

# THE MAJOR PREDISPOSING FACTORS TO HUMAN PAPILLOMA VIRUS (HPV) INFECTION AMONG PATIENTS WITH CANCER OF THE CERVIX AND THEIR KNOWLEDGE OF THE DISEASE



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## OPSOMMING

**Doel:** Die doel van hierdie studie was om die vernaamste predisposisionele faktore tot Menslike Papilloma Virus (HPV) infeksie te identifiseer by pasiënte met kanker van die serviks, insluitende hulle kennis en bewustheid van die siekte, ten einde opvoedkundige programme tot stand te bring en te ontwerp wat die hoë voorkoms van die siekte kan minimiseer.

**Plek:** 'n Stedelike tersiëre verwysingshospitaal wat 'n groot ontwikkelende gemeenskap bedien.

**Metode:** Die studie was as 'n beskrywende, nie-eksperimentele, kontekstuele ondersoek ontwerp. Die proefgroep het bestaan uit vyf-entwintig vroue (n=25) by die Combined Gynaecology Clinic (CGC) te King Edward VIII hospitaal. Hulle ouderdomme het gewissel van vyf-entwintig (25) tot vyf-en-sestig (65). Willekeurige seleksie was gedoen soos die pasiënte by die kliniek aangemeld het.

Data was ingesamel deur proefpersone se histologiese skyfies, vraelyste en beskrywende statistiek te ontleed. ASCII teksredakteur was vir dataontleding gebruik.

**Resultate:** HPV infeksieratio was 3.5:1 met 51.9% HPV positief, 18.5% HPV negatief en 29.6% met uitgestelde diagnose. Gemiddelde ouderdom was 43.76 jaar. 96% van proefpersone was in landelike areas gebore. 84% was Zoeloes met geen vroeëre blootstelling aan dwelms nie. 56% het eerste koïtus op ouderdomme tussen 15 en 20 beleef. 64% het meer as een seksmaat gehad en 92.3% van getroude/geskeide proefpersone het onbesnede eggenotes.

84% proefpersone was van kanker bewus en het geglo dat dit voorkom kan word. 72% het geglo dat dit betyds gediagnoseer moet word ten einde dit te genees. 80% was bewus van die noodsaaklikheid van roetine ginekologiese toetsing maar het dit nagelaat tot die siekte hulle daartoe gedwing het.

**Gevolgtrekking:** Geïdentifiseerde HPV-predispositionerende faktore kan help om opvoedings - en ondersoekprogramme te ontwerp om die hoë voorkoms van kanker van die serviks te verlaag. Sodanige behoefte spreek duidelik uit proefpersone se swak kennis van die siekte en gebrek aan roetine-ondersoeke. Studies oor die rol van die HIV-virus by servixkanker-pasiënte en die rol van die HIV-virus in die reaktivering van latente HPV, in toekomstige navorsing, word aanbeveel.

## ABSTRACT

**Objective:** The purpose of this study was to identify the main predisposing factors to human papilloma virus (HPV) infection among patients with cancer of the cervix as well as establish their knowledge and awareness of the disease, so as to design educational programmes to minimise the future occurrence of the disease.

**Place:** A tertiary urban reference hospital which provides health services to a large developing community.

**Method:** The study was descriptive, non-experimental and contextual. The sample group consisted of twenty five women (n=25) randomly sampled from the Combined Gynaecology Clinic (CGC) at King Edward VIII hospital. Their ages varied between twenty five (25) to sixty five (65).

Data was obtained through the analysis of the subjects' histological slides, questionnaires and descriptive statistics. ASCII text editor was used during data analysis.

**Results:** The infection ratio was 3.5:1 with 51.9% of subjects HPV positive, 18.5% HPV negative and 29.6% with deferred diagnosis. The average age was calculated as 43.76 years. 96% of subjects was born in rural areas. 84% of subjects was Zulus who had no previous exposure to drugs. 56% experienced first coitus at ages 15-20. 64% had had more than one sex partner and 92.3% of married/divorced subjects, had had uncircumcised husbands.

84% of subjects was aware of the existence of cancer and believed that it can be prevented. 72% believed that if diagnosed during the early stages, it can be cured. 80% were of the importance of routine gynaecological check-ups but had never bothered until the disease forced them to.

**Conclusion:** Through the identification of the predisposing factors to HPV, educational and scanning programmes can be designed, which will contribute to the decrease in the occurrence of cancer of the cervix. The need for such programmes arises from the subjects lack in knowledge of the disease and the shortage in regular gynaecological visits. It is recommended that the role of the HIV virus in cervical cancer patients, as well as the role of the HIV virus in reactivating latent HPV, is studied in future HPV research.

## INTRODUCTION

The incidence of cervical cancer in South Africa is evidently on the increase with an average of five hundred and fifty (550) new cases reported at King Edward VIII Hospital alone in 1995. Many causes have been identified as attributable to the disease but no one cause chiefly responsible for the disease has thus far been identified. There has not been much association of infection with neoplasia previously. With modern techniques of microscopic studies, there has been much documentation of the association of infection with neoplasia especially in female genitalia. This is important as the accumulation of mutations in an assortment of genes precedes the development of neoplasia (Gu, *et al.* 1994:629). If this can be detected early, the disease can be prevented or treated successfully at its early stages. Among viruses associated with neoplasia are Human Papilloma Virus (HPV) and Human Immunodeficient Virus (HIV) (Hildeshein; Mann; Brinton; Szklo; Reeves & Rawls, 1991:335 & Van Doornum; Van den Hoek; Van Ameijden; Van Haastrecht; Roos & Henquet, 1993:185).

HPV has been shown to be among the sexually transmitted pathogens associated with cervical neoplasia (Kharsamy; Hoosen; Moodley; Bagaratee & Gouws, 1993:357). Some correlation has been studied between HPV and HIV because HIV associated immune suppression may activate latent HPV infection and therefore lead to the development of cancer of the cervix (Tweddel; Heller; Cunnane; Mulhaupt & Roth, 1994:161). Little has been done regarding the predisposing factors to infection as regards these viruses, with specific relation to cancer of the cervix.

In technologically advanced countries where screening programmes are found, the incidence of cancer of the cervix has been reduced (Wyne, 1993:2) In contrast, cancer of the cervix remains one of the leading causes of cancer-related deaths in underdeveloped countries. To design a screening programme which will be more effective, knowledge pertaining to the predisposing factors to infection, with respect to these viruses, is essential.

## RESEARCH OBJECTIVE

The aim of this study was to identify the major predisposing factors to HPV infection among patients with cancer of the cervix, including their knowledge and awareness of the disease in order to establish and design educational programmes to reduce or minimise the high incidence of the disease.

The researcher identified that the disease mostly affect the Blacks in KwaZulu-Natal Province. This may be related to certain predisposing factors to infection with viruses that may lead to the development of cancer of the cervix.

## LITERATURE REVIEW

Cancer of the cervix is one of the leading causes of cancer deaths in women. It has been shown to be the most common gynaecological cancer in South Africa (Bloch, 1989:309). In England and Wales, it has been reported as the second most common gynaecological malignancy (Bomford; Kunkler & Sherriff, 1993:401). Several factors have been identified as attributable to the high incidence of the disease including high parity, age at first coitus, multiple sexual partners, genital tract infection, smoking, and change in sexual behaviour (Bomford, *et al.* 1993:401-402; Charlewood, 1972:343-344).

The incidence of the disease is more pronounced in more

sexually active people yet rare in virgins. There has been suggested correlation of the highest incidence with circumcision but studies done between 1964 and 1966 showed that there is no great difference in the incidence between Hindus and Moslems (Charlewood, 1972:343, 346). Certain viruses have been identified to be more responsible for cancer of the cervix, although, in most cases these viruses do not solely lead to the disease without the presence of other factors. Bloch (1989:310) gives the following as sources of evidence linking viruses with the causes of cervical cancer :- epidemiology; clinical studies; cytology; histology; immunochemistry; DNA-DNA hybridization; serology; human models and animal models. The assumption is that there is a causal link between an infective organism and cervical cancer (Kirnbauer; Booy; Cheng; Lowy & Schiller, 1992:1280). Infection with HPV is believed to be essential for the initiation of the disease (Gu; Pim; Labreque; Banks & Matlashenski, 1994:629 & Holleb; Fink & Murphy, 1991:145).

HPV induces cell transformation without integration into the cellular DNA. The high risk factors to infection with this virus include early commencement of sexual activity, early marriage, multiple sexual partners, multiple marriages, smoking and straw mattresses (Bloch, 1989:312).

With the present day knowledge of some association of HIV, HPV and cancer of the cervix, it is of crucial importance to have these patients tested for these viruses. A better understanding of the role of HIV in promoting the clinical manifestation of HPV infection is essential to the control of the disease. In order to achieve this, screening and educational programmes should focus not only on diagnosed individuals, but on all patients who attend the primary health care centres. The screening programme should be designed essentially to screen all women systematically.

## RESEARCH DESIGN AND METHODS

A descriptive and contextual survey was performed. It had two kinds of data: primary and secondary. Primary data was obtained from the responses of the subjects to the questionnaire. Secondary data comprised the results of histology slides screening and the current literature relating to the study.

### Sampling Technique

Selection of subjects was done randomly among patients presented to the Combined Gynaecology Clinic (CGC) at King Edward VIII Hospital. An arrangement was made for the screening of histology slides of the subjects for the presence of HPV.

Initially, the study was planned to include HIV as an infective agent, prompted by studies that have revealed some correlation between HIV and HPV. Due to time frame and the unavailability of resources, HIV had to be excluded from the study.

### Selection Criteria

Only Black women diagnosed for the first time with the disease were selected for the study. Their age ranged between twenty five (25) and sixty five (65) years. For the purpose of the study, treatment was withheld. Voluntary participation was encouraged.

### Ethical Consideration

Permission to conduct this research was obtained from the

hospital authorities and from participants. The study involved less than minimal risk. Data available was used only to gain the knowledge about the known possible predisposing factors to infection with HPV. It was later correlated to the results of the questionnaire. It was also compared with studies done in the past relating to cancer of the cervix.

#### Tool Construction

The tool was developed by the researchers as a team, since there were no tools identified to address all the aspects of this research. It contained seven sub-sections which were based on the literature reviewed by the researchers. The following sub-sections were contained in the questionnaire: 9 demographic questions, 2 questions on the history of pregnancy, 4 items on history of family planning, 2 items on social history, 4 items on family history, and 8 items on knowledge regarding cancer and predisposing factors to the disease. Once the activity of constructing a tool was completed, the tool was given to researchers and health professionals to assess if it was appropriate to the purpose intended for. It was found by experts to be adequate. It was then administered to a group of five subjects who were not part of the study, this was done to see if there were no problems with its use. No difficulties were identified.

#### Histopathology

Tissue for histology was obtained either as a result of surgery (when hysterectomy was done), or by the cone biopsy approach. Slides were reviewed with regard to the presence of HPV infection assessed on architectural and cytological alterations characteristic of the infection. In those cases where there was no representation of cervical epithelium with only invasive tumour tissue present, assessment of HPV infection was deferred. The architectural alterations included papillomatosis, acanthosis, parakeratosis and hyperkeratosis. The cytological alterations included koilocytosis (manifested by perinuclear cytoplasmic cavitation, nuclear enlargement and atypia) and multinucleation. Architectural alterations, in the absence of koilocytes were not considered diagnostic. The Southern Blot Hybridization (SBH) technique was used for detecting HPV DNA.

#### Validity and Reliability of this research

The researchers in this study took a number of factors into consideration in order to ensure that the results of this

research were valid and reliable. The following was ensured: A literature review was conducted to prevent duplication and to control the findings of this research study. The findings of this research were not generalised but contextualised to one hospital in Kwa Zulu Natal Province due to the small number of subjects. Not just any Black woman was included in this research, but only those who met the prescribed criteria for inclusion in the study. Triangulation was used to combine various data sources by using three researchers from radiography, a pathologist and one nurse, the design used was both descriptive and contextual; data collection strategies used were questionnaires, histopathology slides and the literature reviewed; and a panel of experts consisting of health personnel to review the tool used for data collection.

The questionnaire was based on literature reviewed. For construct validity, the tool was further given to researchers and health professionals to evaluate if it was measuring what it was intended to measure. A pilot survey was conducted among five subjects who were not part of the study and there were no problems identified with the tool.

#### Data Analysis

Descriptive statistics were used as means of data analysis.

## RESULTS

A total of fifty four (54) subjects was initially selected to participate in the study between May and June 1995. The results obtained from HPV- testing of these subjects are depicted in Tables 1 and 2. Because of the difficulty experienced in reaching all the subjects with the questionnaire, the study group was subsequently reduced to twenty five (25). Table 2 depicts results specifically for  $n=25$ . On analysis, subjects were classified according to histological diagnosis. "Diagnosis deferred" referred to those cases where the subject's slides could not be traced, where only tumour tissue was present with no evidence of epithelium, or those cases where there was no cervical tissue present.

The ratio of HPV infection was 3.5:1 with 51.9% of subjects being HPV positive, 18.5% HPV-negative and 29.6% with deferred diagnosis. The mean age was found to be 43.76 years although this was of no significance to the study. A considerably significant finding was that the geographical

**Table 1:** Exhibiting the results obtained on screening for HPV (n=25)

	Squamous cells carcinoma	Adeno squamous carcinoma	Adeno carcinoma	Undifferentiated carcinoma	Total 100% (25)
HPV infection	56% (14)	0% (0)	8% (0)	0% (0)	64% (16)
No HPV infection	16% (4)	0% (0)	4% (1)	0% (0)	20% (5)
Diagnosis deferred	16% (4)	0% (0)	0% (0)	0% (0)	16% (4)
Total 100%	88% (22)	0% (0)	12% (3)	0% (0)	

distribution of participants yielded results which revealed that most subjects 96% were born and (grew up) in rural areas. Results also showed that 68% of the subjects still reside in rural areas with the remaining percentage now living in the townships. Marital status did not yield results of significant difference with only 44% of respondents single and 40% married.

The majority (84% of the subject group) were Zulus which may suggest bias due to the fact that the study was conducted in KwaZulu/Natal where the majority of the black population is Zulu. There was no evidence of previous exposure to drugs. A significant percentage of the subject group had no history of contraceptive usage.

The majority of the subjects had had early / first coitus between the ages of fifteen and twenty. More than half of the subject group had had more than one sexual partner. From the married group (including divorced) ( $n=12$ ), 92.3% had wed uncircumcised husbands. Furthermore, 53.8% of these individuals remain married to polygamous husbands.

**Knowledge of subjects' about the disease:**

In testing the subjects knowledge of the disease, the following emerged (as shown in Table 2): About 72% were aware of the fact that cancer is a fatal disease as compared with the 16% who believed cancer is not a fatal disease. As to the prevention of the disease, most of the subjects believed the disease can be prevented. In terms of the curability of the

disease, more than half of the subjects believe it can be cured provided it is diagnosed in its early stages. Relatively fewer subjects believe it is not safe to have multiple sexual partners. Results also indicated that most subjects acknowledged the importance of having pap smears or gynaecological examinations performed, but on interviewing these individuals it was established that none of them had ever had these tests done routinely. About 72% were aware of the fact that infection with certain types of viruses can predispose to the development of cancer.

**DISCUSSION**

HPV infection has been shown to be linked with Cervical Intra-epithelial Neoplasia (CIN), cervical cancer and similar changes in the vulval and vaginal epithelium (Bloch & Dehaeck, 1987:557). In this study, this became evident, considering that 64% of the study group were proved to be HPV positive whilst 16% were found to be negative. From this statistical difference it may well be accepted that most women with cancer of the cervix are infected with HPV which in turn may have led to the development of cancer. HPV usually affects epithelia (Specter & Lancz, 1986:373) and from the results (see Table 1 & 2) it was shown that most of the subjects had squamous cell carcinoma more than any other form of histological diagnosis.

**Table 2.** Distribution of subject knowledge and awareness of the disease

Statements about Cancer of the Cervix	Strongly Agree	Agree	Uncertain	Disagree	Strongly Disagree
Cancer of the cervix is fatal	18 (72%)	3 (12%)	4 (16%)	-	-
Cancer of the cervix can be prevented	7 (28%)	3 (12%)	11 (44%)	2 (8%)	2 (8%)
Cancer of the cervix can be cured if diagnosed early	14 (56%)	4 (16%)	7 (28%)	-	-
It is safe to have sex at an early age	-	-	5 (20%)	6 (25%)	14 (56%)
One can have many sexual partners and its safe	-	-	-	-	25 (100%)
Smoking does not predispose to cancer	5 (20%)	2 (8%)	5 (20%)	5 (20%)	8 (32%)
It is very important to have tests or papsmear done even if one does not suspect any disease	19 (76%)	1 (4%)	3 (12%)	1 (4%)	1 (4%)

Currently available data gives certain factors as possibly predisposing to HPV infection:

- (i) possible sexual transmission due to the fact that infection of the genital mucosa and genitals is increasing and involves thousands of new cases each year, usually among sexually promiscuous individuals (Zuckerman; Banatvala & Pattison, 1990:534);
- (ii) high risk factors viz-a-viz early commencement of sexual activity, early marriage, multiple sexual partners, multiple marriages, smoking and straw mattresses (Bloch, 1989);
- (iii) certain individuals with a rare autosomal recessive disease-epidermodysplasia verruciformis (EV)-harbour a number of virus types not found in normal people, among which is HPV (Zuckerman, *et al.* 1990:534);
- (iv) the virus is also commonly found in warts on the skin of individuals in the meat industry especially those handling fresh carcasses (Zuckerman, *et al.* 1990:534);
- (v) transplanted individuals experience either new infections or reactivation of persistent virus as stated by Zuckerman *et al.* (1990:534);
- (vi) as given by Smith and Ritchie (1980:157), transmission is the same as other viruses i.e. they may be transmitted vertically from parent to offspring or they may be arthropod-borne.

Results also showed that 96% (n=24) of the women interviewed came from the rural areas. It is thus debatable whether there is some viral aetiology associated with lifestyles in rural areas. This may also be related to the fact that most women in rural areas have husbands or sexual partners who work and stay away from home. It has been shown in a study done in Addington Hospital (Durban), that, due to the negative effects of socio-economic and cultural factors such as male promiscuity, unemployment, lack of social and recreational facilities, and also the migratory nature of the work force, there is a high incidence of sexually transmitted diseases in males (Govind, 1986:35). These men can therefore act as a reservoir for re-infection of their wives or sexual partners when they return home.

The results confirmed that no statistically significant difference existed between married 40% (n=10) and unmarried 44% (n=11) subjects. This may be due to the fact that in today's society, married women are as sexually active as their single counterparts. Another important fact (although this was not statistically proven) is that it is possible that most single women tend to have more than one sexual partner which, therefore, increases the risk of infection.

The statistical difference according to ethnic distribution may not be considered to be of significance since the study was conducted in an area occupied predominately by Zulus. Previous exposure to drugs or people using drugs did not prove to be a predisposing factor in this study. Smoking has been documented as one of the high risk factors in females (Bloch, 1989). Early commencement of sexual activity was shown to be among the predisposing factors to infection since 56% (n=14) of the subject group had first coitus between fifteen and twenty years of age.

Results contradicted those of studies conducted as early as 1964 (Charlewood, 1972:343, 346) that dismissed circumcision as a major etiological factor causative of cancer of the cervix. In this study it was shown that more than half of the married subjects had uncircumcised husbands. Non-circumcision may render certain individuals unhygienic thus providing a reservoir for the virus in males. Nevertheless, it remains debatable as to whether circumcision increases the risk of infection on its own, whether, it depends on other factors such as sexual behaviour. This is because in certain races where

circumcision is not practised traditionally (eg. Indians), but sexual behaviour differs from that of Blacks, the incidence of cancer of the cervix is not as high. It may therefore be possible that these individuals do harbour HPV but rarely develop cancer of the cervix. The role of circumcision in predisposing to HPV infection could be verified if in future studies are done on individuals who do not have cancer of the cervix but have sexual partners who do not traditionally, practice circumcision.

Subjects showed some knowledge about the disease, but it became evident in this study that the knowledge they have is knowledge they acquire after diagnosis. In terms of prevention of the disease, provided that certain measures are taken, most subjects were uncertain of this as a possibility. Prevention of the disease emanates from within the context of observing the predisposing factors so that one is not prone to developing the disease. With the results showing that most subjects acquire knowledge after diagnosis of the disease, it is recommended that, in future screening of knowledge and awareness of the disease be applied to people who do not have the disease.

Results showed that most subjects are aware of the importance of gynaecological examinations even if there are no signs of the disease present. However it was also established that none of these subjects ever had any of the gynaecological examinations done routinely without being compelled by the presence of the disease. There are two debatable possibilities to explain this :

- i) they may not have had these tests done because of the lack of facilities in the rural areas, or
  - ii) if these facilities were available and within reach, they ignored the importance of using them.
- Educational and screening programme implementation may address both sides of the coin. These programmes may reach to the unreached and at the same time encourage those who are negligent to appreciate the importance of having these tests done.

## LIMITATIONS

Due to the fact that the sample size of this research was too small to generalize from the findings to the total population in KwaZulu-Natal Province, the results were contextualised within a single institution. There is a need for follow up research to validate the findings of this research.

## RECOMMENDATIONS

The recommendations in this study were discussed in two broad sub-headings. The researchers felt that the planning of educational programmes and future research were major areas to be addressed.

### Educational Programmes

For any programme aimed at reducing the high prevalence of this virus to succeed, the disciplines of Virology, Pathology, Oncology, Obstetrics & Gynaecology and nursing must be harnessed and employed in concert. In light of the above-mentioned, it is well worth considering the fact that, in the area where the study was conducted numerous projects are underway regarding the primary health care approach. Furthermore, primary health care centres are in the process of being built. Therefore, these programmes may well become incorporated into these centres.

## Future Research

It is recommended that future research be aimed at identifying the role of HIV in patients with cancer of the cervix as some correlation between HIV and HPV, and HIV and cancer of the cervix has been documented (Tweddel, *et al.* 1994:161 & Van Doornum, *et al.* 1993:185). Such research may determine whether or not the same causative factors responsible for HPV are to a considerable degree related to those of HIV. Future research should also include individuals not infected with the disease (cancer of the cervix) in order to document the prevalence of HPV in these individuals.

## CONCLUSION

Early detection of the virus through the knowledge of the predisposing factors to infection should result in a decrease in the number of women afflicted with this disease in its late stage, bearing in mind that treatment only gives poor prognosis.

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