Original Article

Cervical cancer in women diagnosed at the National Health Laboratory, Sudan: A call for screening

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Abstract

Background: Cancer of the cervix is the second most prevalent cancer of women to date in the Sudan, in a concerted review of the records of the hospital-based cancer registry of the Radiation & Isotope Centre of Khartoum (RICK). However, in spite of a wealth of data, this is the first study to date describing the histopathologic prevalence of cervical cancer in the Sudan.

Objectives: To identify the percentage and clinicopathological pattern of cervical cancer cases diagnosed at Histopathology Department, National Health Laboratory (NHL) in Khartoum, Sudan.

Material and Methods: This is a cross-sectional, descriptive study conducted at the NHL. All cases with histopathological diagnosis of cervical neoplasm in the period from 2004-2009 were reviewed. Patients' clinical data were obtained from clinical records. Exclusion criteria included inadequate clinical information and unavailability of both Hematoxylin and Eosin stained (H&E) sections and formalin-fixed paraffin-embedded (FFPE) blocks. The WHO classification of cancer of the cervix (2003) was used to describe disease type.

SPSS data analysis was applied.

Results: A total of 287 cases were reviewed and 195 cases were included in the study. The mean of cervical cancer cases diagnosed per year at NHL is 7.9%. The commonest age group affected was patients grouped between 41- 60 years (52%) followed by 61-80 years (26.3%). Histologically, 95.9% of the cases were carcinomas. Squamous cell carcinomas were 90.9%, Adenocarcinomas 4.8%, and other epithelial tumours were 4.3%. Of the Squamous carcinomas, 98.8% were invasive and 1.2% intraepithelial (cervical intraepithelial neoplasia).

The majority of case presentations were that of a protruding cervical mass. We noticed the commonest symptom being bleeding per vagina.

Conclusion: To determine the incidence of cervical cancer in the Sudan a national population-based registry is necessary. The mean age of patients presenting with cervical cancer to NHL is 53.25 years. This is in keeping with the natural history of the human papilloma virus (HPV). The late presentation of patients with aggressive disease necessitates health education and cervical cancer screening as well as strict guidelines for medical record keeping in line with good medical practices, enabling good data collection for the newly established population-based cancer registry.

Key words: HPV, invasive squamous cell carcinoma.

CANCER of the cervix uteri is the second most common cancer among women worldwide, with an estimated 529,409 new cases and 274,883 deaths in 2008[1].

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About 86% of the cases occur in developing countries, representing 13% of female cancers[1].High-risk regions are East and West Africa with age-standardized incidence rate (ASR) greater than 30 per 100,000. These are followed by Southern Africa (26.8 per 100,000), South-Central Asia (24.6 per 100,000), South America and Middle Africa (ASRs 23.9 and 23.0 per 100,000)[1]. Rates are lowest in Western Asia, Northern America and Australia/New Zealand (ASRs less than 6 per 100, 000) [1]. Some Eastern and Central European countries have relatively high incidence such as Serbia[2] where the ASR of

cervical cancer is 27.2 per 100,000 - twice as high as in Western European countries[3]. The decline in rates of cervical cancer in Europe and North America is mainly due to the rigorous preventive measures adopted in these societies of cervical cancer screening via the Pap smear.

According to hospital-based statistical data from the Radiation and Isotopes Centre of Khartoum (RICK), cervical cancer is the second most common cancer type among women in Sudan[4].

To date there is no national registry or epidemiological study published about this heath problem.

It is almost two decades since Haral zur Hausen discovered the DNA of Human Papilloma Virus (HPV) type 16 and 18 in cervical cancers and implicated them as causative agents. Since then HPV has been well characterized as a causative agent for cervical cancer[5]. Of the more than 100 subtypes of the HPV have been identified with forty implicated or associated with genital infection but persistent genital infection with oncogenic HPV causes virtually all cases of cervical cancer[6, 7]. HPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 66 are considered to be high risk (HR HPV) and closely related to cervical oncogenesis [8-10].

Copies of HPV viral DNA are detected from 90% of cervical cancer cells. Their E6 and E7 gene products are known to inactivate the major tumor suppressors, p53 and retinoblastoma protein (Prb) and drive cells into an immortal phase with E6 gene products affecting the activity of telomerase[5].

The commonest cancer causing subtypes in Africa appear to be similar to other countries in both the developed and developing world[11-14].

Other factors such as smoking, immunosuppression, chlamydia infection, diet, oral contraceptives, multiple full-term pregnancies, young age at the first full-term pregnancy, poverty, diethylstilbestrol and family history of cervical cancer, may predispose to cervical cancer[15]. But the causal role of HPV in all cancers of the uterine cervix has been firmly established biologically and epidemiologically[16]. Other associations such as co-infection with HIV have also been established in some sub-Saharan African countries[17].

The aim of this study is to identify the percentage and the clinicopathological pattern of cervical carcinomas found in the records of the Histopathology Department, National Health Laboratory (NHL) in Khartoum, Sudan, which receives the majority of specimens from different regions of the country.

Material and Methods:

This is a cross-sectional, descriptive study conducted at the Histopathology Department, NHL in Khartoum, Sudan. All cases diagnosed histopatholgically as cervical tumour in the period 2004-2009 were studied and reclassified according to the WHO (2003) classification system by two histopathologists. An experienced third histopathologist was consulted in some cases. Squamous cell carcinomas were reclassified using the recommended two-tiered classification (keratinized and non-keratinized) and assessed histologically for the degree of differentiation. The patient's information was collected from the clinician's request forms. Exclusion criteria included inadequate information and unavailability of both the Hematoxylin and Eosin (H&E) sections and the formalin-fixed paraffin-embedded (FFPE) blocks. The data were analyzed using the Statistical Package of Social Sciences (SPSS). P value less than 0.05 was considered statistically significant.

Results:

In a review of the NHL histopathology department a total of 287 cervical cancer cases diagnosed during the period 2004-2009 in the NHL, 195 cases were included in the study. Exclusionary criteria for the 92 cases included insufficient clinical data or demographic information or unavailability of FFPE blocks. In the year 2004, 65 invasive cervical cancer (ICC) cases were diagnosed. It represents 12.87% of all cancer cases diagnosed in the same year. In the 2005, 11.82% of cancer cases were ICC, while it

was 8.10% in 2008. In average, cervical cancer accounts approximately for 7.9% of cancer cases diagnosed annually in the NHL. The commonest age group at presentation was 41- 60 (52%) followed by 61-80 (26.3%) (Figure1).

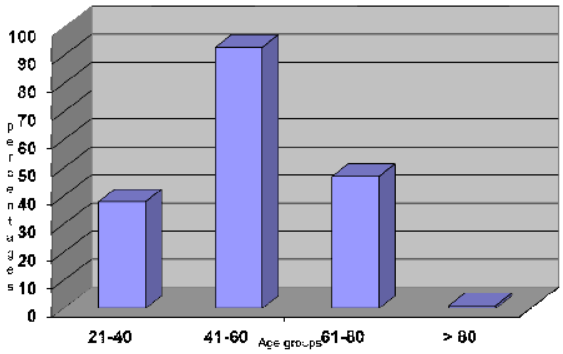

Figure1:Distribution of cases according to age.

Mean age at presentation was 53.3(± 3.5 SD). Vaginal bleeding was the presenting symptom in 88.7% of the studied cases and presence of a cervical mass protruding through vagina accounted for 54.3% of the studied cases in which vaginal examination findings were registered (Figure 2).

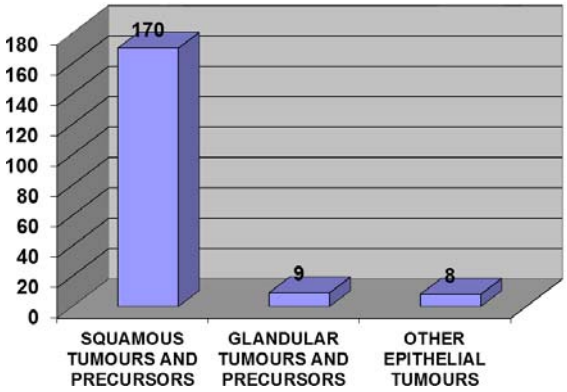

Figure 2: Distribution of epithelial tumors among the studied cases (No=187).

Histologically, 95.9% of the cases reviewed were carcinomas. Of the carcinomas 90.9% were squamous, 4.8% were adenocarcinomas, and 4.3% were other epithelial tumours (Figure 3). The squamous cell carcinomas were 98.8% invasive and 1.2% intraepithelial (Figure 4).

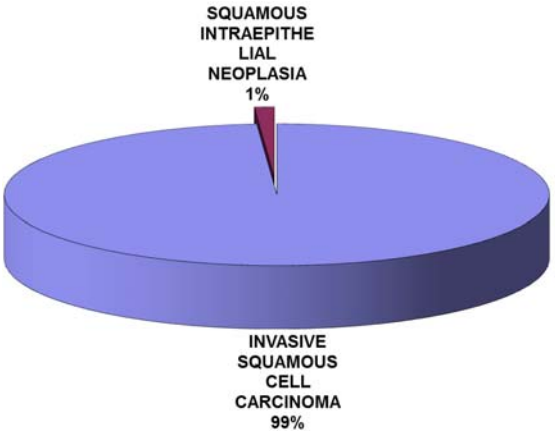

Figure 3: Distribution of squamous neoplasms among the studied cases.

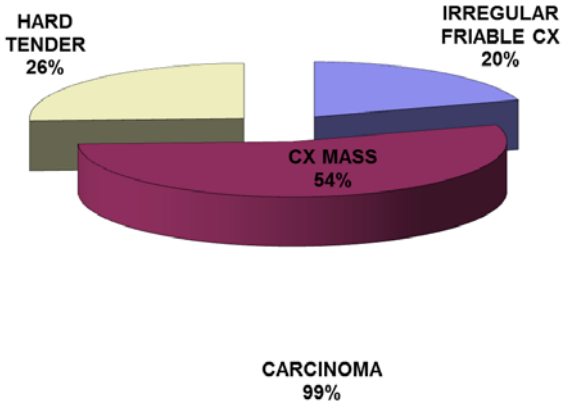

Figure 4: Findings of vaginal examination among the studied cases.

Non-keratinizing squamous cell carcinomas (SCC) accounted for 66.1% and the keratinizing SCC for 24.4% of SCC types. Grading revealed 22.8% well differentiated, 44.9% moderately differentiated and 22.8 were poorly differentiated SCC.

Discussion:

The declining incidence of ICC in the NHL in this study did not reflect the real situation, as many patients who were diagnosed in private or newly established histopathology laboratories were not included in the study. More systematic and national population-based registries and accurate medical record keeping are needed to better determine the incidence of cervical cancer in Sudan.

In a meta-analysis, de Sanjose S et al found that worldwide HPV prevalence in women

with normal cytology at any given point of time is approximately 10.0% indicating that it is one of the most common sexually transmitted infections. About 70.1% of invasive cervical cancers in the world are attributed to HPVs 16 or 18. HPV-16 is consistently the most common type and HPV-18 the second with some minor regional differences[18, 19].

Detrimental to HPV infection and transmission are sexual behavior patterns across populations and age groups rather than individual sexual practices, particularly sexual behavior considered high risk, such non-monogamous relationships, early or premature sexual practice as a teenager[20]. Another pertinent issue studying population patterns and their sexual behavior is that of migrant population with high risk behavior puts those of host country at high risk of developing cervical cancer, particularly so because they too are at high risk of developing ICC related to HPV infection[20].

Sudan has a large migrant population from neighboring African countries. The current study showed that women diagnosed at the NHL as having cervical cancer are at a higher age (Figure 1). This is in keeping with the natural history of HPV infection. The mean age at presentation is 53.3 which is higher compared to some studies [21-24] while similar to others where HPV infection is still prevalent[25-27]. A similar study published recently from Iran described a similar average age group incidence of 53.6 years as ours and higher percentage of adenocarcinomas (20%) when compared to this study. However other similarities include a very low rate (< 2%) of cytology screening in Iran[28].

The most common histopathological type in this study was squamous cell carcinoma and the majority of cases (66.1%) were large cell non-keratinizing. The histopathological features of cervical carcinomas in Sudan appear to be similar to those found in United States, Europe, Asia, and Africa[24, 29-32]. Nearly all studied cases were invasive cervical cancers (98.8%) and where vaginal examinations findings were registered, 54.3% of the patients presented with a protruding cervical mass, i.e. stage II or more. This late presentation is found only in developing countries[21]. Late tumour stage correlates with unscreened populations, however if at risk populations are screened regularly, mortality is reduced by (70%) [33, 34]. Screening for cervical cancer, particularly the Pap smear, has saved multitudes of lives in developed countries. However, this is not the case in developing countries where the majority of women remain unscreened and at high risk of developing invasive cervical cancer, due to the limited resources of their health infrastructure. Incidence too, remains very high for cervical cancer at 86%[35, 36].

The Pap smear for short is the Papanicolaou test, a cytopathology screening test, developed by Georgios Papanikolaou in the 1950s of the last century, and has been instrumental in decreasing the incidence of cervical cancer in the Americas and Europe. Organized and systematic programs of cervical cytology that have been established worldwide in both developed countries have lowered the rates of cervical cancer and increased the detection of preinvsive and dysplastic lesions, which can be easily cured. However, cervical cytology programs require well organized, quality assured, infrastructure and trained health professionals and financing [37, 38].

Hurdles, exist to date to establishing cervical cytology screening programs in developing countries as has been identified in countries of Latin America, where cervical cancer incidence is fluctuating. Many impediments to proper screening have been identified, including, poverty, poor health infrastructure, and lack of awareness of the at risk population[39-41].

Therefore, a number of different tests have been developed and investigated over the years as alternative screening tests to cytology, particularly for low income settings, where programs cannot be implemented properly. They include: HPV-DNA testing, Visual inspection methods, Colposcopy, Polar Probe and optical detection methods[41]. Visual inspection (with acetic acid or Lugol's iodine) and HPV-DNA testing which is being

considered as an additional test to the conventional Pap screening test and as a primary screening test in older women are the two most widely studied alternative approaches to cervical cancer prevention. Cervical precursors that are most likely to progress to cervical cancer are better identified by molecular tests, particularly tests that could detect integrated HPV-DNA or its products[41]. Maintaining routine quality controls of the screening procedures and organizing the proper follow-up of women with abnormal screening results are essentials of the success of the screening program [42].

In the 2009 New England Journal of Medicine publication, Sankaranarayanan et al, described a cluster-randomized trial of Indian women from 52 villages, more than 130 000 women participated. In the study they compare HPV genotype testing (a one time event), cytology based screening and thirdly visual inspection of the cervix with acetic acid. The conclusion of this study suggests that perhaps a one time HPV test of a sexually active female, between the ages of 30-60 years may be more accurate and more affordable of limited resource settings[13].

In Sudan, cervical cancer screening programs has not been implemented by the Federal Ministry of Health although it has been prioritized in its WHO supported National Cancer Control Program and the majority of women have never been screened. The authors think that lack of screening, women's lack of knowledge about reproductive health issues, centralization of health care services, and personal barriers that women experience in accessing health care may attribute to the late presentation of cervical cancer cases in Sudan. In spite of other experiences in other African and developing countries, there still exist barriers to proper cervical cancer screening and this even in our societies were awareness of the severity and knowledge that cervical caner can be cured[11,12,43]. This highlights the need for screening of cervical cancer for early detection and management in addition to educational and organizational preventive strategies, as well as further studies understanding factors leading to lack of access to knowledge and basic infra structure needed to establish programs, particularly in rural settings.

Therefore, a serious and concerted effort is needed to reduce the prevalence of cervical cancer in Sudan. The authors of this paper would like to acknowledge the role of the Regional and Federal Ministries of Health in the Sudan and local NGOs in their efforts to combat and decrease the incidence of cervical cancer, particularly with the initiation of a population based caner registry in 2010. However, policy makers need to get on board to prevent this otherwise fatal disease by endorsing a feasible screening program for women, who are the backbone of our society.

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