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REVIEW ARTICLE

Carcinoma of the cervix and cervical cytology — short epidemiological review

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SUMMARY

Carcinoma of the cervix is an important disease of well-documented epidemiology but uncertain cause. It causes appreciable morbidity and mortality in all countries, including Zimbabwe, with a significant load on curative services. Epidemiology and the role of cytology are reviewed. Cytology screening programmes have suffered from an inability to cover whole populations, particularly less affluent and/or socially disadvantaged groups, which are most at risk.

Despite this difficulty, the magnitude of the problem makes it necessary to continue its study. In particular, efforts are needed in developing countries to study incidence, to better define high risk groups and to devise economical ways of detecting more cases in the earlier stages.

INTRODUCTION

Squamous carcinoma of the cervix uteri is an important disease with a well-documented

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epidemiology (including high incidence in less developed countries) but of uncertain cause. It causes appreciable morbidity and mortality in all countries, including Zimbabwe, and is a significant load on curative services. It is, therefore, essential to make a careful study of the origins of the disease and of possible means of preventing it or detecting it in its early stages.

Incidence and Geographical Distribution: Annual incidence per 100 000 females is one way of measuring the importance of the disease. Table I gives figures for a number of countries, derived from Doll *et al* (1966[1]). To put it another way, it has been stated that two pc of all women in one developed country may expect to develop the disease.

Many less developed countries are believed to have greater incidences of carcinoma of the cervix in absolute terms, and in comparison with other gynaecological malignancies and malignancies in general. Table I illustrates this. Breast carcinoma in particular is the commonest malignancy in Western women, but is far behind carcinoma of the cervix in incidence in Zimbabwe[2] and South Africa.[3] The differences would become more obvious if the different age structures of the populations being compared were taken into account.

Accurate figures are especially difficult to obtain for less developed countries, so that valid comparisons are difficult to make. It seems nonetheless that practitioners in these countries are at least no less obliged to consider the problem of carcinoma of the cervix. As young (growing) populations age, and to some extent as improvements in living standards and health care decrease deaths from other causes, this malignancy and others will become more prominent than they already are.

Age distribution: Median ages at diagnosis were shown in New york City[4] to be 47 years for invasive carcinoma, 35 years for carcinoma *in situ*, and 28 years for cervical dysplasia. It has been suggested that incidence and mortality in younger women are increasing in some developed countries but it is too early to conform any such historical trend.

Other epidemiological features: Early age of first coitus or first marriage has been linked with invasive carcinoma of the cervix, carcinoma *in situ* and cervical dysplasia.[5]

An association with number of sexual partners has been found. There are more broken marriages, more multiple marriages and fewer never-married women among carcinoma cases than among controls.[4,6] A very high rate (37/1 000) of carcinoma *in situ* was

Table I: Incidence and relative incidence of carcinoma of the cervix in several countries (Figures derived from "Cancer in five Continents" [1]

	CA in Situ	Annual incidence all ages/100 000 females	pc of all female malignancies	pc of all female genital* malignancies
Mozambique (Maputo) 1956–60	excluded	18,6	21,3	85,7
Johannesburg (black women) 1953–55	one case included	29,8	41,9	85,5
Jamaica (Kingston & St Andrew) 1958–63	included	37,9	28,9	75,8
Columbia (Cali) 1962–64	excluded	62	35,0	78,5
England & Wales (South Western region) 1960–62	excluded	17,3	6,0	31,9
Denmark 1953–57	excluded	34,0	11,9	48,5
U.S.A. (Connecticut) 1960–62	excluded	16	5,2	29,0
Israel 1960–62	excluded	5,5	2,5	19,6

* W.H.O. (1957) International List Numbers 171–176.

found in a prison population which included many prostitutes and had a high rate of syphilis, gonorrhoea and trichomoniasis. The very low incidence of carcinoma of the cervix in nuns provides further evidence that coitus is in some way important for the development of the disease.

Parity and age at first pregnancy appear to be less directly related to risk of developing the disease.

Low socio-economic status is a known risk factor, perhaps because of greater promiscuity, earlier coitus/marriage/pregnancy, poorer hygiene and less opportunity for and/or acceptance of medical care. As implied, the reasons are not definitely known.

Low incidences have been reported in Jewesses, Muslims in India and South-Western American Indians. A high incidence has been reported in American Negroes.

Users of oral contraceptives have been found to have a significant excess of invasive cervical cancer, although this was offset by a decrease in ovarian and endometrial cancer.[7] An increase in carcinoma *in situ* of the cervix was more marked.

Circumcision has been suggested as the protective factor accounting for low incidence in some populations such as Jews and Muslims. A laboratory based study in Lebanon failed, however, to find a difference in incidence of cervical carcinoma in circumcised and uncircumcised populations living in the same environment.[8] A carcinogenic effect of smegma has been postulated, but there has been no laboratory evidence of such an effect.

Contacts of men with carcinoma of the penis appear to be a high risk group.

Occupational status of the husband[9] has been linked with increased incidence of carcinoma of the cervix. Wives of seamen are an example and it may be that their spouses' itinerant life-style and presumed greater promiscuity are responsible. However, wives of commercial travellers are not at increased risk. It may be that the seamen are occupationally exposed to carcinogens (such as in tar) which they pass on to their wives.

Smoking is strongly associated with carcinoma of the cervix and is now recognised as a major risk factor.[10] It is unclear whether the association is causal or the result of some unknown confounding factor.

Various authors report discrepancies between the epidemiological features of the dysplasias and of more advanced lesions. This is consistent with the current view that dysplasia is a heterogeneous category, which includes many lesions without malignant potential. Richard *et al*[11] found that true cervical intraepithelial neoplasia (CIN) shows aneuploidy on micro-spectrophtometry whereas other lesions without neoplastic potential show euploidy or polyploidy.

Constitutional predisposition must also be considered, for example alpha 1 antitrypsin deficiency.[9]

A sexually transmitted carcinogen?: Many of the epidemiological features outlined above (smoking being one exception) suggest a coitally-transmitted carcinogen or carcinogens to which the cervix may be more susceptible during adolescence or the first pregnancy. Endocervical columnar epithelium exposed to the acid environment of the vagina undergoes physiological squamous metaplasia. This process is most active in the late foetal/neonatal stage, in early adolescence and during the first pregnancy. Reid and Coppleson[12] have proposed that future malignant potential may be determined during a very brief period of peak vulnerability during the transformation process, if an appropriate stimulus is present. This potential may then not be realised for many years.

Histones from the heads of spermatozoa could have carcinogenic activity, more so in males with higher than usual proportions of basic amino acids in their histones.[9]

The evidence is very much in keeping with an infective cause. Associations with syphilis, gonorrhoea and trichomoniasis are thought to be incidental. At association between *Chlamydia trachomatis* and CIN has been found and the suggestion made that 'mild CIN' may be reversed by tetracycline.

Viruses have been studied extensively because they can be sexually transmitted and because of the known oncogenic potential of some viruses. *Herpes simplex* virus type two (HSV-2) antibodies are found in higher titres in cervical carcinoma cases than in controls, although some cases lack these antibodies. Progression of CIN I or VIN II to CIN III has been shown to be more likely in the presence of HSV-2 antibodies, whereas HSV-1 antibodies appeared to have a protective effect. The role of HSV-2 remains unproven.

There has been recent interest in non-condylomatous cervical wart virus infection (NCWVI). (Some prefer the term subclinical papillomavirus infection or SPI). Reid *et al*[13] described diagnostic features of this and pointed out that such infection is common and may co-exist with CIN. Very strong associations of NCWVI with cervical carcinoma and CIN have been found in a study of hysterectomy specimens.[14]

The papillomaviruses in general are especially noted for causing benign epithelial tumours in humans and animals. Conversion to squamous carcinoma is known to occur in many such tumours following exposure to various agents. For example, human juvenile multifocal laryngeal papillomas may become malignant if treated by radiotherapy. Zur Hausen[15] has suggested that papillomavirus may be a promoting agent for cervical carcinoma, with HSV–2 infection acting as an initiating agent.

Cervical Cytology: In the absence of a known cause, attempts to control carcinoma of the cervix have been directed towards early diagnosis through cytological screening. This condition has perhaps the best potential for such an approach for reasons summarised by Miller:[16] (1) the accessibility of the cervix; (2) the propensity of cells to exfoliate from precancerous lesions; (3) the existence of a spectrum of histological changes from mild atypias through to frank malignancies; (4) the apparent long natural history.

Progression of lesions through the 'spectrum' is not clear-cut. The existence of a 'yawning gap' between the incidences of *in situ* and invasive carcinoma suggests that lesions up to and including carcinoma *in situ* may regress spontaneously.[16] Studies of invasive carcinoma cases have revealed that many have had recent negative cytology. It has been suggested that there is a rapidly growing form of the disease, but a probable explanation is sampling error when the smears were taken.

Intensive screening is believed by many to have favourably influenced incidence and mortality figures, for example in Alameda County, California and in Aberdeen. On the other hand, not all are convinced that such conclusions were justified. Mass screening aside, there is no doubt regarding the benefit to an individual woman with microinvasive carcinoma detected and treated, and to at least a proportion of those with carcinoma *in situ* detected and treated, assuming death from other causes does not supervene.

The optimum screening frequency is uncertain. Annual smears have been advocated, but according to one computer study most women need to be screened only once every three to five years. Gordon Grant[17] suggested annual screening for two negative smears then once every three years.

False negatives may be caused by sampling error. It is recommended that the squamocolumnar junction be scraped in its entire circumference (as by an Ayre's spatula). Adequacy is suggested by the presence of both endocervical and ectocervical elements in the smear. The false negative rate is less if a second smear is made at the time of initial screening, but this has not been universally adopted. Bleeding, exudate or inflammation may prevent the cytologist from making an adequate assessment of the smears. Abnormal cells may be lost if the cervix is swabbed or otherwise disturbed prior to taking the smear.

Clerical error may result in unnecessary procedures, therefore abnormal smears are generally repeated. Patients may also be lost to follow-up through clerical error.

Cytologists may make errors and may not always agree among themselves. Abnormal cytology should in general be confirmed by histology, preferably on a colposcopically directed biopsy, before definitive treatment is given. Histology may be misleading if biopsies are too small, or are unrepresentative, or have been damaged by cleaning of the cervix or the recent taking of a smear.

Distinguishing carcinoma *in situ* from microinvasive carcinoma may be difficult. Difficulties may also arise in distinguishing severe dysplasia from carcinoma *in situ*. These last two entities are together approximately equivalent to CIN III in newer terminology. Mild and moderate dysplasia are thought to have a very low risk of progressing to invasive carcinoma in comparison with more advanced lesions, so the newer terminology is logical in this respect. (Direct transformation from CIN I or II to invasive carcinoma has, however, been postulated.) The duplication of terminology and the use of histological terms by cytologists may cause confusion.

Screening programmes tend to miss the women who are most at risk: Antenatal/postnatal and contraceptive clinics are frequented mainly by

younger women. Older women may avoid pelvic examination and tend to attend less regularly for follow-up. A study in Manchester found that widows and divorcees, a high risk group, constituted 17,5 pc of women aged 20 or more in the district, but only 3,6 pc of those being screened by cervical cytology were in this category. Lower socio-economic groups are at greater risk, but may be less well informed about or less accepting of medical services.

CONCLUSIONS

Carcinoma of the cervix is an important disease world-wide with apparent relative prominence in developing countries. The epidemiology is well known but the cause is uncertain. It causes appreciable morbidity and mortality in all countries, with a significant load on curative services. Cytology screening programmes have suffered from an inability to cover whole populations, particularly less affluent and/or socially disadvantaged groups, which are most at risk. Despite this difficulty, the magnitude of the problem makes it necessary to continue its study. In particular, efforts are needed in developing countries to study incidence, to better define high risk groups and to devise economical ways of detecting more cases at an earlier stage.

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