"Gynecologic malignancies at a tertiary care center in Mozambique"

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Running head: Gynecologic cancer in Mozambique

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Abstract word count: 249

Text word count: 2031

Abstract

Objective: To determine the frequency of gynecological cancers and the temporal trends in their incidence over an 18-year-period in Maputo (Mozambique), a city located in South Eastern sub-Saharan Africa, an area in which comprehensive statistics on cancer are limited

Methods: A retrospective review of the pathological records of gynecologic cancers from the Department of Pathology of the Maputo Central Hospital, a quaternary care center, in Mozambique from January 1991 to December 2008 was performed, which is the cancer registry of Maputo City. The frequency of involvement at various sites, histological subtypes and age at diagnosis were determined.

Results: 3,726 gynecologic cancers were reported. Malignant neoplasms of the uterine cervix (64.0% of all tumors) were the most frequent cancers, followed by breast (23.2%), vulvar-vaginal (4.1%), ovarian cancers (3.8%), cancers of the uterine corpus (3.3%), and gestational choriocarcinoma (1.7%). Tumors of the uterine cervix, vulva/vagina, uterine corpus and ovary increased in number three times, whereas breast cancers increased five times during the study period, whereas minimal increase was observed for choriocarcinoma. Mean age of the women with gynecologic cancer was 47.7 ± 14.2 years (range 1 to 96). Gestational choriocarcinomas affected younger patients (29.2 ± 10.0 years), and malignant tumors of the uterine corpus affected older women 59.8 ± 12.6 years.

Conclusions: Malignant tumors related to human papillomavirus infection (cervix, vagina and vulva) accounted for over two thirds of all gynecologic malignancies. Screening for cervical cancer and vaccination against human

papillomavirus infection should be considered a health priority in sub-Saharan Africa.

Key words: Gynecologic cancer, cervical cancer, human papillomavirus, sub-Saharan Africa

Introduction

The cancer burden affecting a specific population is an important issue in health care, and the burden of the morbidity and mortality of gynecologic cancers is enormous throughout the world [1-4]. The data available from various centers worldwide are indicative of the vast geographical variability in the incidence, anatomical site, age and stage at presentation of these cancers. While information on these parameters is available in many of the developed regions, countries of sub-Saharan African have irregular and limited knowledge on the incidence of cancer and the distribution of malignant tumors [2;3;5-8]. Indeed, data on cancer is very scarce not only in Mozambique, but also in the whole South Eastern sub-Saharan Africa and information on the trends in cancer incidence over large periods of time in this region is exceptional. One previous report on cancer in Maputo city (at that time Lourenço Marques) including the period from 1950-1960 was published in 1965, [7] while our group recently published data on cancer related to the period 1992-2008 [9].

The aim of this study was to compile and retrospectively analyze the information on gynecologic malignancies over an18-year period (1991-2008) registered at the Maputo Central Hospital, Mozambique, which receives virtually all the specimens of Maputo City. The ultimate objective was to establish patterns of disease that could help in guiding health care interventions and preventive policies.

Materials and Methods

Study Site

This study was performed at the Department of Pathology of the Maputo Central Hospital (MCH), a 1500-bed hospital that is the only quaternary health care facility in Mozambique. The Department receives virtually all the specimens of the city of Maputo. The Department has a database of all the samples received for pathological diagnoses including specimens of most types of cancers (with the exception of leukemia and clinically diagnosed cancers).

This study was approved by the National Bioethics Committee of Mozambique, and the Mozambican Ministry of Health (Ref. 389/CNBS).

Study Design

The analysis included all gynecological cancer cases registered in the Department of Pathology of the MCH from January 1, 1991 to December 31, 2008. Data were entered into a Microsoft Access database (Microsoft Co, Redmond, WA, USA) which, upon data entry, prevents the use of nonexistent codes and performs checks for internal consistency among variables. The database was carefully reviewed (name, age) to confirm that no duplications had been registered. Information about previous analyses in the same patient was also obtained in order to identify potential duplicate registrations. Cases were identified in the registries as histological studies (including biopsies and surgical pathology), cytological specimens (aspiration or cervical scrape smears), and autopsies. All gynecological tumors, including gestational trophoblastic neoplasms, breast cancers, primary gynecological Kaposi sarcomas and primary gynecological lymphomas were included in the analysis. Multiple primary cancers occurring in the same patient were entered as separate cases. Metastases to genital organs from other primary sites were excluded. Cases with only a clinical diagnosis were not excluded.

Basic demographic data were collected for each case identified, including age, gender and address. For each specimen, the date and method of diagnosis, site from which the specimen was taken (topography), and microscopic morphology were recorded. Patient records/information were anonymized and de-identified prior to analysis. All topographic and morphologic classifications were made according to the the 10th version of the International Classification of Diseases for Oncology (ICD-O). [10-12]

Statistical Analysis

Data were stored in SPSS (version 18.0; SPSS, Inc, Chicago, IL). Some analyses were also performed using STATA (Version 11.0, StataCorp, College Station, TX, USA). The frequency of various malignancies was determined both for the entire cohort and for specific age groups. Comparison between two groups was performed using Fischer's exact test and chi square tests as applicable. Cut off for a significant *P* value was calculated using Bonferroni correction.

Results

A total of 3,726 gynecological cancers were diagnosed during the study period. Of these, 3,025 (81.2%) had a histological diagnosis made either on biopsy or resection specimens, 570 (15.3%) were diagnosed by fine needle aspiration biopsy or cervical cytology, and 131 (3.5%) were identified at autopsy. The mean age of the patients was 47.7 ± 14.2 years, with information on age not being available in 93 women.

The cancer sites included the uterine cervix (2,383 cases, 63.9%), the breast (865, 23.2%), vagina and vulva (152, 4.1%), ovary and fallopian tube

(140, 3.8%), and uterine corpus (122, 3.3%). Gestational choriocarcinoma was identified in 64 (1.7%) women (Figure 1). The absolute numbers of cases and the percentage of each gynecologic cancer in the different age groups are shown in Table 1.

Cancer of the uterine cervix was the most frequent gynecologic cancer over the whole study period in all the age groups, except in pediatric patients. The mean age of women with cervical cancer was 47.8 ± 13.4 years (median 46 years). The histological types of cervical cancer are presented in table 3. Patients between 30 and 44 years of age constituted the commonest age group affected. One hundred and ninety-five cervical cancers (5.7%) were detected in patients younger than thirty years of age. The histological types of malignant neoplasms of the uterine cervix are presented in table 2. Both squamous cell carcinomas and adenocarcinomas or adenosquamous carcinomas increased by over three times during the period of study (Figure 2), with no differences between both histological diagnoses.

Carcinoma of the breast was the second most frequent gynecologic malignancy, with the mean age of these patients being 49.3 ± 13.6 years. Most breast tumors (829 out of 865, 95.8%) were carcinomas (either ductal or lobular). Twenty-one of the tumors were sarcomas, six arising in phyllodes tumors. Eleven malignant lymphomas and four Kaposi sarcomas were diagnosed during the study period.

Carcinomas of the vulva and vagina were most commonly squamous cell carcinomas (131 out of 152 tumors; 86.2%). Ten vaginal adenocarcinomas, three vaginal leiomyosarcomas, two Kaposi sarcomas, 2 verrucous carcinomas of the vulva and one fibrosarcoma were identified. The mean age of the patients

with vaginal cancer was 47.2 ± 17.9 years while that of patients with vulvar cancer was 45.2 ± 16.7 years.

Women with ovarian malignancies had a mean age of 41.3 ± 18.1 years. Epithelial ovarian cancers were the most frequent tumors (114 out of 137; 83.2%). Non-epithelial neoplasms included 12 germ cell neoplasms, 4 sex-cord stromal cell tumors, 5 malignant lymphomas and 1 leiomyosarcoma. Three carcinomas of the Fallopian tube were identified.

Malignant tumors of the uterine corpus were mostly of epithelial origin (85 tumors, 68.0%), but 39 (32.0%) were sarcomas. The most frequent epithelial tumor was endometrioid adenocarcinoma (65 tumors; 53.3%) followed by serous/clear cell carcinomas (11 tumors, 9.0%) and carcinosarcomas (7 tumors, 5.7%). The mean age of patients with epithelial tumors was 59.8 ± 12.6 years. The mean age of patients with sarcoma was 44.4 ± 15.9 years. Women with choriocarcinoma had a mean age of 29.2 ± 10.0 years.

In the pediatric age group (≤ 14 years) the ovary was the most frequent location of malignant neoplasms (9 out of 21 tumors). The histological diagnoses were germinal cell tumors in 7 cases (4 dysgerminomas, 2 immature teratomas, and 1 choriocarcinoma), one malignant lymphoma and one granulosa cell tumor. Other tumors included three additional malignant lymphomas (2 in the uterine cervix and 1 in the vagina), three rhabdomyosarcomas (uterine cervix, vagina and vulva), a Kaposi sarcoma of the uterine cervix, a gestational choriocarcinoma, and three squamous cell carcinomas of the uterine cervix.

Discussion

Cancer of the uterine cervix is a malignant tumor almost always associated with human papillomavirus (HPV) infection [16] and this was found to be by far the most common cancer registered in Mozambican women during the study period, representing 64.0% of all the gynecologic cancers. Cancers of the vulva and vagina, most of which were associated with HPV [17;18], accounted for an additional 4.1% of the malignant neoplasms. Thus, in this series from Mozambique, cancers associated with HPV infection represented approximately two thirds of all gynecologic cancers. Indeed, HPV infection has been shown to be very prevalent in Mozambique, with over 50% of the women being positive at 20 years and with a prevalence of between 20-30% in women older than 30 years of age. [19-21] These results are in agreement with previous evidence showing that cancer of the cervix is the most common cancer among African women, with the highest incidence in eastern and southern Africa [22-24]. Cervical cancers have increased during the period of study at an average of over 10% per year. Moreover, the prevalence of cancers of the uterine cervix has shown a marked increase compared with data published from the same region in the period from 1956 - 1961 (20.3 per 10^5 to 54.3 per 10^5). [7] In a recent community-based survey the prevalence of HIV infection was described to be very high in Mozambique (over 45% in women older than 28 years of age) [25] and it has been proposed as the most likely explanation for a large part of the increase in the incidence of cervical cancer observed in several sub-Saharan countries. Linkage studies of HIV/AIDS and cancer registries have indicated a 2- to 22-fold increase in cervical cancer in HIV-positive compared with HIV-negative women. [26;27] However, although cervical cancer is considered to be an AIDS-defining condition, it is not clear whether the

association between HIV and cervical cancer is simply due to the increased prevalence of HPV infection observed in HIV positive women as suggested by a number of studies. [21;28-33] Squamous cell carcinoma was the predominant histological type during the study period, representing over 88% of all cervical cancers. The decline in the incidence of squamous cell carcinomas with increasing trends in adenocarcinomas observed in several western countries in which cytological screening is widely implemented, [34;35] was not observed in this population. The health care infrastructure in Mozambique does not support Papanicolaou or HPV testing, and cervical screening is virtually nonexistent and confined to a very limited number of opportunistic examinations in a small percentage of women. A recent clinical trial in rural India found that a single round of HPV DNA testing was associated with about a 50% reduction in the risk of developing advanced cervical cancer and associated deaths, with this decrease being significantly higher than that observed with Papanicolaou testing. These findings indicate that strategies based on HPV detection are probably more adequate for low resource settings [36] and should be considered as the most appropriate alternative when screening programs are implemented. Finally, there are high expectations that cervical cancer in developing countries may be prevented by vaccines that protect against the most common oncogenic types of HPV infections (HPV types 16 and 18), which cause about 70% of cervical cancers, [16] and have been shown to cause most cervical cancers in Mozambique. [20] The feasibility and acceptability of HPV immunization are currently being evaluated before national widespread implementation of this vaccine to young adolescent girls is carried out. [16;19]

Breast cancer, the most frequent neoplasm in women around the world, was the second most frequent gynecologic cancer in Mozambique, being much less prevalent than cervical cancer throughout the whole study period. Nevertheless, breast cancer increased much faster during the study period than any other gynecologic cancer. The Ugandan (Kampala) cancer registry has recently reported similar results with rates of breast cancer incidence, having nearly doubled over the past 20 years. [23] Thus, the shift in the predominance of cervical cancer to breast cancer that has occurred in developed countries [2;3;37] is very likely to occur in the near future in Mozambique. Indeed, although the rates still remain much lower than those in black women in the United States and several Western countries, [1-4] breast cancer has already become the most commonly diagnosed cancer in women in several Sub-Saharan African countries [2;4;37;38]. The reasons for the increase of this hormone-related cancer are not yet known but may include increases in the prevalence of risk factors such as early menarche, late childbearing, lower fertility, obesity, and increased awareness and detection, which are associated with urbanization and economic development.

Cancers of the ovary and uterine corpus were infrequent in this series, representing only 3.8% and 3.3% of all the gynecologic tumors respectively. In contrast, data from Globocan 2008 showed a much higher incidence of these tumors in most countries, particularly in Western countries. [2;3;37] This low incidence of these cancers in our study can be explained, at least in part, by the low age of this population, as uterine and ovarian cancers tend to affect older patients. However, during the study period significant increases were observed for both cancers, particularly for the cancers of the uterine corpus.

Finally, gestational choriocarcinoma accounted for 1.7% of all gynecologic malignancies. This is in agreement with the decrease in prevalence reported in other countries, which has been related to improved socioeconomic conditions and dietary changes. [39] However, these results should be considered with some caution, as only cases with pathological confirmation were included in the registry and gestational trophoblastic disease can currently be diagnosed on the basis of clinical and biochemical data. [40]

In summary, a significant increase in cancers in Mozambique it is found during the past 2 decades. Cancers related to HPV infection (cervix, vagina and vulva) account for approximately two thirds of all gynecologic malignancies. Widespread implementation of screening for cervical cancer and especially vaccination against HPV infection should be considered a health priority in sub-Saharan Africa since it could potentially prevent the early death of many African women. The rapid increase in the rates of breast cancer observed indicates that the emergence of cancers associated with westernization of lifestyles is likely to represent a major challenge in the near future.

Conflict of Interest Statement:

None of the authors report any conflict of interest.

No financial support was received for this study.

Acknowledgement section

The authors are grateful to *Ministério de Saúde da República de Moçambique* and *Instituto Nacional de Estatística* for their support and collaboration. We thank Donna Pringle for the English revision of the manuscript.

Table 1. Age at diagnosis of the different gynecologic cancers. Data are presented as absolute numbers and percentages (in brackets).

	Age group							
	0-14	**15-29**	**30-34**	**35-50**	**51-74**	**≥75**	**Unknown**	**All ages**
Cervix	7 (33.3)	137 (49.3)	871 (68.2)	791 (64.2)	428 (61.8)	78 (59.1)	71 (76.3)	2383
Vagina/vulva	3 (14.3)	28 (10.1)	37 (2.9)	40 (3.2)	32 (4.6)	7 (5.3)	5 (5.4)	152
Breast	1 (4.8)	42 (15.1)	286 (22.4)	328 (26.6)	156 (22.5)	40 (30.3)	12 (12.9)	865
Ovary/Tube	9 (42.9)	27 (9.7)	40 (3.1)	37 (3.0)	22 (3.2)	2 (1.5)	3 (3.2)	140
Uterus	0 (0.0)	9 (3.2)	21 (1.6)	31 (2.5)	54 (7.8)	5 (3.8)	2 (2.2)	122
Trophoblast	1 (4.8)	35 (12.6)	23 (1.8)	5 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	64
Total	21	278	1278	1232	692	132	93	3726

Table 2. Histological types of the carcinomas of the uterine cervix. Data are presented as absolute numbers and percentages (in brackets).

	n	**(%)**
Squamous cell carcinoma	2107	(88.4)
Adenocarcinoma	168	(7.0)
Adenosquamous carcinoma	50	(2.1)
Undifferentiated carcinoma	29	(1.2)
Carcinosarcoma	11	(0.5)
Small cell carcinoma	7	(0.3)
Malignant lymphoma	4	(0.2)
Leiomyosarcoma	3	(0.1)
Kaposi's sarcoma	2	(0.1)
Rhabdomyosarcoma	2	(0.1)

Table 3. Histological types of the carcinomas of the uterine corpus. Data are presented as absolute numbers and percentages (in brackets).

	n	%
Adenocarcinoma, endometrioid	65	(53.3)
Adenocarcinoma, serous/clear cell	11	(9.0)
Carcinosarcoma	7	(5.7)
Leiomyosarcoma	30	(24.6)
Endometrial stromal sarcoma	6	(4.9)
Kaposi's sarcoma	3	(2.5)

Figure 1. Sites of involvement of the 3726 gynecologic tumors identified in the Maputo Central Hospital from 1991 to 2018

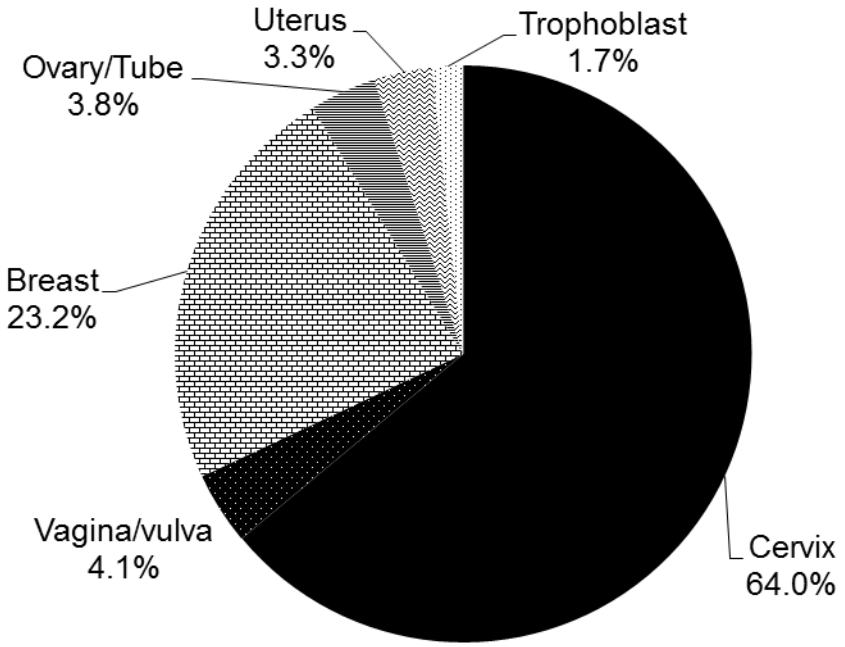


Figure 2. Evolution of the histological types of carcinomas of the uterine cervix during the period of study

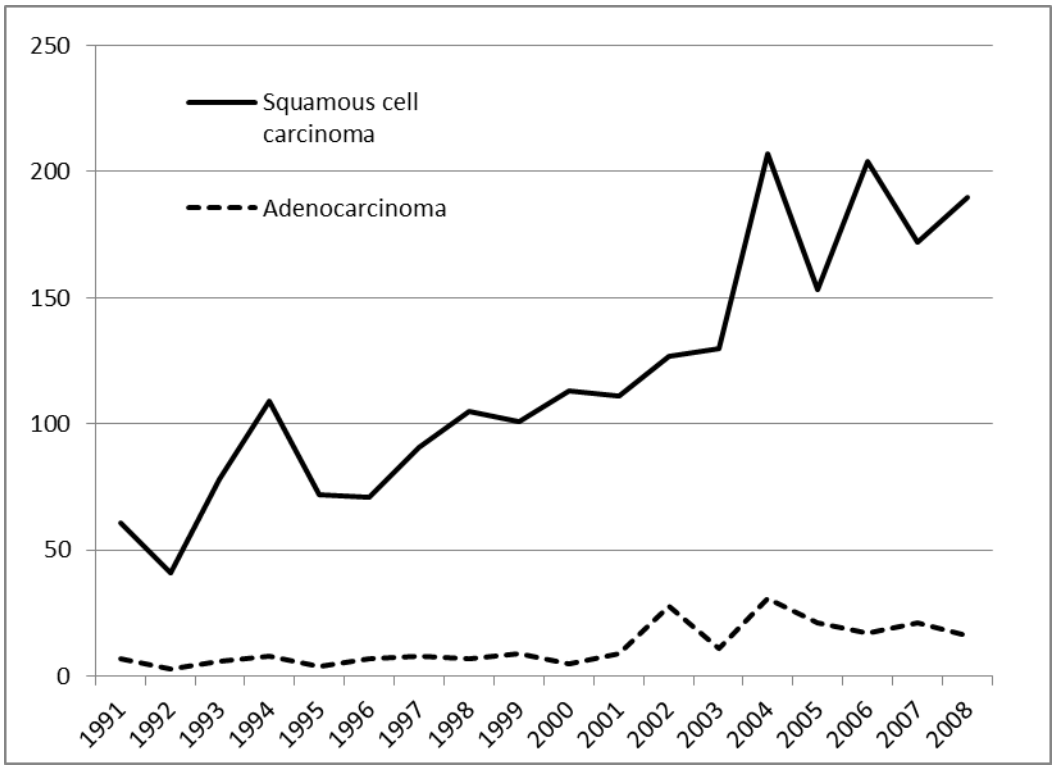
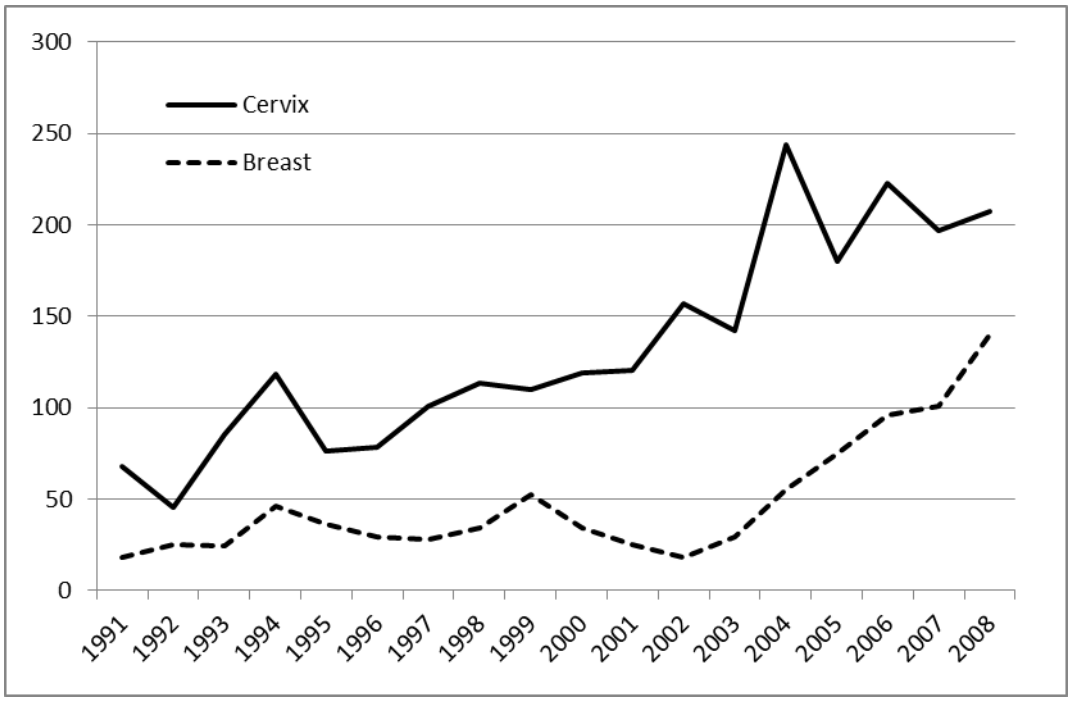


Figure 3. Evolution of the carcinomas of the uterine cervix and carcinomas of the breast during the period of study



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