

# Trends of histopathology of cervical cancer among women in Durban, South Africa

**M. Moodley, K. Moodley**

*Department of Obstetrics and Gynaecology, Gynaecological Oncology, Nelson R. Mandela School of Medicine, University of KwaZulu Natal, Durban (South Africa)*

## Summary

**Introduction:** Cervical squamous cell carcinoma has traditionally been the commonest histological type of cervical cancer. Adenocarcinoma has recently been reported to occur with increasing frequency. **Methods:** This retrospective study was conducted on 2,930 patients with cervical cancer over an eight-year period (1995-2002) recruited from the combined Gynaecology Oncology Clinic at King Edward VIII Hospital (KEH), Pathology Laboratories at KEH, and from the private sector. **Results:** In the public sector squamous cell carcinoma was found to be the commonest type of cervical cancer irrespective of ethnicity and age. It was found to occur in over 80% of patients and remained fairly static over the time period. In the private sector, a slightly higher proportion (38.8%) of women had adenocarcinoma, however since the total number of patients were small (85) there was no statistically significant increase in adenocarcinoma relative to squamous cell carcinoma. There was no correlation between the documented risk factors i.e., smoking, contraception and human papillomavirus and histological type of cervical cancer. Similarly, there was no statistically significant relationship between ethnicity, differentiation, type of cervical cancer and age of the patient in both sectors. **Conclusion:** This study has not revealed an increasing incidence in cervical adenocarcinoma in the public setting. However, in the private sector, a significant proportion of black women (38.8%) had adenocarcinoma. All Asian women had adenocarcinoma while 25% of the white women had adenocarcinoma. Although the total number of patients in this group are small (85), these results cannot be ignored.

**Key words:** Histopathology; Cervical cancer; Durban South Africa.

## Introduction

Cervical cancer is the second commonest cancer throughout the world with an annual prevalence of about 493,000 [1]. The majority of cases are in the developing world, especially Sub Saharan Africa. The mortality is about 50% mainly due to absence or inadequate screening facilities and late-stage presentation [1]. Invasive cervical cancer remains predominantly a disease of woman over 45 years of age, although there has been a suggestion that the incidence in younger women is changing [2]. This may be related to changes in the natural history of the disease and tumour biology, perhaps associated with the human papillomavirus (HPV) infection and human immunodeficiency virus (HIV) infection.

Time trends in the incidence of cervical adenocarcinoma and adenosquamous carcinoma during 1973 to 1998 have been reported using data provided by 60 population-based cancer registries [2]. The data derived from 32 defined populations in 25 countries describe a significant increase in the cumulative incidence of cervical adenocarcinoma in women born in the mid-1930s and in successive cohorts thereafter in some populations in the United States, Australia, New Zealand, United Kingdom, Japan and Singapore [2]. Approximately 4,000 new cases of invasive cervical cancer occur in

England and Wales annually, whereas in the United States of America there are about 16,000 cases each year [2]. In total these figures are reasonably static except that there appears to be a trend in the younger age groups (30-59 years) and a rising trend towards adenocarcinoma [2] but not a disproportionate rise in mortality [2]. There is general evidence that the incidence of adenocarcinoma of the cervix has been rising particularly in young women [3, 4].

While the average annual age-adjusted incidence of invasive squamous cancer is decreasing, the rate of adenocarcinoma is reported to be increasing at a rate of 1.4% per year [5]. In the United States (Alabama, 1974-1980) the percentage of adenocarcinoma relative to squamous cell carcinoma of the cervix increased from 7% in 1974-1978 to 19% during the period 1979-1980 [2]. These trends are generally restricted to younger women, i.e., those less than 35 years of age: adenocarcinoma incidence approximately doubled from the early 1970s to the early 1980s. Available data, although scanty, consistently show that the frequency of cervical adenocarcinoma rises with the number of partners and with decreasing age at first intercourse, suggesting a potential role for sexually transmitted (viral) factors [2].

Findings of studies comparing outcome of adenocarcinoma and squamous cell carcinoma are controversial. It has been reported in a controlled study that there is no difference in survival but only a three-year survival period was documented [2].

---

Revised manuscript accepted for publication June 11, 2008

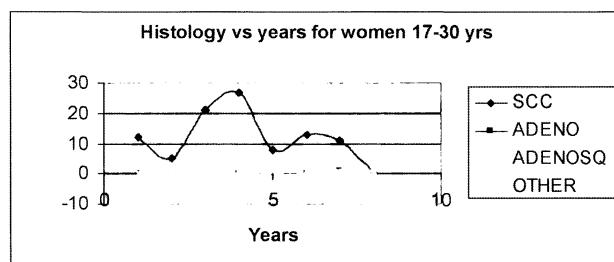


Fig. 1

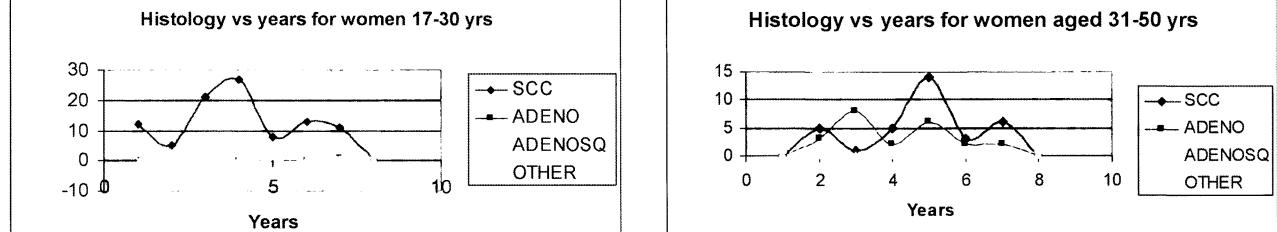


Fig. 2

Figure 1. — Trends of histopathology of cervical cancer for women aged 17-30 years.

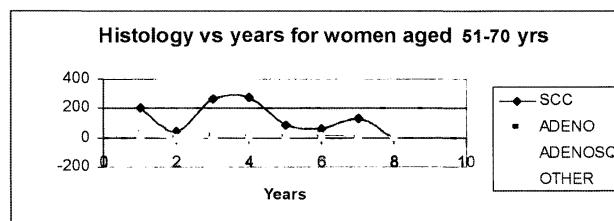


Fig. 3

Figure 3. — Trends of histopathology of cervical cancer for women aged 51-70 years.

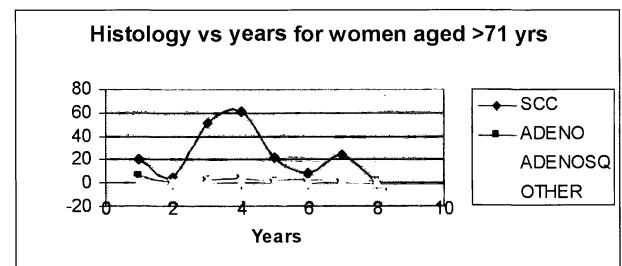


Fig. 4

Figure 4. — Trends of histopathology of cervical cancer for women aged > 71 years.

Scandinavian studies comparing survival in unmatched groups of cervical cancer patients show a significant difference in survival [4]. Patients with adenocarcinoma showed a 15% lower survival in each stage of the disease.

Information regarding trends of cervical adenocarcinoma and squamous cell carcinoma in South Africa is lacking. This study was conducted among different ethnic groups from both the state and private sector, Durban, South Africa, to determine time trends in incidence of squamous cell carcinoma relative to adenocarcinoma.

## Patients and Methods

This retrospective study was based on a total of 2,930 patients with histologically confirmed cervical cancer diagnosed between 1995 and 2002. The study included patients from both the public and private sectors. Information was collected from records stored at the Combined Gynaecology Oncology Clinic at King Edward VIII Hospital (KEH) in the public sector and from Bouwer and Lancet Pathology Laboratories in the private sector. At the time of the study, these were the only two private laboratories in existence in the private sector. The relevant information was documented after institutional ethical approval was obtained.

### Statistical methods

Age (range and mean) and parity was calculated using the Student's t-test and the signed rank S test. The chi-square test was used to calculate the association between contraception and histology type, ethnicity and differentiation, histology versus the different age groups, and histology versus human papillomavirus. The Kruskal-Wallis test was used to assess the relationship between parity and histological type of cervical cancer.

## Results

### Public sector

There were a total of 2,845 patients in the public sector. The mean age of all patients was 52 years (17-93 years). The median parity was 1 (0-12). Most patients in the public sector presented with advanced stage disease. Stage III B disease accounted for 42.7% of all cervical cancers. There was no relationship identified between any of the documented risk factors and the histological type. Smoking was not documented in the majority of patient records in the public sector and could therefore not be analysed. Among women in whom contraceptive use was known, there was no relationship between contraceptive use irrespective of the type of contraception used and histological type of cervical cancer ( $p = 0.6627$ ). In 94.3% of patients contraceptive use was unknown.

No statistically significant relationship was identified between the presence of HPV recorded in the histopathology report and the different histological types of cervical cancer. There was no relationship between HPV and the different age groups. HPV was only recorded in approximately 1% of patient's histology reports. Squamous-cell carcinoma was the commonest type of cervical cancer in the public sector accounting for 85.1% of all cervical cancers. Adenocarcinoma accounted for 6.7%, while adenosquamous and other types accounted for 2.7% and 5.5%, respectively.

There was no statistically significant relationship between the histological types of cervical cancer and the different age groups ( $p = 0.0603$ ) or parity ( $p = 0.3575$ ). An analysis of age versus parity versus histology showed no statistical significance ( $p = 0.2315$ ). There was no

relationship between the differentiation of cervical cancer and the age of patients ( $p = 0.3140$ ). In the public sector histology-confirmed cervical cancer was recorded in only three ethnic groups. These included black, Asian and coloured (mixed black and white) women with a 98.6%, 1.3% and 0.1% prevalence in each group, respectively. There was no statistical significance between the different ethnic groups and the histological findings ( $p = 0.8765$ ). Among black patients, 85% had squamous cell carcinoma, while 15% had adenocarcinoma, adenosquamous carcinoma and other types of cervical cancer. Among Asian women, 86% had squamous cell carcinoma and 14% had the other types of cervical cancer. Squamous cell carcinoma accounted for 100% of cervical cancer among coloured women.

Likewise, there was no relationship between ethnicity of patients and their histological differentiation ( $p = 0.8294$ ). The majority of patients in the public sector had moderately differentiated cervical cancer.

The trends of cervical cancer over the 8-year period in the public sector revealed:

1. Squamous cell carcinoma was relatively static over the 8-year period in women who presented to KEH VIII with no significant rise in adenocarcinoma or adenosquamous carcinoma.

2. In the 17-30 year age group (group 1) (Figure 1) squamous cell carcinoma showed an increasing trend in the first four years followed by a slight fall in the latter four years. Adenocarcinoma and the other types of cervical cancer remained fairly static with no significant increase or decrease.

3. In the 31-50 year age group (group 2) (Figure 2) there were two increases of adenocarcinoma relative to squamous cell carcinoma from years 2 to 6, but thereafter squamous cell carcinoma was the dominant type.

4. In the 51-70 year age group (group 3) (Figure 3) and > 71 year age-group (group 4) (Figure 4), there was a similar trend as in group 1.

5. There was also no specific trend identified in the stage of disease versus the different age groups.

#### *Private sector*

The mean age of patients in the private sector was 47 years (range 25-70 years). Clinical data was not available and only the histological reports were utilised for analysis. Parity, stage of disease, smoking, contraceptive use and the presence of HPV could not be analysed. There were a total of 85 patients in the private sector. Of this, 72% of patients were black, 4.7% were Asian and 23.5% were white females. There were no coloured patients with invasive cervical cancer recorded in the private sector.

There was a statistically significant relationship between ethnicity and the histological subtype ( $p = 0.0285$ ). The commonest type of cervical cancer among women from the private sector was squamous-cell carcinoma, accounting for 60% of the total. There were 38.8% of patients with adenocarcinoma and 1.2% with adenosquamous carcinoma. Among black women, squa-

mous cell carcinoma contributed 61% of all cervical cancers, while adenocarcinoma accounted for approximately half the amount (38.8%). Among Asian women, 100% of the patients had adenocarcinoma, while among the white population group, 70% had squamous cell carcinoma, 25% adenocarcinoma and 5% adenosquamous carcinoma.

There was a statistically significant relationship between the ethnicity of patients and differentiation of cervical cancer ( $p = 0.0371$ ). There was no statistically significant relationship between the type of cervical cancer and the different age groups ( $p = 0.4210$ ). The presence or absence of HPV infection was unknown in 97% of patients as this finding was not recorded in the histology results.

The trends over the 8-year period in the private sector revealed:

1. Squamous cell carcinoma remained the predominant histological type of cervical cancer.

2. There was no significant increase in adenocarcinoma or adenosquamous carcinoma.

3. There was no relationship between histological types versus the different age groups.

#### *Comparison between the public and private sectors*

- A. There was a marked difference in the number of patients between the two groups with 2,845 in the public sector and only 85 documented in the private sector over the past eight years (total = 2,930). The mean age was comparable in both groups.

- B. No comparison could be drawn between parity, stage of disease and the associated risk factors such as smoking, contraceptive use and human papillomavirus as these were not documented in the private sector records.

- C. The largest proportion of invasive cervical cancer occurred among black ethnic groups in both sectors being 98.6% and 71.7% in the public and private sectors, respectively. There were no white patients documented in the public sector and no coloured patients in the private sector.

- D. Overall, squamous cell carcinoma was the predominant type of cervical cancer in both sectors. However, adenocarcinoma was found in a significant proportion of the Black population (38.8%) in the private sector. Furthermore, adenocarcinoma was the only reported type of cervical cancer among Asian women (100%) in the private sector.

- E. The majority of patients had moderately differentiated lesions in both public and private sectors.

- F. The trends were comparable over the 8-year period as regards type of cervical cancer versus the different age groups with squamous cell carcinoma remaining the predominant histological type of cervical cancer.

#### **Discussion**

Cervical cancer accounts for over 250,000 deaths annually, 70% of which occur in developing countries where it is the leading cause of cancer mortality. Histologically,

squamous cell carcinoma is the most common type of cervical cancer while adenocarcinoma accounts for only 10-15% of all primary cervical cancers. This finding was confirmed in this retrospective study with squamous cell carcinoma and adenocarcinoma accounting for 85% and 7.6% of all cervical cancers, respectively, in both the public and private sectors.

The incidence of cervical squamous cell carcinoma has declined during the past decades throughout the developed countries largely because of Papanicolaou (Pap) screening [6]. By contrast, the incidence of cervical adenocarcinoma has been increasing, particularly among younger women. In the USA, the rate of cervical cancer has increased among Hispanic and white women but not among black women. In this study black women in the private sector accounted for 72% of the total number with cervical cancers. Squamous cell carcinoma contributed 61% of all cervical cancers while adenocarcinoma accounted for half this amount (38.8%). While it has been realised that conventional cervical cytology screening may not be effective for adenocarcinoma there may be other reasons to explain the absolute increases in the rate of adenocarcinoma and adenocarcinoma *in situ*. Increasing and intensified surveillance, changes in diagnostic, classification, and birth cohort phenomenon have been examined but do not appear to account for all the increases [7]. Increasing sexual activity with a number of partners including earlier age of coitarche, cigarette smoking and the use of oral contraceptives have been suggested as contributing factors [7]. HPV is a necessary causal factor for both histological types of cervical cancer, type 16 dominating in squamous cell carcinoma and type 18 in adenocarcinoma [8]. According to the International Agency for Research in Cancer (IARC) working group, type 18 has been linked to approximately 50% of cervical adenocarcinomas [6]. Even if HPV is the main causal link to cervical adenocarcinoma it has remained unclear why it causes cancer of two different histological types, differing much in incidence and time trends.

The incidence and mortality rates for cervical cancers have declined dramatically in the United States over the last 35 years. These trends vary, however, by race, age, histological type and geographical area. In recent years the decreases are moderating, particularly among white women [7]. Declines are more evident among black women narrowing the racial differences in rates at younger ages. When analysed by cell type, adenocarcinoma increased among white women aged < 35 years during the 1970s and more recently among those aged 35-54 years [9]. Women with adenocarcinoma increased from 13/100,000 women/years to 38/100,000 women/years in the < 35 age group and from 82/100,000 women/years to 104/100,000 women/years in the 35-54 age group in Atlanta, Connecticut, Detroit and Iowa (USA). This trend was not evident in our analysis.

During the 1970s and 1980s declines in invasive cervical cancers and invasive squamous cell carcinoma were also observed in Seattle and Los Angeles (USA) from 14.2/100,000 in 1973 to 7.4/100,000 in 1995. This data is

consistent with the results of the Finnish Cancer Registry data, where 88% of all cervical cancers were classified as squamous cell carcinoma and 6% as adenocarcinoma during the 1953-1957 period. However, by 1978-1982 the proportion of squamous cell carcinomas had declined to 81% and the proportion of adenocarcinoma had increased to 17%. A report of trends from 13 European countries demonstrates that the age-adjusted adenocarcinoma incidence rates increased throughout Europe from 0.5% per annum in Denmark, Sweden and Switzerland to ≥ 3% in Finland, Slovakia and Slovenia [10]. Increases in cervical adenocarcinoma among young women in the USA were also reported in Los Angeles and in the Surveillance, Epidemiology and End Result Programme (SEER) areas [3, 12].

Major risk factors for cervical cancer include multiple sexual partners and early age at first intercourse. A case-control study conducted in five United States cities during the early 1980s revealed that the mean lifetime number of sexual partners increased from an average of two among white controls aged 35 years and older to more than five [9]. The average age of coitarche declined from 22 years to younger than 19 years. These large differences reflect the 'sexual revolution' of the last several decades, but changes in sexual activity are not reflected in the trends for cervical cancer.

This study did not include data on the sexual history of the women with cervical cancer as documentation in records was not available for analysis. We could not establish a relationship between the presence of HPV and ethnicity of patients, type of histology or different age groups as there was no documented HPV result in more than 90% of patient histology records in both sectors. Reporting of HPV in histopathology reports is not an accurate means of establishing presence of HPV in cervical cancers. Studies show that while HPV infection is extremely common in the general population particularly among young sexually active females, HPV 18 is less common [11]. This observation might explain why the absolute number of cases of adenocarcinoma is low, relative to the overall HPV infection rate in the general population.

However, HPV infection cannot explain the reason for a relatively large increase in adenocarcinoma among white females, since the number of sexual contacts is considered to be the most important determinant of genital HPV infection and black females were reported to have a greater number of sexual partners and a younger age at commencing sexual activity than white females in each age group as previously cited. The absence of clinical data for women among the private sector in this study represents a limitation of the analysis and is reflective of poor-record keeping in the private sector.

Cigarette smoking appears to increase the risk of squamous cell carcinoma independent of the association with sexual factors [12]. In this study there was no relationship between smoking and histological cell type. Other studies have shown that among females, the prevalence of smoking increased from the 1930s through the 1960s, plateaued and declined slightly in recent years [9]. In this

study, smoking was not evident as black women accounted for the majority of patients in whom smoking was not a common practice.

A link between oral contraceptives and cervical cancer, both squamous cell cancer and adenocarcinoma, has been suggested with some evidence that high-dose oestrogen pills may be most hazardous [9]. This was not confirmed in this study, as no statistically significant relationship was found between contraceptive use, ethnicity or histological subtype, where contraceptive use was recorded. Oral contraceptive use became widespread during the 1960s, peaked during the early 1970s and generally decreased thereafter. The pills declined in strength and potency over time as the compositions were modified and effective formulations improved. For these reasons and because young women have been the major users of oral contraception, the maximally exposed cohorts of women were in their 20s during the 1960s, 30s during the 1970s and 40s during the 1980s. This may explain the plateauing of adenocarcinoma among women younger than 35 years of age after increases reported earlier as well as rising rates since the late 1970s among middle-aged women.

A history of having a Pap smear and the interval from the last examination is strongly related to cervical cancer risk [9]. Lower use of such screening among black women in the past may partly explain their higher cervical cancer rates. Narrowing of the racial differences in rates would be expected if screening became more widespread. The proportion of both black and white women in the United States who ever had a Pap smear increased from 1973 to 1987. During the 1980s the proportion who ever had a Pap smear was about 90% in each group, with Black women being screened more frequently. These patterns are consistent for the observed trends in cancer rates.

However, since the Pap smear was reported to be less efficient in identifying adenocarcinoma than squamous cell carcinoma of the cervix, the increase in adenocarcinoma observed could be attributed to failure to detect precursor lesions or women having not been adequately screened [11]. Other studies have suggested that missing or failing to detect precursor lesions with Pap smear screening is an unlikely explanation for the observed incidence patterns in the United States [11]. By examining time trends for adenocarcinoma *in situ*, it was found that there was an increase in *in-situ* adenocarcinoma among white women [11].

Missing or failing to have Pap smear screening also cannot explain why white women have had a much higher increase in adenocarcinoma than black women, since the proportion who ever had a Pap smear was quite comparable between black and white women (90%) in the 1980s. Black women may even have a lower intensity of Pap smear screening, especially below the age of 50 years. Therefore, if failing to have screening is responsible for the observed increase in invasive adenocarcinoma, we should anticipate a larger increase in incidence of invasive adenocarcinoma among black women even in the public sector. However, from this study 85% of the

black women had squamous cell carcinoma while only 15% had adenocarcinoma with no significant increase in adenocarcinoma over the last eight years.

Low socio-economic class has long been recognised as a major risk factor for squamous cell carcinoma but does not play much of a role in the aetiology of adenocarcinoma. Adenocarcinoma occurs with predominance in women characterised by a high social class. This could explain the relatively high percentage of patients with adenocarcinoma in the private sector in this study or among the Asian women and black women with access to private medical care. This is in keeping with a larger percentage (38.8%) of black women in the private sector who had cervical adenocarcinomas and is similar to an increasing trend noted among black women in the United States [12].

Birth-cohort studies in the United States have shown clearly that invasive adenocarcinoma is on an increasing trend in both black and white women since the late 1970s. The rates increased from 0.9/100,000 in 1976-1978 to 1.29/100,000 in 1988-1990 among white women and from 0.86/100,000 in 1976-1978 to 1.11/100,000 in 1988-1990 among black women [11]. The increase for white women has been the most dramatic since the early 1980s. The overall incidence rate of cervical adenocarcinoma for white women has in fact surpassed the rate for black women [11]. A recent report from Korea describes no increasing trend of cervical adenocarcinoma (1.2 in 1993-1995 and 1.4 in 1999-2002) but a decline in squamous cell carcinoma of the cervix from 15.1 in 1993-1995 to 12.2 in 1999-2002 [13].

## Conclusions

Results from univariate analyses and age-period-cohort modelling indicate that invasive adenocarcinoma of the cervix has increased in both the White and Black population groups while the increase is more pronounced among white women. The results also showed that the increase in invasive adenocarcinoma started among those born in the mid 1920s. Early studies in the United States and in other countries around the world have shown that oral contraceptive use, smoking and human papillomavirus might possibly be risk factors for the observed increase in adenocarcinoma.

Current knowledge regarding these factors, however, cannot entirely explain the observed incidence patterns for invasive adenocarcinoma. This knowledge is particularly lacking in our local South African context. This study has not revealed an increasing incidence in cervical adenocarcinoma in the public setting. However, in the private sector, a significant proportion of black women (38.8%) had adenocarcinoma. Black women comprised 72% of all the patients with cervical cancer in the private sector. All Asian women had adenocarcinoma while 25% of the white women had adenocarcinoma. Although the total number of patients in this group is small (85), these results cannot be ignored.

## References

- [1] Denny L., Ngan H.Y.S.: "Malignant manifestations of HPV infection. Carcinoma of the cervix, vulva, vagina, anus and penis". *Int. J. Gynecol. Obstet.*, 2006, 94, S50.
- [2] Vizcaino A.P., Moreno V., Bosch F.X., Muñoz N., Barros-Dios X.M., Borras J.: "International trends in the incidence of cervical cancer: Adenocarcinoma and adenosquamous cell carcinomas". *Int. J. Cancer*, 1998, 75, 536.
- [3] Smith H.O., Tiffany M.F., Qualls C.R., Key C.R.: "The rising incidence of adenocarcinoma relative to squamous cell carcinoma of the uterine cervix in the United States - A 24-year population-based study". *Gynaecol. Oncol.*, 2000, 78, 97.
- [4] Parazzini F., Vecchia C.L.: "Epidemiology of Adenocarcinoma of the Cervix". *Gynaecol. Oncol.*, 1990, 39, 40.
- [5] Plaxe S.C., Saltzstein S.L.: "Estimation of the duration of the preclinical phase of cervical adenocarcinoma suggests that there is ample opportunity for screening". *Gynecol Oncol.*, 1999, 75, 55.
- [6] Sasieni P., Adam J.: "Changing rates of Adenocarcinoma and Adenosquamous carcinoma of the cervix in England". *Lancet*, 2001, 357, 1490.
- [7] Hamminki K., Li X., Mutamien P.: "Age-incidence relationships and time trends in cervical cancer in Sweden". *Eur. J. Epidemiol.*, 2001, 17, 323.
- [8] Bosch F.X., Manos M.M., Muñoz N., Sherman M., Jansen A.M., Peto J.: "Prevalence of human papillomavirus in cervical cancer: a worldwide perspective". International Biological Study on Cervical Cancer (IBSCC) Study Group. *J. Nat. Cancer Inst.*, 1995; 87, 796.
- [9] Devesa S.S., Young J.L., Brinton L.A., Fraumeni J.F.: "Recent trends in cervix uteri Cancer". *Cancer*, 1999, 64, 2184.
- [10] Bray F., Carstensen B., Moller H., Zappa M., Zakelj M.P., Lawrence G.: "Incidence trends of adenocarcinoma of the cervix in 13 European countries". *Cancer Epidemiol. Biomarkers Prev.*, 2005, 14, 2191.
- [11] Zheng T., Hulford T.R., Ma Z., Chen Y., Liu W., Ward B.A.: "The continuing increase in adenocarcinoma of the uterine cervix: a birth cohort phenomenon". *Int. J. Epidemiol.*, 1996, 25, 252.
- [12] Brinton L.A., Schairer C., Haenszel W., Stolley P., Lehman H.F., Levine R., Savitz D.A.: "Cigarette smoking and invasive cervical cancer". *JAMA*, 1986, 255, 3265.
- [13] Wang S.S., Sherman M.E., Hildesheim A., Lacey J.V. Jr., Devesa S.: "Cervical adenocarcinoma and squamous cell carcinoma incidence trends among White women and Black women in the United States for 1976-2000". *Cancer*, 2004, 100, 1035.
- [14] Chung H.H., Jang M.J., Jung K.W., Won Y.J., Shin H.R., Kim J.W.: "Cervical cancer incidence and survival in Korea: 1993-2002". *Int. J. Gynecol. Cancer*, 2006, 16, 1833.

Address reprint requests to:

M. MOODLEY, M.D.  
 Private Bag 7, Gynaecological Oncology, Room 109  
 Department Obstetrics and Gynaecology  
 Nelson R. Mandela School of Medicine,  
 University of KwaZulu Natal  
 719 Umbilo Road - Congella - 4000 Durban  
 (South Africa)  
 e-mail: moodleym29@ukzn.ac.za