Roles of human papillomavirus (HPV) and human immunodeficiecy virus (HIV) in Cervix Uteri Cancer

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Skrevet av: Gilbert B. Moatshe kull -97

Veileder: Bjørn Straume

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ABSTRACT

Cervical cancer is the most common cancer among women in the developing countries. In the developed countries it is a different picture, a decline in incidence and mortality rates of cervical cancer has been observed from the late 1960's and 1970's. This decline is attributable to screening for pre-malignant conditions in the cervix using cytology/Papanicolaou smears and treating them before they become invasive. Most of the developing countries, if not all, do not have organised screening programs for cervical cancer.

Several factors have been associated with increased risk of cervical cancer, including; HPV infection, smoking, high parity, use of oral contraceptives, early sexual debut, multiple sex partners and having other lower genital tract infections such as herpes simplex virus type 2. Infection with high-risk human papillomavirus (HPV) seems to play a central role in the development of cervical neoplasia, with human papillomavirus (HPV) being a necessary but not sufficient cause of cervical cancer. Since the early 1990's, increased risk of cervical neoplasia was observed among women infected with human immunodeficiemcy virus (HIV). In 1993 the Centre for Disease Control in Atlanta, USA included cervical cancer among AIDS defining illnesses in HIV infected women.

HIV prevalence is high in most developing countries, especially in Africa south of the Sahara. These are the countries that also have high incidence and prevalence rates of cervical cancer. In this paper I look at the roles of human papillomavirus (HPV) and human immunodeficiency virus (HIV) in pathogenesis of cervical cancer. Several studies indicate that human papillomavirus (HPV) is the etiologic agent of cervical neoplasia and human immunodeficiency virus (HIV) infection increases the risk of cervical neoplasia.

Data from Botswana, a developing country in southern Africa, was analysed to see if it supports the studies that have shown increased risk of cervical cancer among HIV-infected

women. The data was collected from the Central Statistics Office, which keeps records of all health statistics in the country. The aim was to see if incidence and prevalence of cervical cancer has increased in the wake of outbreak of HIV infection, and to se which age groups are mostly affected. Data was also collected from Gaborone Private Hospital – Oncology department, a local private hospital in the capital of Botswana. This data was analysed to see what proportion of women treated there for cervical cancer were HIV-seropositive; age difference between HIV-seropositive women and HIV-seronegative women; if HIV-seropositve women presented with advanced disease (advanced disease in this case being FIGO stage III and IV) when compared to HIV-seronegative women; and if elderly women presented with advanced disease (advanced disease in this case being FIGO stage III and IV) when compared to younger women. Older women in this case were 55 years and above, and younger women were below 45 years of age.

The number of consultations and hospital admissions with diagnosis 'cervical cancer' increased between the time periods 1980-1986 and 1990-1998. Since the Central Statistics Office recorded the number of admissions where patients suffered from cervical cancer and not persons, the actual incidence and prevalence was not known. It is assumed though that the observed increase is because of increasing incidence of cervical cancer between the two periods, but it could also be due to increasing population or easier access to hospitals in the period 1990-1998 compared to the period 1980-1986.

Data from Gaborone Private Hospital suggests that HIV-seropositive women present with cervical cancer at an earlier age than HIV-seronegative women (mean ages: 42.8 +/- 11.7 years for HIV-seropositive and 56.4 +/- 12.6 years for HIV-seronegative women). HIV-seropositive women do not have advanced disease when compared to HIV-seronegative women. 8 of the 13 (61.5%) stage IV cases were HIV-seronegative compared to only 1 (7.7%) who was HIV-seropositive. The other 4 patients who had stage IV were of unknown

HIV-serostatus. A total of 38 women had stage III cervical cancer and of these, 18 (47.4%) were HIV seronegative, 16 (42.1%) were HIV-seropositive and 4 (10.5%) were of unknown HIV-serostatus.

51 women had advanced disease (stage III and stage IV). 19 (37.3%) of these women were below the age of 45 years and 20 (39.2%) were 55 years and above.

In conclusion: some increase in cases of cervical cancer has been reported in Botswana but this increase cannot be attributable to increasing HIV infection rates.

HIV-seropositive women present with cervical cancer at an earlier age when compared to HIV-seronegative women. This could suggest faster progression from pre-invasive lesions to invasive cervical cancer in HIV-seropositive women compared to HIV-seronegative women. The disease stage was the same in both groups and age did not affect the stage of the disease.

1. INTRODUCTION

In the developing world, more women die from cervical cancer than any other form of cancer. Worldwide, there are at about 450 000 new cases of cervical cancer per year, and about 250 000 women die each year from the disease. 80 percent of cervical cancer cases occur in developing countries [1]. Since cervical cancer generally develops slowly and has a readily detectable and treatable precursor condition (dysplasia, CIN I – III), it can be prevented through screening. Many Western countries have managed to reduce the incidence and mortality of invasive cervical cancer by as much as 70 percent through screening programmes based on routine cytological examination of Papanicolaou (Pap) smears, and treatment of pre-cancerous conditions [2]. In Norway it has been said that mortality of cervical cancer can be reduced by at least 50 percent through a screening programme. There are those who argue that

mass screening for cervical cancer is not scientifically justifiable [**3**]. They argue that the methods used to support screening are based on assumptions that incidence rate and mortality rates are constant over time, such that other factors that are known to play a role in the pathogenesis of cervical cancer should be taken into consideration. One of those factors is the general decrease in parity observed in the western world.

The same reductions in incidence and mortality rates have not been accomplished in developing countries since most do not have organised screening. Reason for failure to implement screening programmes can be grouped in to two: client barriers and system barriers.

Client barriers include inadequate knowledge of cervical cancer, and purposes of Pap smear tests, embarassment with test, fear of death and pain, culture, beliefs, values, and individual beliefs related to cervical cancer and Pap smear screening. Other barriers include, ethnicity, age, level of education, socio-economic status, distance from health facility and time constraints due to family and work resposibilities [**4**]. It can be noted at this point that in USA it was observed that cervical cancer was still more prevalent among ethnic minorities, African-Americans and Latin Americans, who respond poorly to screening programmes primarily because of financial and cultural barriers [**5**].

System barriers include ineffective health policies, inadequate or inaccessible health services [**4**]. Others are shortage of staff, and financial constraints.

Because of the above stated reasons, most of the cervical cancer cases found in developing countries are found at a late stage if they ever get diagnosed at all. Mass screening has been

found to be more cost effective than opportunistic testing in reducing mortality from cervical cancer.

Some 'cheaper' methods have been suggested for use in low cost setting to screen for pre-cancerous lesions in the cervix. These include:

- Targeting older women (age 35 years and older)
- Screening all at-risk women relatively infrequently (for instance, every 10 years)
- Treating only women with severe dysplasia, based on the recognition that most mild dysplasia does not progress to more severe disease.
- Using relatively inexpensive outpatient treatment techniques to eradicate cervical lesions.
- Aided Visual Inspection (AVI). Using a simple magnifying glass to view cervices treated with acetic acid solution to highlight abnormal tissue, alone or with back-up cytology to identify high-grade dysplasia.

The prevalence of HIV is high in many of the developing countries especially in Africa south of the Sahara. If, as some studies suggest, HIV increases the risk of invasive cervical cancer we could expect an increase in the incidence of invasive cervical cancer in those countries. Botswana is a country in southern Africa with one of the highest HIV prevalence rates in the world according to UNAIDS reports [**6**]. Considering that cervical cancer is one of the most common cancers among women in the developing world, and its association with HIV, I was interested in looking at the roles of human papillomavirus (HPV) and human immunodeficiency virus (HIV) in cervical cancer. I searched the published literature on the subject and also looked at epidemiological trends in Botswana, how cervical cancer incidence and prevalence rates have changed over time, and especially in the wake of high HIV prevalence.

I use data from a private hospital in Gaborone to find out if there is an association between cervical cancer and human immunodeficiency virus infection.

2. BACKGROUND

Cervical tumorigenesis is believed to be a multi-step process following HPV infection. It is believe to follow a regular pattern with initial HPV infection followed by persistence of virus expression, and eventually resulting in well-defined cellular changes, which can end up with invasive cervical cancer (Figure 1) [7]. Progression from CIN to invasive cervical cancer takes about 10-20 years. Since not all HPV infections lead to invasive cervical cancer, other factors must be at play.

2.1 Cervical Intraepithelial Neoplasia

These are precursor lesions to cervical cancer. These lesions are characterised by cytological atypia and abnormal cellular proliferation. Cytological abnormalities include hyperchromatic nuclei, abnormal chromatin distribution and increased nuclear:cytoplasmic ratio (N/C ratio). Lesions are graded from I – III (1-3) based on the thickness of the abnormality involving the mucosa. CIN I affects the lower 1/3 of the epithelium, CIN II 2/3 of the epithelium and CIN III the whole epithelial thickness without the abnormal cells breaching the basement membrane. CIN III is often referred to as carcinoma in situ.

Cervical dysplasias can also be classified using the Bethesda classification system; low-grade squamous intraepithelial lesions (SIL) encompass mild dysplasia/cervical intraepithelial neoplasia (CIN) I and koilocytic change induced by HPV; high-grade squamous intraepithelial lesions include moderate dysplasia (CIN II) and severe dysplasia (CIN III).

2.2 Cervical cancer

Cervical cancer is characterised by an infiltration of neoplastic cells through the basal membrane into the surrounding tissues (stroma). Different histologic types have been described. Squamous cell carcinoma is the most common, accounting for about 80-90% of all the cases of cervical cancer, and adenocarcinoma (originating from the columnar epithelium of the cervix) account for about 8-10% of the cases. 2-5% are classified as adeno-squamous carcinoma and 2% are rare tumours such as small cell neuroendocrine tumours, sarcomas and melanomas.

Cervical cancer is usually staged using International Federation of Gynaecology and Obstetrics (FIGO) staging, which is based on the extent of invasion and spread of cancer.

2.3 Risk factors for cervical neoplasia

Several factors have been postulated to increase the risk of cervical cancer, and these include:

- Parity: Muñoz et al, found that there is a direct association between the number of full term pregnancies and squamous cell cancer risk: OR for seven full term pregnancies or more is 3.8 (95% CI 2.7-5.5) compared with nulliparous women, and 2.3 (1.6-3.2) compared with women who had one or two full-term pregnancies [**8**].

- Use of oral contraceptives: Long-term use of oral contraceptives could be a cofactor that increases the risk of cervical carcinoma. Some had suggested that the increased risk could be due to low use of barrier contraceptives in women who use oral contraceptives and thus leaving them at risk of contracting human papillomavirus. Moreno et al, found that long term use of oral contraceptives increases the risk of cervical cancer by up to four-fold in women who are positive for cervical HPV DNA. Compared with never-users, patients

who had used oral contraceptives for fewer than 5 years did not have increased risk of cervical cancer (OR 0.73; 95% CI 0.53-1.03). The OR for use of oral contraceptives was 2.82 (95% CI 1.46-5.42) for 5-9 years, and 4.03 (2.09-8.02) for use for 10 years or longer [9].

- Smoking

- Other microbial agents such as herpes simplex virus type 2 (HSV-2) and Chlamydia trachomatis.

- Genetic susceptibility: it is postulated that certain individuals have increased risk of getting cancer (cervical cancer included) because of their genotype [7]

- Immune status of patient: the host immune response, particularly cellular immunity is an important factor in the incidence of infection, and outcome (regression, persistence or progression) of HPV-associated lesions. Persons with altered cellular immune response show an increased incidence of HPV infection and malignant conversion of HPV-associated lesions, as can be seen in patients with genodermatosis epidermodysplasia verruciformis [**10**], and organ transplant recipients receiving immunosuppressive drugs [**11**]. An increased incidence of genital HPV infection in HIV-infected individuals has been observed since mid 1980's [**12**]. Increased incidence of squamous intraepithelial lesions (SIL) has also been observed in HIV-infected women. The relationship between HIV serostatus and invasive cervical cancer is not conclusive since different studies have different observations.

- Dietary factors: insufficient intake of vitamin A, vitamin C, folate and riboflavin have been associated with increased risk of cervical neoplasia.

- Infection with human papillomavirus [**13**].

2.4 Human papillomavirus (HPV) and cervical neoplasia

Human papillomavirus (HPV) is now considered to play a central role in the pathogenesis of cervical cancer. The worldwide prevalence of HPV in cervical carcinomas has been found to be 99.7% [**13**]. HPV are small DNA viruses that cause benign and malignant epithelial proliferations. There are about 80 known types of HPV, 30-40 of which may infect the ano-genital area causing an array of diseases, ranging from asymptomatic infection, benign proliferations to invasive cancers (see Table 2) [**14**]. Certain types of HPV are strongly related to cervical neoplasia, and based on the strength of their association with cervical neoplasia, they can be put into different risk categories; high risk: types 16, 18, 31, 45 (each found in at least 5% of invasive cancers, with type 16 found in 50% of cervical cancers, and types 18, 31 and 45 in another 30% of cervical cancers); intermediate risk: types 33, 35, 39, 51, 52, 56, 58, 59 and 68 (each found in 1-5% of invasive cervical cancers); low risk: types 6, 11, 42, 43, 44 and many others (rarely found in invasive cervical cancers) [**13**,**15**].

HPV prevalence in women varies according to age group and sexual behaviour. Younger women have higher prevalence (range 20-46%) compared to older women (3-15%). In a Norwegian study, HPV was found in 15% of women aged between 20-44 years [**16**]. A Finnish study estimated that about 70% of all women would have an HPV infection sometime in their life [**17**]. Most HPV infections are transient in nature and only 2-3% of women develop dysplasia. Ho et al found the 36-month incidence of HPV infection to be 43% (confidence interval 36-49%); the median duration of incident infection to be 8 months

(range: 95% CI: 7-10 months), with rates of persistence of only 30% after 1 year and 9% after 2 years among college female students [**18**]. Low grade squamous intra epithelial lesions are attributed to both high and low risk types of HPV, with 30% of lesions having more than 1 type of HPV, and less than 10% of lesions having only low risk type HPV. About 25% of low grade lesions will progress to high-grade lesions, with most regressing spontaneously [**19**]. A question then arises as to which low-grade lesions progress to high-grade lesions and which ones regress. One can also wonder why only 2-3%of women develop dysplasia while HPV infection in the general population is higher. It has been suggested that even though HPV is necessary for development of cervical cancer, it is not the lone cause, suggesting that there should be other factors acting in concert with HPV.

HPV is strictly epitheliotrophic and tissue specific, with mucosal and cutaneous types forming two distinct groups. The HPV virus targets receptors on the epithelial cells, a possible candidate being alpha-6beta-4 integrin receptor [**20**]. After entry into the basal cells of the epithelium, the virus multiplies in the nuclei of the infected cells. The majority of people manage to clear the infection without any clinical disease. Most of those who develop lesions manage to mount a cell-mediated immune response regulated by CD4 T-cell dependent mechanism, with subsequent regression of the lesion. Natural killer cells and antigen specific cytotoxic T lymphocytes seem to have a role in combating the infection but it still unclear. Antibodies against the major virus protein L1, do not seem to have a protective value as is the case in animals [**21**]. It appears the antibodies are lost immediately after resolution of productive infection.

Persistent viral infection ensues if the cell-mediated response fails to clear the viral infection and induce lesion regression. Integration of the viral genome into the host genome with the

subsequent disruption of the E1 or E2 reading frames and survival of epithelial cells containing this viral DNA is the postulated mechanism of development of high grade SIL. Viral E1 protein has a helicase activity that is important for viral DNA replication. Viral E2 protein is a DNA binding protein involved in regulation of viral transcription. Integration of the viral genome into the host cellular genome appears to be the hallmark of viral infection persistence and progression of lesions. Viral genome integration typically occurs within the viral E1 or E2 genes. Disruption of the E1 or E2 genes during viral integration allows for dysregulated expression of the E6 and E7 viral oncoproteins.

E6 oncoprotein inactivates the p53 tumour suppressor protein and enhances telomerase activity. P53 protein functions as a transcriptional activator that regulates the expression of growth suppressor proteins including cell cycle inhibitory protein, p21, and a repressor of p53. It is responsible for mediating cellular growth arrest in response to DNA damage and growth factor deprivation. It also regulates apoptosis in cells that have undergone irreparable injury. When the function of p53 is disrupted by E6 protein, genomic abnormalities in cells infected with HPV (where HPV genome is integrated into the host cellular genome) cannot be controlled and they persist. Other mutations that could lead to cancer may occur and persist in the absence of p53-protein control.

E7 oncoprotein is able to form complexes with several host cellular proteins including retinoblastoma tumour suppressor gene product (pRb) leading to their inactivation. The hypophosphorylated form of retinoblastoma protein is known to form complexes with the transcription factor E2F and inhibit its ability to transactivate genes. E7 disrupts the function of retinoblastoma protein in inhibiting E2F transcription factor resulting in the release of transcriptionally active E2F that is able to induce transcription of growth related proteins. High-risk E7 protein have also been found to up-regulate the G1-S cyclins, cyclin A and cyclin E, and to activate cyclin dependent kinase 2 (cdk2). Cyclin/cyclin-dependent kinase

complex control the phosphorylation events of the retinoblastoma gene product and its subsequent functions. Cyclin-dependent kinase inhibitory protein (CKI) can be inhibited by E7 oncoprotein. E7 oncoprotein seems to bypass the G1-S checkpoint in the cell cycle [**22**].

The high-risk types of HPV have more efficient E6 and E7 molecules. Integration of the HPV genome denotes irreversibility, with between 33% and 50% eventually progressing to cervical cancer [**20**].

It is postulated that high-grade squamous intraepithelial lesions may originate from mild dysplasia or may arise directly from infection by high risk HPV [**23**]. High-grade SIL contain high-risk HPV genotypes in 90% of cases, with high expression of oncoproteins E6 and E7. The oncogenic potential of the HPV type (i.e. different HPV types have different potential to cause cancer, thus categorised as high risk and low risk types) is a well established factor. The viral load appears to have a role to play [**24,25**].

2.5 Human papilloma virus (HPV) and human immunodeficiency virus (HIV)

Co-infection with HPV and HIV could be expected because of similar risk factors for contacting the viruses, including among others; multiple sex partners, early age of first coitus, low use of barrier contraceptives and low socio-economic status. Some studies have shown the incidence of HPV to be higher in HIV positive women compared HIV negative women. These infections often contain multiple HPV genotypes [**26, 27, 28**]

HIV is believed to alter the natural history of HPV progression [**29**]. In the setting of HIV infection, regression of low grade lesions is about 27% (compared to 60% in HIV uninfected women) and the occurrence of cervical cancer in young women with HIV infection suggest rapid progression [**30-33**]. Maiman et al found the lesions in the HIV positive patients to be more extensive with multi-site involvement [**30**]. There are differing views on the effect of

degree of immunosuppression on the evolution of cervical abnormalities. According to Cardillo, et al the degree of immunosuppression appear to contribute to the development of intraepithelial lesions, but once the lesions have been established, the disease progression seem not to have an association with the patients' CD4 T-cell count [**34**]. In the Women's Interagency HIV Study it was found that cervical cytology abnormalities were frequent among HIV positive women, but high-grade lesions were found in only 2.5%. Risk factors for abnormal cytology included; CD4 T-cell count, HIV RNA level, detection of HPV, prior history of abnormal cytology and number of male sex partners in 6 month of enrolment. Progression is significantly increased in the most immunosuppressed (CD4 lymphocyte count < 200/mm3) women while regression is significantly reduced in all HIV sero-positive women except those with the best controlled HIV disease. Rates of incidence, progression, and regression of abnormal cytology did not differ between HIV seronegative women and seropositive women with CD4 lymphocyte counts >200/mm3 and HIV RNA levels <4000/ml of similar HPV status [**35**, **36**].

Even though the relationship between HIV and cervical dysplasia (pre-stadia for cervical cancer) has been established, the relationship between HIV and invasive cervical cancer is more controversial. In 1993 CDC declared invasive cervical cancer an AIDS defining illness in women infected with HIV. In 1993 Klevens, et al found that 1.3% of women 13 years and older who reported with AIDS had invasive cervical cancer [**37**]. HIV related cervical cancer was found to account for about 55% of AIDS related malignancies in women with AIDS related malignancies. Women with AIDS related cervical cancer tend to be less immunosuppressed (based on CD4+ cell count) than women with other HIV related malignancies, and sometimes the diagnosis of cervical cancer preceded the diagnosis of AIDS [**38**], something which has led some to believe that cervical lesions predispose these women

to contact HIV. Fruchter et al ' s study was not conclusive as to whether HIV infection is a risk factor for advanced cervical cancer [**39**] while other studies in USA and Italy found clearly increased rates of cervical cancer in women with HIV [**40, 41**]. Epidemiological studies in South Africa in 1997 and Kenya in 2001 did not show proportional increase in incidence of cervical cancer in the wake of increasing HIV prevalence in these countries [**42, 43**]. A late study done by Sitas in South Africa showed a significant excess risk of cervical cancer in HIV positive women [**44**].

2.6 Molecular pathogenesis

AIDS related cervical cancer cannot be sorely attributed to immunodeficiency, unlike other AIDS related malignancies such as Kaposis' sarcoma, Non-Hodgkin's Lymphoma. Several mechanisms have been postulated to explain AIDS related cervical cancer.

Tumour progression: two pathways for tomorigenesis have been postulated; loss of suppressor genes, referred to as the loss of heterozygosity (LOH) pathway, and genetic instability at microsatelite loci, which is believed to arise as a result of defects in the mismatch repair (MMR) genes making them unable to repair slippage errors that occur during replication. In cervical cancer, loss of tumour suppressor genes seems to be the usual pathway of progression through E6 and E7 proteins [**20**], while microsatelite instability (MSI) is not common [**45**]. Increased rate of microsatelite instability (MSI) has been described in a number of HIV related malignancies including Kaposi's sarcoma, Non-Hodgkin's lymphoma, anal intraepithelial neoplasia and HIV related lung cancer, and HIV related CIN lesions [**46**,**47**].

CD4:CD8 ratio: CD8 cells are increased in CIN lesions [**48**], but an inverse (decrease) in CD4:CD8 ratio is seen in CIN lesions of HIV positive patients, something which suggest that

in the setting of HIV infection the CD4 cells might be ineffective in activating the recruited CD8 T cytotoxic cells [**49**]. This is not really surprising considering that HIV infects CD4+ cells.

The low CD4 count in AIDS patient might favour progression of cervical lesions since regression of cervical dysplasia appears to be mediated by cell-mediated immunity particularly Th1 lymphocytes and macrophages.

Th Cell profile: Lymphocyte protection against viral infection, HPV in this case, and associated neoplasms is mediated by Th1 cells and impaired by Th2 cells. IL-2 (secreted by Th1 cells) have been shown to be decreased and IL-4 and IL-10 (secreted by Th2 cells) to be increased in proportion to HPV infection, something which has also been observed in Hodgkin's disease, renal cell carcinoma, gliomas and HIV positive asymptomatic women. It has been suggested that this Th2 profile is associated with persistence of viral infections and the development of neoplasms [**50**], but it remains to be determined which one is the cause of the other.

Langerhans Cells: these are antigen-presenting cells in the cervical squamous epithelium. They have been found to be significantly decreased in number in CIN lesions of HIV patients [**51**]. HIV may directly deplete or affect their function, as it is known that HIV targets cells of the macrophage-monocyte lineage. This finding may explain persistence of HPV in the cervix and increased rate of progression seen in HIV positive patients. HPV itself might affect Langerhans cells.

HPV-HIV interaction: HIV and HPV infect different cells; HIV infects CD4+ cells which include infiltrating lymphocytes and local macrophage lineage cells while HPV infects

epithelial cells, therefore interaction between these two viruses should be mediated by soluble factors such as cytokines or through viral transactivator factors such as *tat* [**52,53**]. *Tat* and *rev* are two control mechanisms for viral gene expression found in HIV. *Tat* protein enhances the transcription of viral genes, whereas *rev* acts post transcriptionally shuttling viral mRNA from the nucleus to the cytoplasm. These proteins appear to modify HPV expression e.g. exposure to *tat* protein has been found to increase the expression of E1 and L1 genes [**52**], increase E2 dependent HPV-16 transcription, and long controlled region transactivation and increased HPV E7 expression [**52,55**].

3. MATERIALS AND METHODS

Health facilities in Botswana send patient data to the Central Statistics Office (CSO) in Gaborone where all health information is compiled. Most of cervical cancer patients are seen in the two referral hospitals, Nyangabgwe and Princess Marina Hospitals, which are run by the government. There is a private hospital in Gaborone, Gaborone Private Hospital, which was built in 1991, has 132 beds and offers a range of medical and surgical specialities. The hospital is not accessible to the majority of the population because it is expensive to be treated there. Since the government hospitals do not have radiation oncology departments, patients diagnosed with cervical cancer who need radiation therapy are either transferred to South Africa or to Gaborone Private Hospital, with the government covering the expenses.
The data used in this report was obtained from the Central Statistics Office (CSO), where all cervical cancer patients diagnosed in all government health facilities are reported, health statistics reports (written by CSO), Department of Epidemiology and Disease Control, Gaborone Private Hospital – Oncology department. Information on cervical cancer cases

reported from 1981-1999 was obtained from the Central Statistics Office (CSO). The data from the Central Statistics Office (CSO) gives the morbidity and mortality rates of cervical cancer by age and by profession. Unfortunately it does not contain other information such as FIGO staging of cervical cancer, socio-demographic characteristics, HIV serostatus, parity or any known risk factors. The data reported to the Central Statistics Office, which is obtained from government health facilities is based on consultations. In the case of cervical cancer, the Central Statistics Office gets the number of admissions and discharges for patients with cervical cancer. This kind of data recording does not say anything on whether the admissions were for the first time or whether the person had been admitted earlier. Since some of the patients might have been admitted in the hospitals more than once a year, it makes it difficult to know the exact number of people with the diagnosis 'cancer of the cervix' and hence difficult to calculate the incidence and prevalence rates. One can assume that an increase in the number of admissions reflects the actual increase in incidence and a reduction in number of admissions to reflect an actual decrease in incidence, but this assumption carries in itself several errors.

From Gaborone Private Hospital I was able to get data on cervical cancer patients seen in the oncology department in the period April 2001-April 2002. The information contained age, parity, HIV serostatus, FIGO staging of cervical cancer. The data from Gaborone Private Hospital was obtained from patients' records.

Literature was found mostly in journals, textbooks and Pub Med.

In the first part of the report the information from Central Statistics Office is used to see how the cervical cancer incidence has changed over time, and whether there is a significance increase in the wake of high prevalence of HIV. There appears to have been an error in compiling data in the period 1987-1989 since there is an increase in number of cases reported

(admissions), which can not be explained, followed by a decrease in 1990 which can not be explained. One of the possible explanations is that data for that time period was entered twice. Population census was done in Botswana in 1981 and 1991, the actual values of which are used for those years, for the other years population projections were used for some calculations.

In the second part of the report I retrospectively look at data for 83 cervical cancer patients seen at Gaborone Private Hospital to see what proportion of patients seen with cervical cancer are HIV seropositive, compare age distribution of the two groups, see if HIV seropositive patients have more advanced stages of cervical cancer than HIV seronegative women.

4. RESULTS

4.1 Cervical cancer prevalence, mortality and Case Fatality Ratio (CFR) trends in Botswana

Cervical cancer is the most common genitourinary cancer among women in Botswana (Figure 2). When comparing the time periods 1982-1986 and 1990-1997, there has been an increase in number of cervical cancer cases reported (figure 3). In the period 1990-1997 the 'prevalence' fluctuates between a lowest of 43/100 000 in 1994 and a highest of 56/100 000 in 1991 (figure 4). It can be noted here as already stated in the methods part that it is the number of episodes that is recorded, not actual persons. An increase in the number of cases/episodes recorded could be a result of the increasing population in the country. The word '*prevalence*' is put in parentheses here because episodes (number of hospital admissions) were used to calculate the 'prevalence', and this might not be as the actual prevalence.

The HIV prevalence is assumed to be higher in the period 1990-1997 than in the period 1982-1986. This assumption cannot be proven since HIV testing was not done until the late 1980's

in Botswana, such that the prevalence before then is not known. This assumption carries in itself that HIV/AIDS is a new disease (syndrome).

There appears to be a moderate increase in mortality between the periods 1982-1986 and 1990-1997 but no significant increase in mortality within each time period.

Case Fatality Ratio is very low in the time period 1991-1998 (figure 4). This could be explained by the fact that cervical cancer usually progresses slowly and thus mortality from it might be lower than the incidence.

4.2 Age distribution in the country

The age group 45-54 is the one that has the highest 'prevalence' (reported episodes/hospital admissions) of cervical cancer, followed by the 35-44 age group then the 55-64 age groups (figure 5).

4.3 HIV prevalence in cervical cancer patients

27 of the 83 patients (32.5%) treated in Gaborone Private Hospital for cervical cancer were HIV-seropositive (table 3). According to UNAIDS reports based on HIV sentinel surveillance among ante-natal clinic (ANC) attendees in Botswana, HIV prevalence among this population has increased rapidly from 18.1% in 1992 to 32.4% in 1995, 38.5% in 2000 and 36.3% in 2001. In Gaborone the HIV prevalence among antenatal attendees was 39.06% in 2001 [**6**]. The prevalence of HIV among women with cervical cancer is close to that of ANC attendees. Perhaps the similarity just reflects the high prevalence of HIV in the general population and not the association between HIV and cervical cancer, or the fact that the risk factors for contraction HIV and HPV (the causal agent for cervical cancer) are similar.

4.4 Cervical cancer and HIV-serostatus

The data from Gaborone Private Hospital shows that HIV positive women tend to present with cervical cancer at an earlier age when compared to HIV negative women (figure 6 and figure 7). Mean age for HIV positive women with cervical cancer is 42.8 +/-11.7 years while the mean age for HIV seronegative women is 56.4 +/- 12.6 years. In the 2-sample t-test this difference is significant (p 0= 0.000024)

70% of women with cervical cancer who were HIV seropositive were below the age of 45 years, and 44% below the age of 40 years, compared to 23% and 7% respectively for HIV seronegative women (table 3).

The youngest person in the group was 24 years old, HIV seropositive with stage IIIB cervical cancer. These results could suggest that in HIV infected women there is faster progression from HPV infection and pre-cancerous lesions to cervical cancer.

4.5 HIV serostatus and FIGO cervical cancer stage

Only 1 (3.7%) of HIV seropositive women had stage IV cancer compared to 8 (18.6%) in HIV seronegative women. For HIV seropositive women, 10 (37%) had Stage II and 16 (59%) had Stage III, compared to 15 (35%) and 18 (42%) respectively for HIV seronegative women (table 4).

There is therefore no significant difference on the stage of cervical cancer between HIV-seropositive women and HIV-seronegative women (p= 0.9). HIV seropositive women do not have an advanced cancer stage compared to HIV seronegative women.

Since most HIV positive women do not get anti-retroviral treatment, probably most HIV positive women die from other HIV related complications such as opportunistic infections before they reach Stage IV disease.

4.6 Age and stage of cervical cancer

Advanced age does not seem to increase risk of advanced stage of cervical cancer. 5/13 (38.5%) of the patients who had stage IV cervical cancer were below the age of 45 years while 5/13 (38.5%) was above 55 years. For stage III, 14/38 (36.8%) was below the age of 45 years while 15/38 (39.5) were above the age of 55 years (table 5 and figure 9).

5. DISCUSSION

It was unfortunate that the data from Central Statistics Office (CSO) did not have several parameters so that we could be able to assess all the factors that might influence cervical cancer incidence. The only way to get some of the data including demographic data, parity, level of education would be to go back to the patient files which could take a lot of time. I was able though to get the general trends, which gives an idea of whether there is an increase or not. As already stated in the 'Methods' section, the numbers recorded in the Central Statistics Office are those of admissions and not actual persons such that multiple hospital admissions of the same person in a year would give an overestimation of the incidence rate of cervical cancer. The increased number of admissions seen between the periods 1980-1986 and 1990-1998 could be a result of actual increase in incidence of cervical cancer, or it could be because of increased accessibility to health care in the 1990's compared to the 1980s, or it could be because of the general population increase.

It might be noted here that since there is no organised screening programme, there might be under-reporting of cervical cancer cases. Most of the patients seen in the referral hospitals are already at advanced stages of the disease, this could probably be explained by the low use of Pap-smear cytology among the general population as discussed in the introduction part.

In a study done by MacFarlan-Mpotokwane in 1999, it was found that use of Pap smear and knowledge about cervical cancer was limited to those of higher socio-economic status. Some of the reason for low use of Pap smear and limited knowledge about cervical cancer included Shortage of staff and equipment and a lot of work load for the health care providers. Some felt that the nurses who man most of the clinics in Botswana lack the skills and enough knowledge about Pap-smears and cervical cancer, and the general public is not informed about cervical cancer and early detection using Pap-smears. Some feel the problem lies in the

Ministry of Health and other policy makers, which fail to see the importance of screening for cervical cancer and informing the public [**56**].

The referral system in Botswana could also result in a delay such that patients get to the referral hospitals when they are already at an advanced stage, especially for people who live in rural areas. Most of the clinics and health posts are manned by nurses (since there are few doctors in the country and most of them are in hospitals), so it could be an advantage to equip the nurses with more information/knowledge on cervical cancer and screening for cervical cancer. Other people seek alternative medicine practitioners such as traditional healers, and this might also cause a delay in seeking 'western' medicine help.

Botswana being a developing country, has limited resources, and those available are already stretched to the limit by the HIV/AIDS epidemic. It looks like most of the focus now is on combating HIV; some feel that some of the issues including cervical cancer are shoved to the back round. If there is actually an association between HIV and cervical cancer, there might be some problems ahead, considering the shortage of staff and resources as it is at the moment and the high HIV prevalence in Botswana.

HIV has been reported to make cervical cancer advance rapidly by Schwartz et al. [**57**], but this does not seem to be the explanation of advanced cases found in Botswana since the HIV seronegative women were also found to have advanced disease stages.

HIV seropositive women did not have more advanced stage than HIV-seronegative women. This could be because most HIV seropositive women do not take anti-retroviral treatment and they probably die from other opportunistic infection before they could reach an advanced stage.

No age group was at risk of advanced stage (stage III and IV) i.e. advanced disease was found in both young women and older women. One could expect younger women to have earlier

stages of the disease since most of them have better access to health care since they live and work in bigger town and are more open to seeking western medicine than the older generation. Since HIV-seropositive women present with cervical cancer at an earlier age than HIV-seronegative women, this might suggest rapid progression from HPV infection and pre-cancerous lesions to invasive cervical cancer.

The data from Gaborone Private Hospital (GPH) is not representative of the country since the sample size is small, and represents a group of people who can afford to pay the expensive services of Gaborone Private Hospital

The association between HIV and cervical cancer calls for serious measures to combat the seemingly two major diseases affection women in the reproductive age in the developing countries. The effect of these diseases on the socio-economic structure cannot be overlooked, and hopefully more emphasis will be put on addressing women health in Botswana and other developing countries.

It could be interesting to perform a prospective study to see the association between HIV infection and cervical cancer in Botswana, and take into consideration several parameters (such as parity and CD4 count), which were not looked at here.

6. CONCLUSION

The number of discharged women with diagnosis 'cervical cancer' has increased in the time periods 1980-1986 and 1990-1998. Since some women were admitted in hospitals more than once, there was an overestimation. With a certain degree of uncertainty it can be assumed that the increase in number of admissions/discharges reflects the actual increase in incidence and prevalence.

The data from Gaborone Private Hospital suggests that women with HIV infection present with cervical cancer at an earlier age compared to women who are HIV-seronegative.

HIV serostatus does not seem to have an association with the FIGO stage of cervical cancer. Advanced stage of cervical cancer was seen in both HIV seropositive and HIV seronegative women.

Older women do not have a more advanced stage of the disease than younger women.

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Table 1: FIGO staging of cervical cancer.

Stage	*Description*
0	Carcinoma in situ, Full thickness involvement of epithelium with atypical cells no sign of invasion into the stroma
I	Carcinoma strictly confined to the cervix
II	Carcinoma invading beyond the uterus, but not to the pelvic wall or the lower third of the vagina
III	Carcinoma extended to the pelvic wall. The tumour involves the lower third of the vagina. Hydronephrosis.
IV	Carcinoma extends beyond the true pelvis, or has involved the mucosa of the bladder or rectum. Distant metastasis.

Table 2: Spectrum of HPV-associated lesions

HPV group	*HPV type(s)*	*Lesions*
Mucosal		
	6,11	Genital warts, laryngeal papillomatosis
	13,32	Oral focal epithelial hyperplasia
	16	Anogenital intraepithelial neoplasia and carcinoma, oropharyngeal cancer
	18, 31, 33, 35, 39, 45, 56, 58 and more	Anogenital intraepithelial neoplasia and carcinoma
	30	Anogenital, oral, laryngeal carcinoma
	34, 40, 42	Anogenital warts, intraepithelial neoplasia
	61, 62	Anogenital intraepithelial neoplasia
	72, 73	Oral papillomas (ISP)
	72 and 73 variants	Cervical intraepithelial neoplasia
Cutaneous		
	1	Plantar warts
	2.4	Common warts
	3	Flat warts
	5, 8, 20 and many others	Benign and malignant EV lesions
	41, 48 and others	Squamous cell carcinoma (mainly ISP)
	75, 76, 77	Common warts (ISP)

Table 3: Cervical cancer cases according to age and HIV serostatus

AGE	***Number of cervical cancer cases***			
	HIV+	***HIV-***	***UNKNOWN***	***TOTAL***
<34	5	2	1	8
35-44	14	8	5	27
45-54	4	11	2	17
55-64	2	7	5	15
65+	2	15	0	16
TOTAL	27	43	13	83

Table 4: FIGO stage and HIV-serostatus

FIGO Stage	***Number of Cases***			
	HIV+	***HIV-***	***UNKNOWN***	***TOTAL***
I	0 (0)	2(4.6%)	0(0%)	2(2.4%)
II	10(37%)	15(34.9%)	5(38.5%)	30(36.1%)
III	16(59.3%)	18(41.9%)	4(4.8%)	38(45.8%)
IV	1(3.7%)	8(18.6%)	4(4.8%)	13(15.7%)
TOTAL	27(100%)	43(100%)	13(15.7%)	83(100%)

Table 5: FIGO stage of cervical cancer in the different age groups

	Number of cases according to stage				
Age	***Stage I***	***Stage II***	***Stage III***	***Stage IV***	***TOTAL***
<34	*0*	*4*	*2*	*2*	*8*
35-44	*1*	*11*	*12*	*3*	*27*
45-54	*1*	*4*	*9*	*3*	*17*
55-64	*0*	*5*	*9*	*1*	*15*
65+	*0*	*6*	*6*	*4*	*16*
TOTAL	*2*	*30*	*38*	*13*	*83*

Figure 1: Stepwise changes after infection with HPV leading to cervical cancer

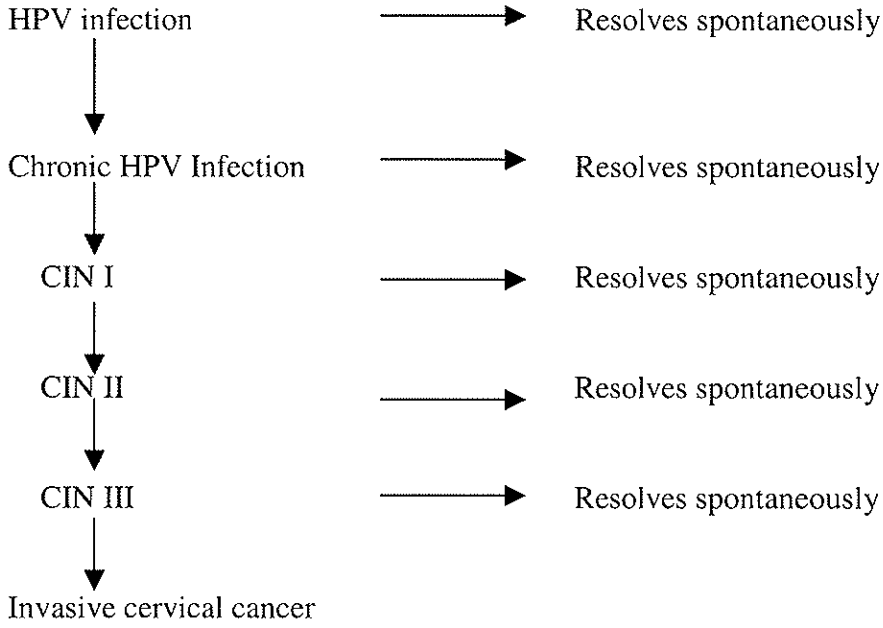

Figure 2: Cancer morbidity: Genitourinary cancers by site in Botswana

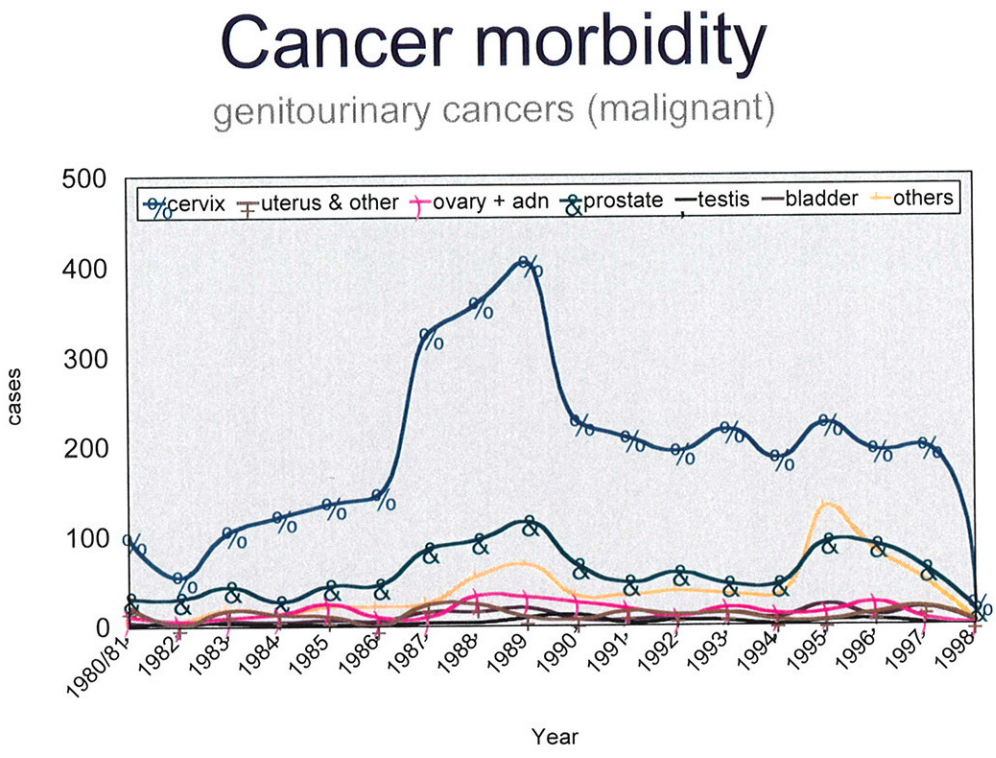

Figure 3: Cervical cancer morbidity and mortality trends (1980/81 – 1998)

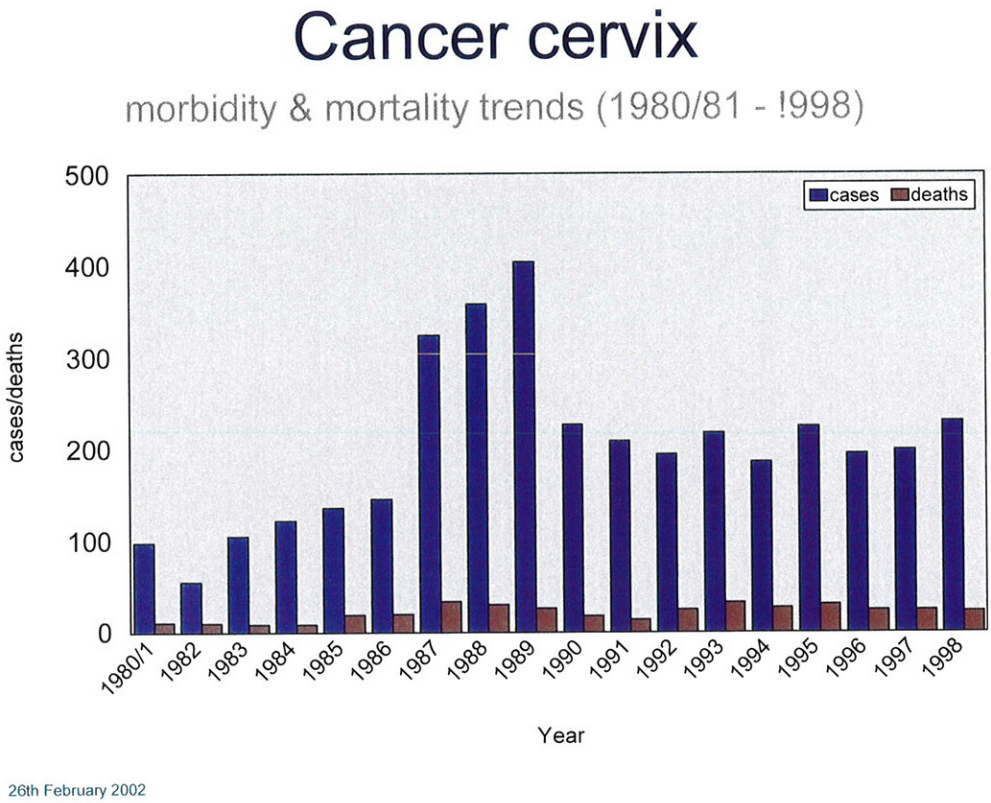

Figure 4: Cervical cancer Prevalence, Mortality and Case Fatality Ratio (CFR) in Botswana (1991 – 1998)

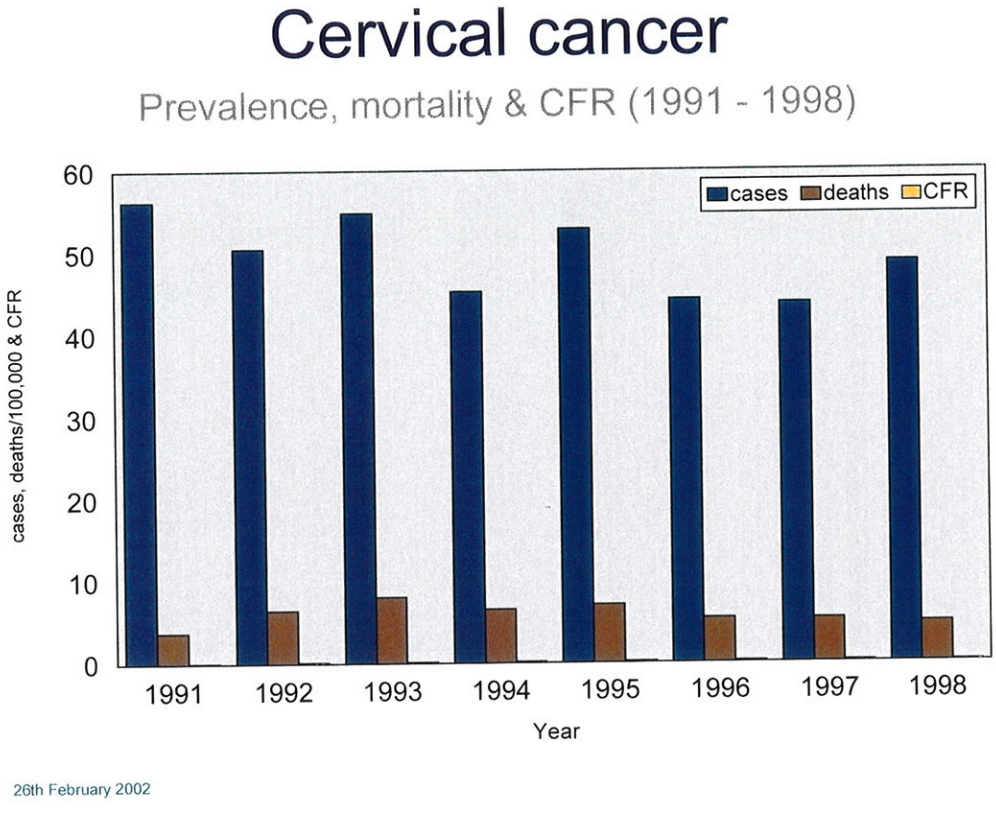

Figure 5: Cervical cancer - Morbidity and mortality trends by age group in Botswana (1980 – 1998)

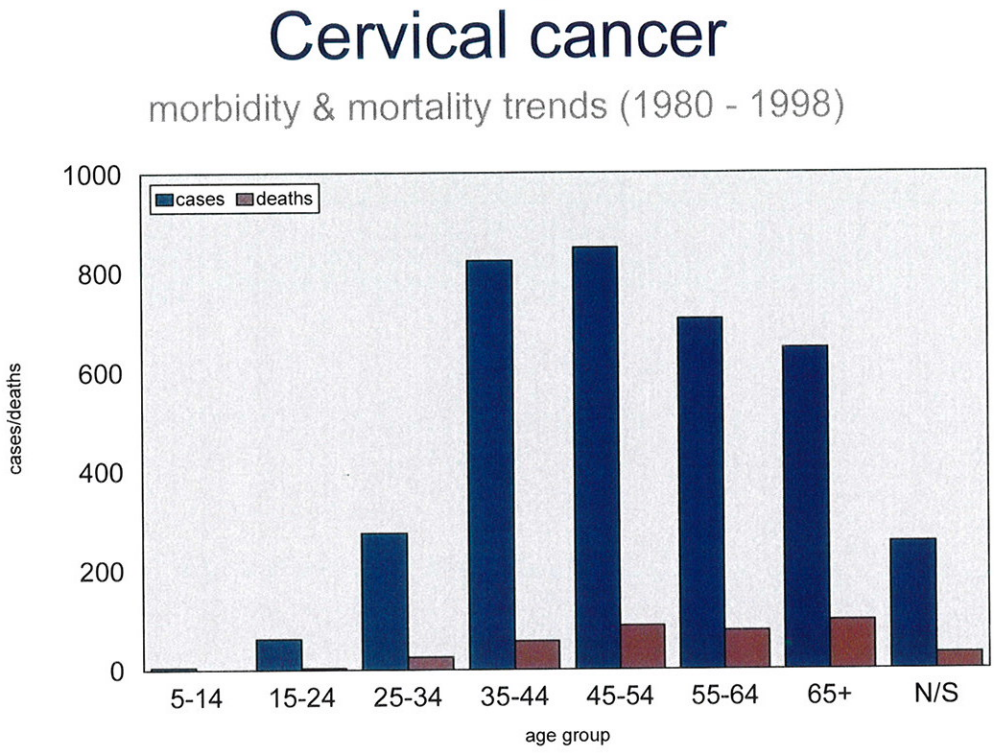

Figure 6: Number of cases of cervical cancer according to age and HIV-serostatus

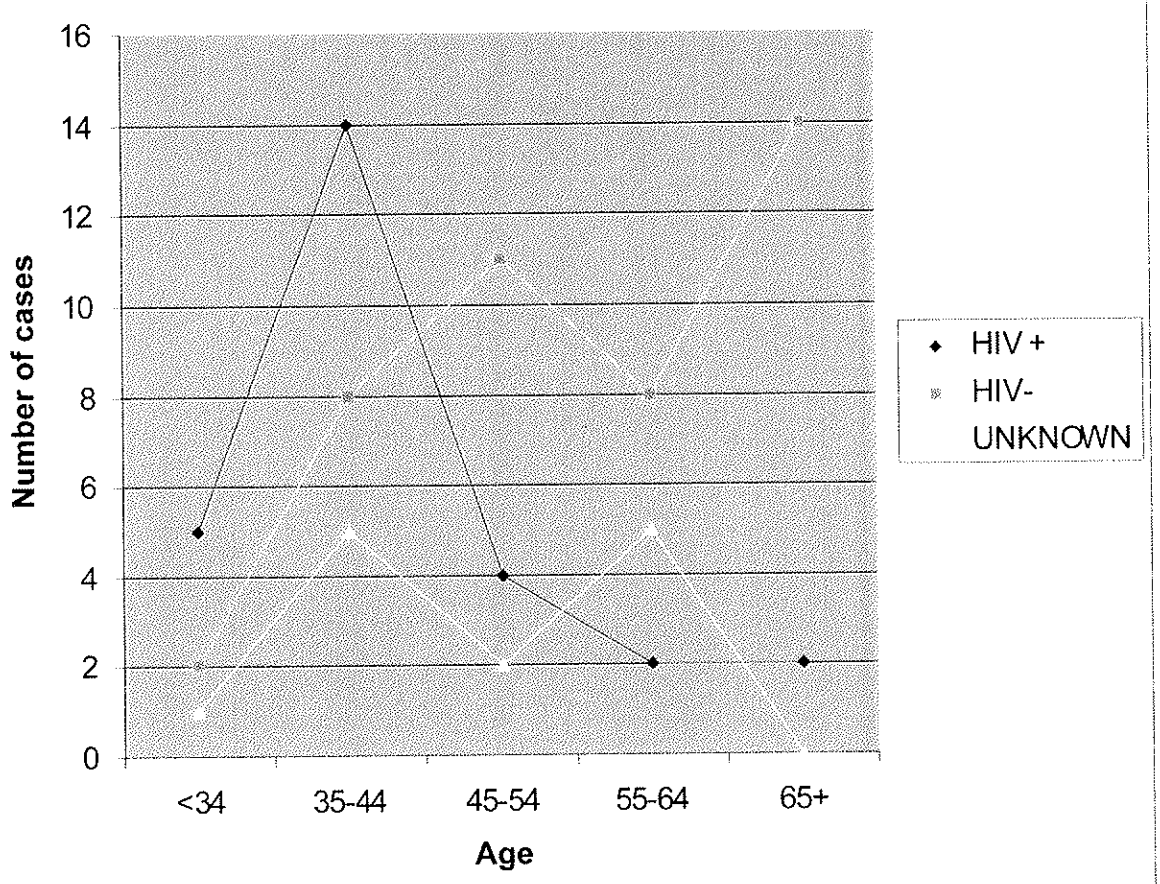

Figure 7: HIV serostatus in the different age groups of cervical cancer patients

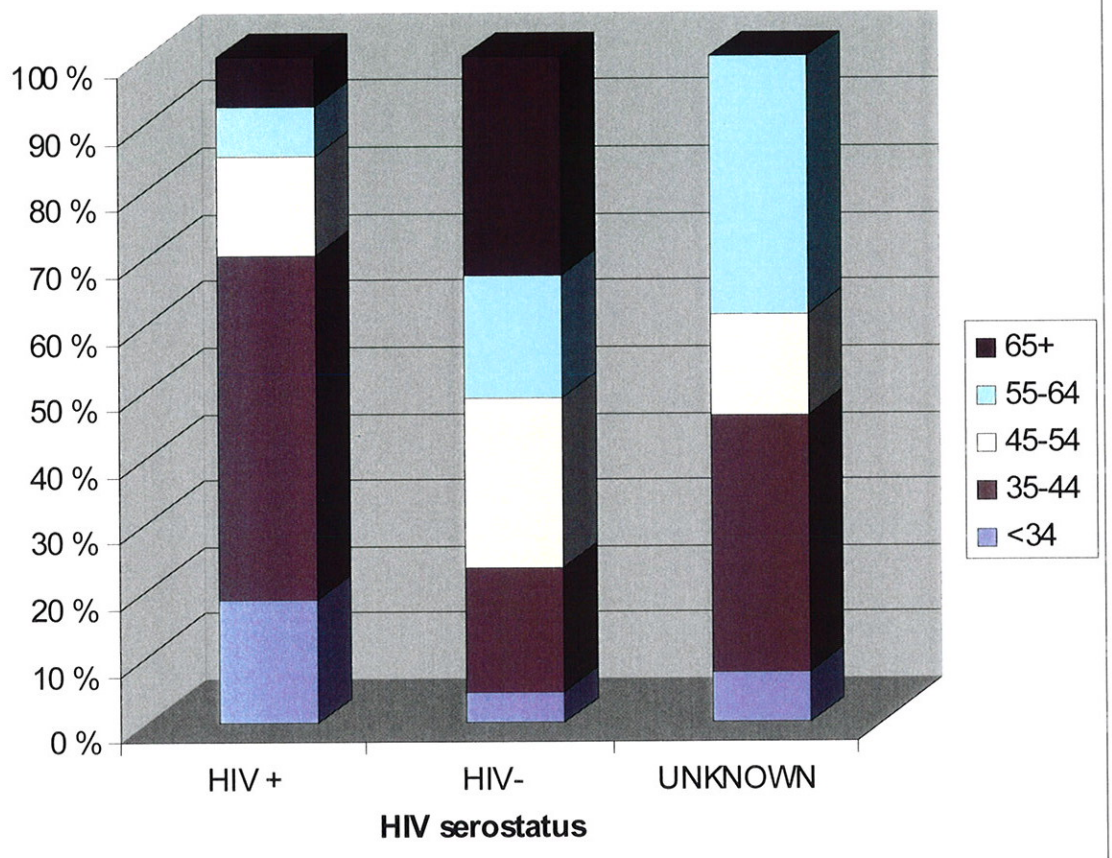

Figure 8: HIV serostatus in the different age groups of cervical cancer patients

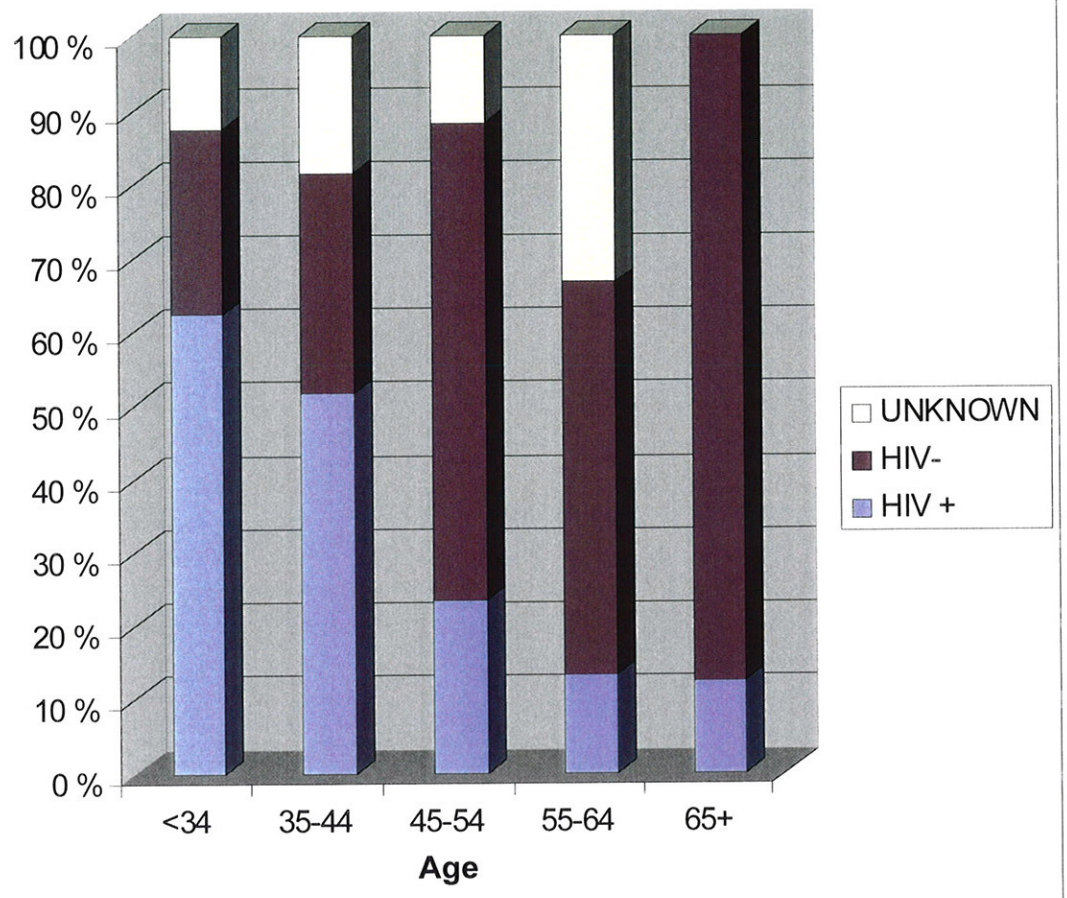

Figure 9: which age groups are affected by each stage of cervical cancer