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THE EPIDEMIOLOGY AND MANAGEMENT OF PROSTATE CANCER IN NEW ZEALAND

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A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Community Health, Faculty of Medical and Health Sciences, The University of Auckland, 2015.

ABSTRACT

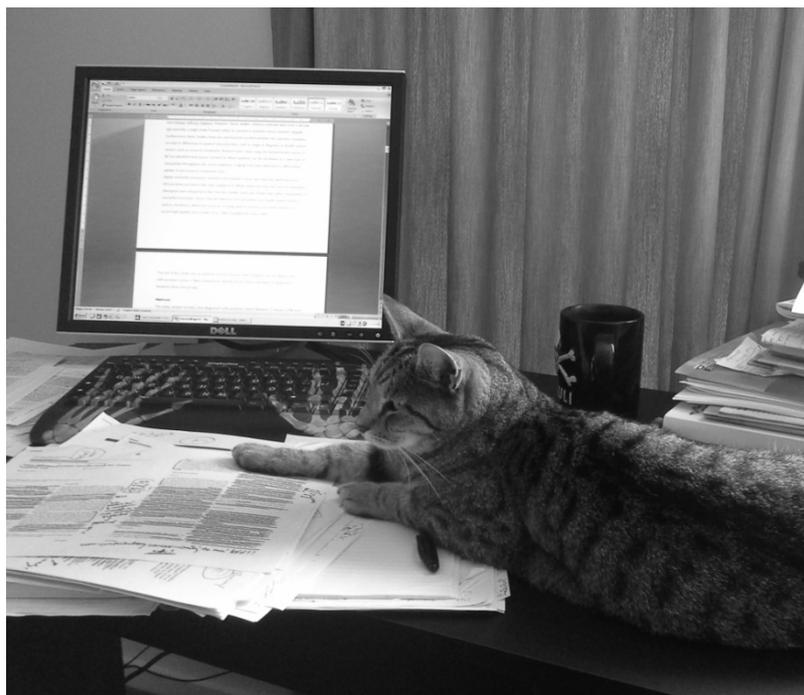
Background: Prostate cancer with its high incidence, prevalence and also relatively high mortality represents a major public health issue in New Zealand (NZ). Ethnic and regional disparities in prostate cancer incidence and mortality have been reported in national and international literature. The aim of this study was to identify causes for the observed differences by obtaining currently lacking information on screening, diagnosis, and management of prostate cancer in NZ men.

Methods: The study was divided into three sections: 1) to describe incidence and survival trends for Māori and non-Māori men and rural and urban men, men aged 40+ years diagnosed with prostate cancer between 1996 and 2010 were identified from the NZ Cancer Registry and Mortality Collection; 2) computerised records of 31 general practices in the Midland Cancer Network (MCN) region linked to laboratory data were reviewed to assess patterns of PSA screening in primary care in 2010, and to examine follow-up investigations, including specialist appointment and biopsy for men with an elevated PSA result by ethnicity, and practice characteristics; and 3) to further assess diagnostic and treatment pathways with a special focus on Māori men, clinical records of all Māori men (150) and three frequency age-matched randomly sampled NZ European men (450) diagnosed with prostate cancer in the MCN region between 2007 and 2010 men were searched retrospectively for information on cancer stage at diagnosis, co-morbidities, and treatment type for localised disease.

Results: Māori men were almost twice as likely to die of prostate cancer compared with non-Māori men. Poorer prostate cancer survival for Māori men is likely explained by lower screening rates, less intensive diagnostic investigations, longer wait times, later diagnosis and differences in treatment observed for Māori men compared with non-Māori men. Although rural men were less likely to be screened, there were little or no differences in diagnostic pathways, incidence and survival of prostate cancer between rural and urban men.

Conclusion: Opportunistic screening for prostate cancer is common in New Zealand but its frequency varies by practice, and by ethnicity. Throughout the prostate cancer care pathway minimal differences were found between rural and urban men, presenting a sharp contrast to disparities observed between Māori and non-Māori men. This study highlighted areas of need for improvement along the prostate cancer care pathway, which will help in guiding policy decisions and resource allocation.

*For my loved ones, who have helped me throughout this journey
And for our precious daughter Sofia*



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ABBREVIATIONS

ADT Androgen deprivation therapy

AS Active surveillance

CCI Charlson Comorbidity Index

CCN Central Cancer Network

CI Confidence interval

DHB District Health Board

DRE Digital rectal examination

EBRT External beam radiation therapy

ERSPC European Randomized Study of Screening for Prostate Cancer

GP General Practitioner

GS Gleason score

HDR High-dose brachytherapy

HOLEP Holmium enucleation of the prostate

HR Hazard ratio

HT Hormonal therapy

LE Life expectancy

LDR Low-dose brachytherapy

LHRH Luteinising hormone-releasing hormone

MCN Midland Cancer Network

NCN Northern Cancer Network

MRI Magnetic resonance imaging

NZ New Zealand

NZCR New Zealand Cancer Registry

PLCO trial Prostate, Lung, Colon and Ovarian trial

PSA Prostate-specific antigen

RCT Randomized controlled trial

RP Radical prostatectomy

RR Risk ratio

RT Radiation therapy

SCN Southern Cancer Network

TRUS Transrectal ultrasound

TURP Transurethral resection of the prostate

WHO World Health Organization

WW Watchful waiting

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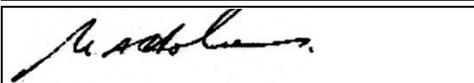
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Certification by Co-Authors

The undersigned hereby certify that:

- ❖ the above statement correctly reflects the nature and extent of the PhD candidate's contribution to this work, and the nature of the contribution of each of the co-authors; and
- ❖ in cases where the PhD candidate was the lead author of the work that the candidate wrote the text.

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Ross Lawrenson	study design, interpretation of data, critical revision of draft, supervision

Certification by Co-Authors

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- ❖ the above statement correctly reflects the nature and extent of the PhD candidate's contribution to this work, and the nature of the contribution of each of the co-authors; and
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Charis Brown		11/06/2014
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Fraser Hodgson	data collection, critical revision of draft
Michael Holmes	critical revision of draft
Charis Brown	data collection, critical revision of draft
Ross Lawrenson	study design, interpretation of data, critical revision of draft, supervision

Certification by Co-Authors

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Fraser Hodgson		11/06/2014
Michael Holmes		11/06/2014
Charis Brown		11/06/2014
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Results; Obertová Z, Hodgson F, Scott N, Brown C, Lawrenson R. 2012. Prostate-specific antigen (PSA) testing in Waikato general practices. Proceedings of the Waikato Clinical School Biannual Research Seminar, Hamilton (New Zealand). N Z Med J 125 (1352) (Abstract)

Nature of contribution by PhD candidate

data collection, data analysis and interpretation, statistical analysis, drafting of the abstract, presentation

Extent of contribution by PhD candidate (%)

80%

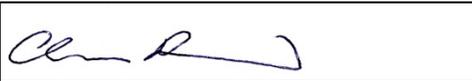
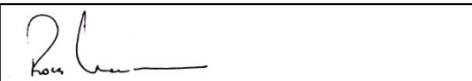
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Nature of contribution by PhD candidate: study design, data analysis and interpretation, statistical analysis, drafting of the abstract, presentation, poster

Extent of contribution by PhD candidate (%): 85%

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Charis Brown	critical revision of draft
Alistair Stewart	critical revision of draft, particularly statistical analysis, supervision
Ross Lawrenson	study design, interpretation of data, critical revision of draft, supervision

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Alistair Stewart		11/06/2014
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Nature of contribution by PhD candidate: study design, data collection, data analysis and interpretation, statistical analysis, drafting of the manuscript

Extent of contribution by PhD candidate (%): 70%

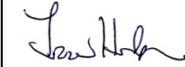
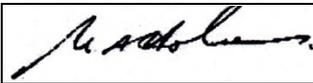
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Results; Lawrenson R, Obertová Z, Brown C, Scott N. 2012. Ethnic differences in screening rates with prostate-specific antigen (PSA) test in New Zealand general practice. 13th Australasian Prostate Cancer Conference, Melbourne (Australia) (Abstract)

Nature of contribution by PhD candidate: data collection, data analysis and interpretation, statistical analysis, drafting of the abstract, poster

Extent of contribution by PhD candidate (%): 75%

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Charis Brown	data collection, critical revision of draft
Nina Scott	interpretation of data, critical revision of draft

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Nature of contribution by PhD candidate

data collection, data analysis and interpretation, statistical analysis, drafting of the manuscript

Extent of contribution by PhD candidate (%)

65%

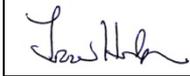
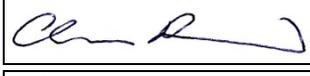
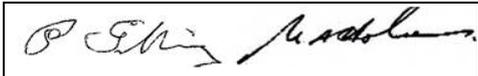
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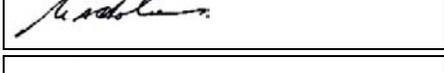
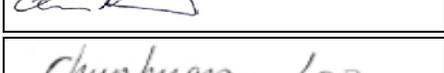
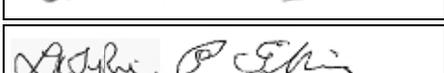
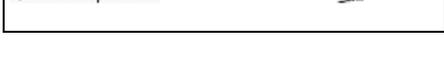
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Nature of contribution by PhD candidate: data analysis and interpretation, statistical analysis, drafting of the abstract, presentation

Extent of contribution by PhD candidate (%): 85%

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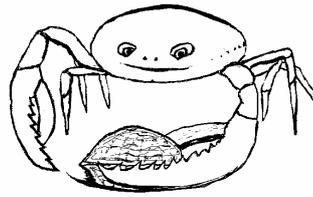
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INTRODUCTION



Prostate cancer (by my talented cousin Dalibor Košš)

Prostate cancer is a major health issue in New Zealand (NZ), with 99.0 incident cases, and 17.4 deaths per 100,000 NZ male population in 2010 [1]. Incidence rate of prostate cancer in NZ is one of the highest in the world, while the mortality rate is higher than in other Western countries, including the USA, Canada and the UK [2]. Similarly to other Western countries, prostate cancer incidence in NZ increased dramatically after the introduction of prostate-specific antigen (PSA) test, raising concerns about over-diagnosis and over-treatment of the disease [3].

As in other countries, ethnic and regional differences in cancer incidence, mortality and survival have been identified for cancer patients in New Zealand [4-6]. Major health disparities have been demonstrated for Māori, the Indigenous people of NZ, who comprise approximately 15% of the total population [4]. Poorer outcomes have been reported for Māori men and women with cancer compared with their non-Māori peers [4, 5]. These have been attributed to differences in stage at diagnosis, access to, timeliness, and quality of health care [4, 7]. In addition, physical distances and financial constraints may pose barriers for accessing optimal health care. Studies from other countries showed that rural men have lower incidence but higher mortality rates of prostate cancer, which may be related to disparities in diagnostic activities and management strategies [8].

Prostate cancer is a complex disease with a variable natural history [9]. Despite advances in molecular biology and genetics, and innovations in imaging techniques and medical instruments that contribute toward a better understanding of prostate cancer development, and identification of novel techniques for prostate cancer diagnosis and management, there are currently still many unknowns and uncertainties regarding prostate cancer risk factors, detection, and management. In the absence of a consensus regarding an optimal detection pathway, and treatment for localised prostate cancer the potential for health system- and patient-related variation is great.

There is currently very little known about prostate cancer detection and treatment and their relation to disease-specific outcomes for NZ men. The aim of this study is to describe patterns of care for men at risk of and diagnosed with prostate cancer, ranging from screening in general practice to management strategies provided by specialist clinicians. This study has also a special focus on identifying differences in prostate cancer incidence, survival and care pathways between Māori and non-Māori men and rural and urban men, with the aim to clarify the causes for any detected disparities.

The first two chapters of this thesis summarise epidemiological patterns and trends of prostate cancer incidence, mortality and survival, and address the intricacies and complexities of prostate cancer screening, diagnosis and management. Chapters 3 to 5 include the results of this study, each opening with a short introduction into the particular area of research, including incidence and survival of prostate cancer for Māori and non-Māori men and rural and urban men, screening for prostate cancer in NZ primary care, and diagnosis and management of localised prostate cancer for Māori and NZ European men. Chapter 6 is divided into four sections: the first three discuss the main findings on the prostate cancer care pathways (for NZ men in comparison with men from other countries, for Māori and non-Māori men, and for rural and urban men), and the fourth section addresses the implications of the results for NZ health policy. In Conclusion (Chapter 7), a better understanding of prostate cancer epidemiology and management and identification of areas of need of improvement within the NZ setting will inform health policy decisions on regional and national level.

CHAPTER 1 EPIDEMIOLOGY OF PROSTATE CANCER

1.1 Natural history of prostate cancer

Prostate cancer is a tumour of the prostate gland in males. The walnut-sized prostate is located in the lower abdomen inferior to the bladder and anterior to the rectum surrounding part of the urethra. In the male reproductive system, the main function of the prostate is to secrete a fluid that comprises 50-75% of the ejaculate [10].

Anatomically, the prostate is divided into four zones [11]: the anterior fibro-muscular zone, the central zone, the transition zone, and the peripheral zone. The anterior fibro-muscular zone encompasses approximately 5% of the prostate and usually does not contain any glandular tissue. The central zone accounts for 20-25% of the prostate mass and surrounds the ejaculatory ducts. In approximately 10% of cases tumours develop in the central zone, and these are often of an aggressive nature [12]. The transition zone is located lateral and anterior of the urethra, and has the ability to grow throughout life, causing benign prostatic hyperplasia (BPH) in elderly men. About 20% of prostate cancers originate in the transition zone. The majority of prostate cancers (up to 75%) develop in the peripheral zone, which represents approximately three-quarters of the prostate gland encompassing the inferior (the apex) to the posterior part of the prostate. Cancerous lesions often develop in multiple foci of the prostate, in more than one zone, and the lesions may have different characteristics [13].

The process of carcinogenesis in prostate cells is currently not fully understood. It is hypothesized that changes in the function of the androgen receptor cause normal epithelial cells to convert into oncocells [14]. In normal epithelial prostate cells the androgen receptor is not expressed, as opposed to epithelial prostate cancer cells, in which the expression of the receptor opens up a signalling pathway directly affecting the proliferation of the prostatic cells [14, 15]. The process involves testosterone in the prostate cells being converted into dihydrotestosterone (DHT) by three isoforms of 5 α -reductase enzymes [16]. Compared with normal prostate and BPH, the expression of isoform I increases in prostate cancer [17]. Type II isoform plays a role in the growth of prostate cancer, while type III isoform is detected mainly in castration-resistant prostate cancer [18, 19].

Based on anatomical, morphological, molecular and genetic observations, high-grade prostatic intraepithelial neoplasia (HGPIN) is considered to be a likely precursor of prostatic carcinoma [20]. HGPIN is characterised by the presence of dysplastic features in the epithelial prostate cells, while the overall structure of the gland remains normal. Following the detection of HGPIN, the risk of developing prostate cancer was 15-80% depending on prostate-specific

antigen (PSA) level [21, 22]. Recently, some studies noted that proliferative inflammatory atrophy (PIA) may precede HGPIN, with the cellular and genome damage due to inflammation potentially contributing to the cancerous transformation of normal prostate cells [23, 24]. Age-related genetic mutations and alterations of metabolic processes may also play a role in the development of prostate cancer [25].

Histopathologically, in 95% of cases prostate cancer is an adenocarcinoma (cancer of the glandular, secretory cells; [26]). Other types of prostate cancer include ductal adenocarcinoma, small-cell carcinoma, basal cell carcinoma, squamous cell carcinoma, and adenosquamous carcinoma of the prostate. These rare cancer types are often aggressive, do not affect PSA levels, and may occur with adenocarcinoma as well as following treatment for prostatic adenocarcinoma [27].

The natural history of prostate cancer varies from indolent tumours with a long pre-clinical phase that may never demonstrate clinically and thus never impact patients' life, to aggressive, incurable metastatic tumours with a considerable impact on patients' quality of life and mortality. Although most prostate tumours are slow-growing, it is currently not known whether indolent cancer can develop into aggressive, rapidly progressing tumours, or whether aggressive cancer follows a different developmental pathway with a shorter pre-clinical phase. The course and potential outcomes of prostate cancer are schematically depicted in Figure 1.

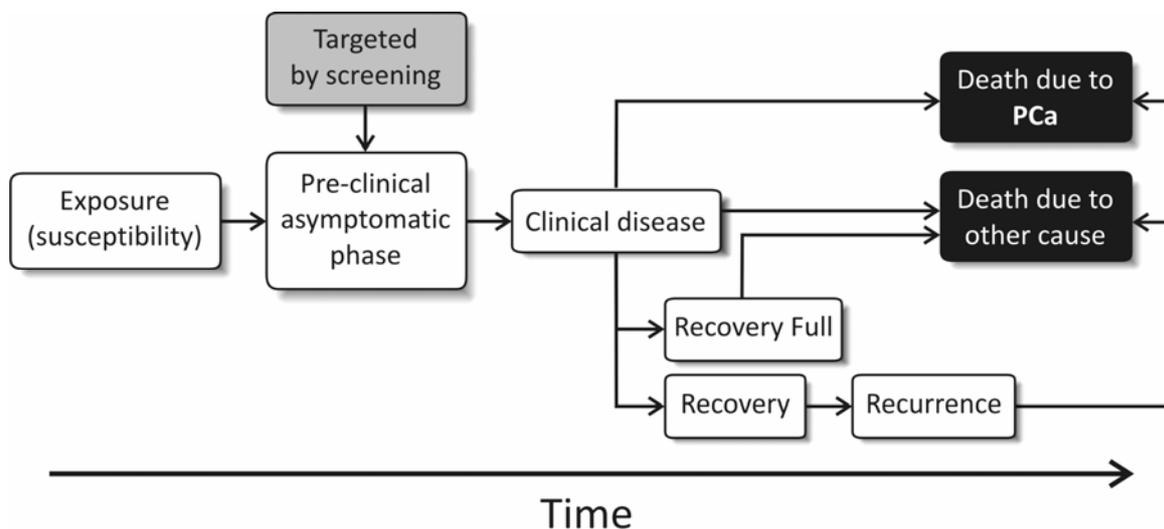


Figure 1 A scheme of the natural history of prostate cancer.

One of the aims of this study is to determine the proportion of prostate tumours detected through screening in the pre-clinical phase as opposed to those detected following symptoms,

and how diagnostic patterns affect mortality in New Zealand men in general, and in Māori and non-Māori men, and rural and urban men in particular.

1.1.1 Risk factors for prostate cancer

The aetiology of prostate cancer is not yet clearly understood. Established risk factors include age, family history, and African-American ancestry [28-31]. In addition, genetic factors, infectious and inflammatory agents [32-34], and exposure to toxic agents, and certain medications [9, 35-37] have been suggested as potential risk factors. The role of diet, mainly polyunsaturated fat intake, obesity, alcohol, cigarette smoking, and sexual behaviour have been discussed as risk factors for prostate cancer but no conclusive patterns have been identified [38-44].

The best-known risk factor for prostate cancer is increasing age. Prostate cancer is extremely rare before the age of 40. Approximately 25-45% of men in their 50s and 60s have histological evidence of prostate cancer at autopsy, with the proportion increasing to 80% for men in their 80s [28, 45, 46].

The risk of prostate cancer increases with a positive family history of the disease. First-degree relatives of men with prostate cancer were found to be two- to three-fold more likely to develop the disease themselves [31, 47]. An increase in risk was also observed with a higher number of affected relatives, and younger age at diagnosis of the affected relative(s) [47-49]. Hereditary prostate cancer accounts for approximately 43% of cancer cases diagnosed in men aged <55 years, in contrast to 9% of tumours diagnosed in older men [49, 50].

It could be argued that family members have an elevated risk of developing prostate cancer because of similar environmental exposures, and potentially more frequent contact with health care providers. However, the hereditary aspect of prostate cancer was confirmed by a higher concordance found for monozygotic than for dizygotic twins [51, 52]. In addition, recent linkage studies have identified a few high-penetrance gene mutations that are related to the development of prostate cancer in families [53], including mutations in the HPC1 locus on the long arm of chromosome 1 [54], and BRCA1 and BRCA2 mutations [55, 56].

In families with prostate cancer linked to HPC1, the diagnosis was usually associated with younger age, and the presence of high-risk and advanced tumours [57, 58]. BRCA1 and particularly BRCA2 mutations have been associated with increased risk of developing prostate cancer, with BRCA2 also being associated with the development of aggressive tumours and consequently higher mortality rate [59-61].

There is currently very little known about the occurrence of hereditary prostate cancer in New Zealand. One study reported that 8% of men visiting private urologists mentioned family history of prostate cancer [62]. However, the reporting pattern was positively associated with higher socio-economic status and education level, which may have resulted in under-estimation of the actual proportion. So far, no studies have investigated whether the presence of hereditary prostate cancer in NZ men varies by ethnicity.

Epidemiological studies have shown that men of African-American ancestry have much higher age-adjusted prostate cancer incidence as well as mortality compared with European-American men [63]. African-American men also tend to be diagnosed at younger age, and with more aggressive tumours [30]. In contrast, Asian men have incidence rates lower than both African-American and European men [2]. Ethnic differences in prostate cancer risk can probably be attributed to a combination of genetic, environmental and lifestyle factors [30, 64].

Differences in genes encoding 5 α -reductase and the enzyme's activity and in the expression of the androgen receptor have been observed between African- and European-American men [65, 66]. Young African-American men have also been found to have 15% higher testosterone levels in blood compared to European-American men, but this difference has not been confirmed among older men [67, 68]. A link between testosterone levels and prostate cancer has been established through observations that eunuchs do not develop prostate cancer, while men who use androgens as anabolics or therapeutics are more likely to develop the disease [9, 37]. However, epidemiological studies have so far provided inconclusive results regarding the association between serum testosterone levels and prostate cancer risk [69, 70].

Although some NZ studies showed a few differences in the frequency of genetic markers between Māori and NZ European people, no information is so far available about whether these differences involve genes or hormones directly related to prostate cancer development [71-73]. One study has reported differences in polymorphisms of drug metabolising genes between Māori and NZ European people, which may indicate that Māori may respond differently to certain medications [74].

Exposure to chemicals, such as pesticides, and Agent Orange (dioxin being most likely the carcinogenic agent in this substance) has been associated with an increased risk of prostate cancer [35, 36, 75-77]. A number of studies have emphasised the close link between farming lifestyle and use of pesticides [35, 76-78]. In New Zealand, farmers were found to have a higher risk of prostate cancer [79]. However, the results of a meta-analysis exploring the association of farming and prostate cancer have been inconclusive [76]. A number of recent studies have

suggested that although there was little evidence for a positive association between farming and prostate cancer in general, the use of certain pesticides was shown to significantly increase the risk of prostate cancer, especially the risk of aggressive tumours [35, 77, 78].

The relationship between prostate cancer and the exposure to Agent Orange has recently been studied in US Vietnam War veterans [36, 75]. Exposed veterans were found to be at greater risk of developing prostate cancer, as well as to have an increased risk of biochemical progression, and more aggressive tumours [36, 75]. Although not part of the present study, future research into prostate cancer incidence and mortality in NZ farmers, and veterans may provide some clarification regarding the distribution patterns of the disease.

The role of environmental factors has been reinforced through migration studies, which showed that prostate cancer incidence of Japanese and Chinese immigrants to the USA, although remaining lower than for African- and European-American men, is higher than for men in Japan and China [80-82]. It is not clear whether the increased incidence of immigrants from low-incidence countries to the USA is due to exposure to Western diet and lifestyle or due to differential health care practices between the two countries regarding PSA screening, and diagnostic procedures [83, 84].

Western diet consisting of high intake of fat and meat has been implicated as one of the risk factors for prostate cancer [38, 85]. However, the results of epidemiological studies on dietary fat intake and prostate cancer risk have been inconsistent [39, 86]. It has been shown that some fatty acids, such as the α -linolenic are associated with an increased risk of prostate cancer [87]. In contrast, a reduced risk of prostate cancer has been associated with high levels of eicosapentaenoic acid (EPA) and docosapentaenoic acid (DHA) [88].

Conflicting results have also been reported regarding the relationship between obesity and risk of prostate cancer [40, 41, 89]. Some studies have shown that obesity was linked to an increased risk of prostate cancer progression, metastases, and cancer-specific mortality [90, 91]. Obesity has been associated with increased levels of insulin-like growth factor I (IGF-1), which promotes normal cell growth but also proliferation of tumour cells [92, 93].

Consequently, higher levels of IGF-1 have been linked to a higher risk of prostate cancer and cancer progression [94, 95].

Considering that Māori men have been shown to have higher rates of obesity, as well as a higher meat intake compared to NZ European men [96, 97], body weight and nutrition may have an influence on prostate cancer patterns in these two groups. However, due to the inconclusive evidence about the effects of these factors on prostate cancer development and

progression, and the lack of individualized information these variables have not been incorporated into the present study.

1.1.2 Prevention of prostate cancer

Considering the natural history of prostate cancer, the disease can be principally prevented either by reducing the rate of transformation of normal into cancerous cells or by delaying the transition from low- to high-risk disease. A number of dietary compounds and supplements, and a few medications have been considered as having the potential to act as protective agents against prostate cancer development or progression.

Chemoprevention studies have targeted two distinct processes thought to be involved in the development and progression of prostate cancer: inflammation, and androgen stimulation [98]. Some epidemiological studies have linked anti-inflammatory drugs to decreased risk of prostate cancer [24], but without randomized prevention trials such association remains inconclusive. Since it has been recognized that the proliferation of prostate cancer cells is dependent on androgens, androgen deprivation therapy (ADT) has been developed as a treatment strategy for men with prostate cancer. However, ADT has not been considered for chemoprevention due to its side effects [99, 100]. Instead, the chemopreventive effect of two 5 α -reductase inhibitors, finasteride and dutasteride has been assessed in large prospective randomized trials – The Prostate Cancer Prevention Trial (PCPT), and the REduction by DUtasteride of prostate Cancer Events (REDUCE) trial [101, 102]. These agents inhibit the transformation of testosterone into DHT within prostate cells, but maintain testosterone levels thereby avoiding the adverse effects associated with ADT. Both finasteride and dutasteride have been successfully used in the treatment of benign prostatic hyperplasia due to their ability to improve urinary symptoms by reducing the volume of the prostate [103, 104].

While both trials showed approximately 20-25% reduced risk of prostate cancer in the 5 α -reductase inhibitors groups compared with placebo groups, the results also showed that finasteride and dutasteride may increase the risk of high-risk cancers [101, 105]. Although several studies have since postulated that rather than increasing the risk of high-risk cancers, the agents only improve their detection [106], the FDA's Oncologic Drugs Advisory Committee decided against recommending the use of finasteride and dutasteride as chemopreventive agents.

The role of diet in prostate cancer development and progression has often been discussed, but there is still little evidence about any single dietary compound being protective against prostate

cancer [107]. Vitamin D and E, selenium, lycopene, isoflavones, and polyphenols have been suggested to decrease the risk of prostate cancer.

Difference in diet, particularly lower intake of dietary fats and higher intake of isoflavones and polyphenols have been used to explain lower incidence of prostate cancer for Asian men compared with African-American and European men [108].

Recent studies have suggested a link between low levels of vitamin D and progression of prostate cancer [109, 110]. Additionally, an ecological study in the USA examining the relationship between UV radiation (the main source of vitamin D) and prostate cancer mortality has provided some evidence about prostate cancer death rates decreasing in a north-south gradient with increasing UV radiation [111]. The findings from epidemiological studies seem to find support in molecular research, which demonstrated that vitamin D inhibits the growth of prostate cancer cells [112].

The positive role of selenium, and vitamin E supplements in preventing prostate cancer had first been established from secondary analyses of skin, and lung cancer prevention trials, respectively [113, 114]. However, the prospective Selenium and Vitamin E Cancer Prevention Trial (SELECT) failed to confirm the protective effect of selenium and vitamin E supplements compared with placebo [115]. Moreover, recent analyses of the trial results showed that vitamin E supplements may actually increase the risk of prostate cancer for healthy men [116]. In contrast, VITamins And Lifestyle (VITAL) study demonstrated that long-term vitamin E supplementation may reduce the risk of advanced prostate cancer [117].

Lycopene intake has been found to be associated with a reduced risk of prostate cancer in some studies but not others, and the results of a meta-analysis showed that the overall positive effect was modest and limited to consumption of high amounts of lycopene/tomato-based products [118-121].

Epidemiological studies have shown that an increased intake of isoflavones in the form of legumes, mainly soybeans reduced the risk of prostate cancer [122, 123]. However, the inverse association between isoflavones and prostate cancer risk has not yet been confirmed by robust prospective randomised prevention trials.

Polyphenols found mainly in green tea have been proposed to have a protective role against prostate cancer based on the association of regular consumption of green tea in Asian populations and lower incidence of prostate cancer in Asian men [124, 125]. Ongoing randomised prevention trials are expected to clarify the relationship between green tea polyphenols and risk of prostate cancer development and progression.

Current knowledge about factors protecting against prostate cancer can probably be best summarised by the results of a study by Arab et al. [126], which found that a healthy lifestyle with balanced diet and regular exercise as recommended by the World Cancer Research Fund is associated with reduced risk of aggressive prostate cancer [107].

In New Zealand, Māori men were found to have similar levels of physical activity as NZ European men, although their dietary habits may differ [96, 97]. Some dietary aspects, such as greater consumption of vegetables and fish by Māori are in accordance with a healthy lifestyle, while greater consumption of meat and smaller amounts of tomato-based products in Māori diet may be seen as potential risk factors for prostate cancer development [97]. One study also explored the exposure to selenium for men with prostate cancer by ethnicity, but found no differences between Māori and NZ European men [127]. Without further studies the preventive or harmful effects of nutritional and lifestyle factors on prostate cancer development and progression remain speculative.

1.2 Screening for prostate cancer

The aim of screening is to identify disease at a stage in its natural history when action can be taken to prevent morbidity and mortality from the disease [128]. Cancer screening targets the disease in the pre-clinical phase, before it progresses to symptomatic disease. For a population-based screening programme to be warranted the disease needs to meet a number of internationally recognized criteria [129, 130]:

- 1) the disease represents an important health problem;
- 2) there is a defined population at risk of the disease;
- 3) the disease has a recognized pre-clinical, asymptomatic period;
- 4) a safe, minimally invasive, acceptable, affordable, highly specific and sensitive, and reliable screening tool exists for the disease;
- 5) there is a best-practice pathway of care, including diagnostic procedures and effective treatment or intervention for early-stage disease;
- 6) there is evidence, preferably from high-quality randomised controlled trials (RCTs) that the screening programme reduces morbidity or mortality;
- 7) the benefits of the screening programme outweigh the harms;
- 8) all steps of the screening programme are ethically, clinically, socially and financially acceptable;
- 9) the screening programme includes strategies for quality assurance and promotes equity.

In case of prostate cancer, the available screening strategies have so far met only few of the above-mentioned criteria. Prostate cancer is certainly an important public health issue, since it is the second most commonly diagnosed cancer, and third most common cause of cancer death in developed countries [2]. It also has a long pre-clinical phase that can be targeted by screening [131]. For the remaining seven criteria the currently available scientific information has been inconclusive. The population at risk is obviously males, most likely older than 40 years. Principally, the risk of having prostate cancer increases with age. However, there is an ongoing debate about whether older men (>70 years) would benefit from screening due to their more limited life expectancy and the presence of co-morbidities that may preclude any intervention if prostate cancer is found [132, 133]. Men with genetic predisposition, and men of African ancestry have been considered to be at higher risk of prostate cancer, therefore screening may be particularly effective for these groups [132, 134]. So far, the effect of other potential risk factors, including environmental, dietary, and physiological characteristics remains unclear. The prostate-specific antigen (PSA) test is currently considered to be the best single test for screening for prostate cancer [135], although it does not meet all of the requirements for an optimal screening tool.

In agreement with the screening criteria, the PSA test is a minimally invasive blood test that is safe, acceptable and affordable. However, the interpretation of the results of a PSA test is not entirely straightforward. With serum PSA level being measured on a continuous scale, there are uncertainties about optimal cut-off values as indicators of prostate cancer. An increase in PSA levels may be caused not only by prostate cancer, but also by other prostatic diseases, including prostatitis, and benign prostatic hyperplasia [136].

For the PSA test, specificity (probability of the test being negative when the disease is absent) and positive predictive value (the probability of having a disease when the test is positive) increase with increasing PSA level, while sensitivity (probability of the test being positive when the disease is present) decreases [137, 138]. At the traditionally employed cut-off point of 4.0 ng/ml about one in four men will have prostate cancer on biopsy, and approximately 20-30% of cancers will be missed [139, 140]. However, prostate cancer may be relatively frequently diagnosed at levels lower than 4.0 ng/ml, and conversely more than a quarter of men with BPH will have a PSA level of >4.0 ng/ml [141, 142]. In a recent study, Holmström and colleagues [143] concluded that no single threshold value for serum PSA level resulted in a positive likelihood ratio (sensitivity/1-specificity) of 10 formally required for a screening test.

Overall, a high number of localized, often indolent tumours are detected through PSA screening [144]. In this respect, a major limitation of the PSA test is its inability to distinguish between indolent and aggressive prostate tumours. It has been estimated that the median survival time for men with early-stage prostate cancer approaches 15-20 years, and even without treatment only approximately one in eight cases of screen-detected prostate cancer will eventually cause death [145-148]. These observations are associated with long lead time (the time by which screening advances diagnosis from the date that clinical symptoms would have occurred without affecting the course of the disease or the time of death) for prostate cancer, estimated to range from 3 to 14 years depending on the data and modelling strategies used and the clinical characteristics of the detected cancers [149-151]. Screen-detected cancers may also represent particularly slowly growing tumours, which may not progress to clinically significant disease during a patient's lifetime, thus introducing so-called length bias to assessments of prostate cancer outcomes [149, 152]. Consequently, detection of indolent tumours may cause more harm than benefit for men, especially if they receive definitive treatment [153].

A definitive diagnosis of prostate cancer can be achieved by prostate biopsy, which is a widely used diagnostic tool with relatively low likelihood of adverse effects [154]. One of the major discussion points in prostate cancer screening is the treatment of early-stage prostate cancer, and whether the existing management strategies lead to improved outcomes for patients [153, 155]. Radical prostatectomy and radiation therapy are the currently available curative treatment types, and they are considered to be equally effective [156]. Since both of these treatment options have been associated with a number of adverse effects that impact on patients' quality of life, there is a concern that men with non-progressive indolent cancers will suffer harm rather than benefit from a definitive intervention [153, 157]. As an alternative, expectant management strategies, active surveillance and watchful waiting have been developed to avoid the harms of definitive treatment but at the same time to closely observe the disease progress, and to intervene with curative or palliative intent if necessary [158, 159]. Although these expectant management modalities have been associated with few physical complications, some studies reported increased anxiety in patients [160]. In addition, there has been so far no consensus about optimal protocols for monitoring the disease progression, so quality assurance may be difficult to assess. Consequently, little agreement currently exists about best practice in the management of early-stage prostate cancer.

The two large published RCTs provided inconclusive results regarding the effect of screening on prostate cancer mortality [161, 162]. However, both trials showed that screening reduces the

incidence of advanced disease, which is an important finding, considering that prostate cancer that spreads outside of the gland is currently not curable.

Due to the many uncertainties concerning screening and management pathways for prostate cancer, it is not clear whether the benefits of a population-based screening programme for prostate cancer would outweigh the harms. Although screening for prostate cancer has been judged as not meeting the criteria for an organised population-based screening programme, unorganised opportunistic screening is common in New Zealand, aggravating the concerns about potential harms of such strategy.

1.2.1 Screening tools for prostate cancer

Prostate-specific antigen (PSA) test and its derivatives

Prostate-specific antigen (PSA) is a kallikrein-related serine protease secreted by prostatic epithelial cells into the seminal fluid. The expression of PSA is regulated by androgens, and its main function is to liquefy seminal fluid [163].

PSA was first identified by forensic scientists in search for a substance in the seminal fluid that may be used as an indicator of the presence of semen in suspected cases of sexual assault [164, 165].

After a successful purification of the PSA from the prostatic tissue, PSA was also identified and quantified in blood serum [166, 167]. The level of serum PSA has been found to be typically very low in men with a healthy prostate, but its levels increase when abnormalities occur within the prostatic tissue, including benign enlargement, inflammation, infection or cancerous growth [167].

In early 1980s, researchers started to investigate the potential of the PSA as a biomarker for prostate cancer [168, 169]. Initial studies demonstrated that fluctuations in PSA levels may be used as an indicator of prostate cancer recurrence and as a tool for monitoring of the therapeutic response [169-171]. As a consequence, the PSA test was first approved by the U.S. Food and Drug Administration (FDA) in 1986 for the purpose of monitoring prostate cancer recurrence and progression [172].

Shortly after the PSA was introduced as a monitoring tool, clinicians started to use the test for prostate cancer detection in symptomatic and asymptomatic men [173]. In response, the original FDA approval was amended in 1994 to include using the test as an aid for detection of prostate cancer [172]. Following the observation that 97 % of all men aged 40+ years will have

PSA serum levels lower than 4 ng/ml [174] the FDA recommended that values above 4 ng/ml shall be considered as indicators of increased prostate cancer risk [172].

Principally, the risk of prostate cancer increases with increasing PSA level: Patients with a total PSA level of >10 ng/ml and a non-suspicious DRE were found to have a likelihood of >40% to harbour prostate cancer [144]. Among men with serum PSA level between 4 and 10 ng/ml 20-30% had prostate cancer on biopsy [139, 140]. However, a number of studies emphasised that about 25% of men will be diagnosed with prostate cancer with a PSA result of 2.0-3.9 ng/ml [141, 175, 176], so lowering the cut-off point may decrease the number of missed cancers. However, lowering the cut-off would also result in increased detection of indolent tumours, so-called over-diagnosis [137, 138].

Since the serum PSA level was also found to increase with age, age-specific cut-off points were proposed to decrease the proportion of unnecessary biopsies in older men, but also to improve detection in younger men with lower PSA levels who may be at risk of prostate cancer [177].

An Austrian screening study confirmed that by using age-specific PSA thresholds cancer detection increased in younger men by 8% while unnecessary biopsies were reduced by 21% in men aged 60+ years [178]. In contrast, another study showed that the use of the age-specific PSA cut-off values resulted in a significant proportion of organ-confined, potentially curable prostate tumours being missed [179].

Besides other prostatic diseases, physical factors affecting prostatic activity, including ejaculation, biopsy, and transurethral resection of the prostate (TURP) were shown to increase serum PSA levels [180, 181], while increasing body weight, and treatment with 5 α -reductase inhibitors have been associated with decreased levels of serum PSA [182, 183]. For men with BPH treated with finasteride or dutasteride adjustments for PSA levels have been suggested for accurate assessments of prostate cancer risk [183]. Similar adjustments may be needed in the future for men with increased body weight, particularly considering the ever increasing prevalence of obesity worldwide.

Some studies have indicated that PSA levels may also vary by ethnicity [184, 185]. In New Zealand, Gray et al. [186] reported that there were no differences in serum PSA levels between Māori and NZ European men after adjusting for co-variates, including lower urinary tract symptoms.

Recently, a number of studies have suggested that measuring “baseline” serum PSA for men in their 40s and 50s may provide reliable estimates of the future risk of prostate cancer, which in turn may help to determine the need for more or less intensive subsequent monitoring [187-

190]. These studies showed that men aged 45 to 49 years with a PSA result of <0.6 ng/ml have an extremely low risk of being diagnosed with prostate cancer in the next 25 years. Others have pointed out that men aged 60 years with PSA levels of <1.0 ng/ml were unlikely to develop clinically significant prostate cancer by the age of 85 years [191].

Due to the recognized limitations of the traditional total serum PSA test, variant forms of PSA have been intensively studied in the past decades. The investigated derivatives include PSA density, PSA velocity, PSA doubling time, percent free PSA (%fPSA), proPSA, Prostate Health Index (PHI), and prostate cancer antigen 3 (PCA3).

PSA density was suggested as a tool for distinguishing whether an increase in the PSA level occurred due to BPH as opposed due to prostate cancer, since an increase in prostate volume has been associated with rising PSA levels [192, 193]. PSA density is calculated as the total serum PSA level divided by the volume of the prostate measured by transrectal ultrasound (TRUS). Some studies have reported that PSA density above 0.15 ng/ml/g was positively associated with the probability of having prostate cancer for men with serum PSA levels between 4.0 and 10.0 ng/ml [194, 195], while others have not corroborated these findings and emphasised that PSA density does not perform better than the PSA test alone [196, 197].

The assessment of PSA dynamics, encompassing PSA velocity (the change in PSA level over time) and PSA doubling time (the number of months for a PSA level to double) was proposed in an attempt to distinguish between indolent and aggressive prostate tumours [198, 199]. An increase of more than 0.75 ng/ml per year between two PSA measurements was suggested as a prognostic factor for positive biopsy. However, there should be at least three measurements preferably 18 months apart, and when PSA levels fall below 4 ng/ml the specificity and sensitivity of PSA velocity decreases sharply [200, 201]. In addition, recent studies have shown that neither PSA velocity nor PSA doubling time added information beyond a single measurement of serum PSA level [202, 203].

Molecular studies have shown that PSA in serum is principally present as free and complexed PSA [204]. The free to total PSA ratio (%fPSA) has been approved as a diagnostic marker for men with PSA levels between 4.0 and 10.0 ng/ml after a %fPSA value of 25% and less have been shown to highly correlate with finding prostate cancer on biopsy [205, 206]. Some studies have shown that measuring %fPSA also aids diagnosis for men with PSA levels of 2.0-3.9 ng/ml [207]. Moreover, low %fPSA has been associated with more aggressive prostate cancer [208].

Elevated levels of proPSA, which is one of the molecular isoforms of free PSA, have been observed in men with prostate cancer [209]. As a diagnostic marker, it seems to perform better

than %fPSA, but more studies are needed to confirm the initial observations [210]. In combination with %fPSA proPSA has also been shown to positively correlate with the presence of aggressive tumours [211].

The Prostate Health Index (PHI) combines the measurements of PSA isoform p2 (%), free PSA and total PSA in a mathematical formula [212]. The PHI has been recently shown to perform better than total PSA and %fPSA in predicting prostate cancer on biopsy for men with PSA levels of 4.0-10.0 ng/ml [213].

The PCA3 is the only urine marker currently used for prostate cancer detection in the clinical practice, and the only prostate cancer-specific marker overall [214]. The PCA3 test is expressed as a ratio between PCA3 mRNA and PSA mRNA [215]. The test is preferentially performed on urine samples collected after DRE or prostate massage [216]. Initially, the PCA3 test was used as a prognostic tool for the presence of prostate cancer on repeat biopsy following a negative biopsy [217], but it has also been investigated as a diagnostic marker, particularly when combined with the PSA test and DRE [218, 219]. The sensitivity of PCA3 for prostate cancer detection was found to range between 53% and 73%, and specificity between 71% and 84% [220, 221].

So far, none of the PSA derivatives has been convincingly shown to be a superior screening tool when compared to total PSA, although percent free PSA has been recognized as a diagnostic marker, and some derivatives, including PSA dynamics and PCA3 have provided additional value as prognostic and monitoring markers. Apart from the total PSA level test and to a lesser extent %fPSA none of the derivatives are currently regularly used in the NZ clinical practice. In conclusion, even though the PSA test cannot be considered to be an optimal screening tool for prostate cancer, it is currently the best one available. In addition, there is little doubt about its value as a prognostic factor for prostate cancer outcomes and as a monitoring tool following treatment for prostate cancer.

Digital rectal examination (DRE)

Digital rectal examination has been used before and alongside the PSA test as a screening tool [161, 222]. During a DRE, the physician inserts his finger through the rectum and palpates the prostate in order to detect any changes to normal prostate anatomy. General firmness and nodularity are considered to be indicative of prostate cancer, but when nodules are identified, the carcinoma is already advanced in more than 50% of cases [223, 224]. In addition, only the posterior and lateral aspects of the prostate can be reached by palpation, so DRE is not

sensitive enough to detect the 25-35% of tumours occurring in other sections of the prostate [225]. Another limitation of the DRE is that it is associated with relatively large inter-individual variability, even among experienced urologists [224].

A meta-analysis showed that sensitivity of DRE in asymptomatic men ranged from 49% to 69%, and specificity was on average 84% [226]. The positive predictive value fluctuated between 5% and 33%, with an average of 18% [226]. In comparison, the same meta-analysis has noted that the sensitivity of the PSA test at 4.0 ng/ml cut-off was on average 72%, and specificity 93%. However, this meta-analysis considered only studies published until 1999. In more recent studies, sensitivity of 21% was cited for the PSA test, but it can be assumed that for DRE the sensitivity would still be below this value [140, 227].

Some studies examined the performance of DRE for men with PSA levels <4 ng/ml, who may not be considered at risk based on the PSA level, with the positive predictive value of DRE being between 10% and 30% [228, 229]. These studies emphasised that at these low PSA levels almost one in five cancers found through DRE would not have been detected by the PSA test, and as expected the majority was clinically significant.

Although DRE is considered to be an inferior screening tool compared with the PSA test [230], it still provides essential information as a complementary diagnostic tool, and also as a prognostic variable in staging schemes [231-233].

Novel biomarkers

Main limitations of the PSA test as a screening marker are its low specificity for prostate cancer and inability to differentiate between indolent and aggressive tumours. To minimize over-diagnosis and over-treatment, a major avenue in the contemporary prostate cancer research is to find a screening biomarker superior to the PSA test.

Biomarkers can be classified based on the biochemical analyte as protein-based, RNA-based, DNA-based, and metabolic-based [234, 235]. In addition, circulating tumour cells (CTCs) represent a special category of biomarkers that have already been approved by the FDA as a prognostic tool for monitoring disease status in patients with metastatic prostate cancer [236, 237].

Protein-based biomarkers are currently the most used (PSA being one of them) and also the most commonly investigated as novel diagnostic and prognostic tools for prostate cancer.

Novel prostate-specific protein-based markers include human kallikrein-related peptidase-2 (KLK2), prostate-specific membrane antigen (PSMA), and prostate stem cell antigen (PSCA)

[238-240]. KLK2 may provide additional value as a diagnostic marker in combination with total and free PSA, but also as a prognostic marker for prostate cancer progression [241, 242]. PSMA has been mainly investigated with regard to its value as a prognostic marker, but so far the results have been inconclusive [239, 243]. Although not entirely prostate-specific, PSCA has been found to have potential both as a diagnostic and prognostic marker [244]. However, its usefulness may be limited because a study showed that PSCA could only be identified in a small proportion of investigated men [245]. Other protein-based biomarkers, such as chromogranin A (CgA) [246], and Caveolin-1 (CAV1) [247] have been associated with advanced disease. RNA-based biomarkers are often investigated in urine, PCA3 being an example. Another well-researched RNA-based biomarker, which has been shown to be over-expressed in prostate cancer, is AMACR (alpha-methylacyl-coenzyme A racemase) [248]. Although AMACR has a limited application as a diagnostic tool, it has proven valuable in prognostic setting as an indicator of biochemical recurrence [249, 250].

DNA-based biomarkers, including TMPRSS2-ERG and GSTP1 are also mostly evaluated in urine [251, 252]. TMPRSS2-ERG is a gene fusion of TMPRSS2 (the androgen-regulated transmembrane protease, serine 2) and Ets family genes (oncogenic transcription factors) unique to prostate cancer, present in up to 50% of men with the disease [253]. Although several studies demonstrated that TMPRSS2-ERG may improve diagnosis and prediction of aggressive prostate cancer on biopsy [254, 255], other studies found little correlation with diagnostic or prognostic outcomes [256, 257].

GSTP1 (glutathione S-transferase pi 1) is down-regulated in prostate cancer tissue due to an alteration in tumour genes [258]. Consequently, GSTP1 has been found to have a high sensitivity and specificity as a diagnostic marker [252]. In addition, there is some evidence that GSTP1 may be of value also as a prognostic marker [259].

Metabolic-based biomarkers are so far quite rare, with sarcosine being one example. Initially, increase in urine sarcosine levels has been associated with cancer progression [260]. However, other studies have not been able to reproduce this result neither in urine nor in cancer tissue [261, 262].

So far, most of the above mentioned biomarkers need to be further evaluated and validated before they can eventually be introduced into the clinical practice.

1.2.2 Benefits and harms of screening for prostate cancer

The unresolved debate about the benefits and harms of population-based screening for prostate cancer has led to a multitude of different guidelines being published internationally [3, 155, 263-266]. The recommendations vary from fully supporting screening to complete abandoning of screening. Interestingly, recommendations by the American Urological Association and US Preventive Services Task Force are based on the same body of literature but reached different conclusions. While the US Preventive Services Task Force recommends stopping screening altogether [155], the American Urological Association (AUA) guidelines say that the benefits of screening outweigh the harms for men aged 55 to 69 years, providing shared decision making was employed [266]. The AUA does not recommend screening for men aged 70 and older or those with less than 10-15 years of life expectancy, and it clearly recommends against screening for men younger than 40 years and average-risk men aged 40 to 54 years [266].

Apart from the clear pro and con screening groups there are some researchers that suggest targeted screening for high-risk groups [132, 134]. In fact, most guidelines mention groups of men who are at higher risk of developing prostate cancer, such as men with family history of the disease or African-American men [3, 263-266]. Although high-risk groups are thought to benefit from screening, not all risk factors for prostate cancer are currently known, and groups who may be more likely to benefit from screening may vary by country or region.

In New Zealand, the National Health Committee does not advocate a national screening programme, but recommends for men to consult their general practitioner about the advantages and limitations of screening during cardiovascular risk assessment starting from the age of 45, or earlier when known risk factors, such as family history of prostate cancer are present [3]. The Urological Society of Australia and New Zealand recommends that men aged 55-69 years are offered PSA test and DRE after being informed about benefits and harms of screening or men at the age of 40 are offered a single PSA test and DRE to assess their risk of prostate cancer [267]. Prostate Cancer Foundation of New Zealand states that men should start annual PSA testing and DRE at the age of 45 or at the age of 40 for men considered at high risk of prostate cancer [268]. Cancer Society New Zealand recommends that men start discussions about benefits and harms of prostate cancer screening from age 50, or age 40 for men with family history of the disease, while the Society does not recommend screening for men older than 75 years [269].

One of the most recent international guidelines is the Melbourne Consensus Statement, which summarises the opinions about screening from world leading urologists, oncologists, general

practitioners, and specialist nurses, who convened at the Prostate Cancer World Congress in Melbourne in 2013 [270]. In contrast to previously cited recommendations, this Statement is primarily based on professional opinions, not on evidence from the scientific literature. There are five main statements included in the Consensus: 1) PSA screening reduces the incidence of metastatic prostate cancer, and cancer-specific mortality for men aged 50-69 years; 2) there is a need to uncouple prostate cancer diagnosis from definitive treatment; 3) PSA test should be used in conjunction with other methods for early detection of prostate cancer; 4) measuring baseline PSA level for men in their 40s may help predicting future risk of the disease; and 5) fit older men with life expectancy of more than 10 years should not be denied PSA screening. Although clearly pro-screening, the Consensus incorporated statements (2 and 3) that may help to alleviate the limitations of using the PSA test as the screening tool.

Advocates of prostate cancer screening argue that it helps detect prostate cancer at an early, curable stage, and potentially reduces mortality from the disease. Conversely, screening opponents state that using currently available tools, i.e. PSA test and DRE for testing asymptomatic men results in over-diagnosis, and subsequent over-treatment of early-stage disease, which causes more harm than good mainly due to the psychological burden of the diagnostic work-up [271, 272], and numerous side effects accompanying definitive treatment [273, 274].

A number of population-based studies and RCTs showed that screening reduces the incidence of advanced prostate cancer, but at the same time increases the incidence of early-stage tumours [161, 162, 275-277]. Diagnosing the disease early means that men may be eligible for curative treatment, but men diagnosed with low-risk disease may also have the option to avoid treatment-related complications by choosing active surveillance as the initial management strategy.

Screening opponents argue that due to the long lead time and length bias associated with the natural history of screen-detected prostate cancer, the majority of these tumours may never cause any health problems, particularly when detected at older age, thus leading to over-diagnosis [155, 272]. Lead-time bias associated with PSA screening was estimated to reach 12 years for a 55-year-old man, while it would be approximately 6 years for a 75-year-old man [150]. Several studies estimated that 20-55% of prostate tumours may currently be considered to be over-diagnosed [151-153].

Part of the argument against screening is also that most men die *with*, not *of* prostate cancer, and the mean age at death of men with prostate cancer is about 80 years [272, 278].

Furthermore, opponents of prostate cancer screening emphasize the harmful effects pertaining to screening, biopsy and treatment. Although screening- and biopsy-related side effects are usually not very common [154, 161], complications associated with treatment, such as urinary incontinence, erectile, and bowel dysfunction may have long-term adverse effect on men's quality of life [157, 273].

It was hoped that the results from two large RCTs would settle the debate about the benefits and harms of PSA screening, but their results were inconclusive. However, the Prostate, Lung, Colon and Ovarian (PLCO) trial reported that screening does not reduce prostate cancer mortality [161, 279], whereas the European Randomized Study of Screening for Prostate Cancer (ERSPC) reported a 20% mortality reduction in the screened group [162, 280]. However, the ERSPC researchers have cautioned that the observed mortality benefit was limited to men aged 55-69 years [162]. Both the PLCO and ERSPC trials reported that screening increased the incidence of prostate cancer, particularly of low-risk, low-grade localized prostate cancer, but also that ongoing screening reduced the rate of metastatic disease [161, 162, 275].

Table 1 summarises the study designs and results of the PLCO and ERSPC trials. Besides the different overall conclusions, these two RCTs differed with respect to age groups involved, intervention strategies, PSA cut-off values for biopsy, biopsy rates, and most importantly in the contamination of the control groups. In the PLCO trial, 52% of men in the control group were screened compared to 20-31% in the ERSPC [281-283]. In addition, almost half of the men in the PLCO trial had one or more PSA tests before they had been recruited for the study, while the proportion of men screened before the ERSPC trial was minimal [281, 284].

The PLCO trial had an annual screening regime, while most men involved in the ERSPC trial were screened every 4 years. Although the question about an optimal screening interval has not yet been satisfactorily resolved, Roobol et al. [284] reported that 4-year screening interval yielded results comparable to a biennial screening regime. Similarly, modelling studies have shown that screening every two years would reduce the number of unnecessary biopsies, while retaining more than 90% of lives saved when compared to annual screening [285, 286].

Along with the above-mentioned factors, treatment strategies may have influenced the outcomes of the two screening RCTs. In the PLCO trial, the distribution of treatment modalities was similar between the screening and the control group [161, 279]. However, in the ERSPC men in the control group diagnosed with high-risk prostate cancer were more likely to be managed with radiotherapy, ADT, or expectantly compared to screened men, who were more likely to receive radical prostatectomy when diagnosed with high-risk prostate cancer [287,

288]. In addition, screened men were more likely to be managed at a university hospital, with access to modern, potentially more intensive treatment compared with men in the control group [287].

Table 1 Comparison of study designs and results of two RCTs evaluating the effect of screening on cancer-specific mortality.

	PLCO [161, 279, 281]	ERSPC [162, 280, 282, 283]
Study population	38,340 screening group, 38,345 control group Age: 55-74 years Recruitment years: 1993-2001 10 study sites in the USA Median follow-up: 11.5 years	72,891 screening group, 89,352 control group Age: 55-69 years Recruitment years: 1991-2003 7 European countries (multiple centres) Median follow-up: 11 years
Intervention	Annual PSA plus DRE for 4 years	PSA every 4 years (Finland, Italy, Spain, Switzerland, Belgium, Netherlands), PSA biannually (Sweden), PSA+DRE+TRUS (Belgium, Netherlands until 1997)
Compliance with screening	85%	82%
Contamination of control group	52%	20%-31%
PSA cut-off	4.0 ng/ml	3.0 ng/ml (Spain, Sweden, Switzerland, Netherlands since 1997), 4.0 ng/ml (Finland, Italy, Belgium, Netherlands until 1997), 10 ng/ml (Belgium until 1995)
PSA above cut-off	7.9%-8.8% (by study year)	16.7% (11.3%-23.3% by country)
Biopsy rate (from positive tests)	30.1%-40.2% (by study year)	85.9% (62.5%-91.1% by country)
Cumulative incidence of prostate cancer	11.1% screening group, 9.9% control group	9.6% screening group (5.1%-12.9% by country), 6.0% control group (2.1%-8.5% by country)
Risk ratio for cancer-specific mortality (screening versus control group)	1.13[95% CI, 0.75, 1.70] at 11 years 1.09 [95% CI, 0.87, 1.36] at 13 years	0.80[95% CI, 0.65, 0.98] at 9 years 0.79 [95% CI, 0.68, 0.91] at 11 years

Two systematic reviews concluded that prostate cancer screening did not significantly decrease prostate cancer-specific mortality [289, 290]. In their Cochrane review, Ilic et al. [289] considered five RCTs for the meta-analysis of the effect of screening on prostate cancer mortality: one from Quebec, Canada [291], two from Sweden - Stockholm, and Norrköping [222, 292], and ERSPC [163], and PLCO [161] trials.

In the Stockholm trial, men aged 55-70 years were randomized to one-off screening versus no screening. The screening tools included a PSA test, DRE, and TRUS, and PSA cut-off level for

biopsy was 10 ng/ml. The authors of this trial concluded that there was no evidence for cancer-specific mortality difference between screened and non-screened men (RR 1.10 [95%CI, 0.83–1.46]) [222].

The Norrköping trial included men aged 50-69 years, the screening interval was 3 years, the PSA cut-off level 4.0 ng/ml and the screening regime included in the beginning DRE alone, which was later combined with PSA. At 15 years of follow-up, no significant difference was observed in cancer-specific mortality between screening and control groups (RR 1.04 [95%CI, 0.64–1.68]) [292]. A more recent analysis of the Norrköping trial reported a risk ratio of 1.16 [95% CI, 0.78-1.73] for prostate cancer death in the screening versus the control group [276].

In contrast to the Swedish trials, the Canadian trial showed a 62% reduction in cancer-specific mortality for screened men following an annual screening regime with PSA and DRE, and by using PSA cut-off level of 3.0 ng/ml for biopsy [291]. However, this trial had significant cross-over and contamination issues, and a subsequent intention-to-treat analysis revealed no difference in prostate cancer mortality between the screening and the control group (RR 1.01 [95%CI, 0.76–1.32]) [289].

The meta-analysis of the five trials returned a risk ratio of 0.95 [95% CI, 0.85-1.07], showing no difference in prostate cancer-specific mortality between screening and control groups [289].

However, the Quebec, Stockholm, and Norrköping study were considered to have an unsatisfactory methodological quality based on the Cochrane criteria.

The other systematic review by Djulbergovic et al. [290] used the GRADE approach and included results of the RCTs from Quebec, Canada [291, 293, 294], Norrköping, Sweden [292, 295], ERSPC [162], PLCO [161], and Göteborg, Sweden [277] in the meta-analysis of screening effect on prostate cancer mortality. This meta-analysis revealed that the overall risk ratio based on an intention-to-screen analysis was 0.88 [95% CI, 0.71-1.09], showing no significant difference in prostate cancer mortality between screening and control groups. However, in support of the ERSPC findings, the Göteborg trial reported a 44% reduction in prostate cancer mortality for screened men at 14 years of follow-up [277]. The Göteborg trial differed from the ERSPC and PLCO trials in that it included younger men aged 50-64 years, and lower PSA cut-off level for biopsy (2.5-3.0 ng/ml).

The ERSPC determined that among men aged 55 to 69 years 1055 men needed to be invited to screening and 37 men diagnosed with prostate cancer to prevent one prostate cancer death at 11 years of follow-up [280]. Compared to the analysis undertaken at 9 years, both the number of men needed to be invited to screening, and the number of men needed to be diagnosed

decreased with longer follow-up [162]. This finding reflects the natural history of screen-detected prostate cancer with its long lead time. Since it has been shown that at least 10 years are needed for screening benefit to become evident [280], many guidelines do not recommend screening for men with a life expectancy shorter than 10 years [264, 265, 296].

Based on the observed differences in the study designs of the PLCO and ERSPC trials, Albertsen [297] pointed out that the PLCO trial actually evaluated the effectiveness of screening comparing a population-based screening programme with opportunistic screening, while the ERSPC reported efficacy of screening versus no screening. As a result, a population-based screening programme seemed to have a similar effect on mortality from prostate cancer when compared with widespread opportunistic screening in a heavily pre-screened population, while screening versus no screening in a relatively screening-naïve population reduced prostate cancer deaths. In addition, it needs to be kept in mind that opportunistic screening in principle may cause unnecessary harm due to the lack of organisation and quality control, while the prerequisite of an organised population-based screening is the presence of clear protocols for intervention, follow-up strategies and quality control.

The majority of NZ and international guidelines stress the importance of information provision for men, and shared decision making about screening between men and their general practitioners [3, 263-265, 296]. However, due to the variety of guidelines and inconclusive results of the RCTs it has often proven difficult for general practitioners to decide what the content of the debate with men should be, and how to provide information in a balanced manner [298-301]. Within the framework of unorganised opportunistic screening, uncertainties often lead to variation between health providers, and promote inequality and inequity in the provision of health care services. The present study will assess the current situation regarding PSA screening in NZ general practice, provision of follow-up investigations and diagnostic pathways for men with prostate cancer.

1.3 Prostate cancer incidence, prevalence, mortality, and survival

1.3.1 Prostate cancer incidence

Prostate cancer is second to lung cancer in incidence worldwide [2]. In New Zealand men, prostate cancer is the most commonly registered cancer, comprising 28% of male cancer registrations [302]. There are approximately 3000 new cases registered annually in a population of 4.3 million inhabitants [302].

New Zealand has one of the highest age-standardised incidence rates of prostate cancer in the world, along with Australia, the USA, and Canada [2; Figure 2].

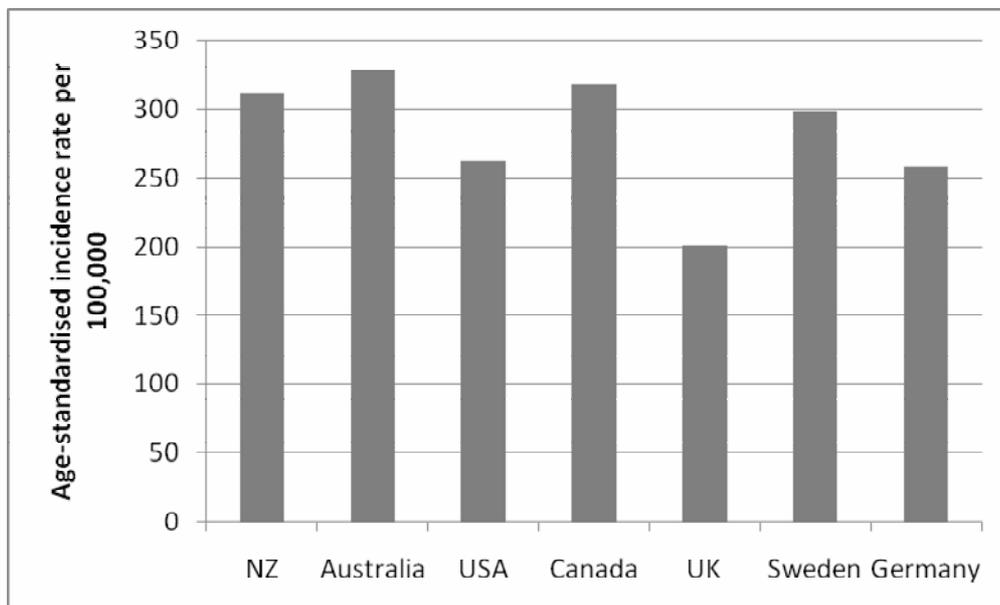


Figure 2 Age-standardised (WHO men 40+ years) prostate cancer incidence rates for NZ, Australia, USA, Canada, UK, Sweden, and Germany [data from Ferlay et al. [2]].

Prostate cancer is generally extremely rare before the age of 40 years, and the incidence increases with increasing age [2, 9]. In New Zealand, the highest age-specific incidence rates of prostate cancer in 2010 were observed in men aged 65-69 years, which likely reflects the high screening rates in this age group [Figure 3].

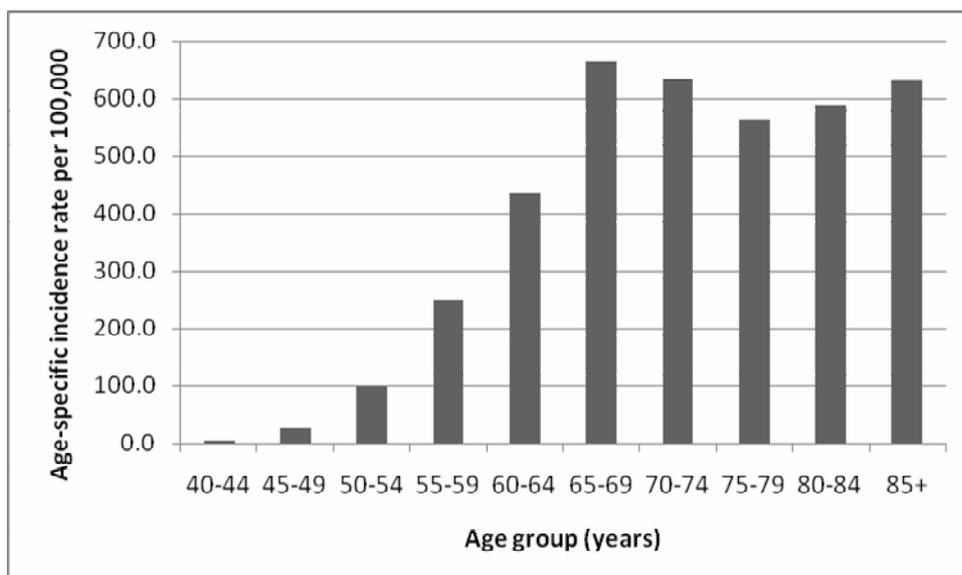


Figure 3 Age-specific prostate cancer incidence rates per 100,000 NZ men in 2010.

The worldwide variation of prostate cancer incidence is more than 25-fold, with the highest rates reported from developed countries of Australasia, Europe, and North America [2]. In contrast, Asian and most sub-Saharan African countries have comparably low incidence rates of prostate cancer [2]. A gradient of decreasing incidence from the poles to the equator and from west to east has been observed, suggesting that environmental factors influence the distribution of prostate cancer [303]. However, the variation between developed and developing countries can also be explained by differences in screening utilization, diagnostic intensity, and potentially lack of completeness of cancer registrations in developing countries [304].

The annual prevalence of PSA testing for men aged 50 years and older has been reported to be about 50% in countries like the USA, Australia, Canada as well as New Zealand, while less than 20% of Japanese and South Korean men in the same age category reported to have a PSA test [3, 305-309]. In comparison, only about 6% of men in the UK were reported having a PSA test [310], which is reflected in the low prostate cancer incidence rate in the country (Figure 2).

A positive association between prostate cancer incidence and the intensity of detection strategies is supported by the fact that the baseline prevalence of prostatic tumours at autopsy seems not to differ between populations [311]. Therefore, increasing incidence rates in developing countries may probably be attributed to changes in both environmental and health care factors, with increasing influence of Western diet and lifestyle potentially increasing the actual risk of prostate cancer, while the adoption of Western cancer detection practices results in diagnosing previously undetected prostate tumours [83, 304].

1.3.2 Prostate cancer prevalence

Second to breast cancer in women, prostate cancer is the most prevalent cancer worldwide [2]. In New Zealand, the estimated 5-year prevalence is about 700 per 100,000 male population, which is similar to countries, such as Australia, the USA, Canada, Sweden and Germany, but higher than the estimated prevalence in the UK (Figure 4). In GLOBOCAN, the 5-year prevalence is calculated as the number of adult persons who have been diagnosed with a given cancer and are still alive at 5 years, regardless of how long ago the initial diagnosis was [2].

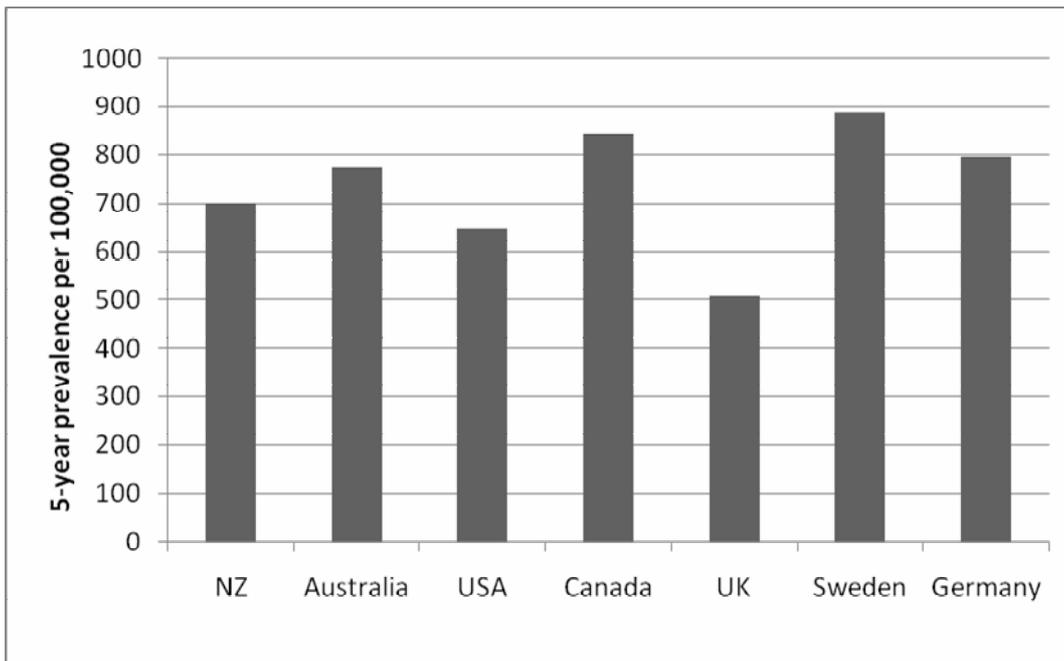


Figure 4 Estimated five-year prostate cancer prevalence for NZ, Australia, USA, Canada, UK, Sweden, and Germany [data from Ferlay et al. [2]].

Currently, prostate cancer in New Zealand is the cancer with the highest 5-year prevalence when compared to other common cancers, such as female breast cancer, lung or colorectal cancer [2; Figure 5]. As prevalence is dependent on both the number of incident cases and the mean duration of the disease, which is relatively long especially for low-risk prostate tumours detected through screening, the already high burden of prostate cancer in New Zealand and other Western countries is estimated to increase with time [312, 313].

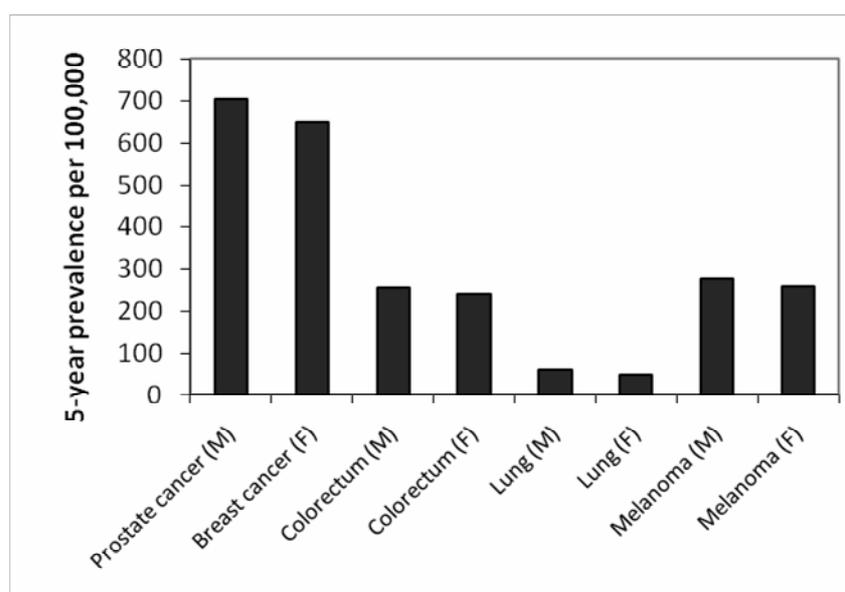


Figure 5 Five-year prevalence of common cancers in NZ; M: males, F: females [data from Ferlay et al. [2]].

1.3.3 Prostate cancer mortality

Prostate cancer is the third most common cause of cancer deaths in developed countries [2]. Prostate cancer is also the third most common cause of male cancer deaths in New Zealand men, comprising 15% of male cancer deaths [302]. The age-standardised mortality rate of 47.3 per 100,000 men aged 40+ years is comparably high, exceeding death rates in Canada, the USA and particularly in the UK, which is a country with low prostate cancer incidence and low screening rates ([2]; Figure 6).

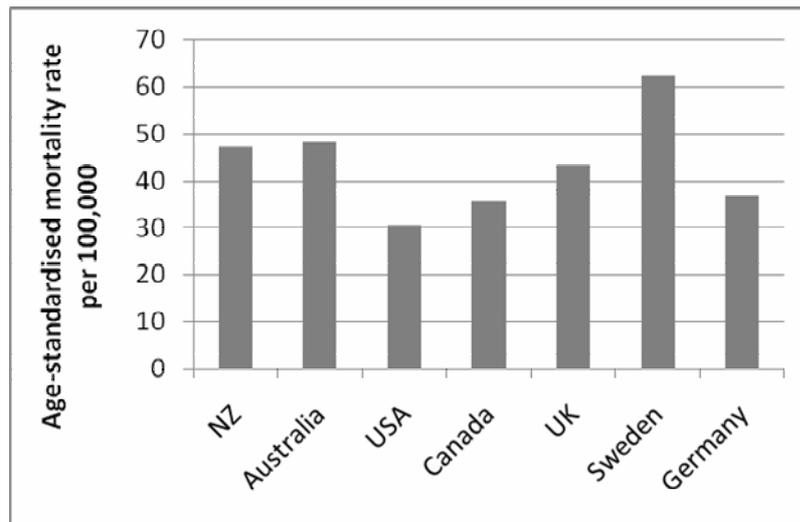


Figure 6 Age-standardised (WHO men 40+ years) prostate cancer mortality rates for NZ, Australia, USA, Canada, UK, Sweden, and Germany [data from Ferlay et al. [2]].

Prostate cancer mortality increases with age and is largely confined to men aged 75+ years [2]. In New Zealand, the age-specific mortality rates for 2008 showed that the majority of deaths occurred in men aged 80+ years (Figure 7).

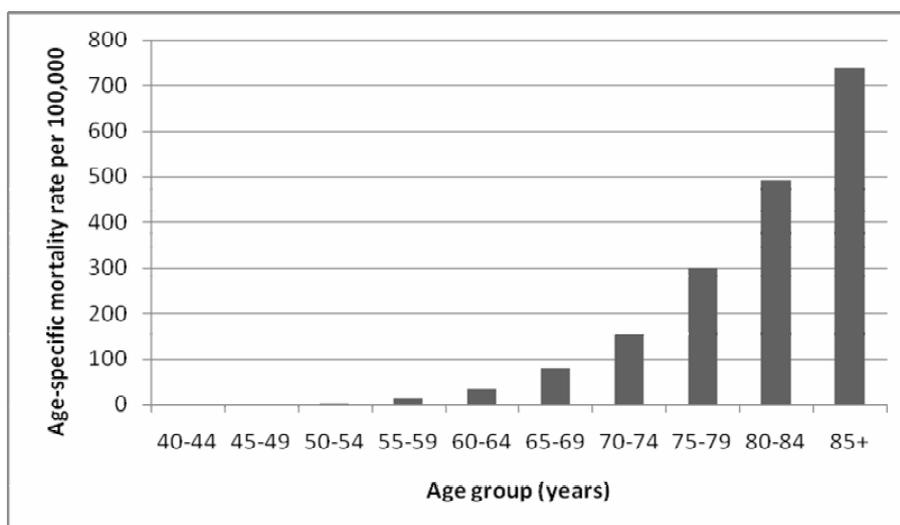


Figure 7 Age-specific prostate cancer mortality rates per 100,000 NZ men in 2008 [data from the Ministry of Health [302]].

Prostate cancer mortality varies considerably around the world, but the differences are less pronounced than for incidence [2]. As with incidence, prostate cancer mortality is mostly greater in Western countries [2]. However, there is currently a trend toward decreasing prostate cancer death rates in Western countries, in contrast to increasing mortality rates in Eastern European and Asian countries [304, 314]. So far, no consistent explanation exists for these trends. It is speculated that in Western countries earlier diagnosis achieved either through screening or intensive diagnostic activity leads to a reduction in the number of advanced prostate cancer cases with poor prognosis, and concurrently innovations in treatment improve outcomes for prostate cancer patients [304, 314-316].

1.3.4 Prostate cancer survival

Cancer survival can be expressed as either relative survival or disease-specific survival [317, 318]. In contrast to cancer mortality (the number of people dying of cancer annually divided by the total population at risk), relative survival compares observed all-cause survival for cancer patients to expected all-cause survival derived from period life tables for the general population. Cancer-specific survival is defined as the probability of surviving a given period of time following cancer diagnosis in the absence of other causes of death. Relative survival is often used for international comparisons, while cancer-specific survival is more suitable for clinical studies and subgroup comparisons within populations.

Relative prostate cancer survival is largely influenced by the “healthy screener effect”, i.e. men diagnosed with prostate cancer are more health-conscious and therefore have a higher life expectancy than the general population [318, 319]. Merrill & Bird [320] found that relative survival has an arc-shaped age distribution, with younger (<50 years) and older men (80+ years) showing poorer survival. This observation may also be partly attributed to the “healthy screener effect”, since screening rates are higher for men aged 50 to 79 years than for those younger and older. Consequently, men younger than 50 and older than 79 years tend to be diagnosed with advanced tumours with poorer survival.

Because of the “healthy screener effect” countries with high screening rates, such as the USA and Canada have prostate cancer relative survival rates close to 100%. The 5-year relative survival was 99% for US men diagnosed with prostate cancer between 2002 and 2008 [63], and 96% for Canadian men diagnosed between 2006 and 2008 (www.cancer.ca/en/cancer-information/cancer-type/prostate/statistics/?region=on). In Australia, the 5-year relative

survival for men diagnosed with prostate cancer between 1998 and 2004 was 85% [321]. In mainland Europe, the 5-year relative survival for men diagnosed with prostate cancer between 2000 and 2002 varied between 58% and 89%, largely depending on the intensity of screening and diagnostic activity in the individual countries [322].

The overall relative survival rates for men with prostate cancer are mainly driven by the proportion and excellent survival rates of men diagnosed with localised disease. Men diagnosed with localised prostate cancer have been reported to survive 15-20 years post-diagnosis, even without treatment, while almost 80% of men diagnosed with distant metastases will die within five years [145-147, 323, 324].

In the USA, the 5-year relative survival for men diagnosed with localised prostate cancer between 2002 and 2008 was 100%, while the 5-year relative survival for men with distant metastases was 28% [63]. Japanese men diagnosed with localised prostate cancer between 2003 and 2005 had also 5-year survival of 100% but the relative survival for men with distant metastases was twice as high as for US men [325]. In Australia, men diagnosed with localised prostate cancer between 1999 and 2007 had 5-year survival of 94% compared with 17% for men diagnosed with distant metastases [326].

In New Zealand, the 5-year relative survival for men diagnosed between 1994 and 2007 was 86% [327]. Interestingly, the 5-year relative survival for UK men diagnosed between 2005 and 2009 was at 81% only slightly lower than for NZ men (<http://info.cancerresearchuk.org/cancerstats/types/survival>). Since screening rates are much lower in the UK than in NZ, it would be expected that NZ would have a higher proportion of men with low-risk localised prostate cancer resulting in a more pronounced difference in survival rates between these two countries. One of the aims of this study is therefore to examine the risk profile of NZ men with prostate cancer in order to clarify the effect of extent at diagnosis on survival patterns.

Difference in survival rates between countries may also be attributed to differential use of treatment for prostate cancer. The USA with excellent survival rates for men with prostate cancer have led the way in implementing innovations in prostate cancer treatment, and have been shown to extensively utilize definitive treatment for localized prostate cancer, and androgen deprivation therapy for men with advanced disease [315, 328]. In New Zealand, very little is known about the distribution of management strategies for prostate cancer and how treatment influences survival of NZ men with the disease.

1.3.5 Temporal changes in prostate cancer incidence, mortality, and survival

Prostate cancer incidence rates in New Zealand revealed similar temporal trends as in other countries with high screening rates, such as Australia, Canada, and the USA, with a rapid increase in the early 1990s, followed by a decline, and subsequent occasional smaller peaks and troughs [63, 304, 329]. The sharp increase around 1990 coincided with the introduction of widespread PSA testing, while the subsequent decline has been attributed to the depletion of the pool of undiagnosed cancer cases [330, 331]. The following occasional smaller peaks with subsequent troughs may be attributed to surges of increased screening and detection activity followed by temporary reduction of prevalent undiagnosed cases [313]. In countries with low or only gradually increasing prevalence of PSA testing, such as Japan and the United Kingdom, incidence rates have continually increased over time, but have not shown the distinct peak with the subsequent decline that has been observed for high-screening countries [304, 314]. In New Zealand, the age-standardised incidence rates increased from 1993, when PSA became widely available [332], to 2000 by 112%, while there was a rate reduction of 26% from 2000 to 2010 (Figure 8).

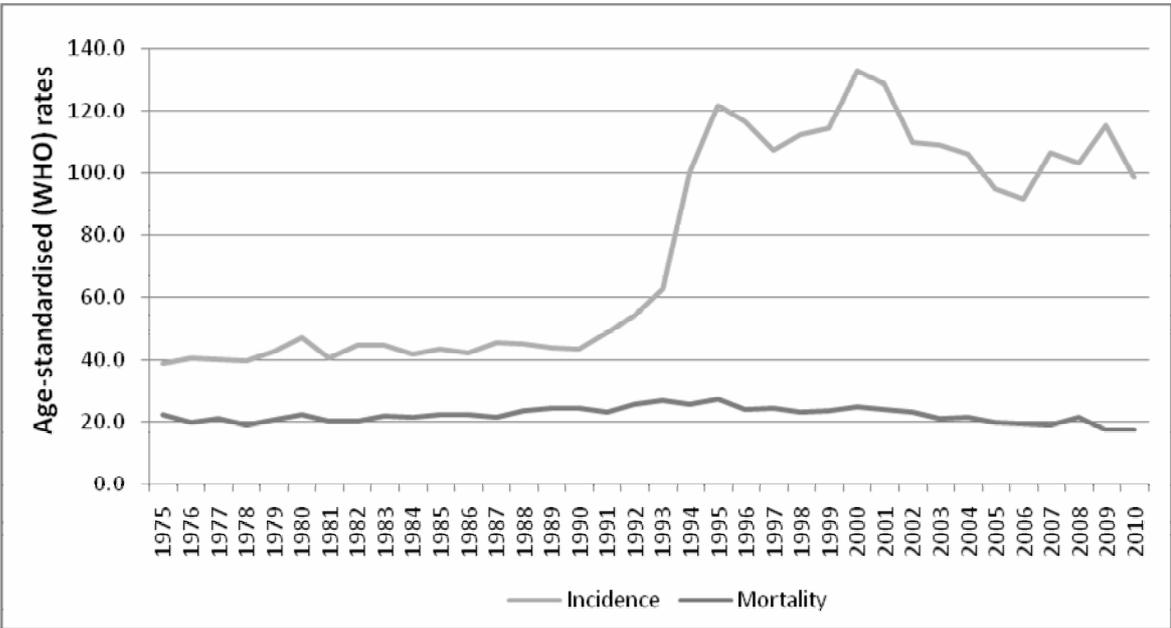


Figure 8 Annual age-standardised (WHO) prostate cancer incidence and mortality rates per 100,000 New Zealand men [data from Ministry of Health [1]].

As the world population ages, a steady rise in prostate cancer incidence would be expected since prostate cancer risk increases with increasing age [28]. However, in most developed countries, incidence of prostate cancer for men aged 75+ years has actually been decreasing over time due to lower screening rates and less diagnostic activity in this age group [304, 313,

333]. The introduction of PSA testing has thus resulted in a reduction of the mean age at prostate cancer diagnosis [304, 333].

Another major shift in the PSA era involves a declining incidence of advanced prostate cancer cases [331, 334, 335]. In countries with a long screening tradition, such as the United States and Australia, more than 80% of men are currently diagnosed with localized prostate cancer [63, 336].

Prostate cancer mortality trends vary more widely than incidence trends [304, 314]. In developed countries, including the USA, Canada, Australia, the UK, and Western European countries prostate cancer mortality rates had been increasing shortly before and after the introduction of PSA testing, but since mid-1990s steady declines have been observed [304, 314]. In contrast, mortality rates are still rising in other countries, mainly Eastern European and South American countries [304, 314].

In New Zealand, the age-standardised mortality rates in New Zealand declined from 1993 to 2000 by 7% and from 2000 to 2010 by 30% (Figure 8). The more rapid decline in the more recent years may be associated with the long-term effects of high screening rates in the country, coupled with continuous innovations in treatment techniques [332, 337, 338].

A number of reasons have been suggested to play a role in the reduction of prostate cancer mortality, including earlier diagnosis, improvements in disease management, changes in the presence of risk factors, and variations in recording of cause of death [304, 339]. The last two alternatives are considered to be the least likely options, since there has been no evidence of distinct changes in coding of causes of death for prostate cancer patients, and a change in risk factors would first cause a reduction in prostate cancer incidence, which had not been the case [304, 329].

The contribution of early diagnosis to declining mortality has been not yet fully resolved. Early diagnosis of prostate cancer has been mainly achieved through screening. Some observational studies have shown a decrease in prostate cancer-specific mortality in regions where PSA screening is common [340-342], while others showed no association between screening intensity and mortality reduction [343, 344].

Since prostate cancer mortality started to decline shortly after the introduction of PSA screening, it has been considered unlikely that PSA screening may have caused such an early change in mortality, especially not with the long lead time of screen-detected tumours [149, 304]. Some researchers have argued, however, that the early waves of widespread PSA testing also detected cancers that had the potential to progress quickly, and through timely treatment

of these cancers mortality could have been improved within a short time frame [331, 345]. Etzioni and colleagues [316] have estimated that 45-70% of the observed decline in prostate cancer mortality in the United States may be attributed to a reduction in late-stage diagnosis as a consequence of screening.

An argument against the positive effect of screening on prostate cancer mortality came from the comparison of temporal trends in the UK and the USA, which found that mortality reduction also occurred in the UK, which is a country with low screening rates [315]. However, the rate of decline was four-times lower in the UK than in the USA, which may actually indicate that extensive screening in the USA has contributed to the decline in mortality [315]. The decreasing trend in mortality rates in the UK may be explained by timely access to diagnosis despite lower screening rates, and also by availability and accessibility of modern treatment modalities for both early and advanced prostate cancer [315, 346].

Improvements in treatment of prostate cancer are the most readily accepted reason for the observed mortality reduction [322, 339, 347, 348]. During the 1990s there were a number of developments for most of the currently available treatment types, such as radical prostatectomy, radiation therapy and hormonal therapy [328], which led to an increase in the proportion of men with prostate cancer receiving these types of treatment [349, 350]. Some researchers have argued that the use of these treatment options, particularly radical prostatectomy, had only increased because through screening more men were diagnosed early enough to fulfil the requirements for curative treatment [331, 351]. In contrast, hormonal therapy, which is not a curative treatment, may have improved prostate cancer mortality by deferring death in patients with advanced disease, who then would have died of other causes [338, 352].

Temporal changes in survival rates largely depend on changes in the proportion of men diagnosed with low-risk disease (mainly through screening) as opposed to the proportion of men diagnosed with metastatic prostate cancer [353, 354]. In contrast to mortality, which can only be improved, i.e. reduced if cancer or death is prevented, survival can also be improved, i.e. increased by diagnosing cancer in the pre-clinical phase. Prostate cancer survival can thus be affected by lead time and length bias introduced through screening. In contrast to mortality, survival improved rapidly in countries with high screening rates, including New Zealand [324, 327]. However, survival substantially improved also in the absence of widespread screening if countries adopted protocols for early diagnosis through rigorous diagnostic work-up [353].

To sum up, temporal trends in incidence, mortality and survival of prostate cancer vary across countries. In developed countries, such as New Zealand, incidence rates have been fluctuating slightly but after a distinct surge and subsequent fall in the early 1990s the number of new prostate cancer cases has been relatively stable. Prostate cancer mortality has been decreasing slowly but steadily, while survival rates have improved rapidly over time, mainly due to the effect of lead time and length bias associated with screen-detected localised prostate cancer cases, which constitute the majority of the incident cases.

1.3.6 Ethnic variation in prostate cancer incidence, mortality, and survival

As shown in Sections 1.3.2 to 1.3.5, prostate cancer incidence, mortality, and survival vary widely between countries. However, these epidemiological parameters have also been found to differ within countries among different ethnic groups [4, 63, 355].

Ethnic differences in cancer incidence, mortality and survival have been associated with genetic factors affecting the biology of the disease, as well as with socio-economic and health-system factors that may lead to inequalities in access to appropriate health services [4, 30, 356-359].

The highest prostate cancer incidence and mortality rates have been reported for African-American men, while Asian-American men have lower incidence rates than European- and African-American men [63]. Recent data from the USA have shown that prostate cancer incidence was almost twice as high, and mortality was more than twice as high for African-American men than for European-American men [63]. In addition, epidemiological studies have observed that African-American men were more likely to be diagnosed with advanced prostate cancer [356, 360], and when treated with radical prostatectomy had a higher rate of disease recurrence compared with European-American men [361, 362]. Apart from genetic factors, the observed disparities between African-American and European-American men may also be partly related to the US health system, since in the UK no differences have been found in cancer stage at diagnosis between men of European and African ancestry [363, 364].

Higher mortality rates for African-American men may be attributed to later stage at cancer diagnosis, more aggressive prostate tumours, but also differences in treatment compared with European-American men [358-360]. Several studies have demonstrated that even when age, cancer stage, and co-morbidities were accounted for, African-American men were more likely to be managed expectantly and were less likely to receive definitive treatment [365-367].

A systematic review of studies focusing on ethnic differences in prostate cancer survival that accounted for clinical and socioeconomic parameters found that African-American men showed

an increased risk of dying of prostate cancer compared with European-American men [368]. Some researchers have argued that while outcomes for localized disease were similar between African-American and European-American men, African-American men were more likely to have poorer outcomes when diagnosed with advanced prostate cancer [30, 63]. However, a number of studies pointed out that after adjustment for demographic characteristics, clinical cancer stage, co-morbidities, socio-economic position and treatment outcome disparities between African-American and European-American men were greatly reduced or even eliminated [359, 365, 369].

In Australia, incidence of prostate cancer has been reported to be lower among Aboriginal men compared with men of European ancestry [370, 371]. Few studies have included information about prostate cancer mortality and survival among Aboriginal men, and the reported patterns have been inconsistent [372-375]. Little is known about the causes of disparities between Aboriginal and non-Aboriginal Australians specifically for prostate cancer, but for other cancers it has been shown that Aboriginal people were more likely to be diagnosed with advanced disease, and were less likely to receive curative treatment [355, 372, 376].

In New Zealand, Robson & Harris [377] reported that between 2000 and 2005 Māori men were about 25 % less likely to be diagnosed with prostate cancer compared with non-Māori men. In contrast, Māori men were almost 50 % more likely to die of the disease than non-Māori men. In 2010, age-standardised prostate cancer incidence rate was 86.4 per 100,000 male population (WHO) for Māori men compared with 100.2 per 100,000 for non-Māori men [1]. It can be speculated that the differences in incidence rates may be explained by variations in screening and detection practices between Māori and non-Māori men, but no studies so far have provided information regarding screening and diagnostic pathways by ethnicity.

Prostate cancer mortality in 2010 was 28.7 per 100,000 male population (WHO) for Māori men compared with 16.7 per 100,000 for their non-Māori peers [1]. From 2000 to 2009, age-standardised mortality rates were reduced by 17% for Māori men compared with a 32% reduction for non-Māori men (Figure 9). It is not clear why prostate cancer mortality improved faster for non-Māori men but it may be assumed that unequal access to screening, early diagnosis and treatment contribute to these disparities.

A number of studies have reported that compared with non-Māori men Māori men had poorer prostate cancer survival [5, 6, 378, 379]. Soeberg et al. [379] demonstrated that although relative survival improved over time for both Māori and non-Māori men with cancer, Māori

men had poorer survival for a number of cancers, including prostate cancer throughout the study period.

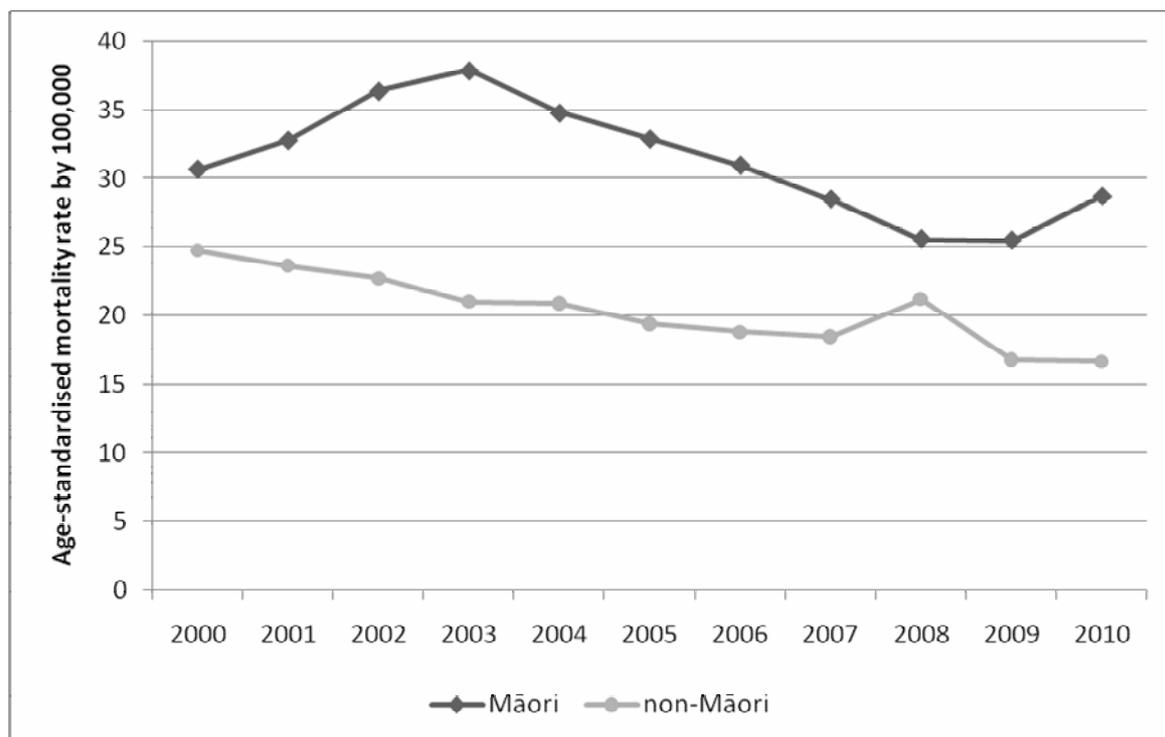


Figure 9 Annual age-standardised (WHO) prostate cancer mortality per 100,000 Māori and non-Māori men [data from Ministry of Health [1]].

Sneyd [378] showed that Māori men were more likely to die of prostate cancer within the first 1-1.5 years post-diagnosis. Sneyd [378] suggested that this finding may be attributed to Māori men being more likely to be diagnosed with advanced disease, but the data provided not sufficient information to support such interpretation. Other explanations for poorer survival for Māori men included differential access to and quality of treatment, and greater burden of co-morbid conditions [5, 6, 378].

Poorer outcomes for ethnic minorities with prostate cancer have been largely explained by differences in socio-economic status; with socio-economically disadvantaged people often experiencing difficulties in accessing health care [358, 359, 364, 371]. In New Zealand, socio-economic position is strongly correlated with ethnicity, with Māori population being more socio-economically disadvantaged [377, 380, 381].

Robson & Harris [377] found that despite lower incidence rates Māori men were more likely to be admitted for prostate cancer to public hospitals compared with non-Māori men. The authors therefore suspected that Māori men may be more likely to present with late-stage disease. An alternative explanation put forward by Robson & Harris [377] was that non-Māori men may be

more likely to be managed in the private sector. Consequently, differences in mortality and survival between Māori and non-Māori men with prostate cancer may be attributed to variations in health care pathways by ethnicity. This study aims to examine prostate cancer care pathways for Māori and non-Māori men to elucidate whether and where along the pathway differences occur.

1.3.7 Rural-urban variation in prostate cancer incidence, mortality, and survival

Assessment of geographical patterns of prostate cancer incidence, mortality and survival is important in order to detect any disparities in access to diagnostic and treatment services. In particular physical distances to access primary and specialist health care have been suggested to disadvantage rural patients [382, 383].

Our recent review of international literature on prostate cancer incidence and mortality for rural and urban men showed that the majority of studies reported higher incidence rates in urban men, while mortality rates showed more heterogeneous trends [8]. Lower incidence rates of prostate cancer for rural men have been mainly associated with lower PSA screening rates for men in rural and remote areas [307, 384, 385]. Apart from screening, the intensity of diagnostic activity for suspected cancer may influence incidence rates, as has been shown by Dey et al. [386], who observed that in Egypt better detection possibilities in a cancer centre increased the incidence rate two-fold.

Interestingly, some of the most recent studies from mid-2000s have reported similar incidence rates between rural and urban men [307, 387]. This trend may reflect a shift toward more diagnostic activity in rural areas or a saturation of new cancer cases in urban areas.

While some studies identified higher mortality rates for rural residents, who faced long distances to cancer services [384, 385], others found no differences in death rates between rural and urban men with prostate cancer [388, 389]. There was some evidence that after PSA testing was introduced, mortality rates tended to be higher for rural men compared with urban men [307, 385]. It has been shown that urban men had higher rates of screening, which is related to earlier diagnosis and potentially improved mortality, while conversely poorer outcomes for rural men may be associated with later stage at diagnosis [307, 384, 385]. Several studies have indeed reported that rural men were more likely to be diagnosed with advanced prostate cancer [384, 390]. Difference in treatment may also contribute to rural-urban disparities in prostate cancer mortality [391, 392].

Similarly to mortality, prostate cancer survival has been shown to be poorer for rural men compared with urban men [383, 391, 393]. However, the differences were reduced after adjustment for stage at diagnosis [393].

The variation in rural-urban incidence and mortality patterns may also be attributed to variable definitions of rurality, and differences in demographic characteristics between rural and urban residents [8]. The concept of rurality and remoteness may vary considerably between countries largely depending on their land mass [4, 307, 394]. In addition, comparisons between countries were also limited by different measures defining rurality, such as settlement size, population density, accessibility to services (i.e., distances or travel times to service centres), economic activity (i.e., employment opportunities) or a combination of these [8].

Rural populations often differ from urban populations with respect to age, overall health status and socio-economic position. In many countries, rural residents tend to be older, poorer and have a higher burden of chronic diseases than their urban counterparts [384, 385, 388]. These factors may affect a man's ability and willingness to travel longer distances for cancer detection or treatment, which in turn may lead to poorer outcomes for rural men.

A number of US studies also showed that differences in ethnic composition between urban and rural populations may considerably influence prostate cancer incidence and mortality rates [388, 390, 395]. Liff et al. [390] showed that rural African-American men were more likely to be diagnosed with distant metastases, and concurrently less likely to be diagnosed with localised prostate cancer compared with urban African-American men, while there was no difference in stage distribution between rural and urban European-American men.

Little information is currently available on rural-urban pattern of prostate cancer incidence, mortality and survival in New Zealand. Studies on gastrointestinal, female breast, and cervical cancer reported that rural-urban residence has little influence on survival [396-398]. In contrast, Robson et al. [4] reported poorer survival for rural residents with prostate, lung, colorectal and uterine cancer. However, the authors acknowledged that these differences may be rather attributed to differences in the demographic structure between rural and urban population than to rural residence as such.

CHAPTER 2 DIAGNOSIS AND MANAGEMENT OF PROSTATE CANCER

2.1 Diagnosis of prostate cancer

In contemporary clinical practice, the most common pathway to prostate cancer diagnosis starts with elevated serum PSA value or a suspicious DRE result, followed by prostate biopsy. The majority of men commence the pathway without symptoms, by being screened [399]. The main concern about this pathway is that many screen-detected tumours may be indolent, resulting in over-diagnosis and over-treatment [333].

About 20-30% of men, who will be later diagnosed with prostate cancer, present with symptoms, including lower urinary tract symptoms (LUTS), erectile dysfunction, tiredness, loss of weight, and bone pain [400, 401]. LUTS may occur when prostate tumour becomes large enough to compress the urethra and thus disrupt the normal flow of urine [402]. The LUTS reported among men with prostate cancer were hesitancy, leakage of urine, urgency, dysuria, weak stream, and frequency [403-405]. However, LUTS have been more commonly associated with BPH [400, 402, 405]. Although prostate cancer and BPH can co-occur, having BPH is not considered to be a risk factor for prostate cancer [402, 406]. The correlation between LUTS and prostate cancer is unclear, since men with LUTS may be more likely investigated by a specialist and as a consequence diagnosed with prostate cancer, even though the real cause of the observed LUTS may be BPH or other diseases rather than prostate cancer [407, 408].

Conversely, the presence of BPH may decrease the likelihood of detecting prostate cancer on biopsy, since the size of the prostate gland is inversely related to tumour yield on biopsy [408]. Some men with prostate cancer may originally present with sexual dysfunction, but it is not clear whether prostate tumour directly influences the development of sexual difficulties [400]. Advanced prostate cancer has been associated with back, hip, and pelvis pain, loss of weight, and general tiredness [409].

Before the widespread use of PSA testing and prostate biopsy, prostate cancer was often identified incidentally from histopathologic examination of prostatic tissue obtained by transurethral resection of the prostate (TURP), holmium enucleation of the prostate (HOLEP), or radical cystoprostatectomy (RCP) for transitional cell carcinoma of the bladder [331, 410, 411]. Approximately 5-15% of men undergoing TURP or HOLEP for BPH were shown to have prostate cancer [411, 412]. Among men undergoing RCP prostate cancer was reported in up to 46%, but the majority of the detected tumours were indolent [413, 414].

In the 1990s, elevated PSA results and abnormal DRE were considered to be the best predictors of prostate cancer, since it has been demonstrated that especially PSA level at diagnosis

correlates well with the likelihood of finding organ-confined tumours on biopsy [415]. At a PSA level of < 4 ng/ml and negative DRE 81–84% of detected tumours were organ-confined, while the likelihood of detecting organ-confined disease decreased to 53-67% for men with a PSA level of 4-10 ng/ml, dropping further to 31-66% for men with PSA level of 10-20 ng/ml [415, 416]. In addition, it has been shown that the likelihood of detecting metastases on bone scan is virtually zero for asymptomatic men with a PSA level below 20 ng/ml [417].

Although PSA level alone or in combination with DRE is still considered to be a sufficient indicator of positive biopsy on a population level, using these two parameters have been shown to be unsatisfactory when deciding on an individual basis whether by performing a biopsy the benefit of detecting a curable tumour would outweigh the harm of diagnosing indolent cancer [418].

Therefore, finding accurate tools that would help to predict detection of potentially progressive, but curable prostate tumours, and concurrently minimising over-detection of indolent tumours has become a research priority [419]. As a solution, so-called risk calculators or nomograms have been introduced that allow for calculating probabilities of detecting prostate cancer on biopsy on a personalised basis [420, 421]. Early risk calculators included PSA level, DRE, age, ethnicity and family history, while the most recent ones have incorporated additional parameters, such as PSA velocity, PSA density and PCA3 to further improve prediction accuracy [419]. Some of the recent risk calculators have been developed to provide also a prediction of detecting indolent tumours on biopsy [419, 422]. Overall, risk calculators have been shown to reduce the number of unnecessary biopsies without missing potentially aggressive tumours [423, 424].

Prostate biopsy

Prostate biopsy is crucial for a histopathological confirmation of the diagnosis of prostate cancer [425, 426]. The decision when to proceed to a biopsy is not a straightforward one, but is typically guided by PSA level, DRE result, patient's age, family history of prostate cancer, co-morbidities, and in some cases by values of PSA derivatives or other biomarkers, such as PSA velocity or PCA3 [264, 265, 296].

Prostate biopsy can be performed transrectally or transperineally. Transrectal ultrasound-guided (TRUS-guided) sextant biopsy of the prostate was introduced approximately at the same time as PSA screening started to be widely used [427]. Therefore, the sharp increase in prostate cancer incidence may also be partly attributed to improved detection of prostate tumours on

biopsy [428]. Since then further advancements in biopsy techniques have included extended biopsy schemes, and three-dimensional transperineal template-guided biopsy.

A number of studies demonstrated that extended biopsy methods including 8-12 cores increase cancer detection by 15-30% compared with traditional sextant biopsies [429, 430]. However, increasing the number of sampled cores beyond 12, as is the case in saturation biopsies, has not provided any additional benefit for prostate cancer detection [430, 431]. Since cancer detection rate decreases with increasing prostate volume, an Austrian team has introduced a nomogram for predicting the number of cores needed for a maximum detection yield of prostate biopsy for men with PSA levels between 2 and 10 ng/ml by accounting for prostate volume and patient's age [432].

Originally, the main advantage of transperineal biopsy was its lower infection rate compared with transrectal biopsy [433], but recently the main benefit of transperineal biopsy is the use of the template-guided method, which allows systematic sampling in small grids of the whole prostate gland [434]. Transperineal template-guided biopsy is commonly used for men with one or more previous negative TRUS-guided biopsies and persistently elevated PSA result, since by using this method significant tumours may be detected, mainly in the transition zone of the prostate [435]. In addition, transperineal template-guided biopsy may also improve risk stratification for men who consider active surveillance as initial treatment and helps targeting prostatic tissue for focal therapy [159, 436].

For men with previous negative TRUS-guided biopsy a repeat biopsy may be considered when PSA levels are rising or PSA derivatives, such as PSA velocity and doubling time indicate changes in the PSA level, when DRE is suspicious, or when the initial biopsy returned a suspicious histology finding, including atypical small acinar proliferation (ASAP) or multifocal HGPIN [437]. In some cases, ancillary staining techniques of the suspicious prostate tissue acquired from the initial biopsy may be employed to clarify its characteristics [438]. A recent US study reported that approximately 40% of men have a repeat biopsy within 5 years of the initial biopsy [439]. Cancer detection rate on repeat biopsies varies between 10% and 40% depending on target zones, and the extent of the initial biopsy [440]. However, the yield of any biopsies following the second biopsy has been shown to be minimal and also these biopsies were associated with increased risk of complications [441].

For an initial TRUS-guided prostate biopsy the rate of significant complications has been reported to be less than 2%, while mortality rate was virtually zero [154, 142, 442]. However,

biopsy is not completely complications-free, with bleeding, sepsis, urinary retention, and severe pain being the most commonly observed adverse effects [154, 442].

Minor bleeding has been found to be relatively common, with 20-80% of patients reporting haematuria, rectal bleeding, or hematospermia [154, 442]. Sepsis has occurred in up to 3% of men following TRUS-guided biopsy but only in up to 0.5% of men who underwent transperineal biopsy [154, 443]. Several studies have reported a rising hospitalization rate after TRUS-guided biopsy due to sepsis caused by antibiotic-resistant strains of *Escherichia coli* [444, 445].

Approximately 5-10% of men experienced urinary retention after transperineal biopsy in contrast to only about 1% of men who underwent TRUS-guided biopsy [154, 443]. Up to 8% of men associated severe pain with TRUS-guided biopsy [442, 446].

The histopathological evaluation of biopsy specimens is summarized by the so-called Gleason score [447]. The Gleason score is generated by adding the most dominant histological tumour pattern to the next most common histological pattern, with the highest (most aggressive) grade being 5 and the lowest 1 [447, 448]. Following recent adjustments, Gleason score including tumours of grade 2 and lower should not be mentioned in the histological report [448, 449].

Some studies have also debated the value of Gleason score 6 (3+3) since labelling such lesions as cancer despite their excellent prognosis may result in over-treatment [450, 451]. However, histopathological evaluations based on biopsy have limitations when compared with evaluations of whole-gland specimens acquired by radical prostatectomy in that the Gleason score derived from biopsy specimens often under- or over-estimates the actual cancer grade identified from the respective radical prostatectomy specimens [448, 452]. While Gleason score of 6 was upgraded to Gleason score of 7 for up to 90%, but mostly for 30-50% of specimens [453], Gleason score of 8-10 was down-graded for 45% of specimens [454].

In New Zealand, recently published prostate cancer management guidelines emphasize the need for improvements in the uniformity and quality-assurance of pathological reporting on regional and national level [455]. An accurate and standardised histopathological evaluation of biopsy specimens is crucial for risk assessment of prostate cancer patients, and consequently for decision-making regarding the management of the disease.

Imaging

In addition to the widely used prostate biopsy, modern imaging techniques provide new, non-invasive approaches for prostate cancer detection, risk assessment, and staging. Traditionally, transrectal ultrasound (TRUS) has been used to visualize lesions suspected to be cancerous in

the prostate, but its specificity and sensitivity in detecting cancer as well as staging prostate tumours are limited, and the readings are largely operator-dependent [456].

Recent advances in imaging technology have provided new avenues for prostate cancer detection, localization, and staging. It is expected that incorporating non-invasive imaging into the prostate cancer detection pathway will allow for better selection of men for prostate biopsy, accurate differentiation of indolent and aggressive tumours, and improved staging, which in turn will aid selecting and planning of disease management strategies. The imaging methods currently used or investigated for prostate cancer detection and staging include computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), bone scintigraphy, single photon emission computed tomography (SPECT), and PSMA-targeted imaging.

Computed tomography (CT) was used for staging advanced prostate cancer but has been recently superseded by MRI [457, 458]. MRI provides superior soft tissue contrast when compared with CT and ultrasound imaging by clearly depicting the zonal anatomy and margins of the prostate [458]. Multiparametric MRI, which combines two or more MR sequences, has been reported to accurately localise cancerous lesions in the prostate and thus may be used as a tool for guiding biopsies [458]. It has also been demonstrated that MRI currently represents the best non-invasive method for staging prostate cancer, particularly for identifying extracapsular spread [459]. In contrast, for detection of lymph node invasion MRI has relatively poor sensitivity and specificity, similar to CT [460]. Both methods use solely lymph node size of 1.0 cm and larger as a criterion for malignancy, although it is known that lymph node metastases can occur in smaller nodes, and node enlargement may have a benign cause [460]. Interestingly, whole-body MRI has been found to provide excellent information about small bone metastases, with a detection rate superior to the widely used bone scintigraphy [461]. MRI may also be helpful in differentiating clinically significant prostate cancer from indolent tumours, thus providing a tool for reducing the number of unnecessary biopsies [462, 463]. However, this approach has not yet been widely utilized due to cost, technological and personnel requirements.

MRI spectroscopy has recently emerged as a method that utilises the metabolic information of citrate and choline, with decreased levels of citrate and increased levels of choline being indicative of prostate cancer [464]. This method has been suggested to be helpful for cancer localization, staging, and progression assessment following treatment [464].

Positron emission tomography (PET) is usually combined with CT to visualize metabolic changes associated with lymph node invasion by using radiotracers [465]. Fluorine-18 2-Fluoro-2-Deoxy-D-Glucose (^{18}F FDG), and ^{18}F - or ^{11}C -choline have been investigated as the positron-emitting radioactive isotopes [465]. Although ^{18}F FDG has been found to be non-specific for early prostate tumours, some researchers have pointed out that it may be used as an indicator of tumour aggressiveness [466]. ^{18}F FDG-PET may also be utilised as a complementary imaging method to bone scintigraphy since it has been shown that ^{18}F FDG-PET has an ability to depict soft tissue and bone marrow metastases [467].

The most commonly used PET radiotracer for prostate cancer detection is currently ^{18}F - or ^{11}C -labeled choline, since it has shown an increased uptake in prostate cancer cells [468, 469]. However, the role of radiolabelled choline for staging of prostate cancer is unclear [470]. ^{11}C -labeled acetate has also been reported to accumulate in prostate cancer cells [471], although as with choline, the potential of using radiolabelled acetate for staging has not yet been clarified [472].

Bone scintigraphy using $^{99\text{m}}\text{Tc}$ -methylene diphosphonate is a well-established imaging technique for identifying metastatic bone lesions in men with prostate cancer [473]. Although the scintigraphic image is of lower resolution than MR or CT images, the advantage of this method is that it reflects functional processes on cellular level, similar to PET imaging [474]. PSA levels higher than 10 ng/ml associated with T2 clinical stage, PSA levels of >20 ng/ml associated with T1c clinical stage, Gleason score of 8-10, and T3-4 clinical stage have been suggested as indicators for undertaking bone scintigraphy in prostate cancer patients [475-477]. Almost three-quarters of men with a PSA level of >100 ng/ml have been shown to have bone metastases [475]. The overall detection rate of metastatic lesions following bone scintigraphy is approximately 15% [345, 475]. After biochemical recurrence following RP, the overall likelihood of a positive bone scan increases to 25% [478].

The majority of bone metastases in prostate cancer have been detected in the axial skeleton therefore they can often remain asymptomatic [479]. The distribution of bone lesions in prostate cancer is characterised by multiple scattered foci mainly throughout the axial skeleton. In some cases, a solitary lesion occurs in long bones [479].

Since the two-dimensionality of bone scintigraphy can be limiting, mainly when assessing solitary lesions, single photon emission computed tomography (SPECT) has emerged as a three-dimensional tool that allows a combined evaluation of functional and anatomical information within the skeleton [480].

PSMA-targeted ^{111}In -Capromab imaging was initially introduced as another potential method for detecting bone metastases, however the technique performed poorly in this context [481]. Later it was shown that the methods may be of value for staging of locally advanced prostate cancer, since the sensitivity and specificity of ^{111}In -Capromab imaging was reported to be better than that of CT and MRI for detecting small metastatic lymph node lesions in high-risk patients [482]. Recently, experimental studies have investigated the potential of another PSMA-targeted imaging technique using radiolabelled humanized J591 for identification of soft tissue and bone metastases with promising results [483].

Despite the benefits that advances in imaging techniques have brought for staging and assessment of cancer progression for patients with high-risk disease, there have been continuing efforts to reduce unnecessary imaging for men with low-risk prostate cancer to better target resources in prostate cancer health care [484]. Prostate cancer management guidelines recommend staging with MRI when the information about potential extracapsular spread is essential for decisions regarding treatment options [159, 455]. MRI, CT, and bone scintigraphy are mentioned in the guidelines as valuable tools for the assessment of metastatic prostate cancer.

2.2 Management of prostate cancer

2.2.1 Staging and risk stratification

Following a prostate cancer diagnosis, it is crucial to correctly assign the cancer stage for each patient to accurately predict the patient's prognosis, and to facilitate decisions about optimal treatment.

Clinical staging can be summarised into three broad categories: localized (organ-confined), regional (locally advanced), and distant (metastatic) disease. The currently most commonly used staging system is the American Joint Committee on Cancer (AJCC) Tumour Node Metastasis (TNM) classification system [485], which was preceded by the Whitmore-Jewett staging system [486]. In the Whitmore-Jewett staging system tumours were basically classified as A, B, C or D: A represented incidentally detected tumours (mostly by TURP), B palpable but organ-confined tumours, C tumours extending outside of the prostate capsule and into seminal vesicles, and D tumours that spread into other parts of the body. This system has been superseded by the AJCC TNM system mainly due to the need of incorporating tumours that were detected solely on the basis of an elevated PSA result. The TNM staging system incorporates three main steps: evaluation of the primary Tumour (T-stage), evaluation of the

involvement of regional lymph **N**odes (N), and evaluation of distant **M**etastases (M).

Information about T-stage has traditionally been obtained by DRE and TRUS, but more recently MRI imaging can also be utilised. Localized (organ-confined) prostate cancer is represented by stages T1 and T2. T1 tumours are divided into T1a, T1b, and T1c groups: T1a and T1b are tumours incidentally detected by TURP or cystoprostatectomy, while T1c tumours are detected by prostate biopsy following an elevated PSA result, but are not palpable on DRE. Since the T1c category was introduced in 1992, the proportion of T1c tumours increased from less than 10% to more than 70% of all newly diagnosed prostate cancer cases [399, 413]. T2 category represents tumours palpable on DRE but confined to the prostate gland. The T2 category is divided into three categories depending on whether the tumour is located in only half of one of the prostate lobes (T2a), in more than half of one of the lobes (T2b) or in both lobes (T2c). Regional (locally advanced) prostate tumours are described as T3a (extracapsular spread), T3b (invasion of seminal vesicles), T4 (invasion of surrounding organs, such as rectum), or N1 (spread to regional lymph nodes). Distant (metastatic) cancer is defined as M1 and includes spread to lymph nodes beyond the regional ones, and to other sites, mainly bones. In case any of the T-stages is associated with a positive N or M stage, the resulting stage will be determined by the N or M category. In order to determine whether cancer spread beyond the prostate, imaging techniques, such as MRI, CT, and bone scintigraphy have often been employed. However, a definitive confirmation of spread into lymph nodes (N1) can only be obtained by lymphadenectomy [426]. Bone scintigraphy is currently the most commonly used imaging method for identifying skeletal metastases originating from prostate cancer.

Risk stratification of prostate cancer patients is crucial for decision-making around management of the disease, and for predicting the outcome of the selected treatment strategy in terms of disease recurrence, progression and cancer-specific survival. Traditionally, combining information about clinical stage based on the TNM classification system, PSA level and Gleason score (GS) derived from prostate biopsy has been considered to provide the best predictions for prostate cancer outcomes [232]. Partin et al. [232] were the first to construct tables with risk categories by taking into account the three factors in order to predict organ-confined disease, extracapsular extension, seminal vesicle invasion, and lymph node invasion. However, the Partin tables have only predicted the clinical characteristics of the RP specimen, not post-treatment outcomes.

The currently most widely used risk stratification predicting biochemical recurrence and survival for patients with localized prostate cancer treated with radical prostatectomy and

radiation therapy was proposed by D'Amico et al. [231] and includes three distinct risk groupings: low risk: GS \leq 6 and PSA $<$ 10 and T1c/T2a; intermediate risk: GS 7 or PSA 10–20 or T2b; and high risk: GS 8–10 or PSA $>$ 20 or T2c. Each of the risk groups is associated with a specific likelihood of biochemical failure and cancer-specific death, therefore patients assigned to the same risk group are expected to have similar clinical outcomes [487, 488]. D'Amico et al. [488] showed that cancer-specific mortality 10 years after initial treatment with radical prostatectomy or radiation therapy was approximately 1% for men with low-risk disease, 5% for men with intermediate-risk disease, and 10-25% depending on the treatment option for men with high-risk disease.

The above mentioned types of risk stratification encountered criticism for the relative heterogeneity of the risk strata, particularly due to categorization of continuous variables, such as PSA level [489]. Nomograms have been suggested as a solution to this problem, since they incorporate continuous variables and also generate individualised predictions. Kattan et al. [233] introduced the first nomogram including pre-treatment PSA level, GS and clinical stage for individualised assessment of risk of biochemical failure 5 years after radical prostatectomy. Another prognostic tool for biochemical recurrence after radical prostatectomy currently gaining interest is the Cancer of the Prostate Risk Assessment (CAPRA) score, which classifies patients based on their PSA level, Gleason score, clinical stage, percentage of positive biopsy cores and age [490].

Other nomograms have used additional characteristics, including percentage of cancer involvement of each biopsy specimen for predicting extracapsular extension [491], or progression-free survival after radical prostatectomy [492], and use of ADT and radiotherapy dose for predicting biochemical failure following radiation therapy [493]. More recently, novel biomarkers, and gene expression profiling have been incorporated into nomograms for predicting biochemical failure after radical prostatectomy [494].

Nomograms have been shown to provide more accurate risk estimates compared with those derived from risk groups, such as D'Amico risk strata or CAPRA score, or with prognosis assessments made by experienced clinicians [489, 495]. However, nomograms have also some limitations, such as that they are group-specific, and therefore need to be validated before they can be used for patients treated at other institutions. As a consequence, the discriminatory power of a nomogram may vary for different groups of patients [496]. Another limitation of nomograms is that the definitions of outcome variables, such as biochemical failure, which vary with time and treatment, need to match between the original and the assessed sample [497].

Predicting indolent tumours post-biopsy has gained importance in the recent years due to a rising interest in preventing over-treatment of indolent prostate cancer and avoiding complications from definitive treatment by using expectant management strategies, mainly active surveillance [498]. The definitions of indolent tumours vary slightly but mostly incorporate one or more of the following criteria: low PSA (<10 ng/ml), GS not higher than 6, T1c or T2a clinical stage, small tumour volume (<0.5 cc), few positive cores (<3), and less than 50% of each positive core altered by the tumour [499]. The indolent or low-risk tumours have been associated with excellent survival even without definitive treatment [145-147]. Kattan et al. [500] constructed a nomogram for predicting indolent tumours following biopsy by using PSA level, GS, clinical T-stage, prostate volume and proportion of cancerous tissue in each positive core.

The decision whether definitive treatment rather than expectant management would be beneficial for a patient also depends on patient's age and life expectancy. Several studies have suggested that patients with a life expectancy of less than 10 years or older than a certain age (most often 70 years) would not benefit from definitive treatment for localized prostate cancer either due to the complications associated with treatment or due to other co-morbidities that affect patients' survival [159, 425, 426]. Nomograms have been constructed to predict 10-year life expectancy or prostate cancer-specific survival at 10 years for patients treated with radical prostatectomy or external beam radiation therapy [501].

To determine follow-up management and outcomes of patients after primary treatment, nomograms have been developed to predict the need for a secondary treatment or further diagnostic workup, including bone scintigraphy for detecting bone metastases [502, 503].

The prognosis and treatment options for men with prostate cancer are closely associated with stage at diagnosis, therefore accurate staging and risk assessment represent key determinants of prostate cancer outcomes.

2.2.2 Management of localised prostate cancer

In Western countries, more than three-quarters of men are currently diagnosed with localized (organ-confined) prostate cancer mostly as a result of screening [63, 336, 504]. Of these men, more than one third has low-grade, slow-growing tumours that are associated with very low likelihood of progression [336, 504, 505]. As a consequence, concerns about over-treatment have arisen since it has been shown that men with localized prostate cancer may live well up to 15-20 years without definitive treatment, and concurrently, all contemporary treatment

options with curative intent are associated with complications that may significantly affect patients' quality of life [145-147, 273]. In contrast, some researchers have voiced concerns about under-treatment for men with high-risk localized prostate cancer, and for some elderly men who may benefit from definitive treatment on the basis of their low co-morbidity burden and relatively long life expectancy [506, 507].

There are a number of definitive treatment options for localized prostate cancer, none of which has been conclusively proven to be superior to the others [156]. In addition to two traditionally employed definitive treatment types of radical prostatectomy (RP) and radiation therapy, which now include a spectrum of different approaches, including open retropubic, laparoscopic, or robot-assisted laparoscopic radical prostatectomy, 3-D conformal or intensity-modulated external beam radiotherapy, and low- or high-dose brachytherapy. There are also two alternative treatment strategies - cryotherapy, and high-intensity focused ultrasound (HIFU) to choose from. However, the last two treatment options are still under evaluation and rarely used, so they will not feature in this study. Recently, pharmacological androgen deprivation therapy (ADT) has also been increasingly offered as a primary or adjuvant treatment to radiation therapy [508].

Active surveillance and watchful waiting are used as expectant management strategies. These approaches have been developed to avoid treatment-related complications by delaying active treatment as long as possible, but at the same time close monitoring of the patient allows for immediate action if cancer progresses [158, 159]. For men managed with active surveillance, the intent is to offer curative treatment when there are signs of cancer progression, while for men under watchful waiting palliative treatment mostly in the form of ADT or radiation therapy is offered to manage disease symptoms when they occur.

As expected, the lack of consensus regarding an optimal management strategy for localized prostate cancer has resulted in a wide variation in utilisation of different treatment modalities among specialist clinicians and regions [350, 509-512]. Although some of the variation may be explained by differing risk profiles of patient groups, it has also been noted that clinicians' preference for treatment options in their own field of expertise may play a significant role [350, 511, 512]. In addition, several studies have found ethnic and socio-economic disparities in management of prostate cancer, which cannot be explained by risk profiles or patient characteristics [336, 365-367, 513].

Informed and shared decision-making has been promoted as a solution to patients' and clinicians' dilemma of choosing the optimal treatment for localized prostate cancer [159, 296,

426, 455]. By discussing all available treatment alternatives, their outcomes and complications, clinicians and patients decide together on a personalized management approach while taking into account clinical features of the cancer, and patient characteristics, such as life expectancy and co-morbidity status. In addition, up to 35% of men who undergo definitive treatment will receive a second treatment within 5 years of the initial treatment, mainly because of biochemical recurrence or disease progression [514, 515], therefore the alternative of failed initial treatment and subsequent management strategies also need to be considered.

2.2.2.1 Radical prostatectomy (RP)

Radical prostatectomy is a surgical procedure involving removal of prostate tumours by a surgical excision of the entire prostate gland. Although this procedure has been known for more than 100 years, the improvements in the technique since the 1980s, including the nerve-sparing [516], and the laparoscopic approach [517] caused a significant increase of its use in the clinical practice, especially after PSA testing was introduced.

A unique advantage of RP over other treatments is the possibility to obtain pathological staging of the tumour based on the whole prostate specimen. In addition, pelvic lymph nodes may also be evaluated if removed along with the prostate gland. Pathological stage, including information about surgical margins and extraprostatic spread, provides an accurate prognostic tool for assessing patients' outcomes [449, 452].

Typically, patients are offered RP as a primary treatment option when they have a low co-morbidity burden, have a life expectancy of more than 10 years and the cancer is confined to the prostate [358, 366, 367]. In some cases, patients with locally advanced prostate tumours may also be considered for RP [296].

There are currently several procedures for RP, including open retropubic, perineal, laparoscopic, and robot-assisted laparoscopic RP. After the introduction of the retropubic procedure, the use of perineal RP has been sharply decreasing [518]. Perineal RP has the advantage of minimal bleeding and postoperative pain, but a concurrent lymph node dissection is not possible, and the preservation of erectile function is inferior compared with the retropubic approach [518].

Robot-assisted laparoscopic prostatectomy (RALP) is currently the most common approach in the USA, while laparoscopic RP without the assistance of a robot predominates in some European countries [517]. In New Zealand, RALP is currently only available in the private health sector, while open retropubic RP is common in the public sector.

The benefits of (robot-assisted) laparoscopic RP are minimal blood loss, lower levels of postoperative pain, shorter hospitalization, and faster recovery compared with open retropubic RP [519-521]. However, some studies pointed out that laparoscopic RP requires a steep learning curve, and is associated with high cost [522, 523].

The early, peri-operative complications associated with RP include bleeding, rectal or urethral injury, recto-urethral fistula, deep venous thrombosis, and pulmonary embolism, and have been observed in up to 20% of patients treated with open retropubic RP [519-521]. For patients treated with laparoscopic RP or RALP respiratory complications were less common, while urethral injuries were more common than for patients treated with open retropubic RP [517]. The two major late complications of RP are urinary incontinence, and erectile dysfunction. The risk for urinary incontinence is difficult to predict, while the likelihood of postoperative erectile dysfunction has been associated with older age, preoperative erectile status, and whether a one-or two-sided nerve-sparing procedure was performed [524-526].

Reported urinary incontinence rates following open retropubic RP vary from 8% to 80%, depending on the definition of incontinence, time since surgery, and surgeon's case load [527, 528]. A temporary decrease in sexual function was observed in the majority of men, but it usually resolved within 6-12 months [524, 526]. Long-term incontinence rates of up to 15% were reported, while erectile dysfunction occurred in up to 50% of patients treated with open retropubic RP [525, 526, 529].

Late complication rate for laparoscopic RP was reported to be equal to or higher than for open RP [517, 519, 520]. Although more than 80% of patients in high-volume centres were reported to be continent within one year regardless of whether they were treated with open retropubic RP, laparoscopic RP or RALP, marked differences between these three techniques were observed for potency rates with more than 90% of patients treated with RALP being potent within a year compared to 55% of patients treated with laparoscopic RP and 60% treated with open retropubic RP [520]. Mortality rate from open retropubic RP was found to be less than 0.5% [530].

Complication rates and oncological outcomes after RP have been found to be closely associated with surgeon's experience and case load, with high-volume centres performing better than low-volume hospitals [531].

After a complete removal of the prostate gland by RP, serum PSA drops to an undetectable level (<0.01 ng/ml) [532]. Overall, up to 30% of patients may show detectable or increasing PSA levels within 5 years after surgery [533]. Rising PSA levels are considered to be the first sign of

cancer recurrence, referred to as biochemical failure in case there is no evidence of clinical recurrence such as palpable nodule on DRE or positive imaging result [534]. Two consecutive serum PSA levels of >0.2 ng/ml are considered to be an indicator of disease recurrence following RP [296]. Some authors suggested a cut-off of 0.4 ng/ml as it tended to be a better predictor of distant metastases [535, 536].

Several studies have shown that oncological outcomes of open retropubic RP were excellent for most patients with low- and intermediate-risk localized prostate cancer; with 10-year biochemical recurrence-free survival higher than 60%, and 10-year cancer-specific survival rate exceeding 90% [537-539]. However, the risk of dying from prostate cancer rapidly increased for patients with high-risk, high-grade (GS of 8-10) disease [538, 539].

Although the follow-up period since RALP utilization started is still too short for an assessment of long-term oncological outcomes, no major differences were found for 5-year biochemical recurrence-free survival between RALP and open retropubic RP [519, 540]. Similarly, no differences in oncological outcomes have been reported between laparoscopic and open retropubic RP [519, 540].

Two RCTs found that patients treated with RP had higher long-term cancer-specific survival compared with patient managed expectantly. However, the benefits were mainly restricted to younger men (<65 years) and men with intermediate- and high-risk localized prostate cancer [541, 542].

The most accepted second-line treatment for patients at high risk of or with signs of disease recurrence following RP is adjuvant or salvage RT [543]. Both of these strategies have the potential to cure the cancer, even though the initial surgical approach had failed [544].

2.2.2.2 Radiation therapy (RT)

Radiation therapy is currently administered by a variety of techniques, including 3-D conformal or intensity-modulated external beam radiation therapy (EBRT), and permanent low-dose or temporary high-dose brachytherapy [545, 546]. The utilization of brachytherapy has been reported to increase over time, while the use of EBRT has remained stable [547].

The advantage of the intensity-modulated EBRT compared with 3-D conformal EBRT is the reduction of radiation exposure of tissues adjacent to the prostate. A systematic review compared the outcomes of 3-D conformal with intensity-modulated EBRT with inconclusive results [548]. Patients treated with intensity-modulated EBRT tended to have lower levels of gastrointestinal toxicity, but higher levels of urinary problems [549]. Some studies reported

improved biochemical recurrence-free survival for patients treated with intensity-modulated EBRT [548].

Several definitions of biochemical recurrence after RT have been used over the years but the most common ones are the American Society for Therapeutic Radiation and Oncology (ASTRO) definition of three consecutive PSA elevations above the nadir (the lowest PSA level observed after treatment) [550], and the Phoenix definition of an increase in PSA value of 2 ng/ml above the nadir [551]. The Phoenix definition was introduced to better predict cancer mortality rather than just biochemical recurrence of the disease. There is no consensus about an optimal value of the nadir following RT, however a PSA nadir of <0.5 ng/ml has been associated with better outcomes [552]. PSA nadirs as well as levels indicating biochemical recurrence following RT differ from those following RP, which renders direct comparisons of recurrence rates between these two treatment strategies difficult. In general, the 10-year biochemical recurrence-free survival following RP would improve by about 10% by using biochemical recurrence definitions following radiotherapy [553].

Recent studies reported 5-year biochemical recurrence-free survival (using Phoenix definition) following intensity-modulated EBRT of 98%, 85%, and 70%, and 8-year biochemical recurrence-free survival rates (using ASTRO definition) of 85%, 76%, and 72% for low-, intermediate- and high-risk patients, respectively [554, 555].

Several studies, including RCTs investigated the effect of dose escalation for EBRT techniques on oncological outcomes and concluded that higher doses were associated with improved biochemical recurrence-free survival by approximately 10% [556-558], but cancer-specific or all-cause survival have not been improved [556, 557]. Higher radiation doses have also been associated with increased likelihood of gastrointestinal toxicity [557].

Besides the trend toward increasing overall radiation doses, the effect of decreasing the number of fractions with concurrent increase in the radiation dose per fraction has been explored [559]. Although there are currently only few studies regarding so-called hypofractionated EBRT, the first data indicate that this approach improved the 5-year biochemical recurrence-free survival compared with conventional EBRT, particularly for patients with high-risk disease [560, 561]. The rate of early gastrointestinal and urinary toxicity was higher for hypofractionated EBRT, but the rate of late complications was similar [560, 561].

In brachytherapy, radioisotopes are placed directly into the prostate gland. In comparison to EBRT, the radiation exposure of other parts of the body is reduced in brachytherapy, while at the same time the cancerous prostatic tissue is subjected to a higher dose of radiation. Another

advantage of brachytherapy over EBRT is that it is usually performed on an outpatient-basis and requires fewer visits to the specialist.

Studies comparing EBRT and brachytherapy have reported improved oncological outcomes for brachytherapy [562-564]. Complication rates varied, with brachytherapy showing lower incidence of late bowel dysfunction, but higher incidence of urinary problems [562-564]. Sexual dysfunction has been reported to increase over time following EBRT, with up to 60% of men having erectile dysfunction at 5 years [565]. In comparison, the rate of erectile dysfunction was approximately 25-35% 5 years after brachytherapy [566].

Some men with localized prostate cancer receive a combination treatment of EBRT and HDR, which has been shown to be beneficial in terms of biochemical recurrence-free survival, and overall survival in comparison to EBRT alone [567, 568]. Studies regarding complication rates following combined treatment in comparison to EBRT or brachytherapy alone have reported conflicting results; some showing higher incidence of complications for men with combined treatment [569], while others demonstrated higher complication rates for EBRT or brachytherapy alone [570].

No studies have directly compared permanent low-dose and temporary high-dose brachytherapy approaches. In low-dose brachytherapy the implants permanently placed into the prostate emit low-dose radiation over weeks and months, while in high-dose brachytherapy the implants emit comparatively high doses of radiation for a pre-specified time period, after which they are removed from the prostate. In contrast to HDR that may be used for treatment of both localized and locally advanced prostate cancer, low-dose brachytherapy is mainly recommended for men with low- risk disease, and for selected men with intermediate-risk prostate cancer [159, 425]. For men with high-risk disease, D'Amico et al. [231] observed that the risk of biochemical recurrence was three-times higher for LDR alone compared with RP or EBRT. The 10-year biochemical recurrence-free survival following LDR has been reported to range from 86% to 92% for men with low-risk, and from 61% to 96% for men with intermediate-risk prostate cancer [571, 572]. Following HDR, the 5-year biochemical recurrence-free survival rate has been reported to range from 75% to 97% [573, 574].

Several recent studies have demonstrated that the pattern of complications differed between HDR and LDR. Although the rates of late complications, such as urinary incontinence, and erectile dysfunction were similar between HDR and LDR, early urinary complications were less common following HDR and gastrointestinal toxicity also resolved earlier after HDR [569, 571, 572]. Several studies reported that oncological outcomes and complication rates for patients

treated with LDR have improved over time, mainly due to advances in intra-operative planning and imaging techniques that allow for better patient selection [572].

In comparison with RP, men with low- and intermediate-risk prostate cancer treated with intensity-modulated EBRT had similar 3- and 5-year biochemical recurrence-free survival, while for men with high-risk disease EBRT was associated with longer biochemical recurrence-free survival [575, 576].

Two large retrospective studies have recently reported higher cancer-specific mortality adjusted for age, year of treatment and risk strata for men treated with EBRT compared with men treated with RP [577, 578]. Both studies showed that the difference was minimal for men with low-risk disease, but increased progressively for men with intermediate- and high-risk disease [577, 578]. No differences in cancer-specific mortality have been reported between men treated with brachytherapy and those treated with open retropubic RP [579].

The incidence, timing and spectrum of complications differ between RT and RP. While RP has been associated with higher incidence of urinary incontinence and erectile dysfunction that mostly resolved within a year or two, patients treated with RT showed a much higher incidence of bowel dysfunction, and complication rates had the tendency to increase over time [157, 273, 580, 581]. In addition, RT has also been associated with increased risk of secondary cancer, mainly bladder and rectum cancer, with the odds of developing secondary cancer being higher for men treated with EBRT than for those treated with LDR [582, 583]. In general, men, who received definitive treatment for prostate cancer, were more likely to report urinary, sexual, and bowel problems compared with age-matched men without prostate cancer [584].

Following biochemical recurrence, patients initially treated with RT may be managed by ADT, salvage brachytherapy or in carefully selected cases by salvage RP [296, 585, 586].

2.2.2.3 Expectant management: Active surveillance and watchful waiting

Active surveillance (AS) and watchful waiting (WW) both describe expectant management strategies for men with localized prostate cancer. Both approaches were developed to defer treatment and thus avoid treatment-related complications for men at low risk of disease progression and/or cancer-specific death. However, AS and WW are clearly distinguished by follow-up strategies and action plans in case of cancer progression: Men managed with AS are regularly monitored by PSA tests and repeat biopsies, and in case of disease progression will be offered curative treatment [159, 296, 425]. In contrast, for men managed with watchful

waiting no consistent monitoring plan has been established, but when symptoms occur patients may be offered non-curative treatment, including ADT and palliative RT [159, 296, 425].

A number of studies demonstrated that men diagnosed with localized, low-grade prostate cancer have a 10-20-year prostate cancer-specific survival rate of more than 80% [145-147]. In addition, other studies found that men older than 65 years are more likely to die of competing co-morbidities rather than of prostate cancer within 10 years of diagnosis, particularly when they have one or more co-morbid conditions [587]. As a consequence, men at low risk of disease progression and prostate cancer death are considered to be suitable for active surveillance or watchful waiting [588-590]. AS is mainly intended for younger men, while WW is usually offered to older men with limited life expectancy [159, 296, 425].

The clinical eligibility criteria for AS vary slightly between different guideline sources, but in general men with T1c or T2a tumours, Gleason score less than 7, PSA <10 ng/ml, fewer than 3 biopsy cores involved and less than 50% of each core containing cancer have been found to benefit from AS [590, 591]. The life expectancy of eligible men should not exceed 15 years, since some studies have shown that the risk of dying of prostate cancer increased for men surviving longer than 15 years [592, 593].

Monitoring protocols for AS include repeat biopsies at 1 year and then at intervals ranging from 3 to 4 years, regular PSA tests every 3 to 6 months, including assessment of PSA kinetics, annual DRE and MRI at initiation of AS [159, 425]. The protocols for the assessment of cancer progression differ between countries and groups of clinicians, although most consider PSA doubling time of less than 3 years, Gleason score 7 and greater and more than 2 biopsy cores, and >50% of each core containing cancer at repeat biopsy indicative of cancer progression [425, 590, 591]. In general, about 30% of men will show disease progression at repeat biopsy and thus become candidates for definitive treatment [590-592].

In case of older men and their suitability for watchful waiting, life expectancy of less than 10 years, localized, and in some cases locally advanced disease (mainly for men with life expectancy of < 5 years), and multiple co-morbidities have been the most commonly cited criteria [425, 506].

Although AS was developed as a management strategy for avoiding treatment-related complications, some studies emphasized that men managed with AS may suffer a different spectrum of adverse effects, including psychological distress and anxiety and complications associated with repeat biopsies [160, 594, 595]. A number of studies have shown that more than 25% of men on active surveillance without any evidence of cancer progression will opt for

definitive treatment, mainly due to increasing anxiety [160, 594]. In contrast, other studies have emphasized that no difference was observed in rates of anxiety and depression between men managed with AS and those treated with curative intent or men without prostate cancer [596, 597].

Another potential limitation of AS is that the risk exists that the window of opportunity for cure may be missed, particularly for patients assigned lower than actual cancer stage and grade [425]. Since up to half of biopsy specimens of Gleason score 6 have been shown to be upgraded to Gleason score 7 at pathological evaluation of radical prostatectomy specimens [453], an accurate staging is crucial for patient selection for AS.

So far, no long-term results were reported from RCTs comparing AS versus definitive treatment. The Prostate Testing for Cancer and Treatment (ProtecT) trial comparing AS, RP, and EBRT is currently underway but it needs a longer follow-up before first comprehensive results can be presented [598]. Men with low-risk prostate cancer identified in the ERSPC, who have not received definitive treatment, have been shown to have a 10-year all-cause survival of 70%, and not a single man died of prostate cancer within 10 years [599].

RCTs comparing WW with radical prostatectomy yielded overall similar, but conditionally different results [541, 542]. In the Scandinavian Prostatic Cancer Group Study Number 4 (SPCG-4) [541] comparing open retropubic RP and WW, the 15-year cancer-specific mortality was higher for men managed expectantly compared with men treated with RP (21% versus 15%). However, this difference was limited to men younger than 65 years. The Prostate cancer Intervention Versus Observation Trial (PIVOT) of men with localized prostate cancer randomised to RP or observation found that 7% of men managed expectantly died of prostate cancer after 12 years compared with 4% of men treated with RP [542]. However, the difference in cancer-specific mortality between RP and observation groups was only significant for men with high-risk disease, while no difference was observed for men diagnosed with low- or intermediate-risk prostate cancer.

Compared to the SPCG-4 study, where only 12% of men had T1c tumours, almost half of the men in the PIVOT study had non-palpable tumours detected solely through an elevated PSA result [541, 542]. The differences in clinical and patient characteristics between these two trials were also reflected in the lower relative reduction in all-cause mortality between the RP and the observation group in the PIVOT trial (12%) compared with 25% in the SPCG-4 trial, and in the lower percentage of men dying of prostate cancer in the PIVOT (7.1%) compared with the SPCG-4 trial (19.6%).

In the SPCG-4 study, no differences were found in the rates of anxiety and depression between men randomized for WW compared with men treated with RP. Men managed with WW had lower rates of erectile dysfunction, and urinary incontinence than men treated with RP [600], but issues with sexual function increased with time for men managed with WW [601]. Another study noted that at 6 to 8 years men managed with WW, and particularly those receiving ADT, reported poorer health-related quality of life compared with men treated with RP [602]. Similarly, a US study showed that with time men managed with WW had poorer quality of life indicators than would be expected due to a normal aging process [603].

Preliminary results from a RCT comparing EBRT and WW in men with localized prostate cancer revealed that at 20 years there was no difference in recurrence-free or overall survival between the two groups [604].

There were also several population-based studies that emphasized that outcomes for men managed expectantly were not inferior to men, who received definitive treatment [145, 146, 588]. However, some studies cautioned against under-treatment, particularly for men with high-risk prostate cancer, emphasizing that also older men may benefit from definitive treatment [506, 507].

2.2.2.4 Hormonal therapy: Androgen deprivation therapy

At the end of the 18th century, John Hunter concluded that the growth of the prostate gland depends on the presence of male (androgen) sex hormone testosterone based on his observation that removal of testes, where testosterone is produced, prevents prostate from growing [605]. In the mid-20th century Charles Huggins and Clarence Hodges recognized that androgens also affects the growth of prostate cancer, and showed that metastatic prostate cancer may be inhibited by suppressing androgen activity by surgical castration or use of oestrogens [606].

In 1971, Andrew Schally described the complete peptide sequence of luteinising hormone-releasing hormone (LHRH), which regulates secretion of the luteinising hormone, which subsequently prompts the production of testosterone [607]. Following his discovery, Schally [607] developed a synthetic analogue of the LHRH, which paved the way for pharmacological androgen deprivation therapy.

For their discoveries and observations, Charles Huggins and Andrew Schally were awarded the Nobel Prize for Medicine and Physiology. More detailed information about methods and

agents used as ADT is presented in section 2.2.3.3 on management of locally advanced prostate cancer.

The use of androgen deprivation therapy (ADT) as a primary treatment for men with localised prostate cancer has increased in recent years [508, 608], although several clinical guidelines do not recommend or even caution against using ADT as primary treatment for men with localised prostate cancer [159, 425]. A population-based study has shown that survival benefits of primary ADT were limited to men with high-risk disease [609]. Moreover, any potential benefit of primary ADT needs to be balanced against the multitude of adverse effects related to hormonal treatment. A recent large retrospective study has reported higher cancer-specific mortality rates adjusted for age, year of treatment and risk strata for men treated with primary ADT compared with men treated with RP [577].

The traditional and recommended use of ADT for men with localised disease has been as a neoadjuvant or adjuvant therapy to radiation therapy [159, 425]. In addition, a course of ADT may be used to reduce prostate volume in order to facilitate the exposure of the cancerous tissue to RT [508]. A number of RCTs were undertaken to investigate the role of ADT as neoadjuvant or adjuvant therapy to EBRT for intermediate- and high-risk prostate cancer [610-612]. These trials showed that a combined treatment of short-term (up to 6 months) ADT and EBRT improved biochemical recurrence-free survival and cancer-specific survival compared with EBRT alone [610-612]. In contrast, retrospective studies showed that when dose-escalated EBRT or brachytherapy was used, ADT did not provide any additional benefit neither for biochemical recurrence-free survival nor for cancer-specific survival [613, 614].

ADT has been associated with a high rate of adverse effects, some of which have a significant impact on the patient's quality of life and survival. Side effects include sexual dysfunction, hot flashes, gynecomastia, fatigue, weight gain, diabetes, cardiovascular disease, osteoporosis, loss of muscle strength, bone fractures, and psychological and cognitive problems [615-625]. Most of the complications, including weight gain, diabetes, cardiovascular disease, osteoporosis, and bone fractures have usually been observed only with long-term use of ADT.

The use of ADT as salvage treatment strategy after failed definitive treatment needs to be weighed against the harms from side effects, and the fact that no overall survival benefit has been demonstrated so far [626, 627].

2.2.2.5 Management guidelines for localised prostate cancer

Table 2a to 2c summarises management guidelines for localised prostate cancer issued by the New Zealand Ministry of Health Prostate Cancer Taskforce [455], Australian National Health and Medical Research Council (NHMRC) [628], English and Welsh National Institute for Health and Care Excellence (NICE) [159], US National Comprehensive Cancer Network (NCCN) [425], and European Association of Urology (EAU) [296].

Clinical guidelines for prostate cancer management typically incorporate three major determinants of treatment: risk profile of the cancer, patient's life expectancy or age, and co-morbidity status. The most commonly used definition of risk in clinical guidelines was introduced by D'Amico et al. [231]. Men with low-risk disease have excellent outcomes, surviving 15-20 years after prostate cancer diagnosis even without definitive treatment [145-147]. Some studies showed that for men with low- and intermediate-risk prostate cancer definitive treatment may provide survival benefit in comparison to watchful waiting, but not earlier than 8-10 years following treatment [280, 629]. In contrast, most researchers agree that men with high-risk disease are likely to benefit from definitive treatment [425, 426, 629].

Table 2a Clinical recommendations for using radical prostatectomy as primary treatment for localised prostate cancer.

	Risk profile ^a	Life expectancy/Age	Additional comments
Prostate Cancer Task Force New Zealand [455]	Low to high risk	>10 years / <75 years	No significant co-morbidity
NHMRC Australia [628]	Low to intermediate risk, selected high-grade	>10 years	No serious co-morbidity
NICE [159]	Intermediate and high risk		
NCCN [425]	Low risk (if ≥10 years life expectancy); intermediate risk (plus T2c); high risk (plus T3a)	≥10 years (low risk)	No serious co-morbidity
EAU [296]	Low, intermediate risk, selected high risk	>10 years	Nerve-sparing RP for low risk

Table 2b Clinical recommendations for using active surveillance as primary treatment for localised prostate cancer.

	Risk profile ^a	Life expectancy/Age	Additional comments
Prostate Cancer Taskforce New Zealand [455]	Very low risk, low risk	Younger men	Older men rather watchful waiting
NHMRC Australia [628]	Low risk	<10 years	
NICE [159]	Low risk, selected intermediate risk, never high risk		
NCCN [425]	Low, intermediate risk	<10 years (low, intermediate risk), <20 years (very low risk)	
EAU [296]	Very low risk		

Table 2c Clinical recommendations for using external beam radiation therapy as primary treatment for localised prostate cancer.

	Risk profile ^a	Life expectancy/Age	Additional comments
Prostate Cancer Task Force New Zealand [455]	Low to high risk		Lower dose for low risk
NHMRC Australia [628]	Low to high risk (PSA <15 ng/ml)	>10 years	
NICE [159]	Intermediate, high risk		Consider plus short-term ADT (intermediate, high risk), long-term ADT (high-risk), Consider plus HDR (intermediate, high risk)
NCCN[425]	Low risk (if ≥10 years life expectancy); intermediate risk (plus T2c); high risk (plus T3a)	≥10 years (low risk)	Consider plus short-term ADT (intermediate risk), long-term ADT (high-risk)
EAU [296]	Low to high risk	Suitable also for older men	Consider plus short-term ADT (intermediate, high risk)

^aclinical factors mentioned separately in case definition varies from the following: very low risk: T1a, T1c, Gleason score (GS)=6, PSA <10 ng/ml, <3 biopsy cores positive, <50% cancer in any core, PSA density <0.15 ng/ml/g; low risk: T1-T2a, GS <7, PSA < 10 ng/ml; intermediate risk: T2b, GS=7, PSA 10-20 ng/ml; high risk: T2c, GS 8-10, PSA > 20 ng/ml; ADT: androgen deprivation therapy; HDR: high-dose brachytherapy

Although some guidelines still use absolute age as a determinant for treatment choices, life expectancy estimates have been promoted as a more accurate tool for predicting treatment outcomes [159, 265, 425, 426, 455]. In addition, health-adjusted life expectancy estimates have recently been introduced to account for differences in survival for healthy and frail individuals [630, 631].

Traditionally, the Charlson Comorbidity Index is used for assessing co-morbidity status in prostate cancer patients, since the Index has been shown to correlate with prostate cancer outcomes [587, 632, 633]. In general, definitive treatment has been rarely recommended for men older than 70 or 75 years at diagnosis or for men with limited life expectancy due to age and/or co-morbidity status since it is assumed that survival in these men would not be improved by definitive treatment [159, 425, 455]. In addition, treatment-related complications have been shown to increase with increasing age and multiple co-morbidities [634, 635]. Since there is currently no consensus about an optimal definitive treatment for localised prostate cancer, the choice is largely driven by clinicians, who ideally take into account clinical characteristics of the cancer, patient's preferences, age and overall health status before deciding on a personalised management strategy [159, 296, 425].

After primary treatment with curative intent, patients should be regularly followed up with PSA and DRE [296, 426]. In case of indications of disease progression, including PSA levels of >20

ng/ml, palpable nodules or bone pain, imaging techniques, such as MRI or bone scintigraphy need to be employed to assess cancer spread. Similarly, men managed with AS should be regularly monitored following predetermined protocols so that curative treatment may be initiated in case the disease progresses [159, 296]. For men managed with WW, development of symptoms and occurrence of clinical indicators of disease progression need to be monitored in order to determine the need for palliative treatment [426].

For up to 50% of patients who had undergone curative treatment signs of cancer recurrence may appear within 10 years of initial therapy, and 16–35% of patients receive second-line treatment within 5 years of initial therapy [514, 515]. As with primary treatment, the decision what treatment modality to choose for second-line treatment and when to commence the treatment following biochemical recurrence depends on a range of factors, such as patient's overall health status, life expectancy, clinical characteristics of the recurring cancer and its prognosis, oncological outcomes, and complication rates associated with the selected management option [159, 425].

2.2.3 Management of locally advanced (regional) prostate cancer

Locally advanced or regional prostate cancer is defined as extraprostatic extension, seminal vesicle invasion, and lymph node invasion of the prostate tumour. Using the TNM staging, locally advanced prostate cancer includes T3 and T4, and N1 clinical stage.

Currently, the only method to confirm lymph node invasion is lymphadenectomy. When performed, extended pelvic lymphadenectomy is recommended, since it identifies twice as many affected lymph nodes compared with standard pelvic lymphadenectomy [426, 636]. Heidenreich et al. [636] also showed that in their study all but one patient with lymph node involvement had a serum PSA level higher than 10 ng/ml and Gleason score of 7 and greater. The number of positive lymph nodes is closely associated with patients' prognosis; the fewer lymph nodes affected, the better the outcomes [637, 638].

In contemporary practice, the prognosis of high-risk patients, including those with extraprostatic extension following primary treatment is still relatively favourable, with a high proportion of these patients surviving 10 or more years without further cancer progression [639, 640].

Treatment options for regional prostate cancer include radical prostatectomy, radiation therapy, ADT or in selected cases watchful waiting. Watchful waiting may be an option for asymptomatic men with T3 disease and limited life expectancy [159, 426]. In contrast, radical

prostatectomy may be considered for men with T3 disease, good health and life expectancy of >10 years [159, 426]. For patients with extensive disease, who are not suitable for RT, ADT may be offered instead of watchful waiting [159, 425]. Treatment strategies combining two or more modalities (radiation therapy, radical prostatectomy, ADT) have been shown to be beneficial for patients with regional prostate cancer [159, 425, 426].

2.2.3.1 Radical prostatectomy

In general, RP for locally advanced prostate cancer should be limited to younger men and men with overall good health status [426]. Radical prostatectomy for men with locally advanced T3 and T4 prostate cancer was investigated in several studies [639, 641-343]. In these studies, the proportion of patients with N1 disease ranged from 6% to 29%. The 10-year biochemical recurrence-free survival was found to be 38-51% while the 10-year overall, and cancer-specific survival were 57-77%, and 75-92%, respectively [639, 641-643].

For men with T3 tumours treated with RP as primary treatment adjuvant EBRT has been shown to improve 5- and 10-year biochemical recurrence-free survival compared with those treated with RP and subsequent observation [644-646]. One RCT also reported better overall survival for men undergoing adjuvant EBRT compared with the observation group [646].

When adjuvant EBRT was compared to salvage EBRT, retrospective studies reported conflicting results, with some studies showing improved biochemical recurrence-free survival for adjuvant EBRT [647, 648], while others demonstrating better outcomes for salvage EBRT compared with adjuvant EBRT [649]. Two RCTs – RADICALS (Radiotherapy and Androgen Deprivation in Combination After Local Surgery), and RAVES (The Radiotherapy-Adjuvant Versus Early Salvage) – have been initiated to address the timing of radiation therapy (adjuvant versus salvage) following RP for patients with locally advanced prostate cancer, but the results are not yet available [650, 651]. The RADICALS trial will also explore the role of concomitant ADT [650]. For patients with N1 tumours, a combined treatment of RP with pelvic lymphadenectomy and ADT resulted in 10-year biochemical recurrence-free survival of approximately 65%, and 10-year cancer-specific survival of more than 80% [640, 652].

2.2.3.2 Radiation therapy

High-dose external beam radiation therapy is a common management strategy for men with regional prostate cancer [426, 646]. The 10-year metastasis-free survival ranged from 23% to 30%, and 10-year cancer-specific mortality from 16% to 30% [653, 654].

HDR may also be used for locally advanced tumours, with reported 5-year biochemical recurrence-free survival rate ranging between 60% and 83% [655]. However, combined therapy of EBRT and HDR has been utilized more commonly than HDR alone [656-658], showing similar or slightly better 5-year biochemical recurrence-free survival than HDR alone. The 5-year overall, and cancer-specific survival ranged was 80-96%, and 90-95%, respectively [656-658]. Few studies reported outcomes for combined treatment with EBRT and LDR for patients with locally advanced prostate cancer, with 12-year biochemical recurrence-free survival ranging from 67% to 89%, and 12-year cancer-specific survival of 94% [659, 660].

A number of RCTs investigated the role of adjuvant ADT for men with locally advanced prostate cancer treated with EBRT, demonstrating improved overall, and cancer-specific survival compared with EBRT alone [653, 654, 661]. The 5-year biochemical recurrence-free survival for EBRT plus ADT ranged from 53% to 96% depending on clinical stage and radiation dose [653, 654]. Several RCTs have also shown that in combination with EBRT long-term ADT was superior to short-term ADT [662, 663]. Clinical guidelines currently recommend EBRT with adjuvant ADT for 3 years as a standard care for men with locally advanced prostate cancer [159, 425, 426].

2.2.3.3 Hormonal therapy

ADT has been commonly used for men with locally advanced prostate cancer, but only as palliative, not a curative treatment [352, 664]. The majority of prostate cancer patients respond to ADT because testosterone influences the growth and development of prostate cancer cells [606]. Prostate cancer growth can be principally controlled by disturbing either of three physiological processes: 1) stopping production of testosterone by surgically removing the testes; 2) reduce testosterone production by the testes by disrupting the LHRH pathway; and 3) counteracting the effect of testosterone by directly blocking the androgen receptors in the prostate [664].

Initially, ADT included surgical castration (orchidectomy) and pharmacological hormonal therapy by oestrogens [665]. Currently, surgical castration is still performed, particularly for patients with metastatic disease in need of rapid decrease in testosterone levels [666].

However, for the majority of patients with locally advanced prostate cancer orchidectomy was largely replaced by pharmacological agents, including luteinising hormone-releasing hormone (LHRH) analogues, and antiandrogens [666, 667]. Oestrogens have been almost completely excluded from contemporary prostate cancer treatment because they were found to be associated with a high risk of cardiovascular complications [668].

LHRH analogues include buserelin, goserelin, leuprorelin, triptorelin, and histrelin. This type of pharmacological castration performs as well as surgical castration in reducing testosterone levels, but the process is slower than with orchidectomy [664, 666]. However, since LHRH analogues actually saturate androgen receptors, they initially stimulate the production of LH, and consequently testosterone. This initial increase in serum testosterone levels called “flare” may cause worsening of clinical symptoms when LHRH analogues are first used [669]. Therefore, concomitant administration of anti-androgens is recommended with the initial use of a LHRH analogue [426].

Anti-androgens are divided into steroidal agents, including cyproterone acetate, and non-steroidal agents, including flutamide, bicalutamide, and nilutamide. They may be used as monotherapy or in combination with LHRH analogues [425]. Non-steroidal antiandrogens block the androgen receptors, but the circulating levels of testosterone remain normal. As a consequence, patients receiving non-steroidal antiandrogens may retain their sexual function [670]. In contrast, steroidal anti-androgens decrease testosterone levels, and have also been shown to adversely affect hepatic, and cardiovascular function [664, 671]. Among non-steroidal anti-androgens, bicalutamide has been reported to have a similar efficacy to LHRH analogues or orchidectomy for patients with locally advanced disease, and to cause less pronounced side effects compared with flutamide [672].

After orchidectomy or pharmacological castration by LHRH analogues, the circulation of serum testosterone may not be completely stopped. Therefore, so-called combined androgen blockade (CAB), which combines orchidectomy or LHRH analogues with anti-androgens has been suggested as a means to manage advanced prostate cancer [673]. However, the results of a meta-analysis showed that the survival benefit of CAB was minimal when compared to monotherapy by orchidectomy or LHRH analogues, while the burden of adverse effects increased [674]. Consequently, the use of CAB has been recommended only for patients that failed initial monotherapy [675].

ADT use is associated with a broad spectrum of significant complications. Besides the commonly observed sexual dysfunction, long-term ADT in particular has been shown to cause weight gain, diabetes, cardiovascular disease, osteoporosis, and sarcopenia [615-625]. The increased risk of osteoporosis in men receiving ADT is closely associated with higher risk of bone fractures for men with prostate cancer [676]. Bone fractures may be associated with significant morbidity and also mortality, particularly in older men [677]. As a consequence, several guidelines prompt utilisation of calcium and vitamin D supplements for men treated

with ADT [296, 425, 426]. In addition, bisphosphonates, such as zoledronic acid, or monoclonal antibody denosumab have been shown to improve bone health of patients receiving ADT [678-680].

Patients receiving ADT need to be regularly evaluated by assessing cancer symptoms and complications and undertaking PSA tests, DRE, and measuring serum testosterone level [425]. The timing of ADT use for men with regional prostate cancer has not yet been fully resolved. A RCT showed that although immediate ADT decreased the risk of death from any cause, cancer-specific mortality has not been improved compared with deferred ADT, i.e. watchful waiting [681]. Another RCT has suggested that men with a PSA level above 50 ng/ml and PSA doubling time of less than 12 months may benefit from immediate ADT [682], while others questioned the use of immediate ADT even for men with N1 disease [667, 683].

There is also an ongoing debate about the benefits of intermittent versus continuous ADT for men with regional prostate cancer. A RCT showed that although oncological outcomes for intermittent ADT were either slightly poorer than or equal to continuous ADT, intermittent ADT was associated with lower rate of significant adverse effects [684]. Other studies also showed that during the breaks from ADT patients may regain sexual function [684, 685]. In addition, some researchers hypothesized that by using intermittent ADT, prostate cancer may retain androgen dependency for longer [685, 686].

RCTs that evaluated pharmacological ADT alone compared with a combined treatment of ADT and EBRT for men with locally advanced prostate cancer clearly showed improved outcomes, including biochemical recurrence-free survival, metastasis-free survival, and cancer-specific survival for the combined approach [687, 688].

2.2.4 Management of metastatic (distant) prostate cancer

Prostate cancer is considered to be metastatic when cancerous prostatic cells spread to distant lymph nodes, skeleton, and soft tissues, such as the liver [485]. Metastatic cancer is progressive and typically fatal within a median time of 24 to 36 months [428]. The disease progression is characterised by a transition from androgen dependent to androgen independent (hormone-resistant) tumours [689]. Metastatic or distant prostate cancer is found at diagnosis in about 5-15% of men in Western countries [63, 336, 346, 504]. Another about 12% of men will progress to metastatic prostate cancer after being diagnosed with less advanced disease [145, 147]. Skeleton is the most commonly affected distant site, with 90% of men dying of prostate cancer showing bone metastases [690, 691]. The most commonly affected areas of the skeleton are

the axial skeleton (spine and pelvis), ribs, extremities, and the skull [692]. The typical appearance of the metastatic spread is that of multiple foci scattered throughout the axial skeleton. In some cases a solitary lesion may occur in long bones, particularly in the femur [479].

Bone metastases cause either bone resorption by increased osteoclastic activity, or bone formation by increased osteoblastic activity. Malignant prostatic cells typically invade the red bone marrow, which results in osteoblastic, rather than osteoclastic activity [693, 694]. As a consequence, prostate cancer bone metastases are characterised by bone formation rather than bone resorption. The invading malignant prostatic cells cause bone marrow failure, changes in calcium metabolism, spinal cord compression, and pathological fractures [695]. The most common clinical manifestation of bone marrow failure is anaemia [795].

The changes in calcium metabolism lead to mild hyperparathyroidism and a chronic increase in bone resorption in skeletal areas not affected by metastases, resulting in osteoporosis and increased fracture risk [696]. Spinal cord compression occurs in up to 10–17% of men with metastatic prostate cancer [697]. The risk of spinal cord compression increases with increased skeletal metastases burden, and long-term continuous ADT [698]. Although pharmacological, surgical and radiation therapy may relieve the symptoms for men with spinal cord compression, the outcomes for these men are generally poor [699].

Men with metastatic prostate cancer have been shown to be at high risk of pathological and osteoporosis-related bone fractures [700, 701]. However, recent studies have reported that the risk of bone fractures was not restricted to men with bone metastases, but was also closely associated with ADT regardless of prostate cancer extent at diagnosis [623, 677, 702]. Overall, up to 60% of men with prostate cancer have been shown to suffer one or more bone fracture [623, 677, 700, 703].

A meta-analysis of studies on prostate cancer and bone metabolism concluded that prostate cancer patients receiving ADT have a higher risk of osteoporosis, and consequently a higher risk of fractures [676]. Recent studies have reported that fracture risk was higher for younger men receiving ADT, which would considerably affect their quality of life, particularly since many of them would still be in the work force [623, 704]. Fractures have also been associated with reduced survival in prostate cancer patients [703, 705, 706].

Since ADT is currently widely accepted as the first-line mandatory treatment for men with metastatic prostate cancer, the reduction of fracture risk for these men has become a priority. Biphosphonates, such as zoledronic acid have been approved for treatment of skeletal-related

complications of prostate cancer, including bone pain, spinal cord compression, and fractures [678, 707].

Although skeletal metastases, particularly those to axial skeleton may remain asymptomatic, the majority of patients with distant prostate cancer experience bone pain at some point during the disease progression [708]. A number of treatment modalities target bone pain, including palliative radiotherapy, radionuclide therapy, analgesics, biphosphonates, and chemotherapeutic agents [707, 709].

Due to the considerable morbidity and mortality associated with metastatic prostate cancer, one of the main aims of recent research into prostate cancer physiology and management is to improve the quality of life and survival of men with distant metastases.

2.2.4.1 Androgen deprivation therapy (ADT)

Androgen deprivation therapy is considered to be the first-line treatment option for men with metastatic prostate cancer [426, 710], since withdrawal of testosterone was shown to be effective for about 80% of men with distant metastases [606]. In asymptomatic men, the use of ADT has a role in delaying the occurrence of symptoms and progression-related complications, with the possibility of deferring treatment in rigorously followed-up men [710]. For symptomatic men, immediate ADT is a mandatory standard of care used to palliate symptoms and to reduce the risk of significant complications, such as spinal cord compression and pathological fractures [710].

LHRH analogues or surgical castration, often in combination with anti-androgens are used for palliation in metastatic prostate cancer [675]. In a number of countries, steroidal and non-steroidal anti-androgens (bicalutamide) have not been approved as monotherapy for treatment of metastatic prostate cancer, because in comparison with LHRH analogues antiandrogens have been shown to reduce overall survival by more than a month [710].

Besides LHRH analogues and anti-androgens, gonadotropin-releasing hormone (GnRH) antagonist degarelix has been approved for treatment of symptomatic metastatic prostate cancer in Europe and North America, but not yet in New Zealand [711]. GnHR antagonists directly block androgen receptors, in contrast to LHRH analogues that only compete for the receptors. The advantage of GnHR antagonists is the avoidance of the initial flare in serum testosterone levels and a more rapid reduction of the testosterone levels compared with LHRH analogues. In a comparison with leuprorelin, a preliminary analysis has shown that degarelix was associated with lower risk of biochemical recurrence and cancer-specific mortality [712].

In order to minimise ADT-related side effects, intermittent instead of continuous approach has been investigated for men with metastatic prostate cancer with promising results. A number of RCTs comparing intermittent with continuous ADT (combination of LHRH analogues and anti-androgens) revealed that intermittent ADT has a similar efficacy to continuous ADT regarding progression-free, and overall survival [684, 713, 714]. In addition, intermittent ADT has been shown to delay the progression to hormone refractory disease [686].

Some patients, who relapse after initial ADT, may respond to secondary ADT consisting of anti-androgen withdrawal or switching to different ADT agent [426, 715], while others become hormone-resistant. These patients may receive chemotherapy or novel therapeutic agents, such as abiraterone acetate as the second-line treatment [716].

2.2.4.2 Chemotherapy

Currently, the most widely used chemotherapeutic agent for patients with hormone-resistant disease is docetaxel in combination with prednisone, after up to 20% improvement in survival was demonstrated compared to a combined treatment of mitoxantrone and prednisone [717-719]. In addition to a median survival improvement of 3 months, docetaxel has been associated with better pain management and improved quality of life compared to mitoxantrone [717-719].

In patients with extensive metastatic disease, high serum PSA levels or a rapid PSA doubling time of less than 6 months, chemotherapy should be started early [426, 710]. However, as any cytotoxic treatment chemotherapy for prostate cancer has been associated with a number of adverse effects, including fatigue and nausea [720].

Patients receiving docetaxel as chemotherapy for hormone-resistant prostate cancer normally show disease progression within 6 to 8 months [721, 722], therefore secondary line of treatment needs to be considered. Docetaxel or mitoxantrone may be used as second-line treatment, while several novel therapies are under investigation [426, 710].

2.2.4.3 Palliative radiotherapy

Symptomatic patients with painful bone metastases may be treated with palliative radiation therapy [723, 724]. Although no survival benefit has been shown, bone pain and the risk of fractures and spinal cord compression have been reduced for men treated with palliative radiation therapy [707, 725].

2.2.4.4 Novel therapeutic approaches

Between 2010 and 2014, six new agents have been approved for management of patients with hormone-resistant metastatic prostate cancer: chemotherapeutic agent cabazitaxel, biologic agents abiraterone acetate and enzalutamide (MDV3100), immunotherapeutic agents sipuleucel-T and denosumab, and radiopharmaceutical agent radium-223 chloride.

Cabazitaxel combined with prednisone was shown to improve overall survival by more than 2 months compared to mitoxantrone, when used as a second-line treatment following docetaxel [726]. Concurrently, cabazitaxel treatment was associated with an increased risk of significant side effects [726].

Since the androgen receptor has been shown to remain active in metastatic prostate cancer [727], two agents that target this receptor – abiraterone acetate and enzalutamide (MDV3100) were developed to provide a second-line hormone blockade beyond initial surgical or pharmacologic castration [728, 729].

Abiraterone acetate is an inhibitor of cytochrome P450-17 (CYP17), a key enzyme that mediates androgen production in the testes, adrenal glands, and in cancerous tissues [728]. A RCT comparing abiraterone acetate plus prednisone to placebo plus prednisone in patients with hormone-resistant metastatic prostate cancer, who failed docetaxel therapy, has demonstrated an overall survival benefit of 4 months and a 35% reduction in risk of death in the abiraterone acetate group [730]. In addition, the time to progression as well as progression-free survival was improved for men receiving abiraterone acetate [730]. Another RCT compared abiraterone acetate plus prednisone with placebo plus prednisone in patients with hormone-resistant metastatic prostate cancer, who had not received chemotherapy. This study showed that progression-free survival was 16.5 months in the abiraterone acetate group compared to 8.3 months in the placebo group [731]. Adverse effects of the abiraterone acetate treatment included hypokalemia, hypertension, and oedema, although severe forms occurred in less than 5% of cases [730, 731].

Enzalutamide (MDV3100) is an androgen receptor antagonist that inhibits androgen receptor function by blocking nuclear translocation and DNA binding [732]. A large RCT comparing enzalutamide versus placebo in patients with hormone-resistant metastatic prostate cancer previously treated with docetaxel has shown that enzalutamide improved overall survival by 5 months, in addition to improvements in time to progression, progression-free survival, and quality of life [733]. The side effects include fatigue, diarrhoea, and 0.6% of patients suffered seizures [733].

Sipuleucel-T is a cellular immunotherapy agent, which was approved by the FDA as a therapeutic vaccine for minimally symptomatic patients with hormone-resistant metastatic prostate cancer [734]. Sipuleucel-T has been shown to improve overall survival by 4 months in comparison to placebo, with manageable complications, such as fever and flu-like symptoms [734]. However, a recent study criticised the trial and pointed out that the survival benefit seemed to be restricted to men older than 65 years [735].

Denosumab is a fully human monoclonal antibody that inhibits osteoclast activity, and thus delays onset of bone metastases [736, 737], as well as reduces the risk of bone fractures in patients with bone metastases, and in prostate cancer patients receiving ADT [680, 738]. A RCT comparing denosumab with zoledronic acid in men with metastatic prostate cancer showed that denosumab was associated with longer time to the first bone fracture, but progression-free and overall survival were similar for the two agents [738]. Hypocalcaemia and osteonecrosis of the jaw were the most commonly reported complications of denosumab treatment, affecting up to 5% of patients [738].

Radium-223 chloride is an α -emitting radiopharmaceutical, which is used for direct targeting bone metastases. Radium-223 chloride has been shown to be more active and less toxic than existing radionuclides strontium-89 and samarium-153 used for palliation in men with hormone-resistant prostate cancer [739, 740]. A RCT comparing radium-223 chloride versus placebo in patients with symptomatic hormone-resistant metastatic prostate cancer demonstrated an improvement of overall survival by more than 3 months, reduction of skeletal related events, and improved quality of life [741].

Emerging approaches for management of metastatic prostate cancer currently under investigation showing promising results include biologic agent cabozantinib [742], monoclonal antibody ipilimumab [743], DNA-based, and virus-based vaccines [744, 745], radioimmunotherapy with monoclonal antibody J591 linked to radionuclides targeting prostate cancer-specific antigen (PSMA) [746], and antibody-chemotherapy conjugates MLN2704, and MMAE targeting PSMA [747].

The access to novel prostate cancer treatment depends on the country of residence, socio-economic position, and ethnicity of the patient [748, 749]. In New Zealand, variations in the use of medication and treatment options were observed both by socio-economic position and ethnicity [7, 379, 750].

CHAPTER 3 PROSTATE CANCER INCIDENCE AND SURVIVAL IN NEW ZEALAND

3.1 Short introduction

Prostate cancer has been identified as being a primary contributor to cancer burden for NZ men [312]. It is therefore important to gain a better understanding of the factors that influence prostate cancer outcomes, and to identify causes of ethnic and geographical inequalities.

New Zealand has one of the highest age-standardised incidence rates of prostate cancer in the world, similar to Australia and the USA [2]. High incidence rates have largely been attributed to high screening rates for prostate cancer in these countries, and consequently a high proportion of the detected cancers is represented by indolent tumours [304].

Prostate cancer mortality rate in New Zealand exceeds death rates in the USA and particularly in the UK, which is a country with low prostate cancer incidence and low screening rates [2, 310]. High mortality rates have often been associated with high proportion of men diagnosed with advanced prostate cancer, and with inadequate access to high-quality treatment [304]. Survival for men with prostate cancer largely depends on disease extent at diagnosis. Men diagnosed with localized disease have excellent survival [145, 146], while men diagnosed with advanced disease, particularly with distant metastases have a very limited life expectancy [323, 324]. Improvements in survival for prostate cancer patients have been associated with more effective treatment but concerns have been raised that with the increased detection of indolent tumours the observed survival improvements may also be an artefact associated with lead time bias [149, 304].

In Western countries, higher cancer mortality has been reported for minorities; for African-American men with prostate cancer in the USA, and also for Australian Indigenous men in comparison to European men [63, 355, 358].

In New Zealand, Māori men are 72% more likely to die of prostate cancer, despite being 14% less likely to be diagnosed with the disease [1]. Low prostate cancer incidence rates coupled with high cancer-specific mortality rates in a population group may indicate that the group experiences difficulties in accessing health services.

Earlier NZ studies have shown that Māori men with prostate cancer have poorer survival than non-Māori men [5, 6, 378]. However, these studies relied on national data from a decade ago and only a single study focused solely on survival for prostate cancer patients [378].

Furthermore, these studies have not satisfactorily clarified whether outcome inequalities

between Māori and non-Māori men with prostate cancer are due to differences in patient characteristics, such as stage at diagnosis or health system factors, such as access to, timeliness and quality of treatment.

Our recent review of international literature on rural/urban prostate cancer incidence and mortality showed that the majority reported higher incidence rates for urban men [8]. Although mortality patterns tended to be heterogeneous, there was some evidence that rural men with prostate cancer experienced higher death rates compared with their urban counterparts. For NZ men, little is known about rural and urban patterns of incidence and survival of prostate cancer.

The understanding of geographical patterns of prostate cancer incidence and mortality is important as it may indicate disparities in access to diagnostic and treatment services. Physical distances to access specialist services are believed to disadvantage rural patients [382, 383]. In New Zealand, the majority of people live in urban settlements close to health care centres, but rural inhabitants may need to travel long distances to health care.

This study as part of the Midlands Prostate Cancer Study was undertaken in the Midland Cancer Network (MCN) region therefore regional comparisons also focus on outcomes for men with prostate cancer diagnosed in this region as opposed to men diagnosed in the other three NZ Cancer Networks.

3.2 Objectives

- 1) to assess temporal trends and current incidence and survival rates for Māori and non-Māori men with prostate cancer;
- 2) to examine incidence and survival rates for rural and urban men with prostate cancer;
- 3) to compare incidence and survival rates for men with prostate cancer by Cancer Network.

3.3 Methods

3.3.1 Sample

This is a cohort study of men diagnosed with prostate cancer (ICD-9 185, ICD-10 C61) between 1 January 1996 and 31 December 2010.

The final study population included 37,529 men from original 41,583 men after double entries (22), men aged younger than 40 years at the time of diagnosis (7), men diagnosed at death (1078), men of unknown ethnicity (2662) and domiciled abroad (212) were excluded. Cases

with morphology codes not consistent with adenocarcinoma (73) of the prostate were also excluded.

3.3.2 Data Sources

Three main information sources for data extraction were used: the New Zealand Cancer Registry (NZCR), the Mortality Collection (MORT), and the NZ Census. The NZCR collects data on all new cases of malignant cancers excluding squamous cell carcinoma and basal cell carcinoma of the skin (<http://www.health.govt.nz/nz-health-statistics/national-collections-and-surveys/collections/new-zealand-cancer-registry-nzcr>). The data requested for this study included: date of birth, date of diagnosis, ethnicity, domicile, District Health Board (DHB) domicile, morphology type, basis of diagnosis, disease extent at diagnosis, and date of death. The MORT contains information on cause of death (<http://www.health.govt.nz/nz-health-statistics/national-collections-and-surveys/collections/mortality-collection>). Data linkage by the National Health Index (NHI) number (a unique alphanumeric code assigned to each health service user in NZ) was used to establish cause of death for deceased men identified from the NZCR. Cause of death was dichotomised into death from prostate cancer and death due to other causes. Data on vital status were collected for the period from 1 January 1996 to 25 May 2011 (the most recent data available at the time of request).

Data available from the MORT were: date of death, date of birth, ethnicity, domicile, DHB domicile, country of birth, years in New Zealand, main cause of death, three contributory causes of death, five other contributory causes (e.g., medical misadventures), and three non-contributory cancers.

For men who died between 1 January 2009 and 25 May 2011 data from original death certificates with a main cause of death and seven contributory causes were provided because these data were not available in the MORT format at the time of the initial request. The cause of death was established by the author and another Study team member based on agreed standards as being due to prostate cancer or due to other causes. To validate our coding strategy, we received data in the MORT format for a cohort of men who died between 1 January 2009 and 31 December 2009 as they had become available during the course of our research. The validation results showed that 99% of our codes matched with those from the MORT.

New Zealand Census (<http://m.stats.govt.nz/Census>) data for years 1996, 2001, and 2010 and annual population estimates for the intermittent years between 1996 and 2010 for male

population aged 40+ years were used as populations at risk for the calculation of annual incidence rates. In order to allow comparisons between years and population groups (Māori versus non-Māori men, urban versus rural men), the 2001 Census population was chosen as the standard population for calculation of the final age-standardised incidence rates.

3.3.3 Predictor variables

This study focuses on Māori men, men residing in rural areas, and men in the MCN, so ethnicity, rural/urban residence and Cancer Networks were the three main exposure variables. Results are presented in three separate sections each targeting one of these three variables. Other variables included in the analyses were: age, year of diagnosis, socio-economic deprivation, and to a limited extent, disease extent at diagnosis. These variables were considered to be potential confounders as it was assumed based on the results of previous studies that they are likely to differ by ethnicity or residence, i.e. be associated with exposure and concurrently may be associated with the outcome (survival). In addition, other studies on cancer epidemiology have treated these variables as potential confounders, and last but not least information on these variables was available from the national collections.

Age is a typical confounder in cancer studies, while year of diagnosis was included as a proxy for changes in diagnosis and treatment strategies, which in turn may have affected both exposure and outcome. With ethnicity and residence as exposures, Cancer Network was included as a confounder because studies showed regional variation in prostate cancer mortality [350, 353] and the exposure categories were assumed to vary by CN.

Residence and socio-economic deprivation may be considered either as confounders or mediators in relation to ethnicity as exposure. In the mediator scenario, being of a certain ethnicity (e.g. Māori) would cause settling in socio-economically deprived areas (or rural areas) and this would in turn cause poorer prostate cancer survival for the given ethnic group possibly through late stage of disease at diagnosis and inadequate treatment that would be caused by the level of socio-economic deprivation. Considering the need for temporal precedence of exposure to mediator, it is so far unclear whether Māori settle in deprived areas or whether areas, where Māori live, become relatively deprived. Moreover, the survival disparities between Māori and non-Māori men remained when stratified by socio-economic deprivation, so even Māori men living in socio-economically least deprived areas had poorer survival to the same extent as those living in the socio-economically most deprived areas. In relation to survival as the outcome, socio-economic deprivation would be a likely mediator for stage at

diagnosis and treatment, but information on these variables was not available so they could not be included in the multivariate models. Residence explained little of the variation in survival when used as a confounder, therefore it would be a weak mediator, if one at all. Therefore, both socio-economic deprivation and residence are used as confounders in this study.

Prioritised ethnicity was used, i.e., if one of three possible self-identified ethnicity responses was Māori, the man was assigned to Māori ethnicity. The system of reporting up to three ethnic affiliations was introduced in the 1996 Census and has been adopted by the Ministry of Health for their national data collection, such as the NZCR and MORT. For the purpose of this study, men not identified as Māori were described as non-Māori. In this group, 95.8% of men were NZ Europeans or other Europeans, 2.4% Pacific Islanders, 1.5% Asians, and 0.3% of other ethnicity. Domicile at diagnosis was used to classify each patient into seven urban/rural residence categories: main urban area (MUA), satellite urban area, independent urban area, rural area with high urban influence, rural area with moderate urban influence, rural area with low urban influence, and highly rural/remote area. This urban/rural classification was developed in 2004 using the 2001 Census meshblock patterns, population size, and the degree of urban influence measured by the usual residence and workplace addresses of the employed population in the respective area [751]. For the purpose of this study, the seven categories were collapsed into two: main urban areas (MUAs), and rural areas (including satellite urban areas, independent urban areas, rural areas with high urban influence, rural areas with moderate urban influence, rural areas with low urban influence, and highly rural/remote areas), since comprehensive health services, in particular Cancer Centres are located in MUAs, while people residing in other areas need to travel shorter or longer distances to access these services.

Domicile at diagnosis from the NZCR was used to assign a deprivation centile for each patient based on the New Zealand Index of Deprivation 2006 (NZDep06). The NZDep06 is a measure derived from nine variables (income, benefit receipt, single parent family, home ownership, employment, qualifications, living space, access to communication and to transport) collected in the Statistics New Zealand 2006 Census of Population and Dwellings and provides a summary deprivation score from 1 (least deprived) to 10 (most deprived) for small geographical areas (with a resident population of approximately 100 people) [752]. For the purpose of this study, deciles were collapsed into tertiles: least deprived (1-3), medium (4-7), and most deprived (8-10).

Rural/urban residence and socio-economic deprivation were used as indicators for access to health care, as opposed to being considered as patient characteristics.

District Health Board (DHB) domicile from the NZCR was used to assign each patient to a Cancer Network. Cancer Networks have a leadership, facilitation and co-ordination role in bringing together and working with stakeholders across organisational and service boundaries to reduce the impact of cancer, reduce the inequalities and improve the experience and outcomes for people with cancer.

New Zealand is divided into four Cancer Networks (CNs): Northern (NCN), Midland (MCN) and Central (CCN) on the North Island, and Southern (SCN) that covers the whole of the South Island [753]. Table 3 lists District Health Boards (DHBs) by Cancer Network.

Table 3 List of District Health Boards (DHBs) by Cancer Network.

Midland Cancer Network (MCN)	Northern Cancer Network (NCN)	Central Cancer Network (CCN)	Southern Cancer Network (SCN)
Waikato DHB	Auckland DHB	Taranaki DHB	Nelson/Marlborough DHB
Bay of Plenty DHB	Waitemata DHB	Whanganui DHB	Canterbury DHB
Lakes DHB	Counties Manukau DHB	MidCentral DHB	Otago DHB
	Northland DHB	Hawke's Bay DHB	West Coast DHB
		Wairarapa DHB	South Canterbury DHB
		Hutt Valley DHB	Southland DHB
		Capital & Coast DHB	
		Tairāwhiti DHB (MCN since 1 July 2012)	

The NCN region has the largest total population of 1,640,000, with the lowest proportion of people aged 70 years and older (7%) and people living rurally, i.e. outside of main urban areas (26%), and the second lowest proportion of Māori people (14%). The MCN region has the lowest total population of 680,000, with the highest proportion of Māori people (25%), and people living rurally (49%). One-tenth of the MCN population is aged 70 years and older. The CCN region has a total population of 1,020,000, of whom 10% are 70 years and older, 19% are of Māori ethnicity and 30% live rurally. The SCN region has a population of 1,040,000, with the lowest proportion of Māori people (8%), and the second highest proportion of people living rurally (45%). As in the MCN and CCN regions, approximately 10% of the population are people aged 70 years and older.

This study as part of the Midlands Prostate Cancer Study was undertaken in the Midland Cancer Network (MCN) region, therefore comparisons of incidence and survival rates between Cancer Networks focus on the MCN and its position within the national framework.

The Midland Cancer Network (MCN) covers the District Health Boards of Waikato, Bay of

Plenty and Lakes. In July 2012, Tairāwhiti DHB has joined the MCN. By this time, data collection for our study was completed, therefore only data for men diagnosed with prostate cancer in the three original DHBs were considered.

The Waikato Hospital in Hamilton is one of six Cancer Centres in NZ and the only one in the MCN providing full spectrum of health care services for prostate cancer patients. In addition, urological services, including radical prostatectomy are offered in both public and private sector in NZ. In the MCN, Hamilton and Tauranga are the two main centres for surgical urological services. In Tauranga, robot-assisted laparoscopic RP is available for private patients. The most common type of radical prostatectomy undertaken in the Waikato Hospital in Hamilton is open retropubic RP. At the time of this study, radiation therapy within the MCN region was only available in the Waikato Hospital in Hamilton.

Age at diagnosis was grouped into 5-year categories for the calculation of incidence rates. Age at diagnosis and year of diagnosis were used as continuous variables for survival analyses. For sample characterisation and subgroup survival analyses, age was dichotomised to <70 and 70+ years. These age groups were chosen considering that for men aged 70+ years biopsy as a cancer detection tool is less commonly used, and expectant management is more commonly offered than treatment with curative intent [333, 506]. For subgroup analyses, years of diagnosis were grouped into 5-year intervals (1996-2000, 2001-2005, 2006-2010).

Extent at diagnosis in the NZCR is coded as B (localised disease), C (invasion of adjacent tissues or organs), D (invasion of regional lymph nodes), E (distant metastases) and F (unknown extent). In this study, categories C and D were classified as “regional” extent. A major limitation of the NZCR is that approximately 75% of prostate cancer registrations have disease extent at diagnosis recorded as “unknown”. This is largely due to the reporting procedure employed for prostate cancer cases. Although biopsy reports containing some staging information are regularly submitted to the national registry, these reports do not include complete staging information. Additional information is collected from hospitalisation records and death certificates; however such data are often obtained with a delay to the biopsy reports. Therefore the current system used in the NZCR for data collection is not sufficient for collating staging information in prostate cancer cases and needs to be revised.

Validation of disease extent at diagnosis in the NZCR was one of the goals of this study (see Chapter 5 for more details). Based on the results of this study, it is assumed that hazard ratios for Māori men (versus non-Māori men) with regional and distant extent in the NZCR can be seen as feasible under conditions identified in the validation study. One of the conditions is that

men with regional extent at diagnosis recorded in the NZCR largely represent a selected sample of men, for whom a pathological report from radical prostatectomy was available as a basis of the extent. Therefore, hazard ratios need to be interpreted as being representative for men treated with radical prostatectomy rather than for all men diagnosed with regional extent. The localised extent at diagnosis was found to be largely underrepresented and also seemed to be selectively recorded depending on the treatment used. Therefore, hazard ratios were not reported for this subgroup.

3.3.4 Outcome variables

Age-specific and age-standardised incidence rates were calculated by year of diagnosis. The Census 2001 New Zealand male population aged 40+ years was used as the standard population at risk (denominator). Men aged younger than 40 years were not considered as being at risk of prostate cancer, since from 1996 to 2010 there were only 7 (0.02%) men younger than 40 years registered with prostate cancer.

Age-standardisation was used to enable comparisons between Māori and non-Māori men, men living in MUAs and rural areas, and CNs.

All-cause and prostate cancer-specific survival was calculated from the date of diagnosis to the date of death extracted from the NZCR. Survival time after diagnosis was measured in months. Men who were still alive on the day of last follow-up (25 May 2011) were censored. For cancer-specific survival, men with prostate cancer listed as main cause of death were considered as cases, while men who died of causes other than prostate cancer or were still alive at the date of last follow-up were censored.

3.3.5 Statistical analysis

Temporal trends were described for age-specific and age-standardised incidence rates by ethnicity, rural/urban residence, and Cancer Network. Incidence rate ratios (IRRs) were calculated for Māori versus non-Māori men, and for men residing in rural areas versus men residing in MUAs for the year 2010.

The probability of surviving one year, five years and 10 years was estimated using the Kaplan-Meier method for Māori and non-Māori men, for men residing in MUAs and rural areas, and for men in the four CNs. The equality of survivor functions was compared by log-rank test.

Cox proportional hazards regression models were used to estimate the relative risk of dying from any cause and from prostate cancer for Māori men (compared with non-Māori men), for

men residing in rural areas (compared with men residing in MUAs), and for men in the NCN, CCN and SCN (compared with men in the MCN). Models were successively adjusted for patients' age at diagnosis, ethnicity, year of diagnosis, residence, socio-economic deprivation, and Cancer Network.

As previously mentioned, management of prostate cancer, including detection and treatment (both of which influence survival) is highly dependent on patients' age, therefore Cox proportional hazards regression models for cancer-specific survival for Māori men (compared with non-Māori men), for men residing in rural areas (compared with men residing in MUAs), and for men in the NCN, CCN and SCN (compared with men in the MCN) were also fitted separately for men aged <70 and 70+ years at diagnosis.

The Kaplan-Meier method was also used to estimate one- and 5-year cancer-specific survival separately for three consecutive time periods (1996-2000, 2001-2005, 2006-2010) by ethnicity, residence, and CN.

Considering the limitations of the NZCR regarding prostate cancer extent at diagnosis, extent was not used as a predictor variable in the models. However, fully adjusted Cox proportional hazards regression models were fitted separately to estimate the risk of prostate cancer death for Māori versus non-Māori men with regional and distant extent of prostate cancer at diagnosis.

Confidence intervals (95%) not including 1 were used as indicators of statistical difference, being analogous to a probability level of less than 0.05.

Ethics approval for the access and use of the data from the national databases (NZCR, MORT) was granted by the Chairperson of the New Zealand Multi-Region Ethics Committee (Ref. No. MEC/11/EXP/044).

3.4 Results

3.4.1 Epidemiology of prostate cancer in Māori and non-Māori men

Study population

The study population included 37,529 men, out of whom 1916 (5.1%) were Māori. Table 4 summarises patient characteristics by ethnicity.

Table 4 Patient characteristics of the national cohort of men diagnosed with prostate cancer between 1996 and 2010 by ethnicity.

	Māori		non-Māori	
	n	%	n	%
Age				
<70 years	1129	58.9	17541	49.3
70+ years	787	41.1	18072	50.7
Residence				
Main urban areas	1053	55.0	24457	68.7
Rural areas	863	45.0	11156	31.3
Cancer Network				
Midland	513	26.8	5235	14.7
Northern	637	33.2	11647	32.7
Central	573	29.9	8668	24.3
Southern	193	10.1	10063	28.3
Extent at diagnosis				
Localised	144	7.5	4547	12.8
Regional	84	4.4	1981	5.6
Distant	186	9.7	2053	5.8
Unknown	1502	78.4	27032	75.9
Socio-economic deprivation (NZDep06)				
1-3 (least deprived)	188	9.8	10004	28.1
4-7	594	31.0	15311	43.0
8-10 (most deprived)	1134	59.2	10298	28.9
Years of diagnosis				
1996-2000	525	27.4	11434	32.1
2001-2005	664	34.7	11782	33.1
2006-2010	727	37.9	12397	34.8
Vital status				
Alive	989	51.6	21882	61.4
Death due to prostate cancer	455	23.7	5792	16.3
Death due to other causes	472	24.6	7939	22.3

The distribution of demographic characteristics of Māori men versus non-Māori men was in agreement with the distribution of these characteristics in the general population. A higher proportion of Māori men were diagnosed aged <70 years compared with non-Māori men. Māori men were more likely to reside in rural and the most deprived areas. The lowest proportion of Māori men lived in the SCN.

Based on the limited data on disease extent at diagnosis, Māori men seemed to be more likely diagnosed with distant metastases. Māori men were less likely diagnosed between 1996 and 2001, indicating that detection activity increased for Māori men with time.

3.4.1.1 Incidence

Age-standardised incidence rates (per 100,000 NZ men aged 40+ years from the 2001 Census) for the total cohort and for Māori and non-Māori men by year of diagnosis are depicted in Figure 10. Although incidence rates fluctuated slightly between 1996 and 2010, a general downward trend was observed. A distinct peak was present in 2000/2001, and a smaller peak was observed in 2009 for the total cohort.

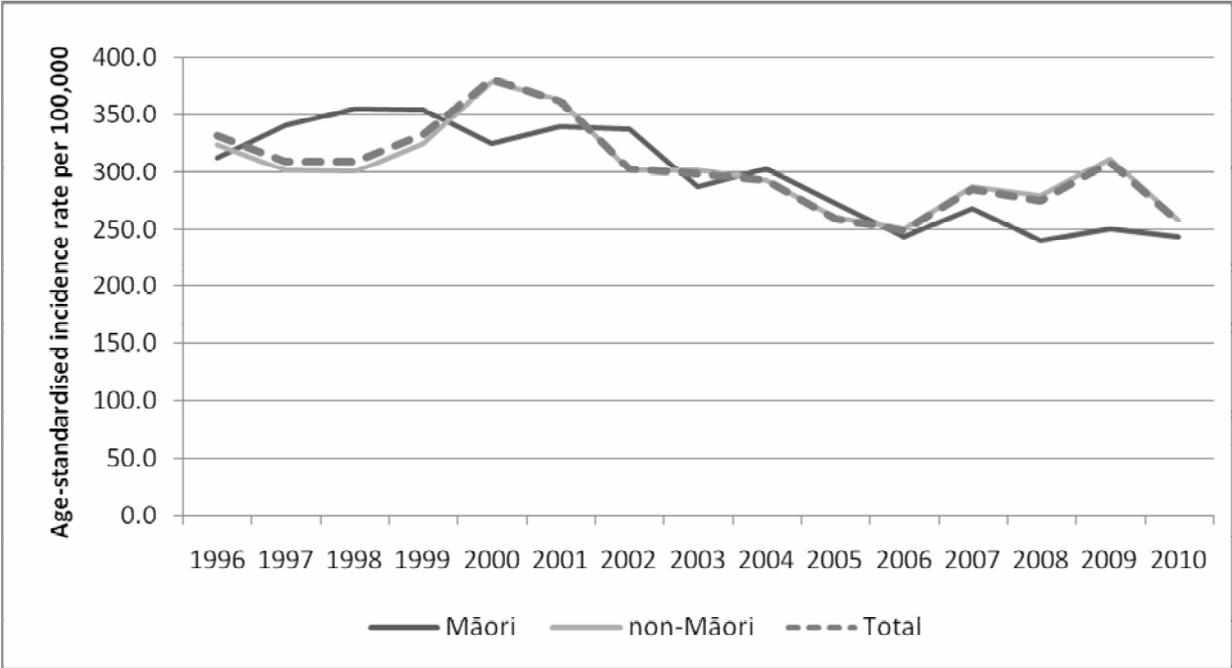


Figure 10 Annual age-standardised (2001 Census NZ men aged 40+ years) prostate cancer incidence rates for the total cohort, and for Māori and non-Māori men.

Incidence of new prostate cancer cases has been declining with time for both Māori and non-Māori men. From 2000 to 2010, age-standardised incidence rates decreased for Māori by 25%, and non-Māori men by 32%, respectively.

An increase in incidence rates for non-Māori men between 2007 and 2009 opened up a gap between incidence rates for Māori and non-Māori men during this period. However, in 2010 the IRR for Māori compared with non-Māori men was 0.95 [95% CI; 0.79, 1.13].

Figure 11 shows age-specific incidence rates of prostate cancer for Māori and non-Māori men by year of diagnosis. A decline of incidence rates over time was observed for both Māori and non-Māori men aged 70+ years. There was a slightly increasing trend in prostate cancer incidence for men aged 40-59 years. Despite some fluctuations, incidence rates for Māori and non-Māori men aged 60-69 years remained relatively stable over time, except for slightly increasing rates for non-Māori men between 2007 and 2009.

Until 2006 (and except for 2001), Māori men aged 70+ years had higher incidence rates compared with non-Māori men. For age groups 40-59 and 60-69 years, incidence rates were

relatively similar between Māori and non-Māori men, although there was a tendency for non-Māori men having slightly higher rates.

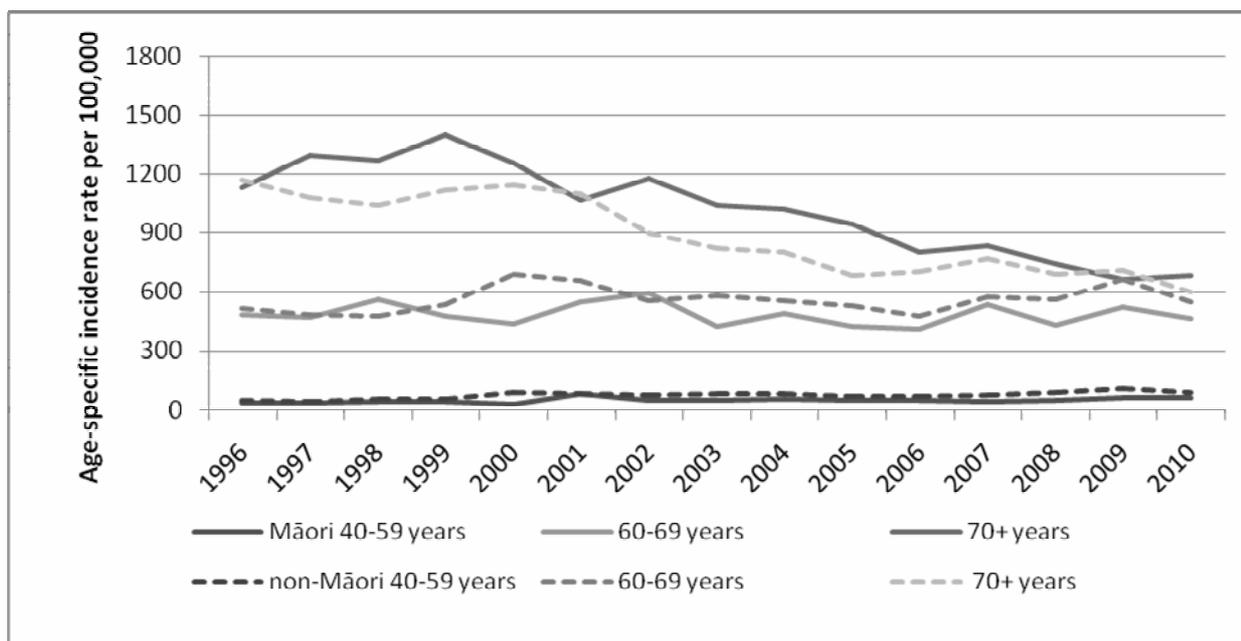


Figure 11 Annual age-specific prostate cancer incidence rates (standardised to 2001 Census NZ men aged 40+ years) for Māori, and non-Māori men.

3.4.1.2. Survival

The Kaplan-Meier method was used to estimate one-year, 5-year and 10-year all-cause and cancer-specific survival by ethnicity (Table 5). Māori men had consistently lower all-cause survival, with 87% surviving 1 year, 59% 5 years and 35% 10 years, compared with 91%, 70% and 49% of non-Māori men, respectively. Cancer-specific probability of surviving one year was 3% lower (92% v. 95%), probability of surviving 5 years 9% lower (76% v. 85%), and probability of surviving 10 years 13% lower (63% v. 76%) for Māori men compared with non-Māori men. The log-rank test returned a probability value of <0.001 for the comparison of both all-cause and cancer-specific Māori and non-Māori survival curves.

Table 5 Kaplan-Meier all-cause and cancer-specific probability of surviving one, five, and 10 years for men diagnosed with prostate cancer between 1996 and 2010 by ethnicity.

	Kaplan-Meier all-cause probability of surviving (%) [95% CI]			Kaplan-Meier cancer-specific probability of surviving (%) [95% CI]		
	1 year	5 years	10 years	1 year	5 years	10 years
Ethnicity						
non-Māori	90.9 [90.5, 91.3]	69.9 [69.3, 70.5]	49.3 [48.5, 50.1]	95.3 [95.1, 95.5]	84.9 [84.5, 85.3]	75.8 [75.2, 76.4]
Māori	86.6 [85.0, 88.2]	58.7 [56.2, 61.2]	35.2 [32.1, 38.3]	91.6 [90.4, 92.8]	75.8 [73.6, 78.0]	62.8 [59.3, 66.3]

Figure 12 shows the Kaplan-Meier estimates for one-year and 5-year cancer-specific survival for Māori and non-Māori men by diagnosis years (1996-2000, 2001-2005, 2006-2010). Survival improved over time for both Māori and non-Māori men, particularly after the year 2000. However, survival differences between Māori and non-Māori men with prostate cancer remained.

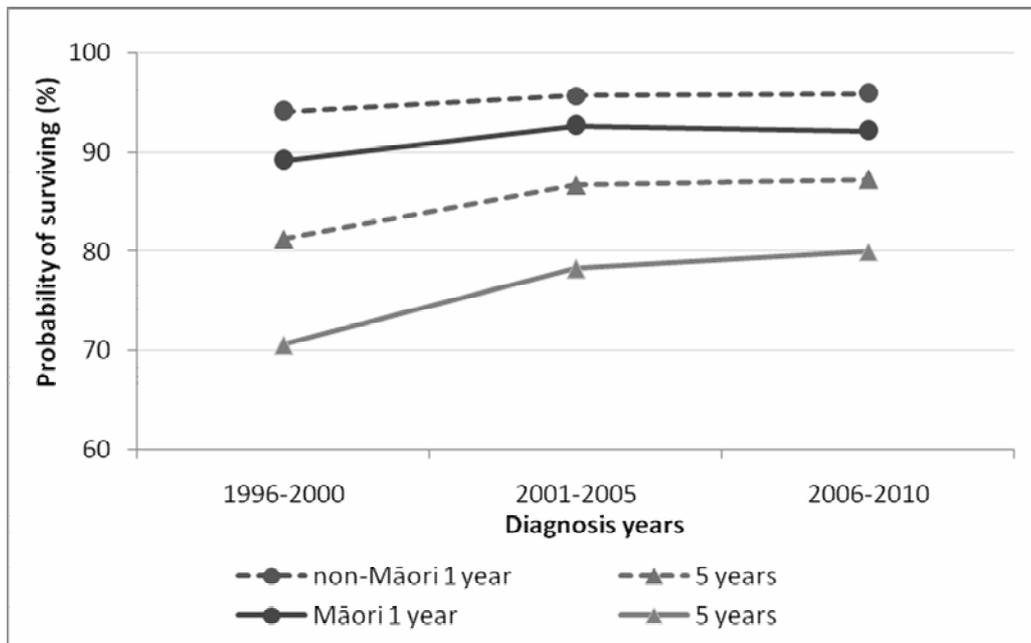


Figure 12 Kaplan-Meier one- and five-year cancer-specific survival estimates for Māori and non-Māori men with prostate cancer by diagnosis years.

Table 6 shows all-cause and cancer-specific hazard ratios for Māori versus non-Māori men derived from the Cox proportional hazards regression models successively adjusted for age, year of diagnosis, residence, socio-economic deprivation and CN. The risk of dying from any cause adjusted for age was 1.93-fold for Māori men compared with non-Māori men. After adjustment for age, year of diagnosis, residence, socio-economic deprivation and CN the risk of dying was reduced to 1.84. For single co-variates, the largest risk reduction from the basic model adjusted for age was observed for the model adjusted for socio-economic deprivation (HR=1.85), which was similar to the risk reduction observed in the full model.

Māori men had 2.09-fold age-adjusted risk of dying of prostate cancer compared with non-Māori men. The full model adjusted for age, year of diagnosis, residence, socio-economic deprivation and CN returned a lower hazard ratio of 1.93. Considering the effect of single variables, the model including socio-economic deprivation showed the largest risk reduction from the basic model adjusted for age (HR=1.98), but the reduction was lower than for the model combining the effect of year of diagnosis, socio-economic deprivation, residence and CN.

Table 6 Hazard ratios derived from Cox proportional hazards regression models for all-cause, and cancer-specific survival for Māori men (v. non-Māori men) diagnosed with prostate cancer between 1996 and 2010.

Hazard ratio (95% CI)						
	Model I adjusted for age	Model II adjusted for age and year of diagnosis	Model III adjusted for age, year of diagnosis and residence	Model IV adjusted for age, year of diagnosis and socioeconomic deprivation	Model V adjusted for age, year of diagnosis and Cancer Network	Model VI adjusted for age, year of diagnosis, socioeconomic deprivation, residence and Cancer Network
All-cause survival						
Non-Māori	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Māori	1.93 [1.81, 2.07]	1.95 [1.83, 2.09]	1.93 [1.80, 2.06]	1.85 [1.73, 1.98]	1.94 [1.81, 2.07]	1.84 [1.72, 1.97]
Cancer-specific survival						
Non-Māori	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Māori	2.09 [1.90, 2.30]	2.11 [1.91, 2.32]	2.05 [1.87, 2.26]	1.98 [1.80, 2.18]	2.06 [1.87, 2.26]	1.93 [1.75, 2.13]

The risk of dying of prostate cancer for Māori men aged <70 years adjusted for age and year of diagnosis was 2.49-fold compared with non-Māori men. After adjustment for age, year of diagnosis, residence, socio-economic deprivation and CN, the risk dropped to 2.32 (Table 7). Socio-economic deprivation was the co-variate with the strongest influence on the risk reduction from the basic model adjusted for age and year of diagnosis. However, other factors not included in the model such as treatment and co-morbidities may potentially explain a large part of the remaining variability.

The age-adjusted cancer-specific hazard ratio for Māori men aged 70+ years at diagnosis was 1.90-fold compared with non-Māori men. The full model adjusted for age, year of diagnosis, residence, socio-economic deprivation and CN returned a lower risk of 1.72 (Table 7). The largest effect of a single co-variate on risk reduction was observed for socio-economic deprivation, followed by CN, and residence.

In order to assess the effect of extent at diagnosis, survival analyses were undertaken separately for groups of men diagnosed with regional and distant prostate cancer. Due to the limited number of cases with known extent of diagnosis in the NZCR, these analyses need to be regarded with caution.

Table 7 Cancer-specific hazard ratios derived from Cox proportional hazards regression models by age group for Māori men (v. non-Māori men) diagnosed with prostate cancer between 1996 and 2010.

Cancer-specific hazard ratio [95% CI]					
	Model I adjusted for age and year of diagnosis	Model II adjusted for age, year of diagnosis and residence	Model III adjusted for age, year of diagnosis and socioeconomic deprivation	Model IV adjusted for age, year of diagnosis and Cancer Network	Model V adjusted for age, year of diagnosis, socioeconomic deprivation, residence and Cancer Network
<70 years					
Non-Māori	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Māori	2.49 [2.16, 2.88]	2.43 [2.10, 2.81]	2.32 [2.01, 2.69]	2.50 [2.16, 2.89]	2.32 [2.01, 2.69]
70+ years					
Non-Māori	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Māori	1.90 [1.67, 2.16]	1.85 [1.62, 2.10]	1.80 [1.57, 2.05]	1.83 [1.61, 2.09]	1.72 [1.51, 1.96]

For men with regional extent at diagnosis (and radical prostatectomy as treatment), the hazard ratio for cancer-specific survival for Māori men (compared with non-Māori men) was 2.73 [95% CI; 1.65, 4.52], when adjusted for age, year of diagnosis, residence, socio-economic deprivation and CN. Māori men with distant metastases at diagnosis were 1.26-fold [95% CI; 1.06, 1.51; model adjusted for age, year of diagnosis, residence, socio-economic deprivation and CN] more likely to die of prostate cancer compared with non-Māori men.

3.4.2 Epidemiology of prostate cancer in urban and rural men

Study population

The study population included 37,529 men, out of whom 12,019 (32.0%) resided in rural areas. Table 8 summarises patient characteristics by residence.

The distribution of patient characteristics is similar between men residing in MUAs and rural areas, except for a higher proportion of Māori men among rural men, a lower proportion of rural men residing in the least deprived areas, and conversely slightly higher proportion residing in the most deprived areas, and the variation of distribution by Cancer Network. The highest proportion of rural men resided in the SCN, and the highest proportion of urban men resided in the NCN.

Table 8 Patient characteristics of the national cohort of men diagnosed with prostate cancer between 1996 and 2010 by residence.

	Main urban areas (N=25510)		Rural areas (N=12019)	
	n	%	n	%
Age				
<70 years	12702	49.8	5968	49.7
70+ years	12808	50.2	6051	50.3
Ethnicity				
Māori	1053	4.1	863	7.2
Non-Māori	24457	95.9	11156	92.8
Cancer Network				
Midland	3069	12.0	2679	22.3
Northern	9980	39.1	2304	19.2
Central	6688	26.2	2553	21.2
Southern	5773	22.6	4483	37.3
Extent at diagnosis				
Localised	3190	12.5	1501	12.5
Regional	1363	5.3	702	5.8
Distant	1479	5.8	760	6.3
Unknown	19478	76.4	9056	75.3
Socio-economic deprivation (NZDep06)				
1-3 (least deprived)	7850	30.8	2342	19.5
4-7	10412	40.8	5493	45.7
8-10 (most deprived)	7248	28.4	4184	34.8
Years of diagnosis				
1996-2000	8417	33.0	3542	29.5
2001-2005	8353	32.7	4093	34.1
2006-2010	8740	34.3	4384	36.5
Vital status				
Alive	15586	61.1	7285	60.6
Death due to prostate cancer	4073	16.0	2174	18.1
Death due to other causes	5851	22.9	2560	21.3

3.4.2.1 Incidence

Age-standardised incidence rates (per 100,000 NZ men aged 40+ years from the 2001 Census) for men residing in MUAs and rural areas by year of diagnosis are depicted in Figure 13. Until 2002, incidence rates were slightly higher for men in MUAs, but since then incidence rates were similar for men residing in MUAs and rural areas. In 2010, the IRR for men residing in rural areas compared with men residing in MUA was 0.98 [95% CI; 0.83, 1.16].

Figure 14 shows age-specific incidence rates of prostate cancer men residing in MUAs and rural areas by year of diagnosis. The trends and age-specific rates were similar for men residing in MUAs and rural areas.

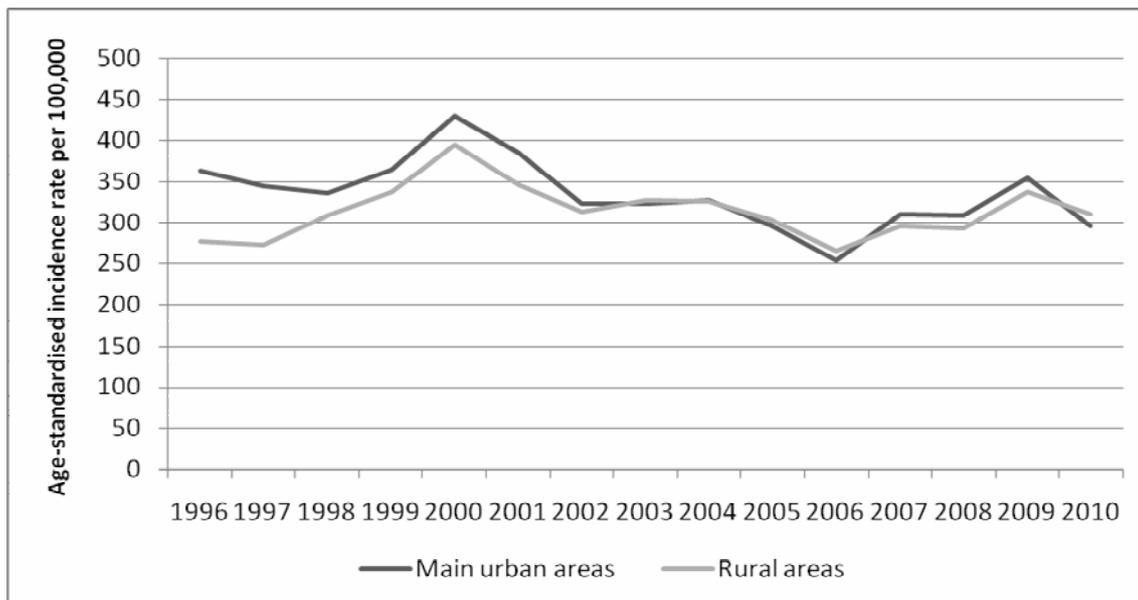


Figure 13 Annual age-standardised (2001 Census NZ men aged 40+ years) prostate cancer incidence rates for men residing in main urban and rural areas.

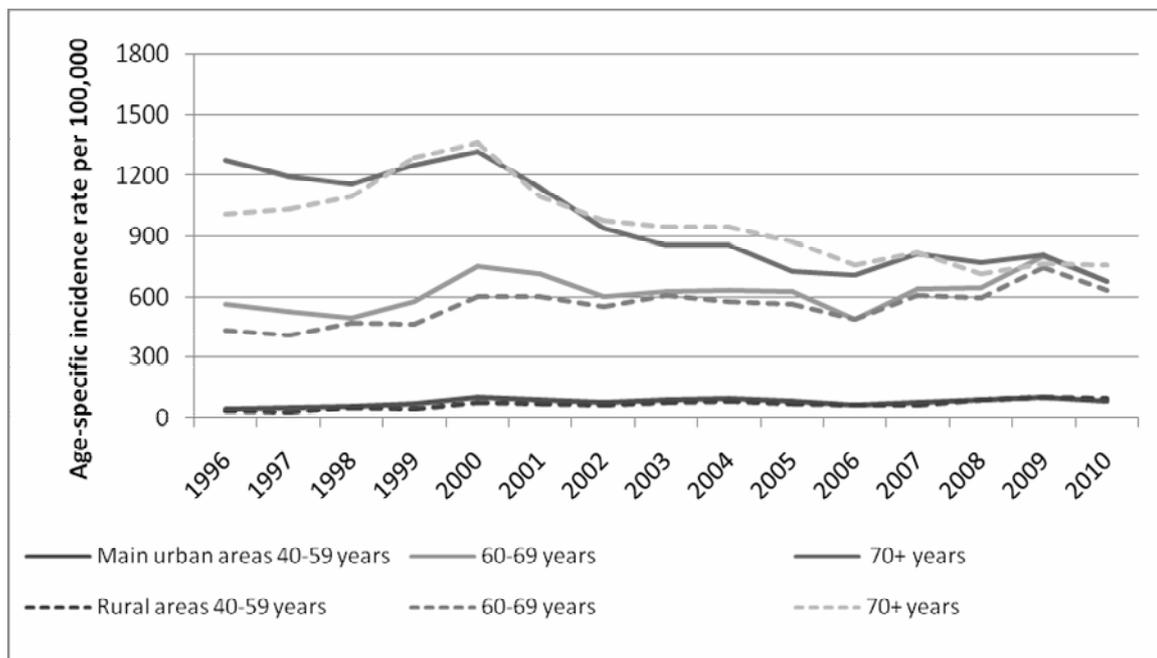


Figure 14 Annual age-specific prostate cancer incidence rates (standardised to 2001 Census NZ men aged 40+ years) for men residing in main urban and rural areas.

3.4.2.2 Survival

The Kaplan-Meier method was used to estimate one-year, 5-year and 10-year all-cause and cancer-specific survival by residence (Table 9). Men in rural areas had consistently slightly lower all-cause probability of surviving, with 90% surviving 1 year, 68% 5 years and 47% 10 years, compared with 91%, 70% and 49% surviving men in MUAs, respectively. Cancer-specific probability of surviving one year was 95% for both urban and rural men, probability of surviving 5 years was 2% lower (83% v. 85%), and probability of surviving 10 years 5% lower (72% v. 77%)

for rural men compared with men residing in MUAs. Although the estimates of probability of surviving were similar between men residing in MUAs and rural areas, the comparison by log-rank test returned a probability value of <0.001 for both all-cause and cancer-specific survival curves.

Table 9 Kaplan-Meier all-cause and cancer-specific probability of surviving one, five, and 10 years for men diagnosed with prostate cancer between 1996 and 2010 by residence.

	Kaplan-Meier all-cause probability of surviving [95% CI]			Kaplan-Meier cancer-specific probability of surviving [95% CI]		
	1 year	5 years	10 years	1 year	5 years	10 years
Main urban areas	90.8 [90.4, 91.2]	70.0 [69.4, 70.6]	49.4 [48.6, 50.2]	95.2 [95.0, 95.4]	85.2 [84.6, 85.8]	76.5 [75.7, 77.3]
Rural areas	90.4 [89.8, 91.0]	67.9 [66.9, 68.9]	47.1 [45.9, 48.3]	94.8 [94.4, 95.2]	82.8 [82.0, 83.6]	72.1 [70.9, 73.3]

Figure 15 shows the Kaplan-Meier estimates for one- and five-year cancer-specific survival for men residing in MUAs, and rural areas by diagnosis years (1996-2000, 2001-2005, 2006-2010). One- and five-year cancer-specific probability of surviving was similar between men residing in MUAs and rural areas, except for a lower probability of surviving 5 years for rural men diagnosed between 1996 and 2000.

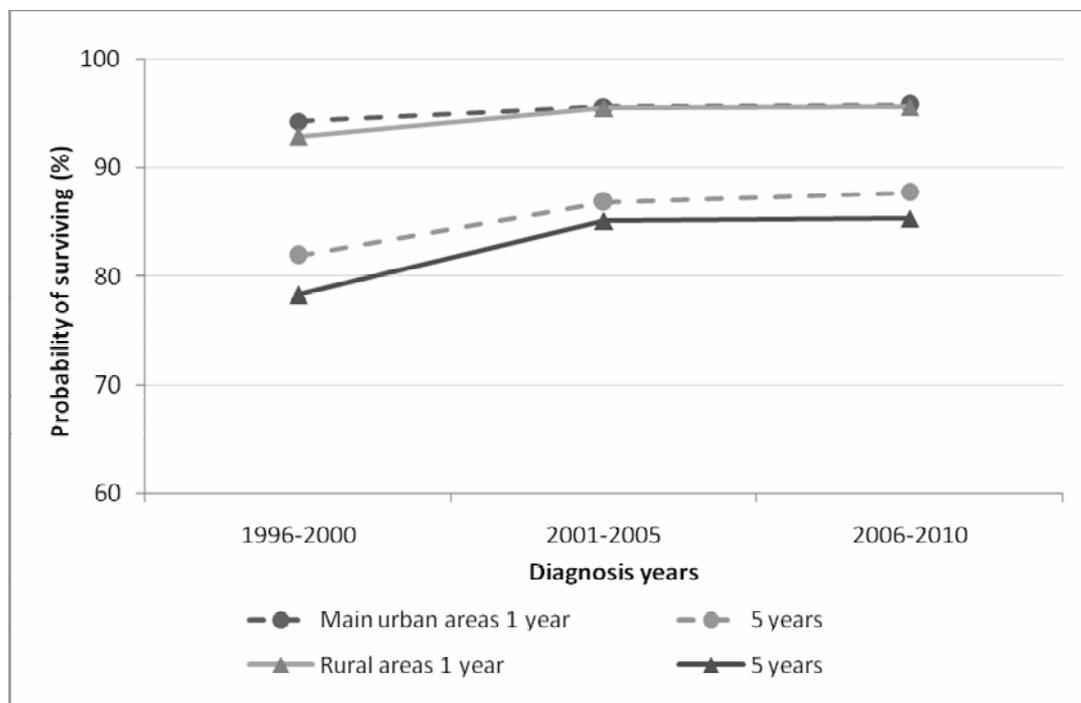


Figure 15 Kaplan-Meier one- and five-year cancer-specific survival estimates for men with prostate cancer residing in main urban and rural areas by diagnosis years.

Table 10 shows all-cause and cancer-specific hazard ratios for men residing in rural areas compared with men residing in MUAs derived from the Cox proportional hazards regression models successively adjusted for age, year of diagnosis, ethnicity, socio-economic deprivation and CN. The risk of dying from any cause for rural men adjusted for age, year of diagnosis and ethnicity was 1.07-fold compared with men residing in MUAs, while adjustment for age, year of diagnosis, ethnicity, socio-economic deprivation and CN reduced the risk estimate to 1.02. The variation in all-cause survival between men residing in rural areas and MUAs can be fully explained by adjusting for the variables in the full model.

Table 10 Hazard ratios derived from Cox proportional hazards regression models for all-cause, and cancer-specific survival for men residing in rural areas (versus men residing in main urban areas) diagnosed with prostate cancer between 1996 and 2010.

Hazard ratio [95% CI]				
	Model I adjusted for age, year of diagnosis and ethnicity	Model II adjusted for age, year of diagnosis, ethnicity and socioeconomic deprivation	Model III adjusted for age, year of diagnosis, ethnicity and Cancer Network	Model IV adjusted for age, year of diagnosis, ethnicity, socioeconomic deprivation and Cancer Network
All-cause survival				
Main urban areas	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Rural areas	1.07 [1.06, 1.14]	1.05 [1.02, 1.09]	1.05 [1.01, 1.08]	1.02 [0.99, 1.06]
Cancer-specific survival				
Main urban areas	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Rural areas	1.18 [1.12, 1.24]	1.16 [1.10, 1.22]	1.13 [1.07, 1.20]	1.11 [1.05, 1.18]

Rural men had 1.18-fold risk of dying of prostate cancer (adjusted for age, year of diagnosis and ethnicity) compared with men residing in MUAs. The full model adjusted for age, year of diagnosis, ethnicity, socio-economic deprivation and CN returned a lower hazard ratio of 1.11. The effect of a single co-variate on risk reduction was larger for CN (HR=1.13) than for socio-economic deprivation (HR=1.16).

3.4.3 Epidemiology of prostate cancer by Cancer Network

Study population

The study population included 37,529 men, out of whom 5748 (15.3%) resided in the Midland CN, 12,284 in the Northern CN (32.7%), 9241 (24.6%) in the Central CN, and 10,256 (27.3%) in

the Southern CN at the time of diagnosis. Table 11 summarises patient characteristics by Cancer Network.

Since this study focuses on the MCN region, this paragraph briefly describes the characteristics of men in the MCN in relation to the other three CNs. The age distribution was similar between Cancer Networks. There was a higher proportion of Māori men in the MCN compared with the other three CNs.

Table 11 Patient characteristics of the national cohort of men diagnosed with prostate cancer between 1996 and 2010 by Cancer Network (CN).

	Midland CN (N=5748)		Northern CN (N=12284)		Central CN (N=9241)		Southern CN (N=10256)	
	n	%	n	%	n	%	n	%
Age								
<70 years	2889	50.3	6437	52.4	4467	48.3	4877	47.6
70+ years	2859	49.7	5847	47.6	4774	51.7	5379	52.4
Ethnicity								
Māori	513	8.9	637	5.2	573	6.2	193	1.9
Non-Māori	5235	91.1	11647	94.8	8668	93.8	10063	98.1
Residence								
Main urban areas	3069	53.4	9980	81.2	6688	72.4	5773	56.3
Rural areas	2679	46.6	2304	18.8	2553	27.6	4483	43.7
Extent at diagnosis								
Localised	742	12.9	1832	14.9	770	8.3	1347	13.1
Regional	285	5.0	708	5.8	280	3.0	792	7.7
Distant	409	7.1	646	5.3	565	6.1	619	6.0
Unknown	4312	75.0	9098	74.1	7626	82.5	7498	73.1
Socio-economic deprivation (NZDep06)								
1-3 (least deprived)	928	16.1	4006	32.6	2093	22.6	3165	30.9
4-7	2580	44.9	4682	38.1	3692	40.0	4951	48.3
8-10 (most deprived)	2240	39.0	3596	29.3	3456	37.4	2140	20.9
Years of diagnosis								
1996-2000	1601	27.9	4225	34.4	2918	31.6	3215	31.3
2001-2005	2001	34.8	4036	32.9	3068	33.2	3341	32.6
2006-2010	2146	37.3	4023	32.7	3255	35.2	3700	36.1
Vital status								
Alive	3468	60.3	7750	63.1	5506	59.6	6147	59.9
Death due to prostate cancer	1094	19.0	1806	14.7	1633	17.7	1714	16.7
Death due to other causes	1186	20.6	2728	22.2	2102	22.7	2395	23.4

The MCN had the highest proportion of rural men and men living in the most deprived areas. Conversely, the MCN showed the lowest proportion of men living in the least deprived areas. For men in the MCN new registrations continually increased up to the most recent period, while for men in the other three CNs new cases of prostate cancer were relatively evenly

distributed in the three time periods. A similar pattern was observed for Māori men, which indicates that this distribution was influenced by the higher proportion of Māori men in the MCN. Similarly, a higher proportion of men with distant metastases in the MCN was probably due to the higher proportion of Māori men in the MCN compared with the other three CNs.

3.4.3.1 Incidence

Temporal trends in incidence rates varied slightly by Cancer Network, but the overall patterns were similar (Figure 16). For men in the MCN a marked decrease in incidence rates occurred between 1998 and 2000, while for men in the other three CNs incidence rates increased significantly during that period. Until 2001 incidence rates were highest for men in the NCN, but in the recent years the incidence was lowest for men in this CN.

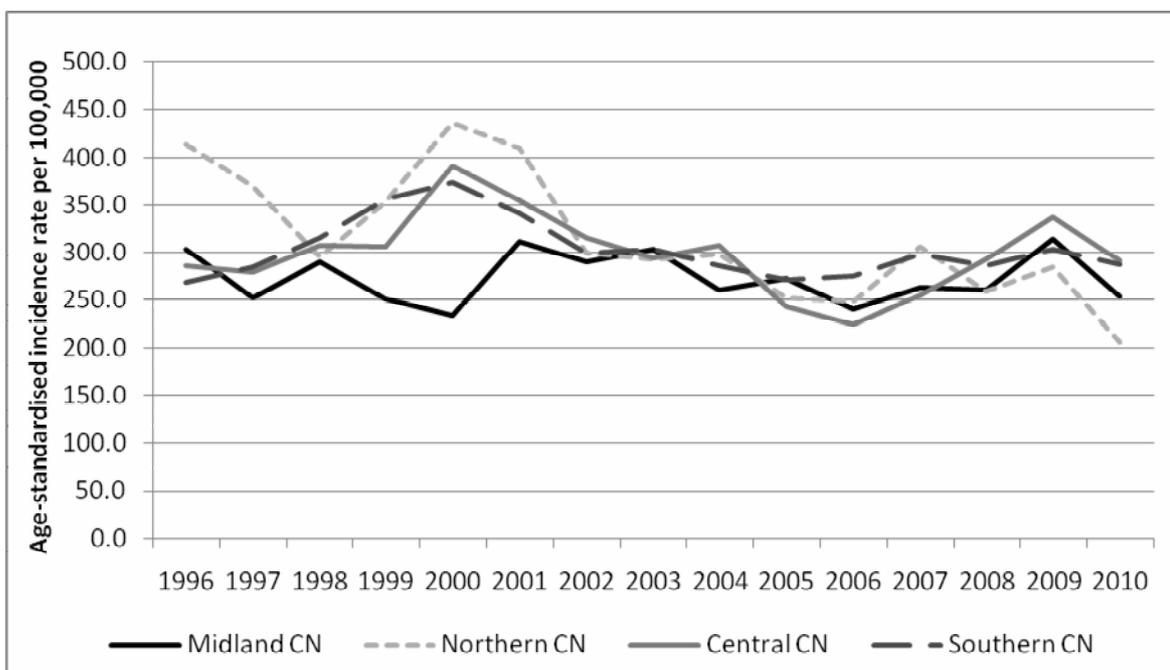


Figure 16 Annual age-standardised (2001 Census NZ men aged 40+ years) prostate cancer incidence rates by Cancer Network (CN).

3.4.3.2 Survival

The Kaplan-Meier method was used to estimate one-year, 5-year and 10-year all-cause and cancer-specific survival by Cancer Network (Table 12). All-cause probability of surviving one and 5 years was lower for men in the MCN compared with men in the other three CNs. The 10-year probability of surviving post-diagnosis was similar between the MCN, CCN and SCN, while it was higher in the NCN. Cancer-specific probability of surviving one, five, and 10 years after prostate

diagnosis was consistently lowest for men in the MCN. The log-rank test returned a probability value of <0.001 for the comparison of all-cause and cancer-specific survival curves between CNs.

Table 12 Kaplan-Meier all-cause, and cancer-specific probability of surviving one, five, and 10 years for men diagnosed with prostate cancer between 1996 and 2010 by Cancer Network.

	Kaplan-Meier all-cause probability of surviving [95% CI]			Kaplan-Meier cancer-specific probability of surviving [95% CI]		
	1 year	5 years	10 years	1 year	5 years	10 years
Cancer Network						
Midland	89.2 [88.4, 90.0]	66.7 [65.3, 68.1]	46.6 [44.8, 48.4]	93.9 [93.3, 94.5]	81.6 [80.4, 82.8]	70.8 [69.0, 72.6]
Northern	91.3 [90.7, 91.9]	72.4 [71.6, 73.2]	53.1 [51.9, 54.3]	95.5 [95.1, 95.9]	86.8 [86.2, 87.4]	79.2 [78.2, 80.2]
Central	90.2 [89.6, 90.8]	68.1 [67.1, 69.1]	46.3 [44.9, 47.7]	94.7 [94.3, 95.1]	83.3 [82.5, 84.1]	73.3 [71.9, 74.7]
Southern	91.1 [90.5, 91.7]	68.0 [67.0, 69.0]	46.4 [45.0, 47.8]	95.6 [95.2, 96.0]	84.2 [83.4, 85.0]	74.1 [72.9, 75.3]

Figure 17 shows the Kaplan-Meier estimates for one-year and five-year cancer-specific survival by Cancer Network and diagnosis years (1996-2000, 2001-2005, 2006-2010). Both one- and five-year cancer-specific survival improved over time for men in all Cancer Networks, particularly the 5-year survival improved after 2000. For men in the NCN, the probability of surviving 5 years post-diagnosis improved steadily after 2005, while for the other three CNs the probability of surviving 5 years remained relatively stable after 2000.

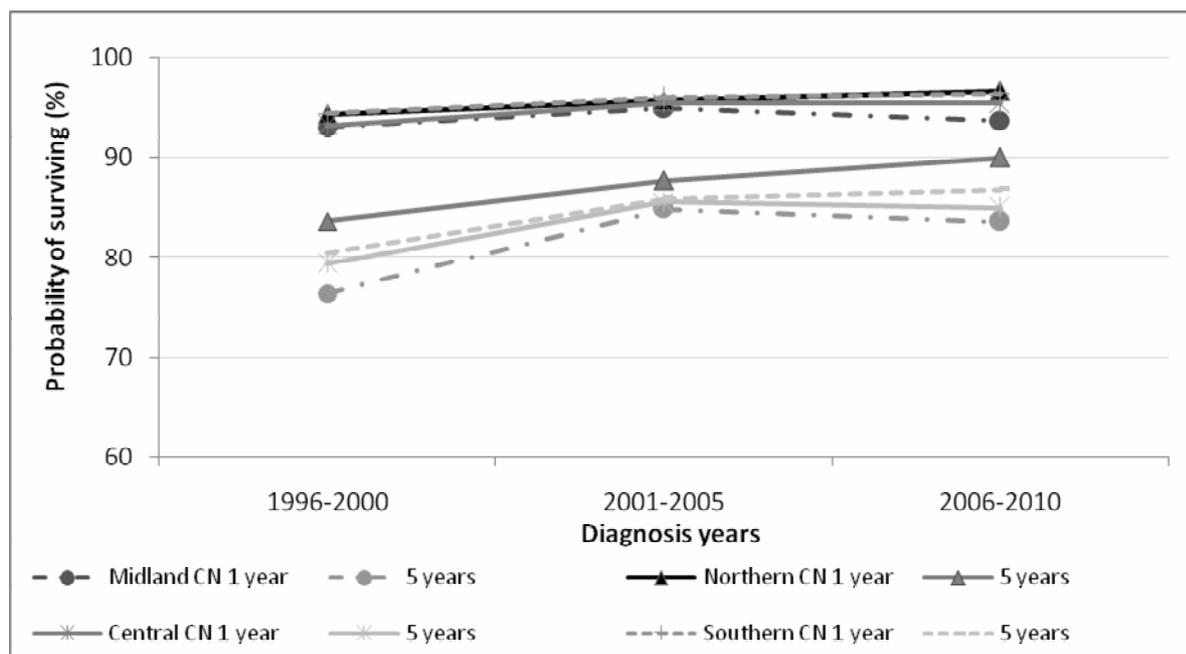


Figure 17 Kaplan-Meier one- and five-year cancer-specific survival for men with prostate cancer by Cancer Network and diagnosis years.

Table 13 shows all-cause and cancer-specific hazard ratios for men in the NCN, CCN and SCN compared with men in the MCN derived from the Cox proportional hazards regression models successively adjusted for age, year of diagnosis, ethnicity, residence and socio-economic deprivation.

Table 13 Hazard ratios derived from Cox proportional hazards regression models for all-cause, and cancer-specific survival for men diagnosed with prostate cancer between 1996 and 2010 in the Northern, Central, and Southern Cancer Network (versus men in the Midland Cancer Network).

Hazard ratio [95% CI]		
Cancer Network	Model I adjusted for age, year of diagnosis and ethnicity	Model II adjusted for age, year of diagnosis, ethnicity, socioeconomic deprivation and residence
All-cause survival		
Midland	1.0 (Reference)	1.0 (Reference)
Northern	0.83 [0.79, 0.88]	0.86 [0.82, 0.90]
Central	0.95 [0.90, 1.00]	0.96 [0.91, 1.01]
Southern	0.94 [0.89, 0.99]	0.97 [0.92, 1.02]
Cancer-specific survival		
Midland	1.0 (Reference)	1.0 (Reference)
Northern	0.71 [0.66, 0.77]	0.75 [0.69, 0.81]
Central	0.88 [0.81, 0.95]	0.90 [0.83, 0.97]
Southern	0.83 [0.77, 0.90]	0.86 [0.80, 0.93]

The risks of dying of any cause adjusted for age, year of diagnosis and ethnicity were lower for men in the NCN (HR=0.83), CCN (HR=0.95) and SCN (HR=0.94) compared with men in the MCN. After adjustment for age, year of diagnosis, ethnicity, residence, and socio-economic deprivation, the risk of dying was still lower for men in the NCN compared with men in the MCN, but the variation in all-cause survival between men in the MCN and men in the CCN as well as in the SCN was fully explained by this model.

Cancer-specific risks of dying adjusted for age, year of diagnosis and ethnicity were also lower for men in the NCN (HR=0.71), CCN (HR=0.88), and SCN (HR=0.83) compared with men in the MCN. The full model adjusted for age, year of diagnosis, ethnicity, residence and socio-economic deprivation returned hazard ratios similar to the basic model, so the risks of dying of prostate cancer were still lower for men in the NCN, CCN, and SCN compared with men in the MCN.

For men aged <70 years at diagnosis, cancer-specific hazard ratio adjusted for age, year of diagnosis, ethnicity, residence and socio-economic deprivation was 0.81 [95% CI; 0.70, 0.93] for men in the NCN, 1.09 [95% CI; 0.94, 1.26] for men in the CCN, and 1.12 [95% CI; 0.97, 1.30] for

men in the SCN compared with men in the MCN. For men aged 70+ years at diagnosis, risk of dying of prostate cancer adjusted for age, year of diagnosis, ethnicity, residence and socio-economic deprivation was 0.72 [95% CI; 0.65, 0.79] for men in the NCN, 0.83 [95% CI; 0.76, 0.91] for men in the CCN, and 0.77 [95% CI; 0.70, 0.84] for men in the SCN compared with men in the MCN.

3.5 Short discussion

3.5.1 Epidemiology of prostate cancer in New Zealand

Age-standardised prostate cancer incidence rates between 1996 and 2010 for NZ men aged 40+ years showed a general downward trend, with a peak in the year 2000 and a period of rising incidence rates between 2006 and 2009. The PSA test became available in NZ in 1993 [332], and incidence rates had been increasing up to 2000. The peak in 2000 coincides with intensified cancer control debate in New Zealand [332, 754]. Between 1997 and 2000 there were several patient and physician surveys regarding PSA testing and prostate cancer detection, which may have resulted in an increase in PSA testing, and thus prostate cancer diagnosis [337, 755]. The subsequent decline after 2000 can be associated with decreased detection of prostate cancer for men aged 70+ years. This seems paradoxical, since prostate cancer incidence biologically increases with increasing age. However, research at that time had started to show that early diagnosis does not improve outcomes for older men and they are more likely to die of other causes rather than of prostate cancer [756].

A possible reason for the surge in new registrations in 2006 may be the fact that sextant biopsy had been replaced by 12-core biopsy for detection of prostate cancer. Twelve-core biopsy results in 15-30% higher yield of positive cores compared to sextant biopsy [429, 430].

Similar temporal fluctuations in prostate cancer incidence rates have been reported in the USA, although the corresponding peaks were observed a few years earlier than in NZ [63]. This shift can be explained by earlier availability of screening and innovations in prostate cancer detection such as the 12-core biopsy in the USA [169, 429]. The troughs following the peaks probably represent periods when the pool of prevalent cases has been temporarily depleted due to the intensified diagnostic activity in the preceding period [313].

3.5.2 Epidemiology of prostate cancer in Māori and non-Māori men

Age-standardised incidence rates of prostate cancer have been decreasing from 1996 to 2006 for both Māori and non-Māori men. Between 2007 and 2009 an increase in incidence rates was

observed for non-Māori men, which opened up a divide between incidence rates for Māori and non-Māori men during this period. This trend may be associated with intensified prostate cancer awareness campaigns such as Blue September and Movember in New Zealand [757]. Since rising incidence rates were mainly observed for non-Māori men aged 60-69 years (the most commonly screened age group), it seems that these men were more likely to have their prostate health checked following awareness campaigns compared with Māori men. However, in 2010 the incidence rate for Māori men was not significantly different from that for non-Māori men.

The unadjusted all-cause and cancer-specific probability of surviving was lower for Māori compared with non-Māori men at one, five and 10 years post-diagnosis. Particularly long-term cancer-specific survival was affected. The cancer-specific probability of surviving 5 years post-prostate cancer diagnosis was 76% for Māori and 85% for non-Māori men, while the 10-year probability of surviving was 63% for Māori and 76% for non-Māori men.

An earlier NZ study reported 5-year relative survival of 68% for Māori men, and 87% for non-Māori men diagnosed between 1994 and 2007, and the 10-year relative survival estimates were 53% and 83%, respectively. The observed differences can be explained by the different approaches used to generate survival estimates. The relative survival approach has been shown to overestimate the actual survival in highly screened population [318]. Since screening rates were higher for non-Māori men, the effect of “healthy screener effect” in this group may be greater, which would explain why the 5- and 10-year cancer-specific survival estimates from this study were lower than the respective relative survival estimates reported by the Ministry of Health [327] for a similar time period. In contrast, the cancer-specific survival estimates for Māori men were greater in this study than the relative survival estimates based on general population, which differed from Māori population by demographic and clinical characteristics, including screening rates, and thus probably underestimated the actual survival for Māori men with prostate cancer.

Cancer-specific survival improved over time for both Māori and non-Māori men, but the survival gap between these two groups has not been reduced. In fact, Māori men diagnosed between 2006 and 2010 have just reached the survival level of non-Māori men diagnosed between 1996 and 2000. The overall improvements in cancer-specific survival over time, particularly for men diagnosed after 2000, coincide with changes in treatment of prostate cancer in Australasia and earlier detection following higher public awareness about PSA testing,

which may have resulted in the diagnosis of indolent tumours with excellent prognosis [332, 337, 504].

Survival differences between Māori and non-Māori men remained after adjustment for age, year of diagnosis, residence, socio-economic deprivation and CN. Māori men were 84% more likely to die of any cause, and 93% more likely to die of prostate cancer compared with non-Māori men. While all-cause survival mainly reflects the effect of treatment and co-morbidities, cancer-specific survival relates also to the effect of early detection, mainly through screening. Greater disparity for cancer-specific than for all-cause survival between Māori and non-Māori men may indicate later stage at diagnosis for Māori men, and concurrently higher proportion of indolent cancers diagnosed in non-Māori men.

The disadvantage of using survival as an outcome measure is that it is difficult to disentangle the effects of early diagnosis and treatment because in contrast to mortality, survival can be improved not only by preventing or curing the disease but also by diagnosing the disease earlier, in its pre-clinical phase. This will result in lead time bias, i.e. survival is artificially prolonged by detection of low-risk tumours with excellent prognosis early in the pre-clinical phase, and in length bias, i.e. more likely detection of slowly growing low-risk tumours as opposed to fast-growing aggressive tumours that may not be detected until symptoms occur. It is possible that the observed survival differences between Māori and non-Māori men may be to some extent explained by differences in lead time and length bias, with non-Māori men surviving longer because of longer lead times and more common detection of slowly-growing cancers with favourable prognosis.

Māori men aged <70 years at diagnosis were 132% more likely to die of prostate cancer, while Māori men aged 70+ years were 72% more likely to die from prostate cancer compared with their non-Māori peers. In prostate cancer patients, age is considered to be a major independent predictor of survival, since disease management, including early detection and treatment options is highly age-dependent [159, 296, 425]. A greater disparity found for cancer-specific survival between Māori and non-Māori men aged <70 years at diagnosis may be related to a more pronounced effect of variations in screening practices and treatment modalities among younger men with prostate cancer. Regardless of ethnicity, men aged 70+ years tend to be more likely diagnosed with advanced disease, and when diagnosed with localised disease, treatment options with curative intent are limited.

Due to insufficient information in the NZCR, extent at diagnosis was not used as a predictor variable in the multivariate survival analyses in this study. Instead, the available data were used

to separately estimate cancer-specific risk of dying for Māori men with regional and distant extent at diagnosis. The survival analysis adjusted for age, year of diagnosis, residence, socio-economic deprivation and CN revealed that Māori men with regional disease were 2.7-fold more likely to die of prostate cancer, while Māori men diagnosed with distant metastases were 1.3-fold more likely to die of the disease compared with non-Māori men. It seems therefore that even when diagnosed with similar extent, survival for Māori men was poorer than for non-Māori men, particularly for those diagnosed with regional extent.

Men recorded in the NZCR as having regional extent of prostate cancer at diagnosis were predominantly treated with radical prostatectomy. Thus, poorer survival for Māori men with regional extent at diagnosis may be partly attributed to factors other than initial treatment, such as co-morbidities, cancer recurrence and follow-up care after surgery. Differences in timeliness and quality of the initial treatment may also have contributed to the observed survival disparities.

In an earlier study, Sneyd [378] used Gleason score as a surrogate measure for extent at diagnosis in a population-based study of 7,647 NZ men diagnosed with prostate cancer between 1996 and 1999. Sneyd [378] found that Māori men were 2.5-fold more likely to die of prostate cancer when diagnosed with Gleason score 2 to 6, but the difference diminished to 1.6 for Māori men diagnosed with Gleason score 8 to 10 compared with non-Māori men. Without further clinical information, Sneyd [378] was not able to assess what proportion of Māori and non-Māori men with a particular Gleason score had cancer spread outside of the prostate, which would have explained some of the variability in survival for the groups defined by Gleason score only.

Socio-economic deprivation explained 12% of the difference between Māori and non-Māori men in cancer-specific survival. Residence and Cancer Network contributed to the models, but their effect on cancer-specific risk of dying for Māori men was marginal compared with that of socio-economic deprivation. Nevertheless, controlling for socio-economic deprivation, residence and CN has not fully explained the variation in cancer-specific survival between Māori and non-Māori men, therefore other factors, such as differences in treatment and co-morbidities may have contributed to the survival disparities by ethnicity.

Studies into colon, lung, and female breast and cervical cancer in NZ have reported that poorer survival for Māori patients can be attributed to a spectrum of patient- and health system-related factors, such as higher co-morbidity burden and health care inequalities throughout the

cancer pathway, ranging from later detection to differential access to and quality of treatment for Māori patients [758-761].

3.5.3 Epidemiology of prostate cancer in urban and rural men

Temporal trends in age-standardised prostate cancer incidence rates were similar for men residing in MUAs and rural areas, although until 2002 incidence rates were slightly higher for men residing in MUAs. The age-specific trends were also similar between men residing in rural and main urban areas. While most studies in our literature review reported that incidence of prostate cancer was higher for urban residents before and after the widespread use of PSA testing, the two most recent studies included in the review reported similar or even higher prostate cancer incidence rates for rural men compared with urban men [307, 387]. This trend probably reflects a shift toward more diagnostic activity in rural areas or a depletion of prevalent prostate cancer cases due to earlier, more intensive uptake of screening in urban areas.

Unadjusted all-cause and cancer-specific probability of surviving were only slightly lower for men residing in rural areas compared with men residing in MUAs. The largest difference between estimates was 5% for cancer-specific probability of dying 10 years post-diagnosis. While the probability of surviving 5 years was lower for rural men diagnosed between 1996 and 2000, no difference was observed between men residing in MUAs and rural areas diagnosed after 2000 thanks to the improvements in long-term cancer-specific survival over time for rural men. Similar trends were reported for Australian men with prostate cancer [391].

The 5-year cancer-specific survival, which was 83% for rural men and 85% for men residing in MUAs, was similar to the 5-year relative survival in Australia reported to be 86% in major cities and 83% in remote areas for men diagnosed with prostate cancer between 1997 and 2004 [321].

After adjustment for age, diagnosis years, ethnicity, socio-economic deprivation and CN, no difference was found for the risk of dying of any cause for rural men compared with men residing in MUAs. The risk of dying of prostate cancer adjusted for age, diagnosis years, ethnicity, socio-economic deprivation and CN was slightly higher for rural men compared with men residing in MUAs.

The overall lack of differences between men residing in MUAs and rural areas may be partly explained by the heterogeneity in access to health with respect to travel distance, particularly within the group of rural men. Nevertheless, findings from this study corroborated conclusions

from earlier studies that found no difference in prostate cancer mortality between rural and urban men in New Zealand [4, 6].

3.5.4 Epidemiology of prostate cancer by Cancer Network

Temporal trends in age-standardised incidence rates varied slightly between Cancer Networks. In particular, incidence rates for men in the MCN showed a distinct low in 2000 as opposed to a peak for men in the other three CNs. Such difference has not been observed since and cannot be readily explained by the current knowledge about prostate cancer detection strategies in the Cancer Networks. One possible explanation is that the incidence decline in the MCN is an artefact of changes in pathology services that occurred during that period.

Any variations observed in incidence rates between CNs may be due to varying screening rates, detection protocols, and pathology reporting, but may also be attributed to differences in demographic composition among the CNs. Studies from Australia, UK and the USA offered similar explanations regarding regional differences in prostate cancer incidence rates [350, 353, 504].

Men in the MCN generally showed the lowest unadjusted all-cause and cancer-specific probability of surviving, while men in the NCN had consistently the highest values. Some of the regional differences can be explained by differences in demographic characteristics among the four CNs: The MCN had the highest proportion of Māori men, rural men and men living in the most deprived areas among the CNs. In contrast, the NCN had the second lowest proportion of Māori men (SCN having the lowest), the highest proportion of men living in the least deprived areas and more than 80% of men living in MUAs. Since Māori men were shown to have higher risk of dying from prostate cancer, CNs with higher proportion of Māori men would show lower cancer-specific survival. Socio-economic position was also shown to contribute to survival disparities in NZ; with men living in the least deprived areas having lower risk of dying of prostate cancer [379].

After adjusting for age, year of diagnosis, ethnicity, residence and socio-economic deprivation cancer-specific risk of dying was still lower for men in the other three CNs than for men in the MCN. The adjusted risk of dying of any cause was lower for men in the NCN compared with men in the MCN, but controlling for ethnicity, residence and socio-economic deprivation fully explained the variation in all-cause survival between men in the MCN and men in the CCN and SCN. The persisting regional differences in cancer-specific survival may be explained by

differences in screening and diagnostic practices among CNs, as well as by differences in treatment.

Due to the limitations regarding information on cancer extent at diagnosis in the NZCR, it is difficult to assess whether variations in cancer extent at diagnosis between CNs may have contributed to the observed differences. For men diagnosed with low-risk localised prostate cancer the likelihood of surviving more than 10 years is high even without treatment [145-147], therefore the high proportion of men surviving 10 years in the NCN compared with men in the other three CNs may be attributed to a high proportion of low-risk tumours being detected in this CN. In addition, based on the distribution of known extent at diagnosis, men in the MCN had a higher proportion of men with distant metastases compared with men in the NCN. Variations in cancer extent at diagnosis associated with lead time and length bias may therefore partly explain the differences in cancer-specific survival between men in the MCN and men in the other three CNs.

It seems that the regional disparities in cancer-specific risk of dying were mainly driven by differences among men aged 70+ years. For men aged <70 years, the difference in cancer-specific survival remained only between men in the MCN and the NCN. Since screening and curative treatment are offered mainly to men younger than 70 years [504, 506, 762], early detection and treatment seemed not to vary among MCN, CCN and SCN. Therefore, other factors, such as treatment for advanced prostate cancer and co-morbidity burden may have caused the regional differences in prostate-cancer survival among older men.

3.5.5 Strengths and limitations

The strength of this study was the population-based information sourced through data linkage of national datasets, including data as current as 2011. A follow-up period of up to 15 years allowed for assessment of temporal changes in prostate cancer incidence and survival.

The use of cancer-specific survival in this study may be seen as a limitation since cancer-specific survival estimates strongly depend on the accuracy of coding of causes of death on death certificates as opposed to relative survival, which is independent from potential miscoding of underlying causes of death. However, in case of prostate cancer relative survival estimates have been shown to overestimate the actual survival because of the “healthy screener effect”, meaning that in high-screening countries like NZ men diagnosed with prostate cancer are on average healthier and have longer life expectancy than the general population. Moreover, other studies have shown that cancer-specific survival estimates are more accurate than

relative survival estimates for heavily screened populations, for which screening behaviour differs by ethnicity or socio-economic position [317, 318]. Since the main focus of this study was comparing survival between Māori men with low screening rates and non-Māori men with high screening rates, cancer-specific estimates were considered to be a more appropriate measure of survival. Based on the results of the regional study, over-diagnosis occurred slightly more likely in non-Māori men compared with Māori men, which would artificially improve survival for non-Māori men, and thus the risk estimates would be biased away from 1.

Other potential limitations of this study were: Firstly, men diagnosed at death were excluded from the analysis. Since we have found that the date of diagnosis in the NZCR was in some instances recorded later than the actual date of diagnosis, these cases may have been men who rapidly died of the disease. There was, however, no difference in the proportion of men diagnosed at death by ethnicity or residence, so the risk estimates would not be affected.

Secondly, approximately 75% of prostate cancer registrations in the NZCR had disease extent at diagnosis recorded as “unknown”. Therefore, using extent at diagnosis as a predictor variable in multivariate analyses assessing survival would not result in reliable risk estimates.

Thirdly, information on treatment and co-morbidity burden was not included in this study. These factors may have explained some of the ethnic variation observed in survival, since they may have acted as confounders due to their association both with ethnicity as exposure and the outcome.

Fourthly, comparing main urban areas against the remaining areas labelled as rural has introduced heterogeneity within the rural group with respect to physical distances to services and socio-economic aspects. However, travel distances to main urban areas are not particularly long in New Zealand, and through pooling, the socio-economic and ethnic structure of the rural areas has become more similar to that of main urban areas. In addition, this grouping allowed for a comparison of the direct spatial access to comprehensive care in MUAs in contrast to shorter or longer travel requirements of rural residents, apart from providing sufficient sample sizes, and consistency across the three studies – from the regional primary care level to the national level. The dramatic drop in sample size, especially for highly rural/remote areas would render the risk estimates imprecise. Although not included in this study, an analysis was undertaken using all seven rural/urban categories, and the risk estimate for survival in men residing in highly rural/remote areas versus those residing in MUAs was actually almost the same as for the grouped analysis. Moreover, earlier NZ studies on other types of cancer, which

distinguished more than two rural/urban categories, found little evidence for association between rural residence and cancer survival [396-398].

It is possible though that some men would move residence to MUAs following the diagnosis of prostate cancer to have better access to care. This would result in risk estimates for survival being biased toward 1.

CHAPTER 4 PSA TESTING IN PRIMARY CARE IN THE MIDLAND CANCER NETWORK REGION

4.1 Short introduction

In 2010, there were approximately 350,000 prostate-specific antigen tests carried out for 945,000 NZ men aged 40+ years [763]. The majority of these tests were ordered by general practitioners (GPs), either as screening or monitoring tests for prostate cancer.

Although population-based screening for prostate cancer is not recommended in New Zealand [3], opportunistic screening is common in NZ general practice [298, 764]. A pilot study showed that approximately 80% of PSA tests in 2010 were undertaken in asymptomatic men [298]. The same study also reported that 80% of PSA testing in NZ primary care was initiated by GPs [298]. A significant proportion of GPs in New Zealand seem to believe that screening for prostate cancer is beneficial and improves prostate cancer mortality [298, 755]. Similar screening behaviour and beliefs have been reported from other countries [300, 765]. However, GPs have also raised questions about what is the best practice for opportunistic screening, and how to explain screening pathways to clients [298, 301].

Practice characteristics and physician preferences have been shown to contribute to variation in screening patterns [766, 767]. Differences in screening practices, such as availability and interval of screening may contribute to ethnic and geographical disparities in prostate cancer incidence and mortality [357].

In New Zealand, Māori men, and men residing in rural areas were found to have lower incidence and higher mortality rates compared with non-Māori men, and urban men [4]. It is unclear whether these disparities are due to differences in detection, i.e. low screening or biopsy rates, resulting in later stage at diagnosis and worse outcomes for Māori men, and rural men, or due to high screening rates and consequently over-detection of indolent cancers with an excellent prognosis for survival for non-Māori men, and urban men.

Despite the high prevalence of PSA testing and screening in NZ primary care, little is known about the follow-up management for these tests. Elevated PSA results are considered to be predictive of prostate cancer, although the PSA test has low specificity, so that an increase in the serum PSA level may be due to other prostatic diseases. This fact may impede GPs' decision-making regarding management of elevated PSA results.

With the worldwide prevalence of prostate cancer rising, the burden on primary health care system regarding the use of PSA test is assumed to increase. GPs may also be increasingly involved in long-term management of patients at different stages of prostate cancer pathway. An in-depth understanding of the patterns of PSA testing in primary care is needed in order to assess the current and future burden on the primary health care system associated with screening for and monitoring of prostate cancer, and to explain the ethnic and regional inequalities in prostate cancer incidence and mortality in New Zealand so that evidence-based interventions can be developed to eliminate inequities.

4.2 Objectives

- 1) to calculate annual PSA screening rates for Māori and non-Māori men and for rural and urban men in the MCN region using computerised records from general practices linked with laboratory data;
- 2) to assess the association of practice characteristics on PSA screening rates;
- 3) to examine follow-up investigations, including specialist appointments and biopsies for men with elevated PSA result by ethnicity and residence;
- 4) to describe clinical characteristics of men diagnosed with prostate cancer.

4.3 Methods

4.3.1 Sample

A cohort of men aged 40+ years enrolled in 31 general practices in the Midland Cancer Network (MCN) region was identified from computerised practice records. Practices were purposefully selected to ensure sufficient numbers of Māori men and rural/urban coverage of the region. The preferential sampling of practices with high Māori population and rural practices has proven successful as shown by comparing the demographic characteristics of this cohort with those of the MCN male population aged 40+ years: In 2010, there were 36,740 men enrolled in the 31 practices, accounting for 24.5% of the estimated overall population of the MCN region in 2010. Similarly, the 31 general practices represent approximately one-quarter of all general practices in the MCN region. Māori men comprised 14.3% (4,986) of the final cohort. The estimated proportion of Māori men aged 40+ years residing in the MCN region in 2010 was 14.4% [753]. The age structure of Māori and non-Māori men of this cohort was similar to that of the total male population in the MCN region (Figure 18).

Approximately 51% of men aged 40+ lived in main urban areas in the MCN region, while 52% of men in this cohort were enrolled in practices located in main urban areas [751].

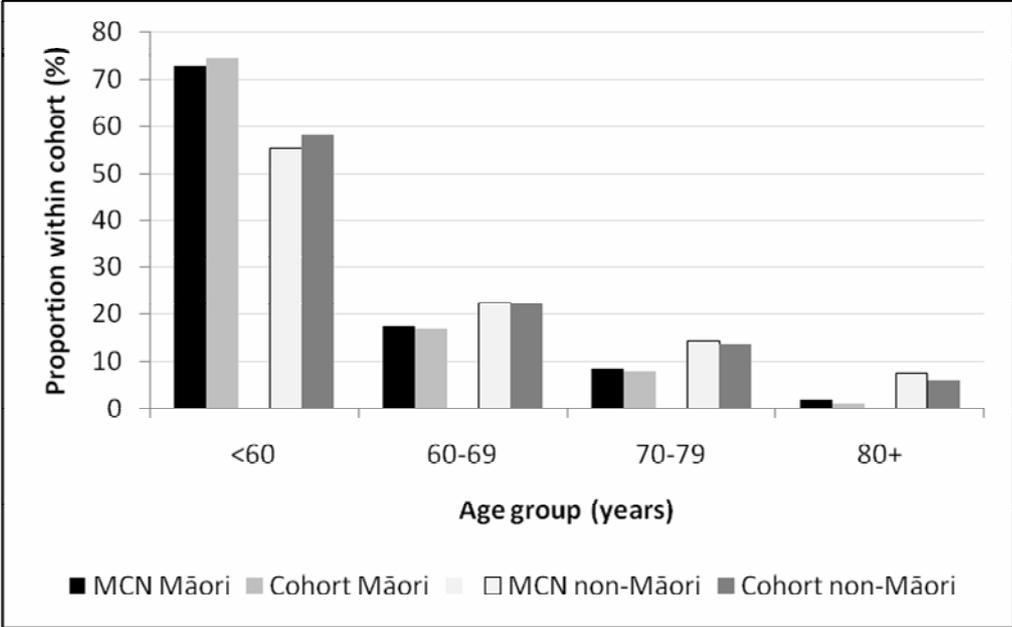


Figure 18 Age distribution of Māori and non-Māori men in the Midland Cancer Network (MCN) region and in the cohort from 31 general practices.

The final study population included 34,960 men aged 40+ years after men diagnosed with prostate cancer before 2010 (1,006) and men with unknown ethnicity (774) were excluded.

4.3.2 Data Sources

All 31 general practices used the Healthtech Medtech software for recording patient data, clinical notes and laboratory results. Each practice provided baseline data (NHI number, date of birth, ethnicity) on all male patients aged 40+ years enrolled with the practice in 2010. Data from the first five practices were extracted by an experienced general practitioner, while the author assisted in three instances to get experience and training with the set-up and content of the databases. The data were entered into a pre-formatted Excel sheet. The subsequent data extractions were undertaken by the author, who was always assisted by one of two colleagues. Men with a PSA test were identified by cross-referencing data from the computerised practice records with laboratory data. The unique NHI numbers were used for data linkage.

All PSA results for the period from 1 January 2007 to 31 December 2010 were obtained from three community laboratories (Pathlab, Waikato Hospital Laboratory, Southern Community Laboratory); with more than 90% of all tests being undertaken in one laboratory (Pathlab). We believe that these data are relatively complete.

Data on prostate cancer registrations for the years 1994 to 2011 were sourced from the NZCR. By linking the NHI numbers of the NZCR and the practice records, 1,006 (2.7%) men with a prostate cancer diagnosis prior to 1 January 2010 or prior to any PSA test in 2010 were identified, and subsequently excluded from the analyses.

Practice records of men with an elevated PSA test in 2010 were searched for information on reasons for testing and on follow-up investigations, including specialist appointments and biopsy. Biopsy information extracted from practice records was cross-referenced with histology reports available from laboratories and suggested there was not a problem with missing data.

4.3.3 Predictor variables

Ethnicity and rural/urban residence were the main exposure variables. Age was considered to be a confounding variable. To better understand clinicians' decision-making, the effect of reasons for PSA test, PSA level at referral, number of previous PSA test, and presence of previous biopsy was explored in relation to follow-up investigations. In order to explore the driving force behind PSA screening, in particular the reasons for ethnic differences (patient characteristics versus practice/GP characteristics) variables describing the size and clientele of general practices were used as a proxy for work-load and care delivery with special focus on Māori clients.

Ethnicity was extracted from general practice records. Clients who enrol with a general practice in New Zealand are asked to report their ethnicity along with other personal information. Men were categorised as either Māori or non-Māori. In the latter group, 91.9% were NZ European or other European, 2.4% Pacific, 3.3% Asian, and 2.4% of other ethnicity. Subjects' age was calculated from date of birth to the date of the first PSA test or to 1 July 2010. Age was grouped into four categories (40-59, 60-69, 70-79 and 80+ years) for the assessment of screening rates, and collapsed into two categories (<70, 70+ years) for assessing the rates of follow-up investigations and regression analyses. The dichotomisation of age groups was used because the age of 70 years has been shown as a threshold for changing diagnostic and treatment strategies for men with prostate cancer, mainly driven by the decreasing life expectancy and increasing co-morbidity burden in older men [333, 506].

For men with elevated PSA results, reasons for PSA testing were categorised as screening (testing of asymptomatic men), symptoms (lower urinary tract symptoms (LUTS), erectile dysfunction, bone pain), and previous prostate problems, including previously elevated PSA

result or negative prostate biopsy in the three years prior to 2010. Urinary retention, reduced flow, nocturia, urgency, frequency, haematuria, and dribbling were classified as LUTS.

Men enrolled in general practices located in main urban areas, i.e. Hamilton and Tauranga were classified as urban. Men enrolled with practices outside of these two cities were classified as rural. The definition of main urban area was based on the New Zealand rural/urban standard classification [751].

General practices were further categorised by governance, size and demographic characteristics of their clientele. Practices governed and managed by Māori organisations were labelled Māori provider practices and were compared to other (not Māori provider) provider practices. Māori provider practices are committed to delivering primary health care in accordance with Māori cultural protocols, customs, and beliefs [768]. Further categorisation was based on the proportion of Māori men aged 40+ years enrolled in the practice in 2010 (<20% versus 20%+), and on practice size based on the number of men aged 40+ years enrolled in the practice (<500 versus 500+), and number of GPs in the practice (1-3 versus 4+).

4.3.4 Outcome variables

In order to calculate screening rates for prostate cancer, all men with a PSA test between 1 January 2010 and 31 December 2010 were identified. For men with more than one PSA test during 2010, the earliest test result was considered in the analysis.

When one of the test results (not necessarily the earliest one) was elevated, the man was categorised as having an elevated PSA value during 2010. PSA values were classified as being elevated when they exceeded age-specific levels used by the local laboratories (adapted from Oesterling et al. [177]; Table 14).

Table 14 Age-specific normal PSA values as recommended by local laboratories (adapted from Oesterling et al. [177]).

Age	Normal value range (ng/ml)
40-49 years	0 - 2.5
50-59 years	0 - 3.5
60-69 years	0 - 4.5
70-79 years	0 - 6.5
80+ years	0 - 7.0

Men were classified as being screened when they had no elevated PSA result or negative prostate biopsy in the three years prior to 2010. In addition, men with an elevated PSA result in 2010 were considered to be screened when there was no record of relevant symptoms for the study period in practice records.

For men with an elevated PSA result (both screened and not screened), data on follow-up investigations, including specialist visit and biopsy results were extracted from practice and laboratory records. Men were followed up until 31 December 2011.

More than 95% of the first specialist appointments were for a urological consultation. Four major hospitals in the MCN region, the Waikato Hospital (the regional Cancer Centre) in Hamilton, Tauranga Hospital, Whakatane Hospital, and Rotorua Hospital, offer specialist urological services. Private urological services are offered in Hamilton and Tauranga.

Men were categorised as having a biopsy when they had either a biopsy or a transurethral resection or holmium enucleation of the prostate (TURP/HOLEP). For men with a positive biopsy, histological and imaging reports were searched for information on PSA level at specialist referral, TNM staging, and Gleason score.

The date of the first elevated PSA result in 2010 and the date of specialist consultation were recorded from practice and laboratory records in order to examine the timeliness of the follow-up investigations.

4.3.5 Statistical analysis

Statistical analysis was performed with SPSS 19.0 and STATA IC/12. Rates of PSA screening were analysed by patient characteristics, including age, ethnicity, residence, and practice characteristics, including governance (Māori versus other providers), size of the practice (1-3 GPs versus 4+ GPs per practice), and clientele (<20% versus 20+% of Māori men aged 40+ years enrolled in practice).

Age-specific proportions and the Mantel-Haenszel (M-H) age-adjusted risk ratios (RR) were calculated to compare screening rates, rates of elevated PSA results, rates of follow-up investigations and rates of positive biopsy results for Māori and non-Māori men, and rural and urban men. The M-H age-adjusted risk ratios (RR) for Māori men (compared with non-Māori men) were also calculated by practice characteristics.

Chi-square test probability values were calculated to assess differences by ethnicity, residence, age group, and reason for PSA testing. Probability level of <0.05 was considered statistically significant.

Multivariate Poisson regression analyses (with “sandwich” robust procedure) adjusted for age and ethnicity were used to explore the effect of PSA level, and medical history (number of PSA tests, negative biopsy between 2007 and 2010) on specialist referral and biopsy as outcome variables. Poisson regression with “sandwich” robust procedure was used because it allows for direct calculation of risk ratios rather than the odd ratios of logistic regression, and provides a reasonable alternative to M-H analysis, when multiple variables are considered [769]. Practices were included as a cluster variable in the models to control for within-practice correlation and between-practice variation in management patterns.

Age-specific mean and median values with 10th and 90th percentiles were calculated from PSA levels at referral for men who visited a specialist and from first elevated PSA levels for non-referred men.

Median values with 10th and 90th percentiles were calculated for intervals in days between first elevated PSA result and first specialist appointment by age, ethnicity, residence, and reason for testing. The difference between medians was tested by the Mann-Whitney test (for two categories), and by Mood’s median test (for more than two categories).

Confidence intervals (95% CI) not including 1 were considered to represent statistical difference, analogous to a probability level of <0.05 .

Access to computerised records of general practices was obtained through close cooperation with general practitioners and practice managers. Ethical approval was issued by the Northern Y Ethics Committee (NTY/11/02/019). Māori consultation included the Midland Cancer Network Māori Advisory Group Hei Pa Harakeke, and Te Puna Oranga (the Waikato District Health Board Māori Unit).

4.4 Results

4.4.1 PSA screening (testing of asymptomatic men)

The final study population included 34,960 men aged 40+ years enrolled with 31 general practices in the MCN region in 2010, of whom 8716 (24.9%) had a PSA test in 2010. Of the 8716 men, 7343 (84.2%) were considered to be asymptomatic screened men. The remaining 1373 men had either one or more elevated PSA tests between 2007 and 2009, had a record of previous prostate problems, such as negative biopsy or symptoms at the time of the first elevated PSA test in 2010.

Table 15 shows age-specific screening rates, proportions of men with elevated PSA and of men with one or more normal PSA tests between 2007 and 2009. The overall screening rate was

21.0%. The highest screening rate was observed for men aged 60-69 years (30.2%), followed by men aged 70-79 years (26.5%). Of the screened men, 168 (2.3%) men had an elevated PSA test in 2010. Men aged 60-69 years had the highest proportion of elevated PSA tests (3.2%).

Of the 7343 men with a screening test in 2010, 4242 (57.8%) had at least one normal PSA test in the previous three years (2007-2009). The proportion of screened men with a normal PSA test in the three years prior to 2010 increased with increasing age, but dropped again for men aged 80+ years (Table 15).

Table 15 Proportions of men with a screening PSA test in 31 general practices in 2010, proportions of men with an elevated PSA result, and with a PSA test between 2007 and 2009 by age group.

Age group (years)	N	Screened men		Men with elevated PSA (from screened)		Men with PSA test (2007-2009) (from screened)	
		n	%	n	%	n	%
40-59	21623	3735	17.3	64	1.7	1695	45.4
60-69	7418	2241	30.2	71	3.2	1557	69.5
70-79	4188	1110	26.5	26	2.3	829	74.7
80+	1731	257	14.8	7	2.7	161	62.6
Total	34960	7343	21.0	168	2.3	4242	57.8

4.4.1.1 PSA screening rates for Māori and non-Māori men

Of the 34,960 men enrolled in the 31 general practices, 4986 were Māori (14.3%). Table 16 shows the cohort characteristics of Māori and non-Māori men.

Māori men were younger than non-Māori men, which is consistent with the age structure of the total Māori and non-Māori population in New Zealand [770]. Māori men were less likely to have a PSA test in 2010. Māori men were also less likely to have a PSA test in the three years prior to 2010 compared with non-Māori men. More than 80% of Māori and non-Māori men had a PSA level lower than 4 ng/ml when tested.

Table 16 Characteristics of men identified from 31 general practices in the MCN region by ethnicity.

	Māori (N=4986)		non-Māori (N=29974)	
	n	%	n	%
Age				
40-59 years	3749	75.2	17874	59.6
60-69 years	805	16.1	6613	22.1
70-79 years	374	7.5	3814	12.7
80+ years	58	1.2	1673	5.6
PSA test in 2010	650	13.0	8066	26.9
Number of PSA tests between 2007 and 2009 (from tested men)				
None	347	53.4	2974	36.9
1	192	29.5	2582	32.0
2+	111	17.1	2510	31.1
PSA level (from tested men)				
0-3.99 ng/ml	554	85.2	6824	84.6
4-9.99 ng/ml	71	10.9	976	12.1
10-19.99 ng/ml	18	2.8	189	2.3
20+ ng/ml	7	1.1	77	1.0

Screening rate for Māori men was 11.2% compared with 22.6% for non-Māori men (Table 17). Māori men were 48% less likely to be screened compared with non-Māori men. When screened, more than twice as many Māori men than non-Māori men had an elevated PSA result (Table 17).

Table 17 Screening rates in 2010 and proportions of men with an elevated PSA result by age group and ethnicity.

	Screening in 2010 n (%)		Men with elevated PSA result n (% from screened)	
	Māori	non-Māori	Māori	non-Māori
40-59 years	350 (9.3)	3385 (18.9)	12 (3.4)	52 (1.5)
60-69 years	146 (18.1)	2095 (31.7)	7 (4.8)	64 (3.1)
70-79 years	55 (14.7)	1055 (27.7)	5 (9.1)	21 (2.0)
80+ years	6 (10.3)	251 (15.0)	0 (0)	7 (2.8)
Total	557 (11.2)	6786 (22.6)	24 (4.3)	144 (2.1)
Mantel-Haenszel age-adjusted risk ratio [95% CI]	0.52 [0.48, 0.56]		2.16 [1.41, 3.31]	

4.4.1.2 PSA screening rates for rural and urban men

Of the 34,960 men in this cohort, 16,646 (47.6%) were enrolled in rural practices. The cohort characteristics of urban and rural men are summarised in Table 18.

Rural men were more likely to be of Māori ethnicity, which is consistent with the demographic structure of the general rural and urban population in New Zealand [751]. Rural men were less likely to have a PSA test in 2010. Rural men were also less likely to have a PSA test in the three years prior to 2010 compared with urban men. This finding may be closely related with the higher proportion of men of Māori ethnicity among rural men.

Table 18 Characteristics of men identified from urban and rural general practices in the MCN region.

	Urban (N=18314)		Rural (N=16646)	
	n	%	n	%
Age				
40-59 years	11648	63.6	9975	59.9
60-69 years	3652	19.9	3766	22.6
70-79 years	2052	11.2	2136	12.8
80+ years	962	5.3	769	4.6
Ethnicity				
Māori	1689	9.2	3297	19.7
Non-Māori	16625	90.8	13349	80.3
PSA test in 2010	5264	28.7	3452	20.7
Number of PSA tests between 2007 and 2009 (from tested men)				
None	1783	33.9	1538	44.6
1	1622	30.8	1152	33.4
2+	1859	35.3	762	22.1
PSA level (from tested men)				
0-3.99 ng/ml	4517	85.8	2861	82.9
4-9.99 ng/ml	592	11.2	455	13.2
10-19.99 ng/ml	113	2.1	94	2.7
20+ ng/ml	42	0.8	42	1.2

Rural men with a screening rate of 17.2% were 32% less likely to be screened compared with urban men with a screening rate of 24.5% (Table 19). Screened rural men were 53% more likely to have an elevated PSA result compared with urban men (Table 19).

Table 19 Screening rates in 2010 and proportions of men with an elevated PSA result by age group and rural/urban practice.

	Screening in 2010 n (%)		Men with elevated PSA result n (% from screened)	
	Rural	Urban	Rural	Urban
40-59 years	1381 (13.8)	2354 (20.2)	28 (2.0)	36 (1.5)
60-69 years	955 (25.4)	1286 (35.2)	40 (4.2)	31 (2.4)
70-79 years	443 (20.7)	667 (32.5)	12 (2.7)	14 (2.1)
80+ years	76 (9.9)	181 (18.8)	4 (5.3)	3 (1.7)
Total	2855 (17.2)	4488 (24.5)	84 (2.9)	84 (1.9)
Mantel-Haenszel age-adjusted risk ratio [95% CI]	0.68 [0.65, 0.71]		1.53 [1.14, 2.07]	

To clarify the effect of ethnicity on the differences in screening rates and in the rates of men with elevated PSA result between rural and urban men, Poisson regression analysis adjusted for age and ethnicity was undertaken. The results showed that rural men were still 28% less likely to be screened compared with urban men (RR, 0.72 [95% CI; 0.56, 0.92]), so the difference in screening rates cannot be fully explained by ethnicity. Similarly, even after adjustment rural men were 24% more likely to have an elevated PSA result compared with urban men (RR, 1.24 [95% CI; 1.08, 1.42]). Although ethnicity contributed to both models, controlling for this variable did not fully explain the observed differences between rural and urban men.

4.4.1.3 PSA screening by practice

Practice characteristics

Thirteen general practices were categorised as urban and 18 as rural. Nineteen practices were located in the Waikato DHB, eight in the Bay of Plenty DHB, and four in the Lakes DHB.

Fourteen practices had one to three attending general practitioners, while the remaining 17 practices employed more than three GPs at a time. Eight general practices were identified as being Māori Health Providers, meaning these general practices are owned and governed by Māori and provide services primarily but not exclusively to Māori. Fourteen practices had 20+% of Māori male clients aged 40+ years.

Screening rates ranged from 4.8% to 34.8% for the 31 general practices (Figure 19). There was a trend for smaller practices (referring to the number of men aged 40+ years enrolled in the practice in 2010) having lower PSA testing and screening rates compared with larger practices.

The majority of smaller practices had a high proportion (20+% of Māori men. Consequently,

practices with a high proportion of Māori men were practices with lower PSA testing and screening rates compared with practices with less than 20% of Māori men.

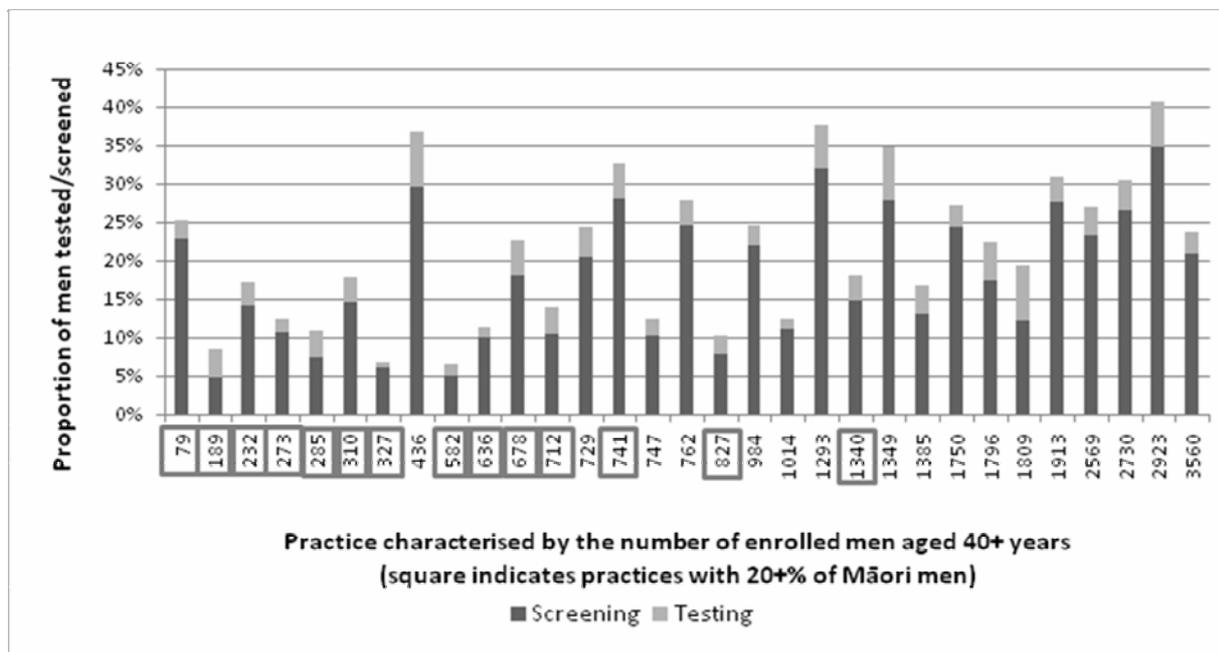


Figure 19 Proportions of men with a screening and non-screening PSA test in 2010 by general practice.

The characteristics of Māori provider and other provider practices are summarised in Table 20. Māori provider practices were smaller with respect to the number of enrolled men aged 40+ years, and to the number of general practitioners in the practice. In each of the Māori provider practices, Māori men represented 20+% of the enrolled men, while only one-fourth of the other providers had such proportion of male Māori clients in their practice.

Table 20 Characteristics of Māori provider, and other provider practices.

	Māori provider practices (N=8)		Other provider practices (N=23)	
	n	%	n	%
Number of men aged 40+ enrolled				
<500	6	75.0	2	8.7
500+	2	25.0	21	91.3
Proportion of Māori men enrolled				
<20%	0	0	17	73.9
20%+	8	100	6	26.1
Number of general practitioners in practice				
1-3	6	75.0	8	34.8
4+	2	25.0	15	65.2
Location				
Main urban area	1	12.5	12	52.2
Rural area	7	87.5	11	47.8

Men enrolled in Māori provider practices were 60% less likely to be screened compared with men in other provider practices (Table 21). The screening rate for men in smaller practices with 1-3 GPs was 14.8% compared with 22.6% for men in practices with 4+ GPs (Table 21). Men in practices with 20+% of male Māori clients were half as likely to be screened compared with men in practices with <20% of enrolled male Māori clients (Table 21).

Table 21 Screening rates in 2010 by age group and practice characteristics.

Screening in 2010 n/N (%)						
	Māori provider	Other provider	Practice with 1-3 GPs	Practice with 4+ GPs	Practice with 20%+ Māori men	Practice with <20% Māori men
40-59 years	119/1751 (6.8)	3616/19872 (18.2)	498/4262 (11.7)	3237/17361 (18.7)	481/4832 (10.0)	3254/16791 (19.4)
60-69 years	81/659 (12.3)	2160/6759 (32.0)	338/1687 (20.0)	1903/5731 (33.2)	313/1766 (17.7)	1928/5652 (34.1)
70-79 years	53/403 (13.2)	1057/3785 (27.9)	205/991 (20.7)	905/3197 (28.3)	186/1054 (17.7)	924/3134 (29.5)
80+ years	7/102 (6.9)	250/1629 (15.4)	34/305 (11.2)	223/1426 (15.6)	31/306 (10.1)	226/1425 (15.9)
Total	260/2915 (8.9)	7083/32045 (22.1)	1075/7245 (14.8)	6268/27715 (22.6)	1011/7958 (12.7)	6332/27002 (23.5)
Mantel-Haenszel age-adjusted risk ratio [95% CI]	0.40 [0.35, 0.44]		0.64 [0.60, 0.68]		0.53 [0.50, 0.57]	

Age-adjusted RRs for Māori men being screened (compared with non-Māori men) by practice characterised by the overall proportion of screened men are depicted in Figure 20. There were two practices that had RRs of Māori and non-Māori screening rates close to (0.97) or above 1 (1.36), both of which were Māori provider practices (Figure 20).

4.4.2 Follow-up investigations for men with an elevated PSA result

In total, there were 1070 men with an elevated PSA result in this cohort. Of these, 168 (15.7%) were screened, 141 (13.2%) had symptoms, and 761 (71.1%) had previous prostate problems (including previously elevated PSA result).

The proportion of men with an elevated PSA result, who were identified through screening, declined with increasing age (24.4% for men aged 40-59 years to 4.6% for men aged 80+ years; Figure 21).

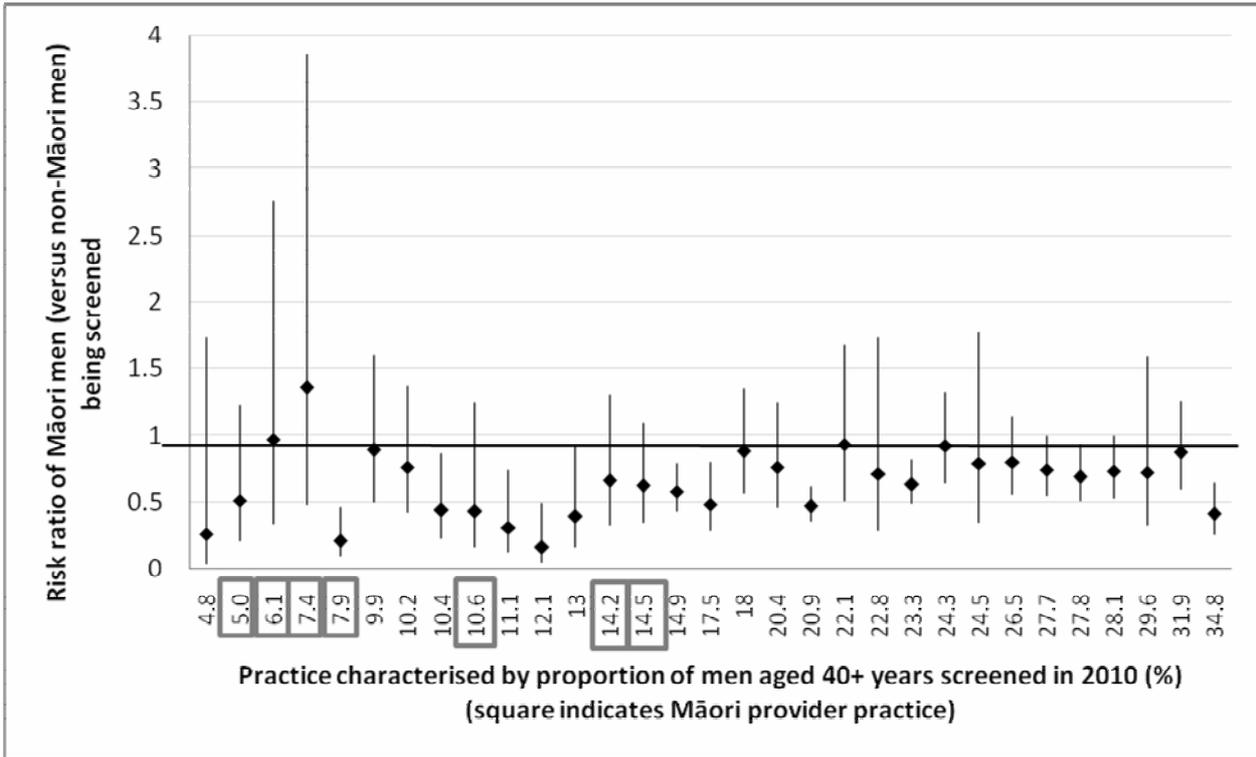


Figure 20 Risk ratios of screened Māori men (versus non-Māori men) by general practice.

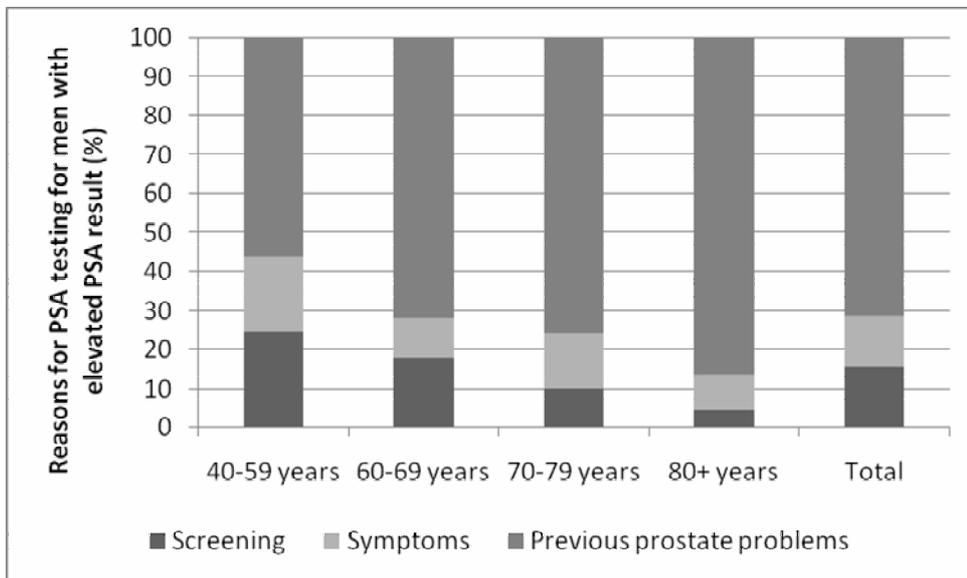


Figure 21 Reasons for PSA testing for men with an elevated PSA result in 2010 by age group.

The distribution of reasons for PSA testing varied significantly by ethnicity (χ^2 test $p = 0.004$) and by rural/urban residence (χ^2 test $p = 0.003$). Māori men had an elevated PSA result more likely following screening compared with non-Māori men (26.1% v. 14.7%; Figure 22). In

contrast, non-Māori men with an elevated PSA result had more likely previous prostate problems than Māori men (72.5% v. 56.5%). Rural men with an elevated PSA result were less likely tested due to previous prostate problems compared with urban men (66.2% v. 75.2%, Figure 22).

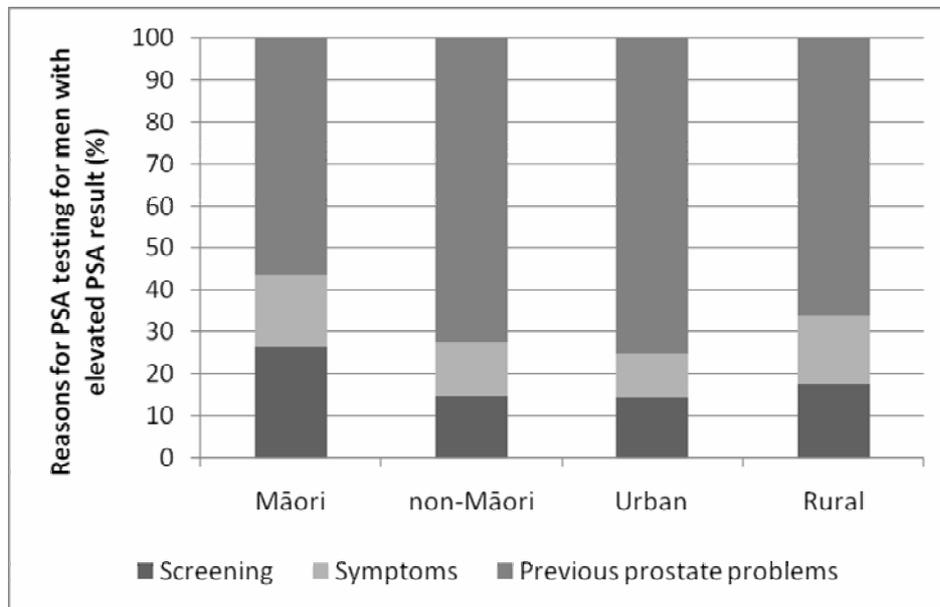


Figure 22 Reasons for PSA testing for men with an elevated PSA result in 2010 by ethnicity and rural/urban practice.

In total, 463 (43.3%) men visited a specialist after an elevated PSA result, and 300 (64.8%) underwent a biopsy following a specialist consultation (Table 22). Of the men, who underwent a biopsy, 165 (55.0%) were found to have prostate cancer. The overall cancer detection rate was 15.4% from all men with an elevated PSA result.

Of the men categorised as having biopsy, 38 (12.7%) men had a TURP/HOLEP, and of these five men (13.2%) were diagnosed with prostate cancer. Five men diagnosed with prostate cancer following a non-elevated PSA result, and two men diagnosed with prostate cancer following clinical symptoms without a biopsy were not included in the analyses. The two clinically diagnosed men were found to have distant metastases.

Following an elevated PSA result 47.6% of men aged <70 years visited a specialist compared to 36.3% of men aged 70+ years (χ^2 test $p < 0.0001$; Table 22). Almost three-quarters of men aged <70 years underwent a biopsy following a specialist consultation compared with less than half of men aged 70+ years (χ^2 test $p < 0.0001$). In particular, only about two-fifths of the older men, who were screened, went on to have a biopsy following a specialist consultation. Following a biopsy, 52.6% of men aged <70 years had a positive biopsy compared with 62.9% of men aged

70+ years (χ^2 test $p = 0.13$). The overall prostate cancer detection rate from all men with an elevated PSA result was 18.4% for men aged <70 years and 10.7% for older men.

Table 22 Frequency of follow-up investigations and prostate cancer diagnosis for men with an elevated PSA result by age group and reason for PSA test.

	Screening	Symptoms	Previous prostate problems	Total
	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Specialist consultation (from men with elevated PSA)				
<70 years	53/135 (39.3)	51/91 (56.0)	210/433 (48.5)	314/659 (47.6)
70+ years	13/33 (39.4)	26/50 (52.0)	110/328 (33.5)	149/411 (36.3)
Total	66/168 (34.8)	77/141 (54.6)	320/761 (42.0)	463/1070 (43.3)
Biopsy (from referred men)				
<70 years	39/53 (73.6)	34/51 (66.7)	157/210 (74.8)	230/314 (73.2)
70+ years	5/13 (38.5)	11/26 (42.3)	54/110 (49.1)	70/149 (47.0)
Total	44/66 (66.7)	45/77 (58.4)	211/320 (65.9)	300/463 (64.8)
Positive biopsy (from men with a biopsy)				
<70 years	22/39 (56.4)	19/34 (55.9)	80/157 (51.0)	121/230 (52.6)
70+ years	5/5 (100)	8/11 (72.7)	31/54 (57.4)	44/70 (62.9)
Total	27/44 (61.4)	27/45 (60.0)	111/211 (52.6)	165/300 (55.0)

Of screened men with an elevated PSA result, 66 (34.8%) men had a specialist consultation, 44 (66.7%) men had a biopsy, and 27 (61.4%) had a positive biopsy result (Table 22). Of the 141 men with symptoms, 77 (54.6%) men visited a specialist, 45 (58.4%) men underwent a biopsy, and 27 (60.0%) were found to have prostate cancer. Of men with an elevated PSA result and previous prostate problems, 320 (42.0%) had a specialist appointment, 211 (65.9%) went on to have a biopsy following the specialist visit, and 111 (52.6%) were diagnosed with prostate cancer following the biopsy. There was a significant difference in the rates of specialist consultation among the three categories of reasons for testing (χ^2 test $p = 0.01$), with screened men being the least likely to have a specialist appointment followed by men with previous prostate problems and men with symptoms. No significant differences were found in the rates of biopsy, and positive biopsy. The overall detection rate calculated from all men with an

elevated PSA result was 16.1% for screened men, 19.1% for men with symptoms, and 14.6% for men with previous prostate problems.

For men with an elevated PSA result, age-specific mean and median PSA levels were only slightly higher for men referred to a specialist compared with mean and median values of the first elevated PSA result for non-referred men (Table 23). The 10th percentiles were similar for referred and non-referred men at any age. The 90th percentiles were similar for referred and non-referred men aged 40-59 years, while they were consistently lower for non-referred men aged 60+ years.

Table 23 Age-specific mean, median, and 10th and 90th percentile of PSA values for referred and non-referred men with an elevated PSA result.

	PSA level at referral (ng/ml)				PSA level for non-referred men (ng/ml)			
	n	mean	median	10 th ; 90 th percentile	n	mean	median	10 th ; 90 th percentile
40-49 years	18	3.7	3.2	2.2; 6.5	26	4.1	2.9	2.6; 5.9
50-59 years	110	9.7	5.9	3.6; 10.7	108	6.9	4.7	3.6; 10.9
60-69 years	186	11.4	7.6	4.8; 17.0	211	8.6	5.8	4.7; 11.9
70-79 years	106	15.6	10.0	6.5; 22.2	153	10.7	8.3	6.8; 15.7
80+ years	43	31.7	16.6	7.2; 49.4	109	14.4	10.5	7.2; 22.0

Table 24 summarises age-specific rates of specialist visit, biopsy and positive biopsy for Māori and non-Māori men. The rate of specialist visits was 34.8% for Māori men and 44.1% for non-Māori men. Following a specialist visit, 18 (56.3%) Māori men and 282 (65.4%) non-Māori men underwent a biopsy. Māori men were 25% less likely to have a specialist consultation and 21% less likely to undergo a biopsy compared with non-Māori men.

Twelve (66.7%) Māori men and 153 (54.3%) of non-Māori men were diagnosed with prostate cancer following a biopsy. The cancer detection rate following an elevated PSA result was 13.0% for Māori men and 15.6% for non-Māori men.

Age-specific rates for specialist visit, biopsy and positive biopsy for rural and urban men are summarised in Table 25. The rate of specialist visits was 43.5% for rural men and 43.1% for urban men. Following a specialist consultation, 147 (69.7%) rural men and 153 (60.7%) urban men underwent a biopsy. Rural men were 13% more likely to undergo a biopsy. Following a biopsy, 78 (53.1%) rural men and 87 (56.9%) of urban men were diagnosed with prostate cancer. The cancer detection rate was 16.1% for rural men and 14.9% for urban men.

Table 24 Frequency of follow-up investigations and prostate cancer diagnosis for Māori and non-Māori men with an elevated PSA result by age group.

	Māori	non-Māori
	n/N (%)	n/N (%)
Specialist visit (from men with elevated PSA)		
<70 years	28/72 (38.9)	286/587 (48.7)
70+ years	4/20 (20.0)	145/391 (37.1)
Total	32/92 (34.8)	431/978 (44.1)
Mantel-Haenszel age-adjusted RR [95% CI]	0.75 [0.56, 1.00]	
Biopsy (from referred men)		
<70 years	16/28 (57.1)	214/286 (74.8)
70+ years	2/4 (50.0)	68/145 (46.9)
Total	18/32 (56.3)	282/431 (65.4)
Mantel-Haenszel age-adjusted RR [95% CI]	0.79 [0.58, 1.08]	
Positive biopsy (from men with a biopsy)		
<70 years	10/16 (62.5)	111/214 (51.9)
70+ years	2/2 (100)	42/68 (61.8)
Total	12/18 (66.7)	153/282 (54.3)
Mantel-Haenszel age-adjusted RR [95% CI]	1.26 [0.90, 1.77]	

Table 25 Frequency of follow-up investigations and prostate cancer diagnosis for rural and urban men with an elevated PSA result by age group.

	Rural	Urban
	n/N (%)	n/N (%)
Specialist visit (from men with elevated PSA)		
<70 years	147/317 (46.4)	167/342 (48.8)
70+ years	64/168 (38.1)	85/243 (35.0)
Total	211/485 (43.5)	252/585 (43.1)
Mantel-Haenszel age-adjusted RR [95% CI]	0.99 [0.87, 1.14]	
Biopsy (from referred men)		
<70 years	114/147 (77.6)	116/167 (69.5)
70+ years	33/64 (51.6)	37/85 (43.5)
Total	147/211 (69.7)	153/252 (60.7)
Mantel-Haenszel age-adjusted RR [95% CI]	1.13 [1.00, 1.29]	
Positive biopsy (from men with a biopsy)		
<70 years	58/114 (50.9)	63/116 (54.3)
70+ years	20/33 (60.6)	24/37 (64.9)
Total	78/147 (53.1)	87/153 (56.9)
Mantel-Haenszel age-adjusted RR [95% CI]	0.94 [0.76, 1.15]	

Table 26 summarises risk ratios for Poisson regression models to explore the effect of PSA level at referral on specialist visit, biopsy and positive biopsy as outcomes. After adjusting for age, ethnicity and reason for PSA test men with PSA levels below 4 ng/ml were shown to be less

likely to visit a specialist, while men with PSA levels of 10+ ng/ml were more likely to have a specialist consultation compared with men with PSA level of 4-9.99 ng/ml.

Table 26 Poisson regression adjusted risk ratios for follow-up investigations and positive biopsy by PSA level at referral, number of previous PSA tests, and previous negative biopsy.

Adjusted Poisson regression model	Adjusted risk ratio for specialist visit [95% CI]	Adjusted risk ratio for biopsy [95% CI]	Adjusted risk ratio for positive biopsy [95% CI]
PSA level at referral*			
0-3.99 ng/ml	0.83 [0.64, 1.08]	0.74 [0.55, 0.99]	1.07 [0.73, 1.58]
4-9.99 ng/ml	1.00 (reference)	1.00 (reference)	1.00 (reference)
10-19.99 ng/ml	1.44 [1.20, 1.74]	1.05 [0.85, 1.30]	0.94 [0.65, 1.36]
20+ ng/ml	1.54 [1.19, 1.99]	1.07 [0.85, 1.36]	1.22 [0.92, 1.63]
Number of PSA tests between 2007 and 2009**			
0	1.00 (reference)	1.00 (reference)	1.00 (reference)
1	0.93 [0.79, 1.10]	0.94 [0.79, 1.12]	1.01 [0.73, 1.40]
2+	0.89 [0.76, 1.04]	1.01 [0.92, 1.11]	0.91 [0.70, 1.18]
Previous negative biopsy**			
No	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	1.13 [0.93, 1.36]	0.94 [0.79, 1.12]	0.73 [0.57, 0.94]

*adjusted for age, ethnicity and reason for PSA test

**adjusted for age and ethnicity

Men with PSA levels of <4 ng/ml were 26% less likely to undergo a biopsy compared with men levels of 4-9.99 ng/ml. There was little evidence for differences in biopsy rates between men with PSA levels of 10+ ng/ml compared with men with PSA levels of 4-9.99 ng/ml. Men with PSA levels of 20+ ng/ml were 22% more likely to have a positive biopsy compared with men with PSA levels of 4-9.99 ng/ml.

Poisson regression models adjusted for age and ethnicity were also separately fitted to explore the effect of number of PSA tests undertaken between 2007 and 2009, and previous negative biopsy on specialist visit, biopsy and positive biopsy as outcomes (Table 26). With increasing number of PSA tests in the three years prior to 2010 men seemed to be less likely to visit a specialist. Rates of biopsy and positive biopsy were not affected by the number of previous PSA tests. Men with a previous negative biopsy were 13% more likely to visit a specialist, while they were 27% less likely to have a positive biopsy. The previous biopsy status had no effect on biopsy rates.

For the total cohort, median interval between the first elevated PSA result and the first specialist appointment was 88 days (10th percentile=8 days, 90th percentile=396 days). There was little evidence for differences in medians by age (Mann-Whitney test p = 0.27), ethnicity (Mann-Whitney test p = 0.24), and residence (Mann-Whitney test p = 0.97; Table 27). Medians

differed between screened men, men with symptoms, and men with previous prostate problems: Men with previous prostate problems showed the highest median values for the interval between the first elevated PSA result and the first specialist appointment, followed by screened men, and men with symptoms (Mood’s median test $p = 0.006$; Table 27).

Table 27 Median (with 10th and 90th percentile) wait times (days) between first elevated PSA test and first specialist appointment for men identified from 31 general practices in the MCN region by age , ethnicity, rural/urban practice, and reason for PSA test.

	First elevated PSA test to first specialist appointment (days)		
	n	median	10 th ; 90 th percentile
Age			
<70 years	297	91	10; 391
70+ years	133	86	7; 427
Ethnicity			
Māori	29	55	2; 396
Non-Māori	401	91	10; 391
Practice			
Urban	221	84	12; 383
Rural	209	98	6; 396
Reason for PSA test			
Screening	58	79	16; 302
Symptoms	72	64	15; 237
Previous prostate problems	300	108	1; 450

4.4.3 Characteristics of men diagnosed with prostate cancer

Clinical characteristics of men diagnosed with prostate cancer are shown in Table 28. Men with a positive biopsy were most likely aged 60-69 years, had previous prostate problems, but did not have a previous negative biopsy, and had a PSA level at referral of 4-9.99 ng/ml. The Gleason score at diagnosis was 6 for 60.6% of men diagnosed with prostate cancer; 27.9% of men had T1c and 30.9% had T2 tumours. Overall, there were 57.6% of men diagnosed with localised disease, 10.9% with regional disease, and 6.1% with distant metastases. For 22.4% of men there was not sufficient information to assign the extent at diagnosis, particularly due to missing information on clinical stage.

Table 28 Characteristics of men with a positive biopsy in 2010/2011 identified from 31 general practices in the MCN region.

	Positive Biopsy (n=165)	
	n	%
Age		
<60 years	42	25.5
60-69 years	79	47.9
70-79 years	39	23.6
80+ years	5	3.0
Ethnicity		
Māori	12	7.3
Non-Māori	153	92.7
Residence		
Urban	87	52.7
Rural	78	47.3
Reason for PSA test		
Screening	27	16.4
Symptoms	27	16.4
Previous prostate problems	111	67.3
Number of PSA between 2007 and 2009		
0	42	25.5
1	40	24.2
2+	83	50.3
Previous biopsy		
Yes	33	20.0
No	132	80.0
PSA level at referral		
0-3.99 ng/ml	9	5.5
4-9.99 ng/ml	102	61.8
10-19.99 ng/ml	33	20.0
20+ ng/ml	21	12.7
Type of procedure		
Biopsy	160	97.0
TURP/HOLEP	5	3.0
Gleason score at diagnosis		
6	100	60.6
7	41	24.8
8-10	24	14.6
Clinical stage		
T1c	46	27.9
T2	51	30.9
T3	20	12.1
T4	3	1.8
unknown	45	27.3
Extent of disease		
Localised	95	57.6
Regional	18	10.9
Distant metastases	10	6.1
Unknown	37	22.4

Clinical characteristics for men diagnosed with prostate cancer by reason for PSA test are shown in Table 29. Men with symptoms were more likely to have PSA levels of 20+ ng/ml at

referral, GS of 8-10 and distant metastases at diagnosis compared with screened men and men with previous prostate problems.

Table 29 Clinical characteristics of men with a positive biopsy identified from 31 general practices in the MCN region by reason for PSA testing.

	Screening (n=27)		Symptoms (n=27)		Previous prostate problems (n=111)	
	n	%	n	%	n	%
Type of procedure						
Biopsy	27	100	25	92.6	108	97.3
TURP/HOLEP	0	0	2	7.4	3	2.7
PSA level at referral						
0-3.99 ng/ml	1	3.7	1	3.7	7	6.3
4-9.99 ng/ml	17	63.0	17	63.0	68	61.3
10-19.99 ng/ml	5	18.5	2	7.4	26	23.4
20+ ng/ml	4	14.8	7	25.9	10	9.0
Gleason score at diagnosis						
6	14	51.9	16	59.3	70	63.1
7	8	29.6	2	7.4	31	27.9
8-10	5	18.5	9	33.3	10	9.0
T-stage						
T1c	8	29.6	5	18.5	33	29.7
T2	10	37.0	12	44.4	29	26.1
T3	4	14.8	4	14.8	12	10.8
T4	1	3.7	1	3.7	1	0.9
unknown	4	14.8	5	18.5	36	32.4
Distant metastases						
Present	0	0	6	22.2	4	3.6

The distribution of Gleason score at diagnosis for men with positive biopsy by ethnicity and residence is depicted in Figure 23. Māori men were more likely to have GS of 8-10 compared with non-Māori men (RR, 1.82 [95% CI, 0.63, 5.24]), but there was no difference in the proportion of Māori and non-Māori men with GS of 6 (RR, 0.96 [95% CI, 0.59, 1.57]). Rural men were less likely to have GS of 6 at diagnosis (RR, 0.78 [95% CI, 0.61, 0.98]), while they were 32% more likely to have GS of 8-10 compared with urban men (RR, 1.32 [95% CI, 0.63, 2.77]). Māori men were more likely to have distant metastases at diagnosis compared with non-Māori men (16.7% v. 5.2%; RR, 3.19 [95% CI, 0.76, 13.37]). A similar proportion of urban and rural men had distant metastases at diagnosis (7.0% and 5.1%, respectively).

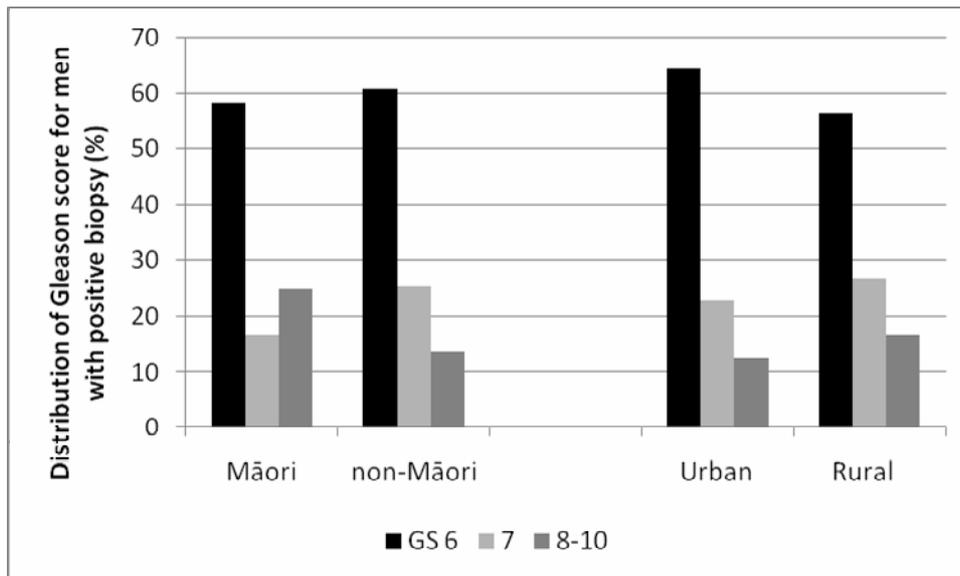


Figure 23 Distribution of Gleason score (GS) for men with a positive biopsy identified from 31 general practices in the MCN region by ethnicity, and rural/urban practice.

4.5 Short discussion

4.5.1 PSA screening rates

Approximately 20% of the 34,960 men aged 40+ years enrolled in 31 general practices in the MCN region were screened in 2010. Of all men with a PSA test in the study period, 84% were considered to be screened. An earlier questionnaire-based NZ study reported screening rates of 18% in 2008 and 22% between 2003 to 2007 [764]. The New Zealand Health Survey found that approximately 50% of men aged 50+ years have had a PSA test within a two-year period, of which 80% were asymptomatic [3].

The highest screening rate was observed for men aged 60-69 years, closely followed by men aged 70-79 years. Although the debate about benefits of screening is still ongoing, two RCTs showed that screening reduces mortality from prostate cancer for men aged 55 to 69 years [162, 277], while there is no evidence that screening improves outcomes for older men [756]. Only 2% of men screened in 2010 had an elevated PSA result. Men were frequently tested, with more than half of the screened men having one or more normal PSA tests in the three years prior to 2010. In an earlier study from the Wellington area, Gray et al. [186] found that 3-4% of men aged 40 to 69 years had an elevated PSA result (>4 ng/ml). The ERSPC reported that PSA screening undertaken on average every four years resulted in 11-23% of elevated tests (above 3-4 ng/ml) [162], and the proportion of men with elevated PSA results (>4 ng/ml) was 8-9% in the PLCO trial with annual screening [281]. In population-based studies, the proportion of men

with PSA levels >4 ng/ml ranged from 8% to 13% [771-773], and a recent US cohort study reported 8.5% of men with a PSA result that exceeded age-specific cut-off values [774]. Māori men were half as likely to be screened for prostate cancer compared with their non-Māori peers. Māori men were also less likely to have a PSA test in the three years prior to 2010 compared with non-Māori men. When screened, Māori men were twice as likely to have an elevated PSA result compared with non-Māori men.

One of the arguments for lower screening rates for Māori men may be that they do not visit their GP as often as non-Māori men do. However, a current NZ Health Survey showed that Māori men were as likely to visit their GPs as non-Māori men in 2011/2012 [96]. There may be also differences between Māori and non-Māori patients requesting PSA screening. However, an earlier NZ study showed that only about 3% of PSA tests are ordered following a patient request, while GPs are the driving force for the overwhelming majority of PSA tests [298]. Similar observations were reported from other countries [310, 767].

There was a seven-fold variation in PSA screening rates between practices. In the vast majority of practices Māori men were less likely to be screened, however, two Māori provider practices showed relatively equal screening rates for Māori and non-Māori men. Concurrently, Māori provider practices showed the lowest overall screening rates among the 31 practices. Māori provider practices differed from other provider practices by having a higher proportion of Māori patients and being smaller in terms of both number of patients and GPs. Overall, it was found that screening rates were lower in smaller practices and practices with a high proportion of male Māori clients.

Compared with urban men, rural men were 32% less likely to be screened, but they were 53% more likely to have an elevated PSA result following screening. Although these differences were reduced after adjusting for ethnicity, they could not be fully explained by this adjustment. Screening in NZ has been shown to be mainly driven by GPs [298]. Despite an on-going international debate regarding the benefits and harms of PSA screening, a questionnaire recently undertaken among GPs in the MCN region confirmed that GPs believe in the benefits of PSA screening, which was corroborated by the fact that all but one GP stated that they opportunistically tested asymptomatic men [298]. The surveyed GPs also noted that they have difficulties to provide patients with balanced information about PSA screening.

4.5.2 Follow-up investigations for men with an elevated PSA result

Of the 1070 men with an elevated PSA result in 2010, more than 70% were men with previous prostate problems (including previously elevated PSA result). Screened men and men with symptoms thus comprised only a small proportion of men considered at-risk of prostate cancer based on an elevated PSA result.

Less than half of the men with an elevated PSA result visited a specialist in the follow-up period, meaning that general practitioners have managed more than half of the men with an elevated PSA result without referring them to a specialist. The proportion of men visiting a specialist following an elevated PSA result (> 4 ng/ml) in other studies ranged from 52% to 75% [762, 775].

Age-specific median and mean PSA levels at referral were consistently higher than the recommended age-specific cut-off points. PSA levels of referred men, although being slightly higher, were not evidently different to the PSA levels of non-referred men. A questionnaire-based study from the UK also reported higher median thresholds for referral than the recommended age-specific cut-off values [776].

The reasons why GPs decide not to immediately refer men with an elevated PSA result are not clear, but a UK survey showed that a high co-morbidity burden and too low PSA value (<10 ng/ml) contributed to GPs decision to monitor men with repeat PSA rather than to refer [777]. Also in this study, men were more likely to visit a specialist when they had PSA levels of $10+$ ng/ml, while the opposite was true for men with PSA levels below 4 ng/ml (compared with men with PSA levels of 4-9.99 ng/ml). In addition, men with previous PSA tests were less likely to have a specialist consultation, while men with previous biopsy were more likely to visit a specialist.

Following a specialist visit, 65% of men went on to have a biopsy. Approximately half of the biopsies returned a positive result. A similar positive biopsy rate was reported for men undergoing biopsy in the Auckland area between 2005 and 2006, and for men undergoing biopsy in Christchurch between 1995 and 2007 [142, 778].

Considering age-specific PSA cut-off values and selective referral, the overall cancer detection rate (from men with an elevated PSA result) was 15%. In comparison, other observational studies reported cancer detection rates between 19% and 30% when using a cut-off value of 4.0 ng/ml [139, 762]. The US-based PLCO trial showed that 8% of biopsies undertaken in men with PSA levels ≥ 4.0 ng/ml were positive [281]. The ERSPC and ProtecT (Prostate Testing for Cancer and Treatment) reported a detection rate of 16% and 26%, respectively, when using a cut-off level of 3 ng/ml [162, 598].

Māori men were less likely to visit a specialist after an elevated PSA result compared with non-Māori men. Following a specialist consultation, Māori men were less likely to undergo a biopsy. The overall cancer detection rate was slightly lower for Māori compared with non-Māori men. Even after adjustment for age, PSA level at referral and reason for testing, Māori men were less likely to undergo a biopsy. Clinical guidelines recommend that the decision when to proceed to prostate biopsy needs to be primarily based on PSA level and the result of the digital rectal examination, with higher PSA levels and palpable tumours warranting a biopsy [265, 455]. The results of DRE before diagnosis were not available in this study, but an earlier study has shown that the proportion of palpable tumours was higher for Māori/Pacific men [778]. However, other factors, including patients' co-morbidities and family history of prostate cancer may have had an effect on specialists' decisions to undertake a biopsy [3, 265, 455]. Similarly, these factors may have influenced GPs' decision to refer for a specialist assessment in the first place. Accounting for these factors in future studies may help to clarify the differences in the diagnostic work-up between Māori and non-Māori men.

Men aged 70+ years were less likely to visit a specialist following an elevated PSA test, and they were also less likely to undergo a biopsy compared with younger men. Men with symptoms were more likely to visit a specialist compared with screened men. Only about one-third of screened men visited a specialist following an elevated PSA result.

No difference was found for rates of specialist visits and positive biopsy between rural and urban men. Rural men were 13% more likely to undergo a biopsy compared with urban men. While the majority of rural men, particularly those younger than 70 years, underwent a biopsy following the specialist visit, only about half of the urban men underwent a biopsy. This pattern may be associated with specialists' findings regarding risk factors and symptoms of rural men at presentation.

Median interval between the first elevated PSA result and the first specialist appointment was 88 days, which often included at least one repeat PSA test in general practice. There was little evidence for differences in intervals between the first elevated PSA result and the first specialist visit by age, ethnicity, and residence. Men with previous prostate problems had higher median wait times between the first elevated PSA result and the first specialist appointment compared with screened men, and men with symptoms.

4.5.3 Characteristics of men diagnosed with prostate cancer

Overall, there were 58% of men diagnosed with localised disease, 11% with regional disease, and 6% with distant metastases. For 22% of men there was not sufficient information to assign the extent at diagnosis.

Gleason score at diagnosis was 6 for 61% of men diagnosed with prostate cancer, while 15% of men had GS of 8-10. A similar proportion (approximately 30%) of men had T1c tumours (detected solely on the basis of an elevated PSA result) and T2 (palpable) tumours.

Men with symptoms were more likely to have GS of 8-10 and distant metastases at diagnosis compared with screened men and men with previous prostate problems. Although the relation between lower urinary tract symptoms and prostate cancer is still unclear [407, 408], men with symptoms in this cohort were diagnosed with more advanced disease than men without recorded LUTS.

Māori men were more likely to have GS of 8-10 and distant metastases compared with non-Māori men, but at the same time the proportion of Māori and non-Māori men with GS of 6 was similar. Rural men were less likely to have GS of 6 at diagnosis, and 32% more likely to have GS of 8-10 compared with urban men.

4.5.4 Strengths and limitations

The strength of this study was that population-based data were acquired from the computerised practice records, which allowed for distinction of reasons for PSA testing, necessary to calculate rates of screening as opposed to rates of testing due to symptoms or disease monitoring. Until now, most studies on PSA screening rates were based on evaluation of questionnaires answered either by patients or general practitioners [300, 755, 764, 778].

These studies may suffer from bias associated with the study design, such as recall bias.

Through data linkage using NHI numbers, information gathered from practice records were validated by laboratory data, and cancer registrations in the NZCR. Comprehensive history regarding PSA testing as well as data on follow-up management, including specialist appointments and biopsy results were extracted from multiple sources. Two main advantages of this study were the good quality of data on PSA testing and sufficient numbers of Māori and rural men for statistical evaluation of the results.

The representativeness of the information on PSA testing gathered from practice and laboratory records was assessed by comparing the number of PSA tests in the cohort with the total number of PSA tests recorded in the MCN region in 2010. There were 57,517 PSA tests recorded in the MCN region. In this cohort, 11,112 PSA tests were undertaken in men without

previous prostate cancer diagnosis. For each of the 1006 men diagnosed with prostate cancer before 2010 two annual tests were estimated. Consequently, the total number of PSA tests would be at least 13,124, i.e. 23% of the total number of tests in the region. The cohort represented 25% of all males aged 40+ in the MCN region, so the estimated proportion of PSA tests corresponds well with the overall percentage.

A number of potential limitations were identified: Practice notes might not be complete, particularly regarding reasons for PSA testing. The note-taking seemed to be individually specific, and it may be assumed that patient request was not always noted. However, this category was grouped with screening, and was not further explored. The category of previous prostate issues was derived both from practice records and laboratory records, therefore can be considered well validated. Symptoms seemed to be noted quite consistently. However, misclassification of reasons for testing may have occurred because information on symptoms was not collected for men without an elevated PSA result. A pilot study of five general practices, which assessed reasons for testing for all men with a PSA test in 2010 reported that 11% were tested due to symptoms [298]. The proportion of screened men in this pilot study was 75% compared with 84% in this study. Consequently, about 10% of men who were considered as screened in this study may have been misclassified. The proportion of symptoms was observed to be slightly higher for Māori men, and rural men, so the risk estimates would be biased away from 1, thus increasing the already observed differences.

Men enrolled in general practices in 2010 were considered as the baseline population, as opposed to men who visited their GP that year. A current NZ Health Survey showed that more than 80% of men older than 40 years visited their GP in 2011/2012 [96]. More than 97% of men aged 40+ years were enrolled with a general practice [780]. The screening rates may therefore be under-estimated.

Residence of each man was dichotomised as urban and rural based on the location (main urban area or rural) of the practice, with which the man was enrolled. However, there may be a proportion of men, particularly those who live in rural areas but have a strong connection to main urban areas, for instance through employment, who may have been enrolled with an urban general practice.

Information on some variables that may have acted as confounders, such as the number and type of co-morbidities, and family history was not acquired. The inclusion of these variables may have helped to clarify the screening behaviour.

The study was powered for the assessment of screening rates so the sample size was not sufficient for a robust analysis of secondary outcomes, i.e. specialist visits and biopsy rates. Especially the risk estimates for biopsy as outcome were based on a small number of Māori men, and therefore lack precision.

Another potential limitation of this study is that data on screening and follow-up investigations were sourced only from the Midland Cancer Network region. Screening rates and follow-up strategies may vary between Cancer Networks in New Zealand.

CHAPTER 5 PROSTATE CANCER IN THE MIDLAND CANCER NETWORK REGION: DIAGNOSTIC AND TREATMENT PATHWAYS FOR MĀORI AND NZ EUROPEAN MEN

5.1 Short introduction

For prostate cancer patients, survival chances as well as decision-making around treatment options are highly dependent on the extent of the disease at diagnosis [159, 426, 455]. Patients diagnosed with localised disease have in general excellent survival and they can potentially opt for being managed expectantly with AS to avoid treatment complications [145, 146, 159]. In contrast, patients diagnosed with advanced disease, particularly those with metastases cannot currently be cured and have considerably reduced survival [323, 324]. In the NZCR, three quarters of prostate cancer patients have extent at diagnosis recorded as “unknown” [4, 378]. Therefore, little is known about the association of extent of prostate cancer and survival for NZ men.

In Western countries, more than three-quarters of newly detected prostate cancer cases are localised, i.e. have not spread outside of the prostate gland [63, 336, 504]. Johansson et al. [145] showed that 80 % of men, who had initially presented with localised disease, were still alive after 15 years of follow-up and survival was unaffected by whether or not they had received treatment. Therefore, concerns have been raised about whether treatment of low-grade tumours is beneficial for patients, particularly regarding known complications associated with reduced quality of life following definitive treatment [3, 273, 333].

The most common treatment modalities for localised prostate cancer are radical prostatectomy, external beam radiotherapy, high-dose brachytherapy, and low-dose brachytherapy. Active surveillance and watchful waiting are increasingly used as conservative treatment options. These approaches were developed to avoid potential treatment-related complications by delaying active treatment as long as possible, but at the same time include close monitoring of the patient, which allows for immediate action if cancer progresses [158, 159]. The main aim of active surveillance is to delay treatment for younger men with low-risk disease in order to avoid treatment-related complications that may impact their quality of life, while watchful waiting has been mainly used for older patients and patients with multiple co-morbidities to avoid complications from androgen-deprivation therapy, since treatment with curative intent, particularly radical prostatectomy is not an option for these patients.

There is currently no consensus about what is optimal treatment for localised prostate cancer [156]. Several countries developed guidelines to help clinicians and patients with decision-making around prostate cancer management [159, 296, 425]. In New Zealand, the first guidelines for prostate cancer management were published in 2012 [455]. Little is currently known about which treatment modalities are used for NZ men with localized prostate cancer, and how the utilization of treatment options corresponds with clinical guidelines.

Although there have been several publications that emphasize high prostate cancer mortality and poor disease-specific survival for Māori men in NZ [5, 6, 378], treatment differences as potentially a major cause for poor outcomes have not yet been investigated. Results from NZ studies on other cancers, such as colon, lung, and breast in women, indicate that inequality in the type, timeliness of and access to treatment exists for Māori compared with non-Māori cancer patients [758, 759, 781]. Research into management pathways for NZ men with prostate cancer is crucial for better understanding of outcome disparities.

5.2 Objectives

- 1) to obtain information from clinical records about disease extent for men diagnosed with prostate cancer between 2007 and 2010 in the MCN region;
- 2) to examine treatment types for men with localised prostate cancer;
- 3) to assess use of treatment modalities for localised prostate cancer in light of clinical guidelines, particularly with respect to patients' risk of cancer progression, life expectancy and co-morbidity status;
- 4) to compare treatment types for Māori and NZ European men with localised prostate cancer;
- 5) to address timeliness of individual steps on the management pathway for prostate cancer.

5.3 Methods

5.3.1 Sample

All men aged 40+ years diagnosed with prostate cancer in the Midland Cancer Network (MCN) region between 1 January 2007 and 31 December 2010 were identified from the NZCR. Men with prostate cancer diagnosed at death were excluded.

All Māori men (150 in total) diagnosed within the defined time period were included for analysis. Three randomly sampled NZ European men were frequency age-matched (± 2 years) to each Māori man, so the final sample consisted of 600 men. Age-matching was used because NZ European patients are in general older than Maori patients. With the focus on Maori, this

method provided an appropriate comparison (NZ European are the predominant ethnic population of New Zealand) and eliminated the difference in age structure of the two groups that would certainly act as a confounding factor in the analysis since treatment for prostate cancer is age-dependent.

5.3.2 Data sources

A retrospective review of clinical records for the study sample of 600 men was undertaken in order to collect comprehensive information on patient characteristics, including demographic data (age, ethnicity, socio-economic deprivation, urban/rural residence), clinical staging at diagnosis, co-morbidities, and treatment types. The data extraction was undertaken by a research assistant specifically trained for this task. The data were entered into a pre-formatted Excel sheet.

Using NHI numbers, information obtained from clinical records sourced from hospitals and specialist practices in the MCN region was cross-referenced with data available from local laboratories (Pathlab, Southern Laboratories, Waikato Hospital Laboratory), and national databases (NZCR, National Minimum Dataset, National Non-Admitted Patient Collection). The National Minimum Dataset (NMDS) is a national collection of public and private hospital discharge information on inpatients and day patients (<http://www.health.govt.nz/nz-health-statistics/national-collections-and-surveys/collections/national-minimum-dataset-hospital-events>). The National Non-Admitted Patient Collection (NNPAC) collates data about non-admitted secondary care events, such as out-patient and emergency department visits (<http://www.health.govt.nz/nz-health-statistics/national-collections-and-surveys/collections/national-non-admitted-patient-collection>).

5.3.3 Predictor variables

Ethnicity was the main exposure variable. A number of variables, including co-morbidity status, D'Amico risk strata, residence, socio-economic deprivation, and health sector were used as confounders, since they were assumed to be associated both with ethnicity as the exposure and with treatment as the outcome. These associations have been shown in previous studies, but were also based on the results of the descriptive statistics for Māori and NZ European men in the current study. Adjustment for age in the analyses was necessary due to the sampling strategy.

The role of socio-economic deprivation as a potential mediator could be suggested in association with stage at diagnosis and thus indirectly with ethnicity, but as explained in Chapter 3 Section 3.3.3 socio-economic deprivation is considered to be a confounder to ethnicity rather than a mediator.

Patients' age was dichotomised as <70 and 70+ years, except for the description of patient characteristics when four age groups were used: 40-59, 60-69, 70-79 and 80+ years.

Prioritised ethnicity was extracted from the NZCR.

For the assessment of the clinical stage at diagnosis according to the AJCC TNM staging system [485], prostate-specific antigen (PSA) levels, results of digital rectal examination (DRE), biopsy results, including Gleason score (GS), and imaging results (radiography, computed tomography, magnetic resonance imaging (MRI), whole body bone scan) were used. Extent of prostate cancer at diagnosis was categorised as localised, regional or distant in accordance with the classification used in the NZCR, where disease extent is coded as B for localised disease, C for invasion of adjacent tissues or organs, D for invasion of regional lymph nodes, E for distant metastases and F for unknown extent. The regional extent in this study includes the NZCR categories C and D. Extent was categorised as regional or distant when imaging was positive for local spread or metastases (mainly to bone) within four months after initial biopsy or other specialist assessment.

Localised prostate cancer was stratified as being low-, intermediate- or high-risk based on the classification by D'Amico et al. [231]. Low-risk localised prostate cancer is characterised by Gleason score of 6, PSA level of <10 ng/ml and T1c/T2a stage. The intermediate risk category includes men with Gleason score of 7, or PSA 10-20 ng/ml or T2b/T2c stage. High-risk localised prostate cancer is defined by Gleason score of 8-10 or PSA>20 or T3-4 stage.

The Charlson Co-morbidity Index (CCI) [632] was used to assess the burden of co-morbid conditions, as its use as a prognostic tool has been validated for prostate cancer patients [633]. The CCI represents a weighted score derived from the presence of specified conditions listed in Tables 30. For the purpose of this study, men were classified as having none, 1 or 2+ CCI score; the higher the score, the greater the burden of co-morbidities, and consequently the higher likelihood of all-cause and cancer-specific death [632]. The data on co-morbidities were extracted from the clinical records and cross-referenced and where needed amended with the information available from the national databases.

Table 30 Conditions recorded for the Charlson Co-morbidity Index.

Condition	ICD-10 code	Index weight
Myocardial infarction	I21-22	1
Congestive heart failure	I50	1
Peripheral vascular disease	I70-89	1
Cerebrovascular disease	I60-69	1
Dementia	F00-09	1
Chronic pulmonary disease	J40-47	1
Connective tissue disease	any M	1
Ulcer disease	K25-28	1
Liver disease, mild	K70-77	1
Diabetes	E10-14	1
Hemiplegia	G81	2
Renal disease, moderate or severe	N00-29	2
Diabetes with end organ damage	E10-14	2
Any malignancy	any C	2
Leukaemia	C90-95	2
Malignant lymphoma	C81, 83-85	2
Liver disease, moderate or severe	K70-77	3
Metastatic solid malignancy	C77-79	6
AIDS	B20-24	6

Domicile at diagnosis from the NZCR was used to assign a deprivation centile for each patient based on the New Zealand Index of Deprivation 2006 (NZDep06) [752]. For the purpose of this study, the deprivation scores were collapsed into tertiles: least deprived (1-3), medium (4-7), and most deprived (8-10).

Domicile at diagnosis was used to classify each patient into seven urban/rural residence categories: main urban area, satellite urban area, independent urban area, rural area with high urban influence, rural area with moderate urban influence, rural area with low urban influence, and highly rural/remote area [751]. For the purpose of this study, the seven categories were dichotomised into main urban areas, and rural areas (including satellite urban areas, independent urban areas, rural areas with high urban influence, rural areas with moderate urban influence, rural areas with low urban influence, and highly rural/remote areas).

Men were classified into two groups based on health care sector: men who received health care in the public health sector only as opposed to men who were fully or partially managed in the private health sector. Health care included specialist consultations, biopsy, and treatment. In New Zealand, secondary public health care is free for all residents, but patients can opt for getting private health care if they are able to carry the cost either out-of-pocket or through a private insurance.

5.3.4 Outcome variables

Treatment modalities were analysed only for patients with localised prostate cancer. Initial treatment type was categorised as radical prostatectomy (RP), radiotherapy (including external beam radiation therapy (EBRT), low-dose (LDR) and high-dose (HDR) brachytherapy), active surveillance (AS), watchful waiting (WW), hormonal therapy (HT; including pharmacological and surgical androgen-deprivation therapy), and unknown treatment. AS and WW were considered as initial treatment when the clinical records explicitly mentioned these management strategies. In addition, when AS was recorded as primary treatment a repeat biopsy needed to be on record within a year from diagnosis. Pharmacological androgen-deprivation therapy used as part of the management pathway before radiation therapy was not considered as initial treatment.

The date of primary care referral for a specialist appointment, the date of first specialist appointment (FSA), the date of positive biopsy, and the date of treatment (RP, EBRT, LDR) were collected retrospectively to assess intervals in days from referral to FSA, from FSA to positive biopsy, and from positive biopsy to active treatment.

5.3.5 Clinical guidelines

The use of treatment modalities in this sample was assessed in light of the English and Welsh National Institute for Clinical Excellence (NICE) [782] and the U.S. National Comprehensive Cancer Network (NCCN) clinical guidelines [425]. The first New Zealand Ministry of Health clinical guidelines for diagnosis and management of prostate cancer were published in 2012, i.e. after this study was finished [455]. The contents of the NZ guidelines are in agreement with the NICE and NCCN guidelines.

Treatment modalities were assessed with regard to the following five statements from the clinical guidelines: 1) active surveillance is recommended for men with low-risk disease; 2) watchful waiting is suitable for men with life expectancy (LE) of <10 years, significant co-morbidities and unlikely disease progression; 3) radical prostatectomy is recommended for medically fit men with LE of 10+ years; 4) treatment with curative intent is recommended for men with intermediate-risk disease and LE of 10+ years; and 5) treatment with curative intent is recommended for men with high-risk disease, except for those with LE of <10 years and significant co-morbidities.

Life expectancy was assessed as being <10 and 10+ years based on patient's age and co-morbidity status. Life expectancy for each patient was derived from national estimates of life

expectancy for Māori and NZ European men in 2010 (http://stats.govt.nz/browse_for_stats/health/life_expectancy/period-life-tables.aspx). NZ European men aged 75 years and Māori men aged 70 years have on average life expectancy of less than 10 years.

The effect of co-morbidity status on LE was adapted from Cho et al. [631], since the average life expectancy reported for European- and African-American men at the age of 65, 70, and 75 was similar to that of Māori and NZ European men in this study. For men with multiple co-morbidities (CCI of 2+) it was assumed that their life expectancy will be decreased by 5 years compared to the average LE of men at that age, while for men with no co-morbidities it was assumed that NZ European men aged 76 and 77 years and Māori men aged 71 or 72 years will have a life expectancy of more than 10 years.

D'Amico risk classification [231] was used as an indicator for the likelihood of cancer progression.

5.3.6 Statistical analysis

Statistical analysis was performed with SPSS 19.0 and STATA IC/12. Since the adopted sampling strategy was focused on acquiring a sufficient number of Māori men for analyses, weights were assigned for each NZ European man based on the likelihood of selection through the matching process. The weights ranged from 1.3 to 9.0 depending on age. All Māori men were sampled, so they were each assigned a weight of 1. These weights were included in calculations of rates of cancer extents at diagnosis and treatment options for NZ European men and in all calculations involving the total sample in order to interpret the results as population-based for the MCN. Weights were also considered in regression analyses.

Design-based F-test probabilities were used to assess the differences in initial treatment modalities between subgroups, such as patient's age group, ethnicity, PSA level at referral, clinical stage and grade, D'Amico risk strata, co-morbidity status, socio-economic deprivation, residence, and health sector.

Multivariate Poisson regression analysis (with "sandwich" robust procedure) was used to calculate risk ratios (RR) comparing treatment modalities between Māori and NZ European men with prostate cancer, while adjusting for patient's age, PSA level at referral, clinical stage and grade, D'Amico risk strata, co-morbidity status, socio-economic deprivation, residence, and health sector. AS and WW were grouped for regression analyses into AS/WW category representing expectant treatment as opposed to active treatment.

The individual effect of co-morbidities, D'Amico risk strata, residence, socio-economic deprivation, and health sector on treatment was explored in analyses adjusted for age and ethnicity as confounders.

Median values with 10th and 90th percentiles were calculated for wait times in days between referral and first specialist appointment (FSA), between FSA and positive biopsy, and between positive biopsy and active treatment. Sampling weights were considered in all these calculations. The difference between medians was tested by the Mann-Whitney test (for two categories), and by Mood's median test (for more than two categories).

To assess the utilisation of treatment for localised prostate cancer in the MCN region, proportions of men not treated in accordance with clinical guidelines were calculated. Sampling weights were not used for these analyses, since the compliance with clinical guidelines was studied in this particular sample and it was not intended to extrapolate the results to the general population.

Confidence intervals (95% CI) not including 1 were considered to represent statistical difference, analogous to a probability level of <0.05 .

Access to clinical records and national databases was approved by Northern Y (Ref. No. NTY/11/02/019) and Multi-Region Ethics Committees (Ref. No. MEC/11/EXP/044).

5.4 Results

5.4.1 Extent of prostate cancer at diagnosis The results of the comparison of disease extent at diagnosis from clinical records and from the NZCR are shown in Table 31. In the NZCR, 414 (69%) men had prostate cancer extent at diagnosis recorded as unknown, while based on clinical records only 31 (5%) men had unknown extent at diagnosis. Assuming that the information about disease extent at diagnosis from clinical records is accurate, 26% of the extent data in the NZCR matched the data obtained from clinical records. The highest proportion of matching extent entries was among patients with distant metastases (40%). Localised extent at diagnosis matched between the NZCR and the clinical records only for 22% of men. There were 408 men with localised prostate cancer identified from clinical records, while there were only 88 recorded in the NZCR. Māori men were more likely to have cancer extent recorded as unknown in the NZCR when they had localised extent at diagnosis based on clinical records compared with NZ European men.

Table 31 Distribution of prostate cancer extent at diagnosis in the New Zealand Cancer Registry (NZCR) compared with clinical records.

	Localised (NZCR)	Regional (NZCR)	Distant (NZCR)	Unknown (NZCR)	Total (clinical records)
Localised (clinical records)	88 (21.6%)*	24 (11 had regional spread on radical prostatectomy)	0	296	408 (68.0%)
Regional (clinical records)	0	19 (30.2%)*	0	44	63 (10.5%)
Distant (clinical records)	0	2	26 (40.0%)*	37	65 (10.8%)
Unknown/excluded (clinical records)	15 (6 no information, 3 uncertain extent at diagnosis, 2 Gleason score (GS) 5, 4 incidental diagnosis from cystoprostatectomy)	4 (1 no information, 1 uncertain extent at diagnosis, 1 GS 5, 1 diagnosed before 2007)	8 (8 diagnosed before 2007)	37 (15 no information, 5 uncertain extent at diagnosis, 6 GS 5 or benign, 11 diagnosed before 2007)	64 (10.7%)
Total (NZCR)	103 (17.2%)	49 (8.2%)	34 (5.7%)	414 (69.0%)	600

*percentage of disease extent matching between the NZCR and the clinical records

It was found that men identified from clinical records as being diagnosed with localised or regional extent were more likely to have extent of disease recorded in the NZCR if they had been treated with radical prostatectomy. For men treated with radical prostatectomy, extent in the NZCR matched the extent from clinical records for 46% of men with localised disease and for 86% of men with regional extent. It should be noted that 11 men initially diagnosed with localised disease were reclassified following a prostatectomy as having regional disease due to the pathologist reporting extension of the tumour outside the prostate gland.

Out of the 600 men, whose clinical records were reviewed, 64 (14 Māori and 50 NZ European) were excluded from the final analysis. The reasons for exclusion are summarised in Figure 24. A similar overall proportion of Māori and NZ European men was excluded (9% and 11%, respectively). The two most common reasons for exclusion were missing information (3% for Māori men, and 6% for NZ European men), and diagnosis prior to the study period (6% for Māori men, and 2% for NZ European men). Nine NZ European men (2%) recorded as having prostate cancer in the NZCR were considered having benign disease based on clinical records.

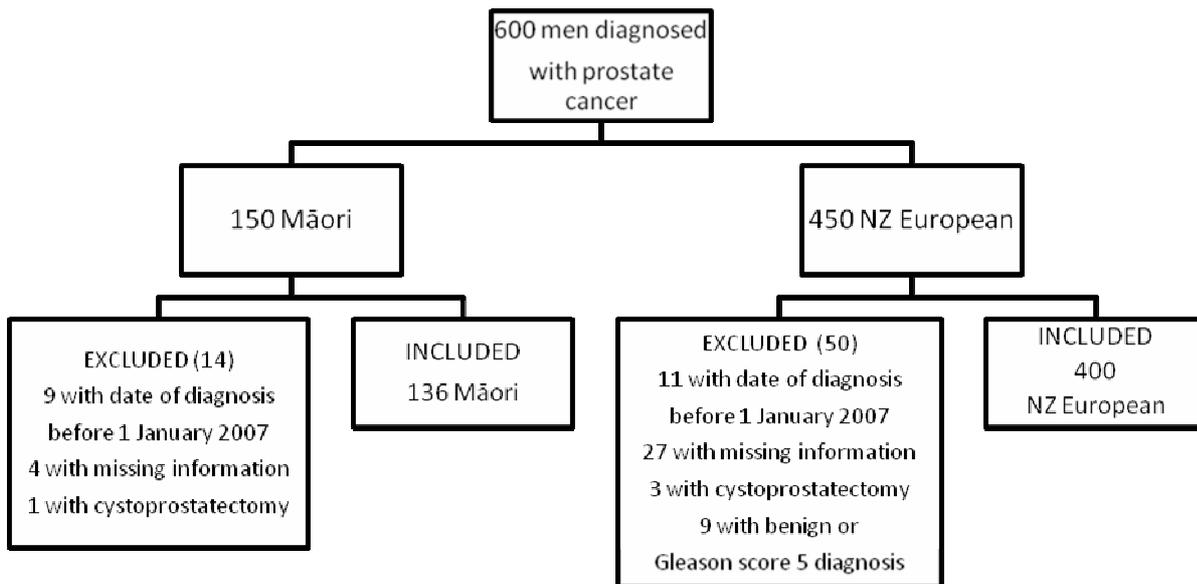


Figure 24 Exclusion criteria and sample size for a sample of Māori and NZ European men diagnosed with prostate cancer between 2007 and 2010 in the MCN region.

The final cohort included 536 men (136 Māori and 400 NZ European), of whom 408 (76.1%) were diagnosed with localised prostate cancer, 63 (11.8%) had regional and 65 (12.1%) had distant extent at diagnosis (Table 32). Of men diagnosed with localised prostate cancer, 33.0% were classified as having low-risk disease, 47.0% intermediate-risk disease, 13.4% high-risk disease, and for 6.6% risk of progression was unknown (Table 33).

Māori men were twice as likely to be diagnosed with metastatic disease as NZ European men (19.1% v. 9.8%; Table 32). The distribution of low- and intermediate-risk localised prostate cancer was similar between Māori and NZ European men, but Māori men were more likely to be diagnosed with high-risk disease (Table 33).

Table 32 Distribution of cancer extent at diagnosis for Māori and NZ European men diagnosed with prostate cancer between 2007 and 2010 in the MCN region.

	Māori	NZ European	Total
Cancer extent at diagnosis	n (%) [*]	n (%)	n (%)
Localised	97 (71.3)	311 (76.6)	408 (76.1)
Regional spread	13 (9.6)	50 (13.6)	63 (11.8)
Metastatic	26 (19.1)	39 (9.8)	65 (12.1)
Total	136	400	536

^{*}actual counts are used, while percentages are calculated with weights

Table 33 Distribution of D’Amico risk strata for Māori and NZ European men diagnosed with localised prostate cancer between 2007 and 2010 in the MCN region.

	Māori	NZ European	Total
D’Amico risk	n (%)*	n (%)	n (%)
Low	27 (27.8)	110 (33.5)	137 (33.0)
Intermediate	44 (45.4)	140 (47.2)	184 (47.0)
High	21 (21.7)	40 (12.5)	61 (13.4)
Unknown	5 (5.2)	21 (6.8)	26 (6.6)
Total	97	311	408

* actual counts are used, while percentages are calculated with weights

The distribution of disease extent at diagnosis by age group (<70 years, 70+ years) is depicted in Figure 25. While men aged <70 years at diagnosis were more likely to be diagnosed with localised disease compared with men aged 70+ (84.2% v. 61.9%), they were less likely to be diagnosed with regional spread (10.3% v. 18.2%), and distant metastases (5.6% v. 19.9%). Men aged <70 years with localised prostate cancer were more likely diagnosed with low-risk disease compared with men aged 70+ years (38.5% v. 19.9%), while men aged 70+ years were slightly more likely to have intermediate- and high-risk disease at diagnosis compared with younger men (Figure 26).

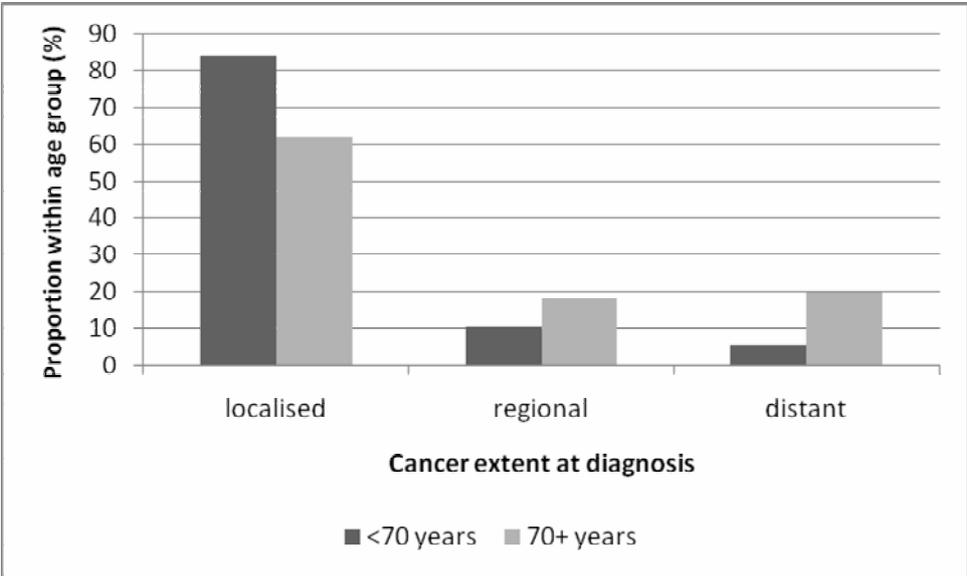


Figure 25 Distribution of prostate cancer extent at diagnosis for a sample of Māori and NZ European men diagnosed with prostate cancer between 2007 and 2010 in the MCN region by age group.

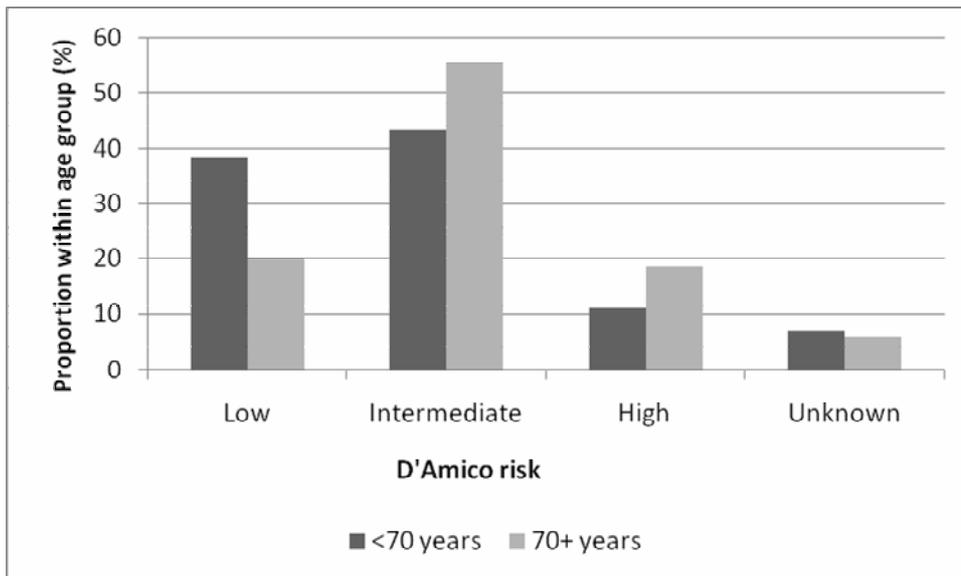


Figure 26 Distribution of D'Amico risk strata for a sample of Māori and NZ European men diagnosed with localised prostate cancer between 2007 and 2010 in the MCN region by age group.

The distribution of cancer extent at diagnosis was similar between men residing in rural areas and those residing in MUAs (Figure 27). Rural men with localised prostate cancer were almost twice as likely to be diagnosed with high-risk disease compared with men residing in MUAs (18.1% v. 9.4%). In contrast, men residing in MUAs were slightly more likely to have low- and intermediate-risk localised prostate cancer compared with men residing in rural areas (Figure 28).

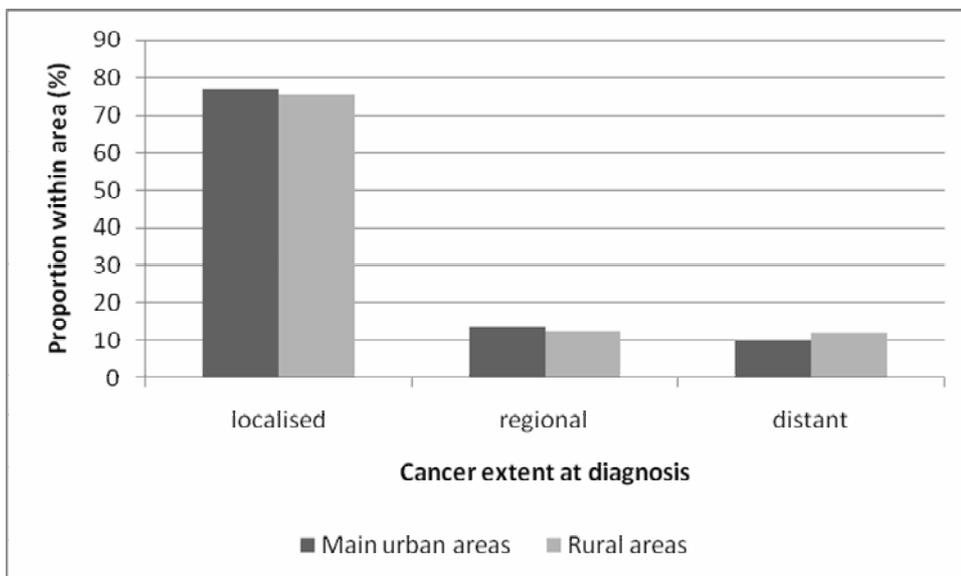


Figure 27 Distribution of prostate cancer extent at diagnosis for a sample of men residing in main urban, and rural areas diagnosed with prostate cancer between 2007 and 2010 in the MCN region.

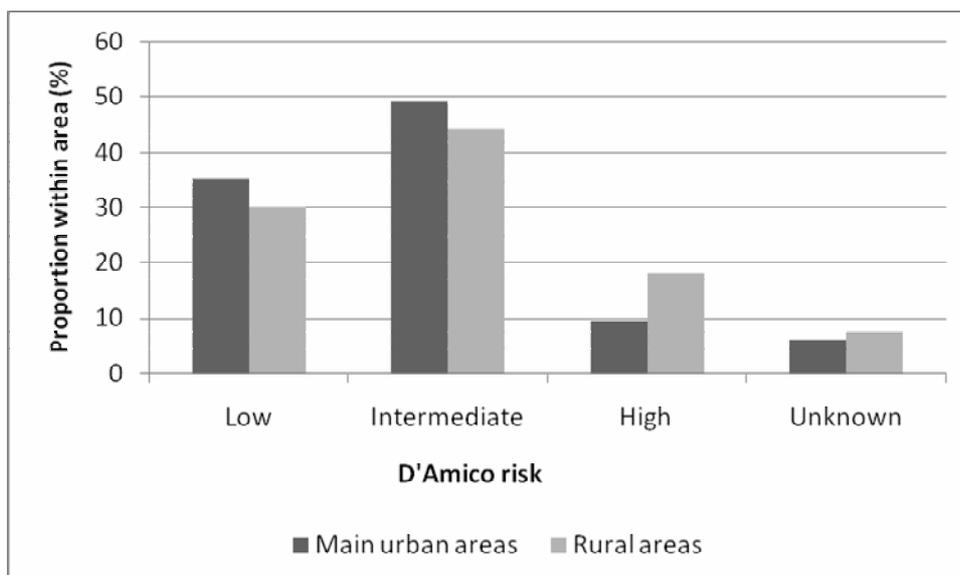


Figure 28 Distribution of D'Amico risk strata for a sample of men residing in main urban and rural areas diagnosed with localised prostate cancer between 2007 and 2010 in the MCN region.

5.4.2 Treatment modalities for men with localised prostate cancer

The distribution of the initial treatment modalities for men with localised prostate cancer in the MCN region is shown in Table 34. Radical prostatectomy with 45.3% was the most common treatment type. Approximately a quarter of men received radiation therapy, including EBRT, HDR and LDR. There were 44 (9.8%) men managed with AS and 45 (12.8%) with WW. Hormonal therapy as the initial treatment option was used for 4.9% of men.

Table 34 Distribution of initial treatment modalities for a sample of men diagnosed with localised prostate cancer between 2007 and 2010 in the MCN region.

Treatment	Total (N=408)
	n (%) [*]
Radical prostatectomy (RP)	182 (45.3)
External beam radiotherapy (EBRT)	51 (10.9)
High-dose brachytherapy (HDR)	20 (4.3)
Low-dose brachytherapy (LDR)	38 (10.4)
Radiation therapy (RT) = (EBRT+HDR+LDR)	109 (25.6)
Active surveillance (AS)	44 (9.8)
Watchful waiting (WW)	45 (12.8)
AS + WW (AS/WW)	89 (22.6)
Hormonal therapy (HT)	20 (4.9)
Unknown	8 (1.6)

^{*} actual counts are used, while percentages are calculated with weights

5.4.2.1 Treatment modalities for Māori and NZ European men with localised prostate cancer

Patient characteristics of Māori and NZ European men diagnosed with localised disease are summarised in Table 35.

Compared with NZ European men, Māori men were more likely to have PSA level of 10+ ng/ml at referral, palpable (T2) tumours and Gleason score of 8-10 at diagnosis. Māori men were also more likely to live rurally, in the most deprived areas, have multiple co-morbidities, and receive health care for prostate cancer solely in the public sector. The sample was frequency age-matched so there was no difference in the age distribution between Māori and NZ European men.

Table 35 Clinical and demographic characteristics of a sample of Māori and NZ European men diagnosed with localised prostate cancer between 2007 and 2010 in the MCN region.

Patient characteristics	Māori (97)	NZ European (311)
	n (%)	n (%)
Age at diagnosis		
40-59 years	26 (26.8)	82 (26.4)
60-69 years	51 (52.6)	149 (47.9)
70-79 years	17 (17.5)	66 (21.2)
80+ years	3 (3.1)	14 (4.5)
PSA level at referral		
0-3.99 ng/ml	3 (3.1)	23 (7.4)
4-9.99 ng/ml	49 (50.5)	185 (59.5)
10-19.99 ng/ml	35 (36.1)	67 (21.5)
20+ ng/ml	8 (8.2)	23 (7.4)
unknown	2 (2.1)	13 (4.2)
T-stage at diagnosis		
T1c	44 (45.4)	155 (49.8)
T2	53 (54.6)	149 (47.9)
unknown	0 (0)	7 (2.3)
Gleason score at diagnosis		
6	48 (49.5)	195 (62.7)
7	31 (32.0)	88 (28.3)
8-10	15 (15.5)	26 (8.4)
unknown	3 (3.1)	2 (0.6)
Charlson Comorbidity Index (CCI)		
0	32 (33.0)	163 (52.4)
1	23 (23.7)	56 (18.0)
2+	42 (43.3)	92 (29.6)
Socio-economic deprivation (NZDep06)		
Least deprived (1-3)	8 (8.2)	67 (21.5)
mid (4-7)	18 (18.6)	142 (45.7)
most deprived (8-10)	71 (73.2)	102 (32.8)
Residence		
Main urban areas	44 (45.4)	168 (54.0)
Rural areas	53 (54.6)	143 (46.0)
Health sector		
Private sector involved	28 (28.9)	154 (49.5)
Public sector only	69 (71.1)	157 (50.5)

The distribution of initial treatment types for Māori and NZ European men diagnosed with localised disease is shown in Table 36. Māori men with localised disease were less likely to be treated with radical prostatectomy and LDR compared with NZ European men. Conversely, Māori men were more than twice as likely to receive EBRT, and HDR. Māori men were also more likely to be managed with AS. Similar proportions of Māori and NZ European men were managed by WW, and received hormonal therapy as initial treatment. The distribution of treatment options was significantly different between Māori and NZ European men (design-based F-test $p=0.003$).

Table 36 Distribution of initial treatment modalities for a sample of Māori and NZ European men diagnosed with localised prostate cancer between 2007 and 2010 in the MCN region.

Treatment/Ethnicity	Māori (N=97)	NZ European (N=311)
	n (%)	n (%) [*]
Radical prostatectomy (RP)	31 (32.0)	151 (46.7)
External beam radiotherapy (EBRT)	20 (20.6)	31 (9.9)
High-dose brachytherapy (HDR)	8 (8.2)	12 (3.9)
Low-dose brachytherapy (LDR)	3 (3.1)	35 (11.2)
Radiation therapy (RT) = (EBRT+HDR+LDR)	31 (32.0)	78 (25.0)
Active surveillance (AS)	15 (15.5)	29 (9.2)
Watchful waiting (WW)	13 (13.4)	32 (12.8)
AS + WW (AS/WW)	28 (28.9)	61 (22.0)
Hormonal therapy (HT)	4 (4.1)	16 (5.0)
Unknown	3 (3.1)	5 (1.4)

^{*} actual counts are used, while percentages are calculated with weights

Multivariate Poisson regression model fitted to compare management with AS/WW versus other treatment types adjusted for patient’s age, D’Amico risk strata, co-morbidities, socio-economic deprivation, residence and health sector showed that Māori men were 55% more likely to be managed expectantly compared with NZ European men (RR, 1.55 [95% CI, 1.00, 2.40]).

Multivariate Poisson regression analysis comparing RP versus other management types adjusted for patient’s age, D’Amico risk strata, co-morbidities, socio-economic deprivation, residence and health sector showed that Māori men were 23% less likely to be treated with RP compared with NZ European men (RR, 0.77 [95% CI, 0.55, 1.08]).

With RT (including EBRT, HDR and LDR versus other treatment types) as the outcome variable, the Poisson regression model adjusted for patient’s age, D’Amico risk strata, co-morbidities,

socio-economic deprivation, residence and health sector showed little evidence for difference in risk between Māori and NZ European men (RR, 1.17 [95% CI, 0.79, 1.72]).

5.4.2.2 Treatment type by patient characteristics other than ethnicity

Figures 29-34 depict the distribution of treatment types by age group (Figure 29), co-morbidity status (Figure 30), D'Amico risk strata (Figure 31), socio-economic deprivation (Figure 32), residence (Figure 33), and health sector (Figure 34). Unknown treatment was not included in the Figures, so the percentages within categories do not add up to 100%. All calculations include weights.

Radical prostatectomy was the most common treatment modality for <70 years old men with localised prostate cancer, while WW was the most common management strategy for men aged 70+. RP, HDR and AS were more likely used as management strategies for men <70 years compared with older men. Radiation therapy, including EBRT and LDR was used relatively equally for men aged <70 and 70+ years. Watchful waiting and hormonal therapy were more likely used for men aged 70+ years. The distribution of treatment types differed significantly by age group (design-based F-test $p < 0.0001$).

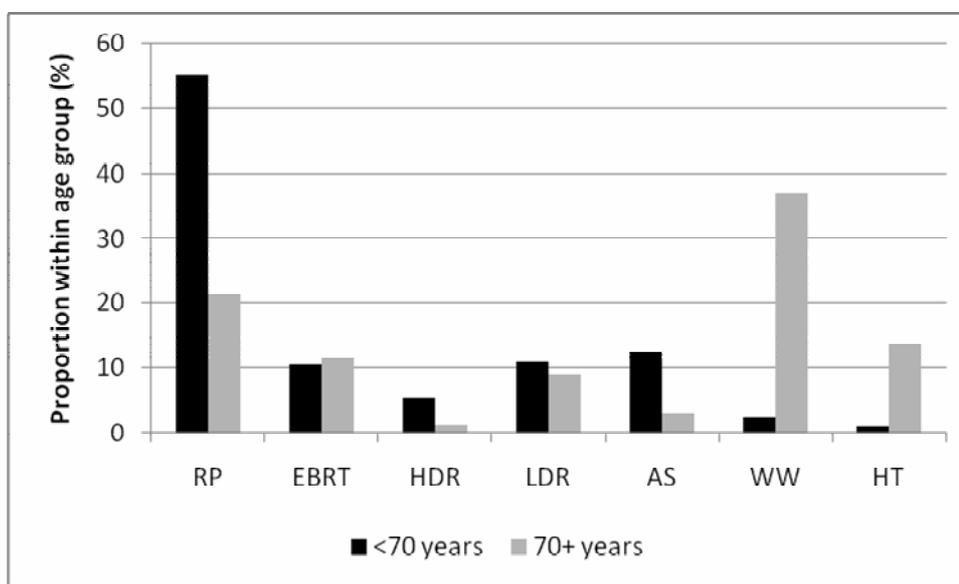


Figure 29 Distribution of initial treatment modalities for a sample of men diagnosed with localised prostate cancer between 2007 and 2010 in the MCN region by age group (RP: radical prostatectomy; EBRT: external beam radiation therapy; HDR: high-dose brachytherapy; LDR: low-dose brachytherapy; AS: active surveillance; WW: watchful waiting; HT: hormonal therapy).

RP and LDR were decreasingly used with increasing number of co-morbidities. Conversely, WW was increasingly used with increasing number of co-morbidities. EBRT was relatively rarely

used for men with CCI of 0, while AS was the least common for men with CCI of 2+. HDR was used to a similar extent for all groups. HT was predominantly used for men with CCI of 2+. The distribution of treatment types differed significantly by co-morbidity status (design-based F-test $p < 0.0001$).

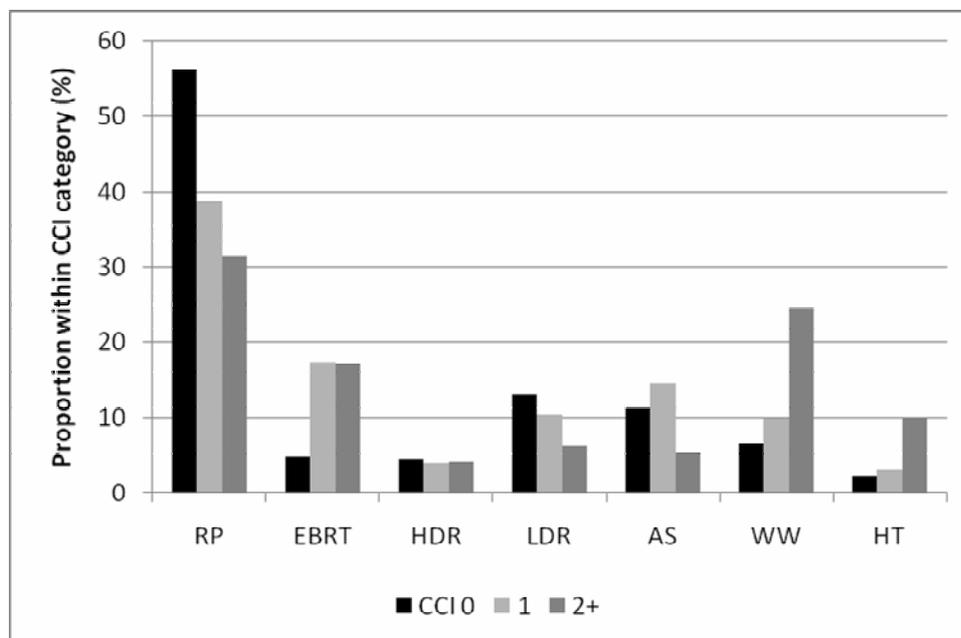


Figure 30 Distribution of initial treatment modalities for a sample of men diagnosed with localised prostate cancer between 2007 and 2010 in the MCN region by Charlson Co-morbidity Index (CCI) (RP: radical prostatectomy; EBRT: external beam radiation therapy; HDR: high-dose brachytherapy; LDR: low-dose brachytherapy; AS: active surveillance; WW: watchful waiting; HT: hormonal therapy).

RP was decreasingly used with increasing D'Amico risk stratum. For men with high-risk disease, EBRT and HT were used with high frequency. AS was used in approximately 15% of men with low-risk disease, thus representing the third most common management option following RP and LDR. EBRT was rarely used for men with low-risk disease, while HDR was rarely used for men with high-risk prostate cancer. WW was relatively commonly used for men with intermediate-risk disease, followed by men with low-risk prostate cancer. The distribution of treatment types differed significantly by D'Amico risk strata (design-based F-test $p < 0.0001$). RP was used to a similar extent across all three deprivation categories, but it was the least likely used for men residing in the most deprived areas. EBRT was increasingly used with increasing socio-economic deprivation, while the use of LDR was declining with increasing deprivation. AS was the least likely used for men residing in the least deprived areas. WW was used with similar frequency across deprivation categories. HDR and HT were rarely used for men residing in the medium deprived areas. HT was relatively commonly used for men residing

in the least deprived areas. There was weak evidence for a difference in distribution of treatment types by socio-economic deprivation (design-based F-test $p=0.19$).

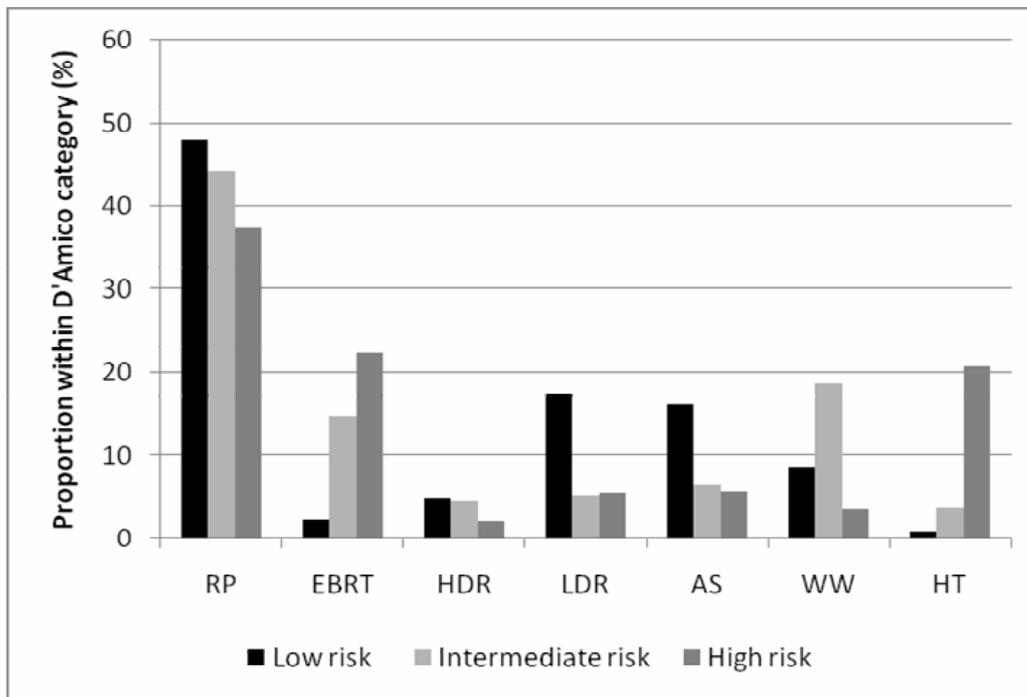


Figure 31 Distribution of initial treatment modalities for a sample of men diagnosed with localised prostate cancer between 2007 and 2010 in the MCN region by D'Amico risk strata (RP: radical prostatectomy; EBRT: external beam radiation therapy; HDR: high-dose brachytherapy; LDR: low-dose brachytherapy; AS: active surveillance; WW: watchful waiting; HT: hormonal therapy).

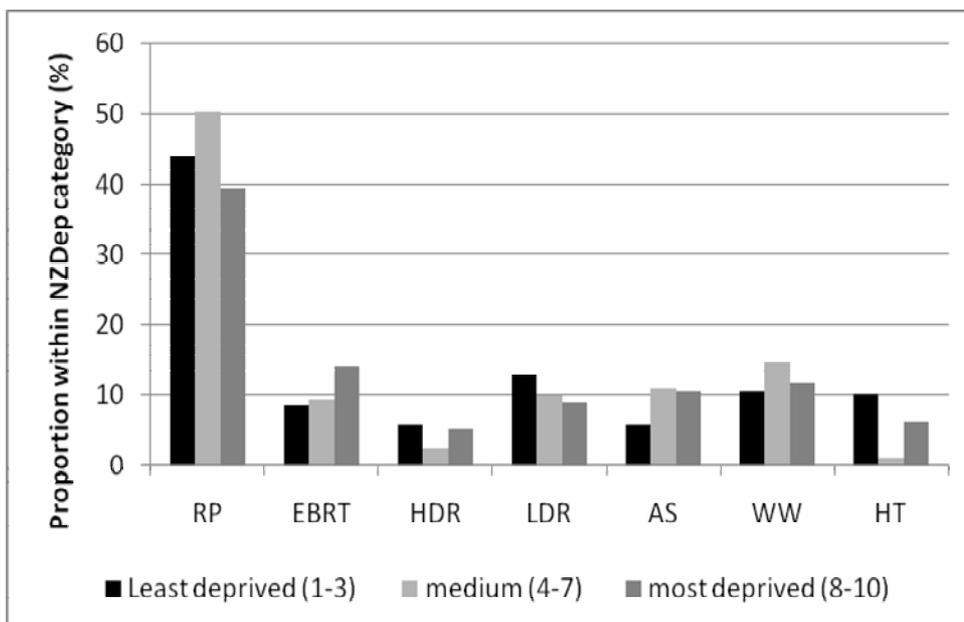


Figure 32 Distribution of initial treatment modalities for a sample of men diagnosed with localised prostate cancer between 2007 and 2010 in the MCN region by socio-economic deprivation (RP: radical prostatectomy; EBRT: external beam radiation therapy; HDR: high-dose brachytherapy; LDR: low-dose brachytherapy; AS: active surveillance; WW: watchful waiting; HT: hormonal therapy).

Although RP, EBRT and HT were slightly more commonly used for men residing in rural areas, and WW and LDR were slightly more commonly used for men residing in main urban areas, there was no significant difference in the distribution of treatment types by residence (design-based F-test $p=0.56$).

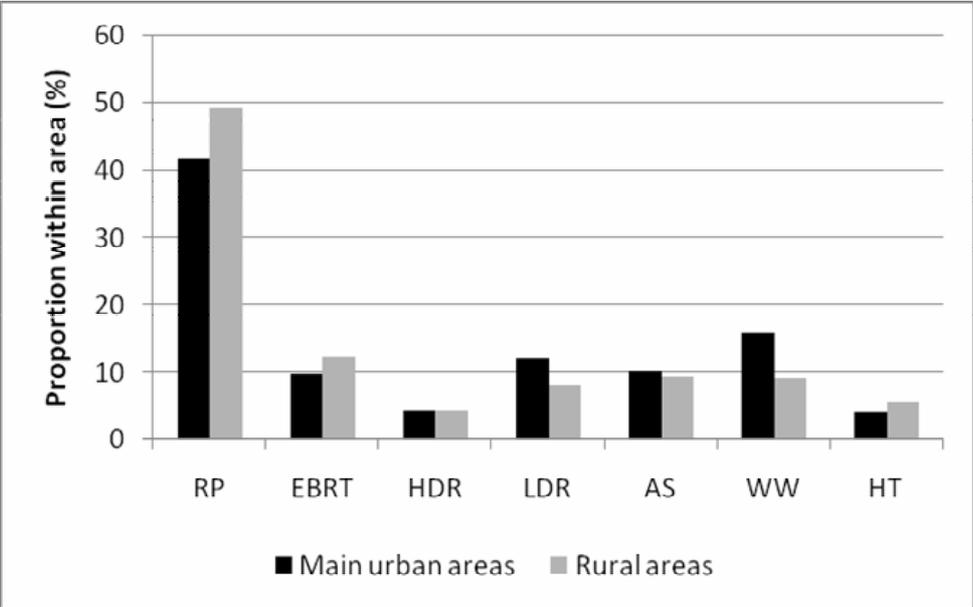


Figure 33 Distribution of initial treatment modalities for a sample of men diagnosed with localised prostate cancer between 2007 and 2010 in the MCN region by residence (RP: radical prostatectomy; EBRT: external beam radiation therapy; HDR: high-dose brachytherapy; LDR: low-dose brachytherapy; AS: active surveillance; WW: watchful waiting; HT: hormonal therapy).

RP was more likely used for men managed in the private sector compared with men managed in the public sector only. LDR was the second most commonly used treatment option in the private sector. In New Zealand, LDR is available exclusively through private sector. All other treatment types, including EBRT, HDR, AS, WW and HT were more likely used for men managed in the public sector only. The distribution of treatment types differed significantly by health sector (design-based F-test $p<0.0001$).

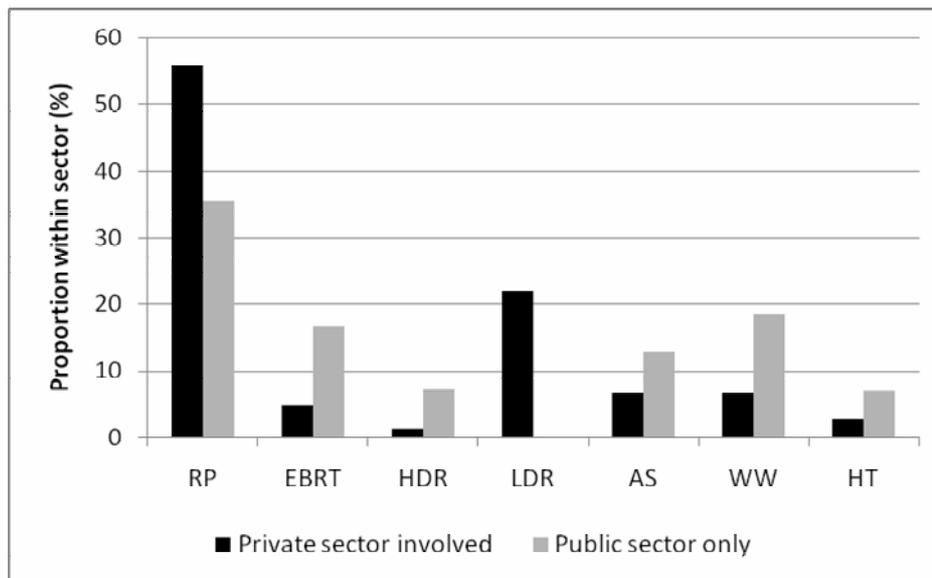


Figure 34 Distribution of initial treatment modalities for a sample of men diagnosed with localised prostate cancer between 2007 and 2010 in the MCN region by health sector (RP: radical prostatectomy; EBRT: external beam radiation therapy; HDR: high-dose brachytherapy; LDR: low-dose brachytherapy; AS: active surveillance; WW: watchful waiting; HT: hormonal therapy).

Poisson regression models adjusted for age and ethnicity were fitted to explore the effect of individual predictor variables (co-morbidity status, PSA level at referral, clinical stage at diagnosis, Gleason score at diagnosis, D'Amico risk strata, socio-economic deprivation, residence, and health sector on expectant management (AS/WW versus other treatment types) as an outcome (Table 37).

The number of co-morbidities, socio-economic deprivation, and residence had little effect on the use of expectant management versus other treatment types. Men receiving health care for prostate cancer solely in the public sector were 91% more likely managed with AS/WW compared with men managed in the private sector.

D'Amico risk stratification is based on PSA levels, Gleason scores and clinical stage, so it would be expected for the effect of these variables being strongly correlated. Expectant treatment was less likely used with increasing risk of progression. Men diagnosed with palpable (T2) tumours, and with GS of 7 and 8-10 were less likely to be managed expectantly compared with men with T1c tumours, and GS of 6, respectively. PSA levels had little effect on the use of expectant management versus other treatment types.

Table 37 Poisson regression age- and ethnicity-adjusted risk ratios for active surveillance/watchful waiting (AS/WW) versus other treatment types; models fitted separately for each of the clinical and demographic factors.

Poisson regression models adjusted for age and ethnicity	AS/WW v. other treatment types
	RR [95% CI]
Charlson Comorbidity Index (CCI)	
0	1.00 (reference)
1	1.23 [0.69, 2.18]
2+	1.15 [0.72, 1.84]
PSA level at referral	
0-3.99 ng/ml	1.70 [0.89, 3.23]
4-9.99 ng/ml	1.00 (reference)
10-19.99 ng/ml	1.24 [0.76, 2.05]
20+ ng/ml	0.85 [0.43, 1.67]
T-stage at diagnosis	
T1c	1.00 (reference)
T2	0.66 [0.43, 1.01]
Gleason score at diagnosis	
6	1.00 (reference)
7	0.39 [0.23, 0.66]
8-10	0.10 [0.03, 0.28]
D'Amico risk strata	
Low risk	1.00 (reference)
Intermediate risk	0.73 [0.47, 1.13]
High risk	0.18 [0.07, 0.46]
Socio-economic deprivation	
Least deprived (1-3)	1.00 (reference)
mid (4-7)	1.61 [0.79, 3.25]
most deprived (8-10)	1.27 [0.61, 2.65]
Residence	
Main urban areas	1.00 (reference)
Rural areas	0.71 [0.47, 1.07]
Health sector	
Private sector involved	1.00 (reference)
Public sector only	1.91 [1.15, 3.19]

5.4.3 Compliance with clinical guidelines for prostate cancer management

The final cohort for this study included 382 men, after excluding 26 men with unknown risk of disease progression from the 408 men diagnosed with localised prostate cancer in the MCN region between 2007 and 2010. Patient characteristics of men classified as having life expectancy (LE) of <10 and 10+ years are summarised in Table 38.

There was no difference in the life expectancy by ethnicity, residence, and socio-economic deprivation. Men with LE of <10 years were more likely to have high-risk prostate cancer, and were more likely managed in the public sector only.

Table 38 Patient characteristics of a sample of men diagnosed with localised prostate cancer between 2007 and 2010 in the MCN region by life expectancy.

Patient characteristics	Men with 10+ years life expectancy (n=308)	Men with <10 years life expectancy (n=100)
	n (%)	n (%)
Age at diagnosis		
40-59 years	108 (35.1)	0 (0)
60-69 years	164 (53.3)	36 (36.0)
70-79 years	36 (11.7)	47 (47.0)
80+ years	0 (0)	17 (17.0)
Charlson Comorbidity Index (CCI)		
0	189 (61.4)	6 (6.0)
1	71 (23.1)	8 (8.0)
2+	48 (15.6)	86 (86.0)
Ethnicity		
Māori	69 (22.4)	28 (28.0)
NZ European	239 (77.6)	72 (72.0)
D'Amico risk strata		
Low risk	121 (39.3)	16 (16.0)
Intermediate risk	130 (42.2)	54 (54.0)
High risk	37 (12.0)	24 (24.0)
Unknown	20 (6.5)	6 (6.0)
Socio-economic deprivation (NZDep06)		
Least deprived (1-3)	61 (19.8)	14 (14.0)
mid (4-7)	116 (37.7)	44 (44.0)
most deprived (8-10)	131 (42.5)	42 (42.0)
Residence		
Main urban areas	160 (52.0)	52 (52.0)
Rural areas	148 (48.0)	48 (48.0)
Health sector		
Private sector involved	153 (49.7)	29 (29.0)
Public sector only	155 (50.3)	71 (71.0)

Figure 35 shows the distribution of treatment types by life expectancy. Men with LE of <10 years were 61% less likely to be treated with RP (RR 0.39 [95% CI, 0.25, 0.58]), and 56% less likely to be managed with AS (RR 0.44 [95% CI, 0.18, 1.08]) compared with men with LE of 10+ years. Conversely, men with LE of <10 years were 88% more likely to be treated with EBRT (RR 1.88 [95% CI, 1.11, 3.16]), and five-times more likely to be managed with WW (RR 4.98 [95% CI, 2.79, 8.87]) compared with men with LE of 10+ years.

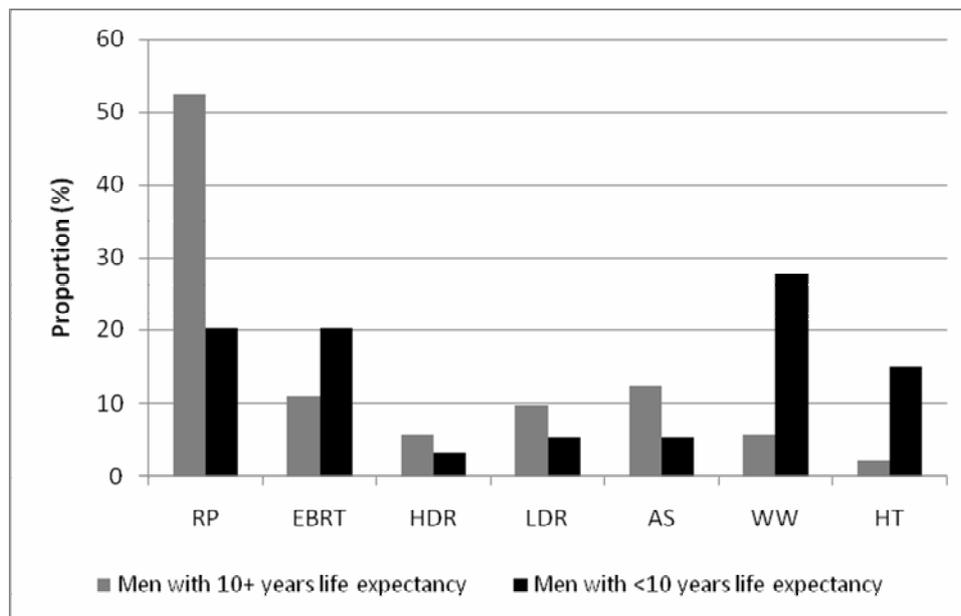


Figure 35 Distribution of initial treatment modalities for a sample of men diagnosed with localised prostate cancer between 2007 and 2010 in the MCN region by life expectancy (RP: radical prostatectomy; EBRT: external beam radiation therapy; HDR: high-dose brachytherapy; LDR: low-dose brachytherapy; AS: active surveillance; WW: watchful waiting; HT: hormonal therapy).

Guideline 1: *Active surveillance is recommended for men with low-risk prostate cancer. Of men managed with AS in this sample, 35% had intermediate- or high-risk prostate cancer at diagnosis.*

Guideline 2: *Watchful waiting is suitable for men with life expectancy of <10 years, significant co-morbidities, and unlikely disease progression. A third of men (33.3%) managed with WW in this sample had an estimated LE of 10+ years and no record of significant co-morbidities.*

Guideline 3: *Radical prostatectomy is recommended for medically fit men with LE of 10+ years. Forty out of 170 men (23.5%) treated with radical prostatectomy in this sample had an estimated LE of <10 years and multiple co-morbidities.*

Guideline 4: *Treatment with curative intent is recommended for men with intermediate-risk disease and LE of 10+ years. Of men with intermediate-risk prostate cancer and an estimated LE of 10+ years in this sample, 16.2% had not received treatment with curative intent.*

Guideline 5: *Treatment with curative intent is recommended for men with high-risk disease, except for those with LE of <10 years and significant co-morbidities.*

Only one man of those diagnosed with high-risk prostate cancer and an estimated LE of 10+ years was not treated with curative intent in this sample.

5.4.4 Timeliness of events on the diagnostic and management pathway for prostate cancer

For the total sample, median wait time between referral and FSA was 46 days (10th percentile=16 days, 90th percentile=80 days), between FSA and positive biopsy 49 days (10th percentile=0 days, 90th percentile=124 days), and between positive biopsy and active treatment 101 days (10th percentile=44 days, 90th percentile=252 days).

Median values with 10th and 90th percentiles for wait times in days between referral and FSA, between FSA and positive biopsy, and between positive biopsy and active treatment are shown in Table 39.

The comparison of median wait times between referral and first specialist appointment showed that men aged 70+ years waited 9 days longer than younger men, Māori men waited 8 days longer compared with NZ European men, rural men waited 3 days longer than men residing in MUAs, and men receiving health care in the public sector only waited 5 days longer compared with men who received care in the private sector. Men with one and more co-morbidities waited 11 days longer than men with CCI of 0. Men with low-risk prostate cancer waited longer (52 days) compared with men with intermediate- (44 days) and high-risk disease (46 days).

There was little difference in median wait times between referral and FSA by socio-economic deprivation, but men residing in the medium and the most deprived areas waited 4 days longer than men from the least deprived areas. Men subsequently managed expectantly with AS and WW waited longer between referral and FSA compared with men treated with RP, EBRT or LDR. Statistical testing showed weak evidence for a difference in median wait times between referral and FSA by treatment type (Mood's median test $p=0.10$).

Median wait times between FSA and positive biopsy were 28 days longer for men aged 70+ years compared with younger men, 24 days longer for Māori men compared with NZ European men, 9 days longer for rural men compared with men residing in MUAs, and 20 days longer for men receiving health care in the public sector only compared with men who received health care in the private sector. Median wait times between FSA and positive biopsy increased with increasing number of co-morbidities from 31 to 70 days, and also with increasing socio-economic deprivation from 32 days for men residing in the least deprived areas to 57 days for men residing in the most deprived areas. Men with intermediate-risk prostate cancer waited longer between FSA and positive biopsy compared with men with low- and high-risk disease. Men subsequently treated with LDR had the shortest median wait time between FSA and positive biopsy (22 days), followed by men treated with RP (42 days), men managed with AS (56 days), men treated with EBRT (74 days), and the longest median wait time was found for men

managed by WW (79 days). There was strong evidence for differences in median wait times between FSA and positive biopsy by age group (Mann-Whitney test $p=0.004$), ethnicity (Mann-Whitney test $p<0.001$), co-morbidity status (Mood's median test $p<0.001$), socio-economic deprivation (Mood's median test $p<0.001$), health sector (Mann-Whitney test $p<0.001$), and treatment type (Mood's median test $p<0.001$).

Table 39 Median (with 10th and 90th percentile) wait times (days) between referral and first specialist appointment, between specialist appointment and positive biopsy, and between positive biopsy and active treatment by clinical and demographic characteristics.

	Referral to first specialist appointment (days)			First specialist appointment to positive biopsy (days)			Positive biopsy to treatment (days)		
	n	median	10 th ; 90 th %ile	n	median	10 th ; 90 th %ile	n	median	10 th ; 90 th %ile
Age									
<70 years	297	43	15; 80	299	42	0; 122	239	102	46; 231
70+ years	98	52	20; 75	99	70	10; 145	55	98	30; 306
Ethnicity									
NZ European	298	44	15;76	301	46	0; 122	228	99	44; 252
Māori	97	52	24; 101	97	70	19; 159	66	127	53; 241
Charlson Comorbidity Index (CCI)									
0	188	41	18; 75	188	31	0; 104	144	87	46; 181
1	76	52	17; 86	77	45	0; 101	55	96	41; 259
2+	131	52	13; 101	133	70	8; 165	95	153	36; 306
D'Amico risk strata									
Low risk	137	52	18; 76	137	45	4; 108	92	96	51; 231
Intermediate risk	184	44	15; 77	184	54	6; 130	132	108	46; 252
High risk	61	46	14; 101	61	47	0; 101	52	85	29; 340
Socio-economic deprivation									
Least deprived (1-3)	74	43	21; 69	74	32	0; 89	57	90	33; 240
mid (4-7)	152	47	13; 92	151	45	0; 119	116	110	48; 288
most deprived (8-10)	169	47	16; 83	170	57	4; 153	121	96	46; 206
Residence									
Main urban areas	209	44	19; 74	209	46	0; 119	145	101	42; 241
Rural areas	186	47	13; 95	189	55	0; 156	149	106	44; 252
Health sector									
Private sector involved	174	44	16; 83	176	37	0; 130	146	90	41; 241
Public sector only	221	49	17; 79	222	57	9; 119	148	118	49; 270
Treatment									
RP	177	40	13; 77	178	42	0; 117	181	89	44; 202
EBRT	50	43	16; 76	50	62	15; 162	51	153	83; 288
LDR	34	44	16; 97	35	22	4; 77	30	124	60; 437
AS	42	57	19; 73	42	56	0; 154	NA	NA	
WW	44	55	21; 75	45	79	21; 156	NA	NA	

There was little difference between median wait times between positive biopsy and treatment by age group and residence. Median wait times between positive biopsy and treatment were 28 days longer for Māori compared with NZ European men, and 28 days longer for men receiving health care in the public sector only compared with men who received care in the private sector. Median wait times between positive biopsy and treatment increased with increasing number of co-morbidities from 87 days for men with CCI of 0 to 153 days for men with CCI of 2+. Men with intermediate-risk prostate cancer had the longest median wait time between positive biopsy and treatment (108 days), followed by men with low-risk disease (96 days), and men with high-risk disease had the shortest median wait time of 85 days. Men residing in the least deprived areas had the shortest median wait time between positive biopsy and treatment (90 days), followed by men residing in the most deprived (96 days) and men residing in the medium deprived areas (110 days). Men treated with RP had the shortest wait time between positive biopsy and treatment (89 days), followed by men treated with LDR (124 days), and men who received EBRT as the initial treatment (153 days). There was strong evidence for differences in median wait times between positive biopsy and treatment by ethnicity (Mann-Whitney test $p=0.01$), health sector (Mann-Whitney test $p=0.004$), and treatment type (Mood's median test $p=0.001$).

5.5 Short discussion

5.5.1 Extent of prostate cancer at diagnosis

Comparison of clinical records and the NZCR

Clinical records of a sample of 600 men diagnosed with prostate cancer between 2007 and 2010 in the MCN region were reviewed to validate extent information for prostate cancer in the NZCR. While in the NZCR 69% of prostate cancer cases had extent at diagnosis recorded as unknown, only 31 (5%) cases had insufficient information for staging following a thorough search of the clinical records.

Localised extent at diagnosis matched only for 22% of men. There was a significant under-representation of Māori men categorised as having localised disease in the NZCR compared with NZ European men. Regional extent matched for 30% of prostate cancer cases. Distant extent in the NZCR matched the extent from clinical records for 40% of cases.

Men identified from clinical records as being diagnosed with localised or regional extent were more likely to have extent of disease recorded in the NZCR when they were treated with radical prostatectomy. This is likely due to the fact that pathological reports from radical

prostatectomy are a straightforward source of staging information preferentially used by the Ministry of Health coders. For men treated with radical prostatectomy, the cancer extent in the NZCR matched the extent from clinical records for 46% of men with localised disease and for 86% of men with regional extent.

Distribution of extent of prostate cancer at diagnosis in the sample

The majority (76%) of men were diagnosed with localised prostate cancer. Twelve percent of men were diagnosed with distant metastases.

An earlier study from the Auckland area reported that 9% of men who underwent a biopsy with a public urological service between 2005 and 2006 were subsequently diagnosed with distant metastases [778]. The lower proportion of men with distant metastases compared to this study can be explained by differences in demographic characteristics between these two samples, with the Auckland study representing an urban population with a low proportion of Māori men. In addition, men diagnosed with metastatic disease may be underrepresented in the selective sample of the Auckland study. In contrast, a Palmerston North study reported that 21% of men undergoing biopsy between 1994 and 1998 were diagnosed with distant metastases, which may indicate that there has been a decrease in late-stage diagnosis of prostate cancer over time [332].

Men aged <70 years at diagnosis were more likely to be diagnosed with localised disease compared with older men. Conversely, 20% of men aged 70+ years were diagnosed with distant metastases compared with 6% of younger men. Men aged <70 years with localised prostate cancer were almost twice as likely to have low-risk disease compared with older men.

Of men diagnosed with localised prostate cancer, 33% had low-risk, and 13% high-risk disease. Māori men were twice as likely to be diagnosed with distant metastases compared with NZ European men. Māori men with localised prostate cancer were almost twice as likely to have high-risk disease. There was little difference between the proportion of Māori and NZ European men diagnosed with low-risk disease. In an earlier study of men diagnosed with prostate cancer in the Auckland area between 2005 and 2006, there was little difference in the proportion of Māori/Pacific and NZ European men with GS of 5-6 and metastatic disease, but Māori/Pacific men were more likely to have GS of 8-10 [778].

The distribution of cancer extent at diagnosis was similar between rural men and men residing in MUAs. Rural men with localised prostate cancer were almost twice as likely to have high-risk disease compared with men residing in MUAs.

5.5.2 Treatment modalities for men with localised prostate cancer

Radical prostatectomy was the most common initial treatment type (45%), followed by radiotherapy (including EBRT, HRD and LDR; 26%). Approximately 23% of men were managed expectantly with AS and WW. Hormonal therapy as the initial treatment option was used for 5% of men with localised prostate cancer, the majority of who were aged 70+ years.

A small NZ study from Palmerston North reported that RP was used for 38% and RT for 15% of men diagnosed with prostate cancer between 1994 and 1998 [332]. Australian studies showed regional differences in the distribution of treatment options for men with localised disease, with RP use ranging from 23% to 46%, RT from 27% to 40%, HT from 4% to 27%, and 6% to 23% of men were managed expectantly with AS or WW [326, 336, 504, 783]. A UK study reported that for men diagnosed with localised prostate cancer between 1995 and 2001 treatment distribution was as follows: 12% radical prostatectomy, 23% radiotherapy, 24% either AS or WW, and 37% hormonal therapy [363]. For US men diagnosed with localised prostate cancer, the proportion of RP use ranged from 40% to 53%, RT from 23% to 38%, AS or WW from 6% to 19%, and HT from 9% to 15% [366, 784-786]. Brachytherapy alone was reported for 12% of prostate cancer patients [784].

The proportions of men treated with RP, and RT in the present study were in accordance with other international studies [326, 336, 363, 366, 504, 783-786]. The use of expectant management with AS or WW was comparatively common, while HT as the initial treatment for men with localised disease was quite rare compared with other studies [336, 363, 366, 504, 783-786].

As expected, the distribution of treatment types depended on patient characteristics, such as age at diagnosis, number of co-morbidities, and D'Amico risk categories [365, 504, 787, 788]. Men treated with radical prostatectomy were more likely to be aged <70 years, have no co-morbidities, and low- or intermediate-risk prostate cancer. Men treated with EBRT were more likely to have one or more co-morbidities, and intermediate- or high-risk prostate cancer. HDR was the least common treatment in this sample. This treatment option was more likely to be used for men with low- and intermediate-risk prostate cancer, and was rarely used for men aged 70+ years. Men treated with LDR were more likely to have no or few co-morbidities, and low-risk prostate cancer.

Active surveillance as a management strategy was more likely to be used for men aged <70 years, who had no or few co-morbidities, and low-risk cancer. In contrast, men managed with

WW were more likely aged 70+ years at diagnosis, had multiple co-morbidities, and intermediate-risk prostate cancer.

Men treated with hormonal therapy were more likely aged 70+ years, had multiple co-morbidities, and high-risk prostate cancer.

There was no evidence for treatment differences by rural/urban residence.

Māori men with localised prostate cancer were less likely to be treated with radical prostatectomy, and with LDR compared with NZ European men. In contrast, Māori men were more likely to be managed with AS, and more than twice as likely to receive EBRT and HDR. These differences in treatment may be related to differences in patient characteristics, with Māori men being more likely to have high-risk prostate cancer and multiple co-morbidities compared with NZ European men in this sample.

There were also differences in characteristics related to access to health care, with Māori men being more likely to live rurally, in the most socio-economically deprived areas and were more likely to receive health care for prostate cancer solely in the public sector. However, even after adjustment for patient's age, D'Amico risk strata, co-morbidities, socio-economic deprivation, residence and health sector Māori men were 55% more likely to be managed expectantly and 23% less likely to be treated with RP compared with NZ European men.

An earlier study from the Wellington area suspected differences in treatment modalities for Māori and Pacific men with localised prostate cancer, particularly a lower uptake of radiotherapy for men with intermediate- and high-risk disease [789].

The distribution of treatment modalities differed by socio-economic deprivation, and utilisation of services in private and public health sector. Men initially treated with RP were more likely to reside in socio-economically less deprived areas, and to be managed in the private sector. Men treated with EBRT were more likely residing in the most deprived areas, and were more likely managed in the public sector only. While HDR was rarely used for men managed in the private sector, the opposite was true for men treated with LDR, who were more likely to be managed in the private sector, since LDR is only available in the private sector in NZ. Men treated with LDR were also more likely to live in the least deprived areas.

Men managed with AS were more likely to live in the more deprived areas and to receive health care in the public sector only. Men managed with WW and HT were also more likely to receive health care in the public sector only, but HT was more likely used for men residing in the least deprived areas.

Multivariate analysis adjusted for age and ethnicity revealed that expectant management with AS and WW was preferentially used for men who received health care solely in the public sector compared with other treatment types. Consequently, men who received health care in the private sector were less likely to be managed expectantly, which suggests that these men were either more likely to opt for or were counselled to have active treatment for localised prostate cancer.

5.5.3 Compliance with clinical guidelines for prostate cancer management

As expected, the use of treatment modalities differed by men's life expectancy. Men with LE of <10 years were 61% less likely treated with RP, and 56% less likely to be managed with AS compared with men with LE of 10+ years. In contrast, men with LE of <10 years were almost twice as likely to be treated with EBRT, and 5-times more likely to be managed expectantly with WW compared with men with LE of 10+ years.

Overall, compliance with clinical guidelines for management of localised prostate cancer was good for men with high-risk disease and LE of 10+ years, but contrary to the guidelines 35% of men managed with AS had intermediate- or high-risk disease, for whom curative treatment is recommended, particularly when their life expectancy is estimated to be more than 10 years. In contrast, only 15% of men with low-risk prostate cancer were managed with AS.

RP is recommended for medically fit men with LE of 10+ years, but in this sample a quarter of men treated with RP had multiple co-morbidities and an estimated LE of <10 years. In contrast, WW is considered to be suitable for men with LE of <10 years and significant co-morbidities, when disease progression is not likely. In this sample, one in three men managed with WW had an estimated LE of 10+ years and no significant co-morbidities. Although other factors, such as patient preferences may have played a role in treatment selection, evaluating prostate cancer treatment in light of clinical guidelines helps to elucidate areas of need of improvement as well as provides information for quality assurance strategies.

Both under- and over-treatment appeared to be an issue for New Zealand men with localised prostate cancer. Treatment with curative intent was under-utilised for men with intermediate-risk disease, while almost a quarter of men seemed to be over-treated with radical prostatectomy. In more than one-third of cases, active surveillance was used in contrast with clinical recommendations.

5.5.4 Timeliness of events on the diagnostic and management pathway for prostate cancer

For men in this sample, median wait time between referral and first specialist appointment was 46 days, between FSA and positive biopsy 49 days, and between positive biopsy and treatment 101 days.

Māori men, men with multiple co-morbidities, and men managed in the public sector only had longer wait times for all the observed steps on the prostate cancer care pathway compared with NZ European men, men with no co-morbidities, and men managed in the private sector, respectively. Māori men waited 8 days longer between referral and FSA, 24 days longer between FSA and positive biopsy, and 28 days longer between positive biopsy and treatment compared with NZ European men. There was little evidence for differences in wait times between rural men and men residing in MUAs.

Longer wait times between first specialist appointment and positive biopsy were observed for men aged 70+ years, men residing in the most deprived areas, men consequently managed expectantly with WW and AS, and those treated with EBRT.

Men with low-risk prostate cancer waited longer between referral and FSA compared with men with intermediate- and high-risk disease, while median wait times between FSA and positive biopsy and between positive biopsy and treatment were longer for men with intermediate-risk prostate cancer compared with men with low- or high-risk disease.

Median wait times between referral and FSA were the longest for men managed subsequently with AS and WW. Men managed with WW had also the longest wait time between FSA and positive biopsy. In contrast, the shortest wait time between FSA and positive biopsy had men treated with LDR, followed by men treated with RP. Both of these treatments are either exclusively (LDR) or commonly (RP) provided by the private sector. Men who opt for these treatment types may be more likely to receive initial consultations in the private sector, which are potentially associated with shorter wait times. Median wait time between positive biopsy and RP was 89 days, between positive biopsy and EBRT 153 days, and between positive biopsy and LDR 124 days.

An earlier NZ study reported that in 1995 approximately 50% of prostate cancer patients waited longer than 6 months between diagnosis and radical prostatectomy [790]. It seems that the wait time for radical prostatectomy has not improved over time in NZ.

Shorter wait times for men treated with RP, and LDR compared with men treated with EBRT may be partly explained by RP and LDR being offered in the private sector, which has been associated with shorter wait times for prostate cancer patients [783]. Alternatively, longer wait

times between positive biopsy and treatment for men treated with RT compared to those treated with RP may be explained by time demands of specific clinical steps necessary to optimise the radiation procedure [791].

An inter-relation was observed between wait times, patient characteristics and treatment types. For instance, Māori men, and men with multiple co-morbidities were found to be more likely treated with EBRT, therefore longer wait times for men managed with EBRT were reflected in differences in wait times by ethnicity and co-morbidity status.

5.5.5 Strengths and limitations

The strength of this study was that comprehensive information was collected from clinical records of prostate cancer patients sourced from multiple locations in the Midland Cancer Network region, such as urology and oncology departments at hospitals, but also from private urology practices. Cross-referencing data from clinical records with national databases through NHI numbers was used to minimise the amount of missing information, and to test the validity of the available data.

A major strength of this study is the comprehensive information on cancer extent at diagnosis extracted from the clinical records, which apart from allowing for extent- and risk-based assessment of management pathways for prostate cancer patients, also facilitated validation of extent information for prostate cancer in the NZCR.

The study design, which involved selecting all Māori men within the region and frequency age-matching each Māori men with three randomly selected NZ European men, is considered both a strength and a limitation of the study. The advantage is that this design allowed us to obtain sufficient numbers of Māori men for statistical evaluation of the results; the disadvantage is that by matching by the age structure of Māori prostate cancer patients, the overall age structure of the sample is younger than that of the general NZ population of prostate cancer patients. However, weights were used to at least partly simulate population data within the respective age range.

Men diagnosed with GS 5 were excluded from this study (9 out of 450 NZ European men), although they are included as being diagnosed with prostate cancer in the NZCR. These men can be considered being over-diagnosed and regardless of their treatment option their survival outcome would likely be excellent. Since only non-Māori men were recorded in this category, including them in the study would mean that the proportion of NZ European men with low-risk localised prostate cancer would increase compared with Māori men. This finding would also

affect the observed survival rates in the national sample; greater proportion of non-Māori men with low-risk disease would contribute to lead time and length bias, which artificially improve survival, resulting in risk estimates biased away from 1.

In contrast, the exclusion of men with an incorrectly assigned later date of diagnosis in the NZCR may have contributed to the under-estimation of the proportion of men with advanced disease. It seemed that these cases were not registered in the NZCR until they had progressed to advanced extent. Since there were more Māori men with an incorrectly assigned date of diagnosis (9 out of 150) compared with NZ European men (11 out of 450), the proportion of Māori men with prevalent late-stage prostate cancer would increase compared with NZ European men. This finding would also affect the observed survival rates in the national sample; a greater proportion of Māori men first registered with advanced disease although they were actually diagnosed with localised disease some time earlier would lower the survival time for these men, thus resulting in risk estimates biased away from 1.

Another potential limitation of this study is that data on treatment types were sourced only from the Midland Cancer Network region. Treatment options and access to specific types of treatment may vary between Cancer Networks and regions in New Zealand.

CHAPTER 6 DISCUSSION

6.1 Prostate cancer care pathway and outcomes in New Zealand in comparison with other countries

Main finding: *Despite high rates of opportunistic screening, twice as many men in New Zealand were diagnosed with advanced disease compared with other high-screening countries, and prostate cancer mortality was reported to be higher than in the UK, which is a country with low screening rates. Apart from late stage at diagnosis, under-utilisation of high-quality treatment may have caused the comparably high death rate.*

Approximately every fifth man aged 40+ years enrolled in 31 general practices in the MCN region was screened in 2010. Similar screening rates were reported from other NZ studies and also from other countries with privatised primary care services, such as the USA, Canada, and Australia [305-307, 764].

The incidence of prostate cancer in New Zealand has been largely influenced by changes in screening, and diagnostic practice such as the introduction of a more effective biopsy procedure. In general, the incidence rate of prostate cancer has been decreasing since 2000 due to the decline in new cancer cases in men older than 70 years. These findings may be partly explained by then emerging research results showing that early diagnosis does not improve outcomes for older men and they are more likely to die of other causes rather than of prostate cancer [756]. A consistent decline in incidence rates for older men was also observed in Australia, the USA and Canada, all countries with high screening rates for men between 50 and 70 years [63, 304, 313, 333].

In this study, the low rate of diagnostic activity for men aged 70+ years was evident in biopsy rates. Almost three-quarters of men aged <70 years with an elevated PSA result underwent a biopsy following a specialist consultation compared with less than 50% of men aged 70+ years. Similar proportions were found in a US study, with 89% of men younger than 70 years and 46% of men aged 70+ years undergoing a biopsy following a specialist visit [762].

The argument for lower diagnostic activity in older men has also been reinforced by reports that treatment options with curative intent were rarely used for men aged 70+ years, mainly because of their high burden of co-morbidities [358, 366, 367, 504]. In this study, the majority of older men were managed expectantly with watchful waiting. When curative treatment was used, it was mainly in the form of radiation therapy. However, some researchers currently

argue that with steadily increasing life expectancy older men fit for their age should be given the opportunity to have their prostate cancer diagnosed and treated when possible [506, 507]. Despite the low diagnostic activity for older men, more than a quarter of men aged 70-79 were screened. Apart from the fact that there is no evidence that screening and potential subsequent treatment would do more good than harm, and that early diagnosis would reduce mortality for this age group [162, 277], the following sequence of events from the present study illustrates the futility of screening in older men: Of 1367 men aged 70+ years screened in 2010, 33 (2%) had a PSA level higher than the laboratory recommended age-specific cut-off level of 6.5-7.0 ng/ml. Following an elevated PSA result, five men (15%) underwent a biopsy, all of whom were subsequently diagnosed with prostate cancer; three with Gleason score of 6 and 7, and two with GS of 8-10. Based on the minimal risk of dying of prostate cancer for older men with GS of 6, only three men out of 1367 screened (0.2%) would potentially benefit from screening in this sample, assuming that they would receive treatment and survive at least 10 years post-diagnosis.

Overall, only 2% of men screened in 2010 had an elevated PSA result based on age-specific cut-off values. The low proportion of men with an elevated PSA result can be partly explained by frequent testing, since more than half of the screened men had one or more normal PSA tests in the three years prior to 2010. Previous studies showed that frequent screening is not beneficial, since two- and four-year screening intervals resulted in a similar number of clinically significant cancers missed [284]. Moreover, frequent screening may result in more than 50% of prostate tumours being over-diagnosed [150].

Less than half of the men with an elevated PSA result had a specialist appointment in the follow-up period. In particular, only about one-third of screened men were referred to a specialist. Factors that prompted a specialist visit were a PSA level of 10+ ng/ml, presence of symptoms (compared with screening), and previous negative biopsy.

Following a specialist consultation, 65% of men underwent a biopsy. Approximately half of the biopsies returned a positive result. As expected, men aged 70+ years, and men with a PSA level at referral of 20+ ng/ml were more likely to have a positive biopsy, while prostate cancer was less likely detected in men with a previous negative biopsy. There was little evidence for differences in positive biopsy rates by the number of previous PSA tests, and between screened men and men with symptoms or men with previous prostate problems. As shown by the study by Roobol et al. [284], frequent PSA screening does not result in higher detection rates of clinically significant cancers.

Out of the 165 prostate cancer cases diagnosed between 2010 and 2011 in men enrolled with the 31 general practices, 58% were localised, 11% regional, and 6% distant at diagnosis. For 22% of men there was not sufficient information to assign the extent at diagnosis, mainly because of unknown clinical stage at diagnosis.

The review of clinical records of a sample of 600 men diagnosed with prostate cancer between 2007 and 2010 in the MCN region showed that the majority (76%) of men were diagnosed with localised prostate cancer, 12% with regional disease, 12% with distant metastases, and 5% had unknown cancer extent at diagnosis.

In high-screening countries, such as the United States and Australia, more than 80% of men were diagnosed with localised prostate cancer [63, 336, 504], while in countries with lower screening rates, such as the UK, Sweden, and Japan the proportion of men diagnosed with localised disease ranged between 51% and 63% [325, 346, 792]. The proportion of men with metastatic disease was less than 5% in the USA and Australia [63, 336, 504], while 13% to 15% of men in the UK, Sweden, and Japan were diagnosed with distant metastases [325, 346, 792]. Although the majority of prostate tumours diagnosed in the recent years in New Zealand were of localised extent, as a consequence of the low diagnostic intensity for men with elevated PSA results about half of the men with prostate cancer were diagnosed with high-risk or advanced disease. In comparison to other Western countries with similar screening patterns, this sample showed double the rate of distant metastases at diagnosis.

For men with localised prostate cancer, the distribution of D'Amico risk categories largely determines the prognosis and treatment needs of prostate cancer patients [159, 425, 455]. In this sample, 33% of men with localised prostate cancer had low-risk disease, 47% intermediate-risk, 13% high-risk cancer, and 7% unknown risk at diagnosis. Australian and US studies reported proportions of men diagnosed with low-risk disease ranging from 33% to 46% [336, 504, 505, 542, 629], while a UK study found 21% of men being diagnosed with low-risk disease [346]. High-risk cancer was found for 21% to 30% of US men [505, 542, 629], for 12% of Australian men [504], and for 39% of UK men with localised disease [346]. Although the proportion of men diagnosed with low-risk cancer in this study was similar to those reported from other high-screening countries, there seemed to be a shift toward a higher proportion of men with intermediate-risk tumours and correspondingly lower proportion of high-risk disease. Since the present study was based on more recent data than the other studies, a similar shift may have also occurred in other high-screening countries over time.

In this study, radical prostatectomy was the most common initial treatment with 45%, followed by radiotherapy, including EBRT, HDR and LDR (26%). Approximately 23% of men were managed expectantly with AS and WW. Hormonal therapy as the first line of treatment was used for 5% of men with localised prostate cancer. As expected, the distribution of treatment types depended on patient characteristics, such as age at diagnosis, number of co-morbidities, and D'Amico risk categories [365, 504, 787, 788].

Men initially treated with radical prostatectomy were more likely to have no co-morbidities and low- or intermediate-risk cancer. In contrast, men treated with EBRT had more likely one or more co-morbidities and intermediate- or high-risk prostate cancer. HDR was the least common treatment type in this sample, used mostly for men with low- and intermediate-risk prostate cancer. LDR was more likely used for men with no or few co-morbidities and low-risk prostate cancer. Active surveillance was used more likely for men with no or few co-morbidities and low-risk prostate cancer, as opposed to watchful waiting, which was more commonly used for men with multiple co-morbidities and intermediate-risk disease. Men initially treated with hormonal therapy had more likely multiple co-morbidities and high-risk prostate cancer.

The distribution of treatment modalities in the present study was largely in accordance with the NZ Prostate Cancer Taskforce recommendations for management of prostate cancer [455], as well as with observational studies from other countries, which noted that older age was associated with expectant management and HT, while RP was preferably offered to men younger than 70 years [358, 363, 366, 367, 504, 784-786]. Radical prostatectomy was typically offered to patients with few co-morbid conditions [358, 367, 784, 785, 788, 793], while expectant management and HT were more likely used for men with multiple co-morbidities [367, 784]. Low-risk disease was associated with a more common use of RP, brachytherapy, AS and WW, while the use of EBRT and HT was shown to increase with increasing risk [350, 784, 785, 788].

Overall, both over- and under-treatment was observed for men with localised prostate cancer in this sample. This finding is in accordance with other studies that reported that patients with low-risk disease often receive aggressive treatment, i.e. they are being over-treated [350, 794], while men with high-risk prostate cancer were shown to be under-treated [366, 794].

There is currently no consensus about optimal treatment for localised prostate cancer. In addition, there is no clear evidence that one management strategy is superior over another with regard to disease recurrence or survival [156]. The choice of treatment is therefore largely influenced by individual preferences of clinicians and patients, which are mainly guided by

known or perceived risk of adverse events and side effects of the given treatment modality. Ideally, the decision process would involve a number of different health professionals, including both urologists and oncologists along with a well-informed patient, and take into account patient characteristics, such as age, life expectancy, overall health status, clinical features of the tumour, and treatment-related aspects, including effectiveness and side effects [159, 296, 425, 455].

Earlier studies showed that patients' preference and understanding of the advantages and limitations of treatment modalities, as well as treating physician's preferences and skills contribute to treatment choice [512, 795]. Moul [511], and Fowler et al. [510] demonstrated that specialist clinicians tend to recommend the treatment type that they undertake themselves, i.e. urologists recommend radical prostatectomy for treating localised prostate cancer, while radiation oncologists are more likely to suggest radiotherapy. Differences in accessibility and availability of treatment types may have an impact on patients' choice of treatment, and subsequently on patients' outcomes [367, 531, 796].

Wait times in the prostate cancer care pathway were generally longer in this study compared with those reported from other countries, except for wait times between first specialist appointment and positive biopsy. The median wait time between the first elevated PSA result and the first specialist visit was approximately 3 months for NZ men compared with less than 2 months for Australian, UK, and US men [777, 797, 798].

The median wait time between FSA and positive biopsy was 49 days, and between positive biopsy and treatment 101 days (3.5 months). Median wait times between specialist consultation and biopsy reported from other countries were approximately 2-2.5 months [783, 797, 799], while the median wait times between biopsy and definitive treatment were approximately 2 months [783, 797].

Median wait time between positive biopsy and treatment was shorter for men treated with RP (89 days) compared with men treated with LDR (124 days), and EBRT (153 days). Studies from other countries reported median wait times from prostate cancer diagnosis to radical prostatectomy, ranging between 48 to 77 days [783, 800, 801], and to radiation therapy 95 to 121 days [783, 791].

In New Zealand, there are currently no guidelines regarding wait times for prostate cancer patients. A questionnaire study showed that wait times of up to six months between diagnosis and treatment were considered acceptable by patients scheduled for radical prostatectomy [790]. In the UK, a "two-week wait rule" between referral and initial specialist consultation for

suspected cancers has been implemented since 2000 [802], which seems to have a positive impact on prostate cancer stage at presentation. Despite low screening rates in the UK, the proportion of men diagnosed with distant metastases in 2009-2010 was 15% [346], only slightly higher than the 12% of men diagnosed with metastatic prostate cancer in this study.

Due to the good prognosis of localised prostate cancer, it is suspected that moderate delays in diagnosis and treatment will not have an adverse impact on outcomes [802-804]. In contrast, O'Brien et al. [805] showed that for men with low-risk localised prostate cancer scheduled for radical prostatectomy, a delay of 6 months and more was associated with an increased risk of high-grade disease at surgery and subsequent biochemical progression, and Nguyen et al. [806] identified a greater risk of PSA failure for men with high-risk localised prostate cancer following a delay to radiation therapy of more than 2.5 months. In addition, longer diagnostic and treatment intervals were associated with greater psychological distress for cancer patients [807].

Differences in cancer-specific survival by Cancer Networks indicate that prostate cancer care pathways, including the distribution of cancer stage at diagnosis and the use of treatment modalities likely vary among regions in New Zealand. Therefore the conclusions based on data from the Midland Cancer Network region may not be representative for the whole of New Zealand. However, with a good representation of Māori men, and rural men this study helped clarifying the reasons for disparities by ethnicity and rural/urban residence, and showed how inconsistencies in diagnosis and management of prostate cancer adversely influence patients' outcomes.

6.2 Prostate cancer care pathway and outcomes for Māori and non-Māori men

Main finding: *Māori men were twice more likely to be diagnosed with metastatic disease, and were also twice more likely to die of prostate cancer compared with non-Māori men. Poorer prostate cancer survival for Māori men can be attributed to a series of differences along the prostate cancer care pathway, including less intensive diagnostic investigations, later stage at diagnosis, longer wait times, and differences in treatment modalities for both localised and metastatic prostate cancer.*

The prostate cancer care pathway for Māori men compared with non-Māori men is summarised in Figure 36.

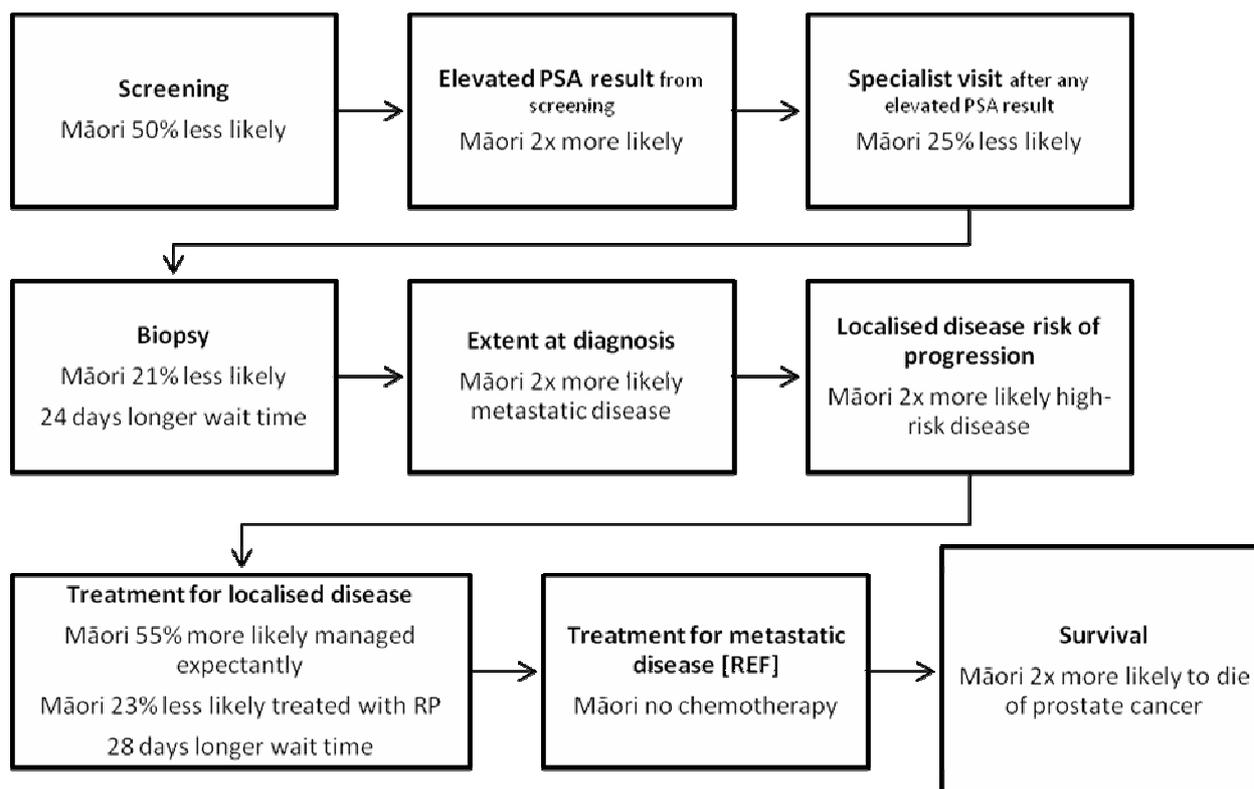


Figure 36 A schematic depiction of the prostate cancer care pathway for Māori men compared with non-Māori men.

Poorer prostate cancer survival for Māori men compared with non-Māori men can be attributed to differences in cancer extent and risk of progression at diagnosis, co-morbidity burden, treatment options, and timeliness of events throughout the prostate cancer care pathway.

Māori men were half as likely to be screened for prostate cancer compared with their non-Māori peers. Due to the persisting controversy about benefits versus harms of prostate cancer screening and about its role in reducing prostate cancer mortality [161, 162], it is unclear whether Māori men would benefit from increased screening rates. Considering that following screening the elevated PSA result indicated an increased prostate cancer risk for twice as many Māori men as non-Māori men, there seems to be a bigger pool of at-risk Māori men compared with non-Māori men. This finding may be partly due to the lower likelihood of PSA testing for Māori men in the three years prior to 2010, implying that there is a greater potential for detecting an elevated PSA result among Māori men compared with more frequently tested non-Māori men. However, this study also showed that compared with NZ European men Māori men were more likely to be diagnosed with advanced prostate cancer, and more likely to die of

prostate cancer. It seems therefore that Māori men may benefit from tailored screening strategies, as suggested by researchers in Australia and the USA [132, 134].

Patient characteristics, such as age and co-morbidities may play a role in GPs' screening behaviour, but GPs' preferences and practice characteristics, including the number of GPs in the practice and the number of patients seen by the GP also influence GPs' decisions around screening [300, 766]. In this study, there was a seven-fold variation in PSA screening rates between the 31 general practices. In the vast majority of practices Māori men were less likely to be screened, however, two Māori provider practices showed relatively equal screening rates for Māori and non-Māori men. Concurrently, Māori provider practices showed the lowest overall screening rates among the 31 practices. Overall, screening rates were lower in smaller practices (with 1-3 GPs) and practices with a high proportion of male Māori clients, which may indicate that due to higher work-load caused by fewer staff or patients with high burden of other diseases preventive measures were less utilised.

Compared with non-Māori men, Māori men were less likely to visit a specialist following an elevated PSA result, even after adjustment for age, PSA level at referral and reason for testing. Following a specialist visit, biopsy was undertaken for 75% of non-Māori men aged <70 years compared with 57% of their Māori peers, and for approximately half of both non-Māori and Māori men aged 70+ years. Since younger men are more likely to profit from early detection, it seems that biopsy is under-utilised in Māori men. Lower biopsy rates were also reported for African-American men with an elevated PSA result compared with European-American men [808].

Since referral and biopsy rates were lower for Māori men, the likelihood of prostate tumours going undetected was probably higher for Māori men compared with non-Māori men. In contrast, higher screening rates and more frequent PSA testing for non-Māori men have not resulted in a higher rate of cancer detection. This was probably due to the fact that the yield of screening actually decreased with increasing number of repeat tests [288].

Although prostate cancer incidence has been declining since 2000, there was a surge in new registrations between 2006 and 2009 for non-Māori men. It seems that prostate cancer awareness campaigns such as Blue September and Movember have prompted non-Māori men to get their prostate health checked. Irrespective of the discussions about the benefits of screening as a detection tool, the cultural appropriateness of prostate cancer health awareness campaigns should be reconsidered considering that they do not seem to reach Māori men, who are more likely to be diagnosed with advanced prostate cancer and die of the disease.

However, in 2010, no difference was observed between prostate cancer incidence rates for Māori and non-Māori men, mainly due to a decline in the incidence rate for non-Māori men. This finding is supported by similar prostate cancer detection rates for Māori and non-Māori men in the MCN region following an elevated PSA result in 2010. The decline in prostate cancer incidence for non-Māori men may be explained by the depletion of the pool of prevalent cases due to the intensified diagnostic activity in the preceding period [313].

Survival disparities between Māori and non-Māori men with prostate cancer have been repeatedly acknowledged for about 20 years now [5, 6, 378], but despite improvements in the disease-specific survival for both Māori and non-Māori men, the survival gap between these two groups has not been reduced with time. In fact, survival rates for Māori men diagnosed between 2006 and 2010 only just reached the survival level for non-Māori men diagnosed between 1996 and 2000. Particularly long-term cancer-specific survival was affected.

The observed survival differences between Māori and non-Māori men may be to some extent explained by differences in lead time and length bias, with non-Māori men surviving longer because of longer lead times and more common detection of slowly-growing cancers with favourable prognosis. However, persistent differences in prostate cancer mortality between Māori and non-Māori men [1], and only slightly higher proportion of low-risk localised tumours observed in non-Māori men compared with Māori men diagnosed between 2007 and 2010 (Figure 37) suggest that the observed differences were determined by the loss of survival time due to more commonly diagnosed advanced disease in Māori men rather than due to gain in survival time through lead time and length bias of low-risk localised tumours in non-Māori men.

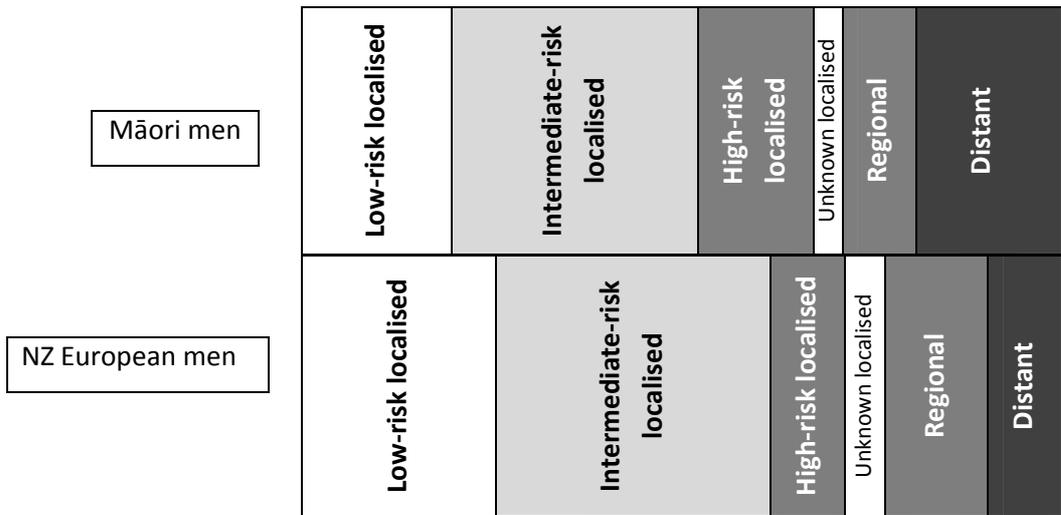


Figure 37 Risk profiles of a sample of Māori and NZ European men diagnosed with prostate cancer between 2007 and 2010 in the MCN region (the width of the box equals 100 mm representing 100%, while the widths of the individual rectangles represent the proportion of respective risk categories).

A greater disparity was found for cancer-specific survival between Māori and non-Māori men aged <70 years at diagnosis compared with older men. This finding may be related to a more pronounced effect of variations in screening practices and treatment modalities among younger men with prostate cancer. Regardless of ethnicity, men aged 70+ years tend to be more likely diagnosed with advanced disease, and when diagnosed with localised disease, treatment options with curative intent are limited.

In prostate cancer patients, age is considered to be a major independent predictor of survival, since disease management, including early detection and treatment options is highly age-dependent [159, 296, 425]. In this as well as in other studies, men diagnosed at an age younger than 70 years were more likely to have been screened, to have undergone diagnostic investigations, and to have received treatment with curative intent for localised cancer, while older men were less likely to have undergone a biopsy following an elevated PSA result, and when diagnosed, may often be counselled to accept expectant management mainly due to their higher co-morbidity burden [504, 506, 762]. The argument for less diagnostic activity for older men is that these men are more likely to die of causes other than prostate cancer when diagnosed with localised disease [756].

Recent US studies suggested that adjusting for age, cancer stage at diagnosis, competing causes of death and treatment fully explained survival differences between African-American and European-American men [359, 365]. Although data on co-morbidities were not available for the national cohort, results from the regional study have shown that Māori men with prostate cancer were more likely to have multiple co-morbidities. Studies from other countries showed that the presence of multiple co-morbidities was associated with poorer outcomes for men diagnosed with prostate cancer; however, the effect was largely confined to overall- and non-cancer-specific outcomes [787, 788].

Cancer extent at diagnosis is a strong predictor of prognosis, since men diagnosed with localised disease may survive up to 20 years even without treatment, while the majority of men diagnosed with distant metastases will not survive longer than 5 years [145-147, 324]. Late diagnosis has been considered as one of the major contributing factors to poorer survival for ethnic minorities with prostate cancer [5, 355, 358, 360, 378].

Based on the results from primary care, Māori men were more likely to have GS of 8-10 and distant metastases compared with non-Māori men. The study of clinical records showed that 19% of Māori men and 10% of NZ European men were diagnosed with distant metastases

between 2007 and 2010 in the MCN region. Of Māori men with localised prostate cancer 22% had high-risk disease, in contrast to 13% of NZ European men.

Later stage at diagnosis for Māori men may probably be attributed to lower PSA screening rates and less intensive diagnostic activity compared with non-Māori men. Although differences in genetic susceptibility and metabolic determinants for aggressive cancers between Māori and NZ European men may also be suggested as potential contributing factors, there is so far little evidence for such a scenario. For instance, higher serum levels of IGF-1 were linked to an increased risk of aggressive prostate tumours, but a recent study showed that there was no difference in serum IGF-1 concentrations between Māori and European men in NZ [809]. More research in this area would help to clarify the baseline risk for different ethnic groups.

Studies from the USA reported higher proportions of advanced prostate cancer for African-American men compared with European-American men, but the difference seemed to have been reduced with time, mainly due to intensified screening for African-American men [63, 360, 810]. One recent study showed that African-American men had higher proportion of high-risk localised prostate cancer and correspondingly lower proportion of low-risk disease compared with European-American men [365]. No differences in the distribution of stage at diagnosis have been observed between UK men of European and African ancestry; UK having a relatively equal-access public health care system [363, 364].

Poorer outcomes observed for Māori men compared with non-Māori men can be at least partly attributed to differences in the management of localised prostate cancer.

Māori men with localised prostate cancer were less likely to be treated with radical prostatectomy, and with LDR compared with NZ European men. In contrast, Māori men were more likely to be managed with AS and WW, and more than twice as likely to receive EBRT, and HDR. These differences in treatment may be related to differences in patient characteristics, with Māori men having more likely high-risk prostate cancer, and multiple co-morbidities compared with NZ European men in this sample. There were also differences in characteristics related to access to health care, with Māori men being more likely to live rurally, in the most socio-economically deprived areas, and to receive health care for prostate cancer solely in the public sector. However, even after adjustment for patient age, D'Amico risk strata, co-morbidities, socio-economic deprivation, residence and health sector, Māori men were 55% more likely to be managed expectantly and 23% less likely to be treated with RP compared with NZ European men.

An earlier study on metastatic prostate cancer showed that treatment varied between Māori and non-Māori men diagnosed between 2007 and 2011, and, in general, ADT and chemotherapy seemed to be under-utilised [811]. Only 72% of men have received medical or surgical ADT, and less than 1% received chemotherapy. Chemotherapy was dispensed only for non-Māori men [811]. In comparison, in the USA 95% patients diagnosed between 1994 and 2002 with stage IV disease received either surgical or pharmacological ADT, while 16% received chemotherapy [812].

Differences in treatment modalities have also been identified between Māori and non-Māori patients with lung, colon, and female breast cancer in NZ [758, 759, 781]. A number of overseas studies reported differences in treatment between men of European and African ancestry, with the latter being less likely treated with definitive treatment, mainly radical prostatectomy, and conversely being more likely managed expectantly [358, 363, 365-367, 786]. One study specifically noted that African-American men with localised prostate cancer of similar risk were less likely to be treated with RP compared with European-American men [365]. Differential use of treatment has been shown to contribute to survival differences between African-American and European-American men [358, 365].

In the absence of a consensus regarding optimal treatment for localised prostate cancer, choosing a treatment may pose a challenge for both patients and clinicians, which may create a greater potential for inequality. Interestingly, Richert-Boe et al. [817] reported that urologists were less likely to offer definitive treatment to African-American men than to European-American men, even when age, cancer stage, co-morbidities and socio-economic position were accounted for.

In this study, Māori men were socio-economically more disadvantaged and were more likely to receive health care in the public sector only compared with non-Māori men. Socio-economic deprivation is often closely associated with ethnicity [377, 381]. Interestingly, in low-income, uninsured US men the proportion of distant prostate cancer was 19%, the same as for Māori men in this study [814]. Other US studies agreed that uninsured or publicly insured US men, and especially African-American men were more likely to be diagnosed with advanced prostate cancer [356, 810, 815].

The observed variation in treatment modalities was also partly explained by socio-economic position and access to private health care. As in other countries, men receiving private health care or having private health insurance, and those residing in socio-economically least disadvantaged areas were more likely to be treated with radical prostatectomy, while men

receiving health in the public sector only, and those living in the most disadvantaged areas were more likely to be managed expectantly or with RT [336, 366, 367, 391, 784].

Considering these findings, it was not surprising that socio-economic deprivation has been identified as an important contributing factor to poorer survival for Māori men. The effect of socio-economic position was also associated with poorer cancer-specific survival for African-American compared with European-American men [816].

Timeliness of diagnosis and treatment has also an effect on patient outcomes. Māori men had longer wait times between the individual steps of the prostate cancer care pathway compared with NZ European men. Differences in wait times have also been identified between Māori and non-Māori patients with lung, and colon cancer in NZ [758, 759]. A US study reported longer wait times between prostate cancer diagnosis and radical prostatectomy for African-American men [800]. However, two other studies that explored wait times between diagnosis and treatment in an equal-access health care setting found no differences between African-American and European-American men [817, 818].

A similar picture of Māori men having longer wait times and receiving less curative treatment was described by Hill et al. [819] who summarised current research into cancer care pathways in New Zealand. The authors pointed out that inequalities in treatment (but also diagnosis) between Māori and non-Māori cancer patients may stem not only from differences in patient level factors, such as co-morbidities, but also from differences in health-care processes and the performance of the health system. Hill et al. [819] suggested that so-called institutional racism, a kind of organisational discrimination in the location, funding, and personnel requirements may contribute to the observed inequalities by ethnicity in cancer patients. Clarity in service provision, such as implementation of national screening programmes may contribute to the elimination of inequalities [820], while the presence of uncertainty and time restrictions may reinforce stereotyping from health care providers [821].

6.3 Prostate cancer care pathway and outcomes for rural and urban men

Main finding: *There was little evidence for differences in prostate cancer survival between rural men and men residing in main urban areas. Although rural men were less likely to be screened, little or no differences were observed for the distribution of extent at diagnosis and treatment modalities for localised prostate cancer between men residing rural and main urban areas. There was also little evidence for differences in wait times along the prostate cancer care pathway.*

The prostate cancer care pathway for rural men compared with men residing in main urban areas is summarised in Figure 38.

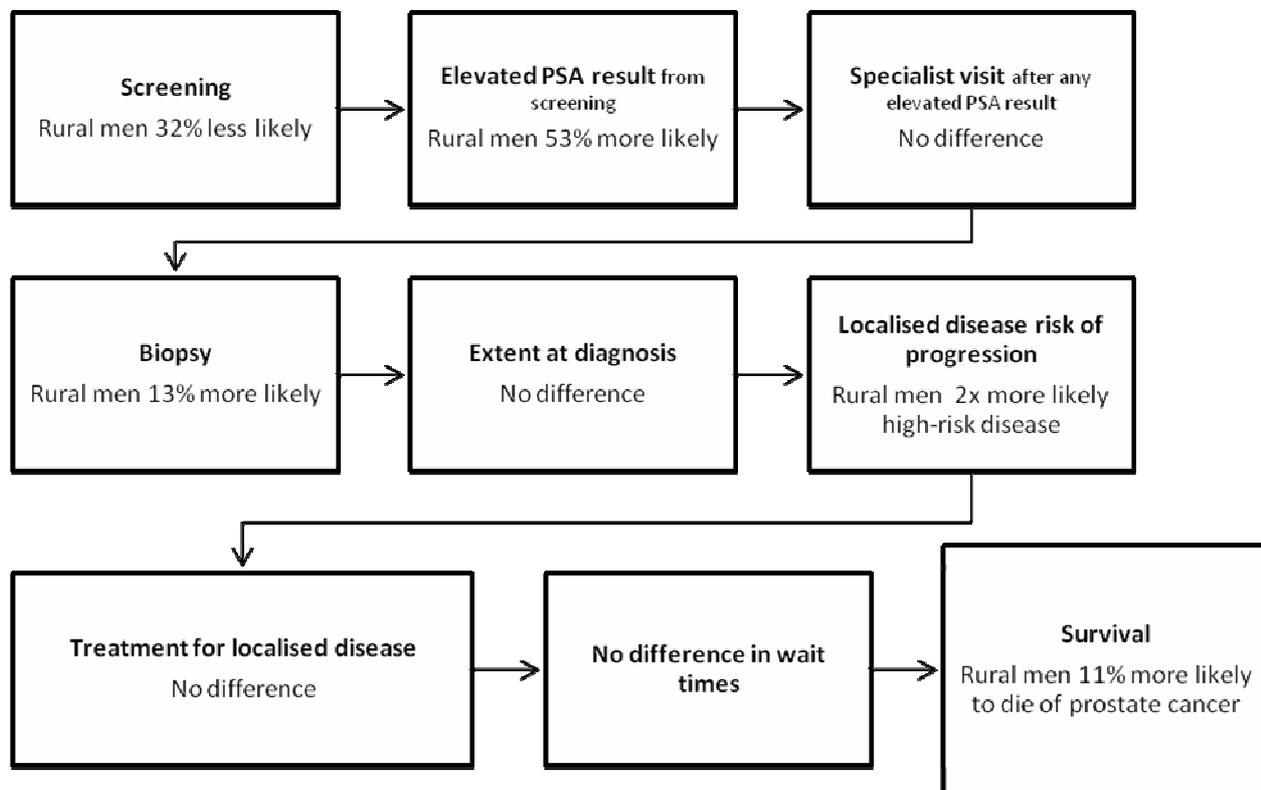


Figure 38 A schematic depiction of the prostate cancer care pathway for rural men compared with men residing in main urban areas.

Rural men were less likely to be screened in 2010, but compared with urban men they were more likely to have an elevated PSA result following screening. Rural men were also less likely to have a PSA test in the three years prior to 2010 compared with urban men. Lower screening rates for rural residents were also reported from Australia, Canada and the USA [307, 384, 385]. The observed variation was so far mainly explained by differences in patient characteristics, including age, socio-economic position and overall health status between rural and urban areas [384, 385, 388], but access to and availability of health services, and awareness of screening benefits may have contributed to these rural-urban disparities [822-826]. Lower screening rates for rural populations have also been reported for other cancers, including colorectal, breast, and cervical cancer [822-826], indicating that preventive measures are less utilised in rural areas.

In New Zealand, there is a shortage of rural general practitioners, and consequently rural practices are often under-staffed, indicating that lower screening rates in rural practices may

be related to higher work-load with a focus on acute health problems. In addition, rural practices have often a high “turn-over” of practitioners and are staffed by international medical graduates, whose screening practice may vary from NZ practitioners [827, 828]. From the present data it is uncertain whether rural men were less inclined to participate in screening or whether rural GPs were less likely to screen. However, a NZ survey showed that while rural patients were as likely to visit their GP as urban patients, rural GPs were less likely to order laboratory tests and investigations, and also undertook fewer preventive measures [829]. Referral, biopsy and cancer detection rates were similar between rural and urban men. Although rural men with localised prostate cancer were more likely to have high-risk disease there was little difference in extent at diagnosis between men residing in MUAs and rural areas. Similarly, an earlier NZ study found no difference in the proportion of distant stage at diagnosis between rural and urban men with prostate cancer [4]. While some overseas studies reported that rural men were more likely to present with advanced prostate cancer, others found no rural/urban difference or even a reverse trend with a higher proportion of urban men being diagnosed with advanced prostate cancer [384, 388, 390, 395].

Rural men showed lower prostate cancer incidence rates between 1996 and 2001 compared with men residing in MUAs, but between 2002 and 2010 there was little difference between incidence rates by rural/urban residence.

There was little evidence for differences in all-cause and cancer-specific survival between rural men and men residing in main urban areas, although the probability of surviving was slightly lower for rural men. It seems that any potential variation in survival related to urban-rural residence can be almost fully explained by controlling for age, ethnicity and socio-economic deprivation. Studies from other countries also suggested that poorer prostate cancer outcomes, including survival for men living in rural areas can be largely explained by differences in demographic and socioeconomic characteristics between rural and urban residents that influence access to and utilisation of diagnostic and treatment services, and not by physical distances to healthcare facilities per se [388, 391, 393, 395]. Although physical distance does not present a barrier for urban residents, other factors, such as low education level and poverty may have similar effects on disadvantaged groups as remoteness [395].

Earlier NZ studies on upper gastrointestinal cancer, female breast and cervical cancer also found little association between rural residence and survival [396-398]. In contrast, Robson et al. [4] reported that rural Māori and non-Māori men diagnosed with prostate cancer between 2002 and 2006 had significantly lower relative survival than their counterparts living in MUAs.

Although the study by Robson et al. [4] also reported poorer survival for rural residents with lung, colorectal, and uterine cancer, they acknowledged that these differences may be linked to other factors, such as ethnicity and age structure of the population rather than rural residence as such.

There was little evidence for differences in treatment modalities by rural/urban residence in this study, opposed to Australian studies that reported that urban men were more likely to be treated with curative intent [307, 336, 392, 504, 793]. There were also no differences in the wait times for the individual steps of the prostate cancer care pathway between men residing in rural and main urban areas.

6.4 Implications for policy

To improve outcomes for New Zealand men with prostate cancer and to diminish and eventually eliminate the inequalities along the prostate cancer care pathway, policy-makers should consider:

1) establishing clear guidelines regarding the use of PSA screening; 2) facilitating compliance with existing recommendations about detection and treatment of prostate cancer by utilising multidisciplinary meetings and external audits provided that structured data on patient management become available on regional and national level; and 3) assessing the needs of the healthcare workforce (e.g. number and type of staff) so patient needs, including information provision, access to high-quality treatment and optimal support throughout the cancer care pathway can be met.

With prostate cancer being the most commonly diagnosed male cancer in New Zealand, and the third most common cause of male cancer deaths, this disease is clearly of public health interest. Due to the cancer's variable natural history, ranging from slow-growing indolent localised disease to aggressive incurable metastatic tumours, management of prostate cancer requires the involvement of a variety of health care specialists and resources. Although there are still uncertainties about best practice for prostate cancer diagnosis and management, it is crucial to gather information about contemporary prostate cancer care pathways in New Zealand and assess these in light of available guidelines and international findings in order to identify areas in need of improvement.

The reporting of new cancer cases is mandatory in New Zealand, with the New Zealand Cancer Registry being linked to other registries to present comprehensive information about cancer

patients. However, one of the major limitations of using the NZCR for prostate cancer research is that cancer extent at diagnosis is recorded as unknown in about 75% of cases. This may be due to lack of uniformity of reporting and the need for collation of multiple sources to obtain complete staging information. Since the natural history of the disease, patients' needs and outcomes are closely associated with prostate cancer extent at diagnosis, it is especially important to improve reporting of clinical and histological cancer stage and grade assessments to at least achieve proportions of known extent similar to colorectal and breast cancer, where more than 80% of cases have known disease extent recorded in the NZCR [377]. Following the example from other countries [504, 830], the New Zealand Cancer Control Council is currently reviewing the reporting of all cancers, which will hopefully lead to improvements in data availability and accuracy in the NZCR, including extent at diagnosis [831].

Although not recommended in New Zealand [3], opportunistic screening for prostate cancer was common in primary care, having been frequently undertaken also in men older than 70 years, for whom there is no evidence of mortality benefit. Of the screened men, more than half had one or more normal PSA results in the previous three years. Screening rates varied widely by ethnicity, residence, and practice. Māori men, and rural men were half as likely to be screened as non-Māori men, and urban men, respectively.

Opportunistic screening has not only been harmful for patients by causing inequality, but it has also been a waste of resources. Despite high screening rates, a relatively large proportion of men was still diagnosed with advanced disease and the death rate due to prostate cancer in NZ was higher than in other high-screening countries. It was even higher than prostate cancer mortality in a low-screening country such as the UK. The minimal benefit of opportunistic screening compared with organised screening with regard to mortality reduction has also been shown for cervical cancer in the UK, Australia and New Zealand [832].

There are basically three alternatives to opportunistic PSA screening, which is selective, causes inequalities and in case of NZ excessively targets men over 70 for whom there is no evidence of benefit from PSA screening. First, to implement population-based screening, which is currently not recommended in any country worldwide, but it can be argued that one large randomized controlled trial, the ERSPC found mortality benefit for screened men between 55 and 69 years [162]. For instance, the group behind the 2013 Melbourne Consensus Statement advocates for screening and early diagnosis of prostate cancer, associated with decoupling of diagnosis and treatment for men with low-risk localised prostate cancer, using active surveillance as a management strategy instead of surgery or radiation therapy in order to reduce over-

treatment [270]. Similarly, the Urological Society of Australia and New Zealand [267] recommended that asymptomatic men aged 55-69 years should be encouraged to get a PSA test and DRE after having been advised on the risks and benefits of PSA screening.

Second, to completely abandon screening following the current recommendations by the US Preventive Services Task Force [155]. This alternative may be difficult to implement since there are many campaigns encouraging men to discuss their prostate health with health professionals, and the PSA test is well-known as a screening tool. Moreover, GPs seem to believe in the benefits of screening since screening in New Zealand is currently mainly GP-driven [298].

Third, to screen high-risk groups, which are currently defined to be older men, men with family history of prostate cancer and African-American men [28-31]. Older age as a risk factor needs to be considered in light of the findings that older men would not benefit from screening due to their shorter life expectancy, greater co-morbidity burden and complications associated with treatment [133, 756]. In NZ, the question may arise whether Māori ethnicity should be classified as a risk factor. Māori men are more likely diagnosed with advanced disease and they are more likely to die of prostate cancer as is the case with African-American men. However, African-American men are more likely to be diagnosed with prostate cancer in general, which is not the case in NZ Māori men.

In these alternatives, the PSA test is considered as the screening tool. The PSA test has a number of limitations in this respect, so ideally the future of prostate cancer screening would lie in a screening tool that would be highly prostate cancer-specific (not just prostate-specific as is the case with PSA) and will detect treatable tumours, but not over-diagnose the disease.

Ethnicity was a major predictor of diagnostic activity, including referral and biopsy rates.

Despite the lower rate of diagnostic activity for Māori men, the overall detection of prostate cancer did not differ by ethnicity, which was also reflected in similar national prostate cancer incidence rates for Māori and non-Māori men in 2010. However, when diagnosed with prostate cancer Māori men were more likely to have high-risk disease and distant metastases compared with non-Māori men. Better understanding of prostate cancer risk on an individual basis, and consistent follow-up strategies for men considered to be at higher risk of prostate cancer may help to reduce the number of men diagnosed with advanced cancer. Considering the low yield of frequent and common screening for non-Māori men as opposed to suboptimal detection of prostate cancer for Māori men, adjusting the distribution of resources in light of the specific

needs of these two groups may prove beneficial for both the patients' outcomes and the health system by reducing the number of unnecessary investigations.

Overall, less than half of the men with an elevated PSA result had a specialist appointment. Moreover, PSA levels at referral were consistently higher than the recommended age-specific cut-off values. Thus general practitioners managed a large proportion of men potentially at risk of having prostate cancer in their practice instead of referring them to a specialist. In addition to monitoring these men, GPs have been increasingly involved in the monitoring of survivors and patients with metastatic prostate cancer [833]. This puts a lot of pressure on the already heavy work-load of many GPs. More research is needed in order to assess the administrative and financial requirements of these arrangements.

A major finding of this study was the identification of disparities throughout the prostate cancer care pathway between Māori and non-Māori men. Lower screening rates, less intensive diagnostic investigations, longer wait times, later diagnosis, and differences in treatment probably all contributed to poorer prostate cancer survival for Māori men. The survival gap between Māori and non-Māori men has not diminished over the last 15 years. Although over-diagnosis for frequently screened non-Māori men may also have explained the observed survival disparity, less than a third of prostate cancer cases diagnosed in NZ European men in the MCN region between 2007 and 2010 were classified as low-risk localised disease, and the difference in the proportion of low-risk cancer between Māori and NZ European men was less than 10%.

Māori men with localised prostate cancer were less likely initially treated with radical prostatectomy, and with LDR compared with NZ European men. In contrast, Māori men were more likely to be managed with AS, and WW, and more than twice as likely to receive EBRT, and HDR. Although some of these disparities may be explained by differences in patient characteristics, such as the number of co-morbidities, and risk of disease progression, even after adjustment for patient- and health system-characteristics Māori men were less likely to be treated with RP, and more likely managed with AS and WW. When compared with NZ European men, Māori men had also longer wait times between referral and first specialist appointment, between FSA and positive biopsy, and between positive biopsy and curative treatment.

Recent comparative effectiveness research on breast cancer showed that screening and early diagnosis are not the driving force behind mortality reduction; instead it is improved treatment and patient care in general [834]. The comparison of outcomes for men with prostate cancer in

the UK and NZ seems to be in accordance with this finding, since screening rates in the UK are much lower than in NZ, but men with prostate cancer have good access to high-quality treatment, and consequently slightly lower prostate cancer mortality than NZ men.

Interestingly, the present study showed that although rural men had lower screening rates and, possibly as a consequence, slightly later stage at diagnosis than urban men, there were no differences in treatment of localised disease and no differences in survival by residence. In contrast, for Māori men, who also had lower screening rates and higher rates of late stage diagnosis compared with non-Māori men, differences in treatment options and timeliness were detected, which have resulted in evidently reduced prostate cancer survival.

Since there are currently several relatively equally effective management options for men with localised prostate cancer, the choice of an optimal pathway of care should be ideally achieved through a close cooperation and availability of a number of specialists and health service providers along with the involvement of a well-informed patient. An increased utilisation of multidisciplinary meetings would be beneficial. In addition, providing culturally appropriate and understandable information on the prostate cancer care pathway and its complexities may facilitate the implementation of shared decision-making.

In this study, non-compliance with existing international clinical guidelines for management of localised prostate cancer was identified in up to 35% of cases, highlighting the need for improvement in this area. In 2012, recommendations for diagnosis and management of prostate cancer were published by the NZ Prostate Cancer Taskforce [455], so the next important step would be to conduct studies about the use of and compliance with these guidelines.

There is also emerging evidence that to reduce inequalities in cancer outcomes it is necessary to better understand the social determinants of health, including community norms and attitudes, in order to provide culturally and socially accepted health services [835-837].

In conclusion, three major areas of focus for researchers and health care policy-makers emerged through this study: 1) development and implementation of strategies that would result in the reduction of the survival gap between Māori and non-Māori men, 2) identification of causes for the variation in survival between CNs, and 3) formulation of a plan for an optimal use of available treatment strategies and timely introduction of novel approaches and medication that have been shown to improve patient outcomes.

CHAPTER 7 CONCLUSIONS

New Zealand men have one of the highest incidence rates of prostate cancer in the world, accompanied by comparably high mortality rates. The prevalence of prostate cancer is estimated to increase dramatically, mainly due to the ageing of the population, but also due to the continuously rising number of survivors, consisting among others of over-diagnosed patients. So far, little has been known about diagnostic and management pathways for prostate cancer in New Zealand, therefore the aim of this study was to gain information about current practice regarding screening, diagnosis and treatment of prostate cancer in New Zealand, and to identify any existing ethnic and regional disparities.

Prostate cancer care pathways for NZ men are very diverse; the diversity originating partly from the naturally complex nature of the disease, but to a large extent also from the uncertainty about the optimal care strategy on the part of health care providers.

As expected opportunistic screening has resulted in ethnic and regional inequalities and in a large variation in screening rates among general practices. Less than half of the men with an elevated PSA result (indicator of increased risk of prostate cancer) had a specialist consultation and those not referred were managed in primary care. Moreover, PSA levels at referral were consistently higher than the recommended age-specific cut-off values.

Both over- and under-treatment of localised prostate cancer was identified in this study. Better compliance with available guidelines for prostate cancer treatment may considerably improve patient outcomes, including quality of life and survival.

Clearer guidelines need to be developed and implemented across health care services concerning the use of PSA testing, follow-up strategies after an elevated PSA result, and management of prostate cancer if detected.

The one finding that needs to be especially highlighted is the poor survival of Māori men with prostate cancer compared with non-Māori men and men in other Western countries. Poorer prostate cancer survival for Māori men compared with non-Māori men can be attributed to a series of differences along the prostate cancer care pathway, including less intensive diagnostic investigations, later diagnosis, longer wait times, and differences in treatment modalities for localised (this study) and metastatic prostate cancer [811]. International research has shown that by improving access to, timeliness and quality of treatment, the effect on outcomes can be significant and almost immediate [834].

Further research into decision-making around management strategies from clinician and patient perspective accompanied by audits of compliance with treatment recommendations

would help to better understand and consequently reduce ethnic and regional variations in the prostate cancer care pathways. In saying this, research into several important issues, including treatment of metastatic disease, new forms of treatment, costs, and patient perspective on prostate cancer pathway has already commenced [811, 838-840].

To conclude, the present study provided an insight into the current practice regarding screening and management of prostate cancer in New Zealand, and how it influences epidemiological outcomes, such as incidence and survival. By identifying inequalities in diagnostic and treatment pathways and their causes, this study highlighted areas of need for improvement, which will help to guide policy decisions and resource allocation.

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