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
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). To put it another way, it has been
stated that two per cent 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 and South Africa. 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 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, carcinoma in situ and
cervical dysplasia. 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. 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"

<table>
<thead>
<tr>
<th>Country</th>
<th>CA in Situ</th>
<th>Annual incidence</th>
<th>pc of all female malignancies</th>
<th>pc of all female genital malignancies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mozambique (Maputo)</td>
<td>excluded</td>
<td>18,6</td>
<td>21,3</td>
<td>85,7</td>
</tr>
<tr>
<td>Johannesburg (black women)</td>
<td>one case</td>
<td>29,8</td>
<td>41,9</td>
<td>85,5</td>
</tr>
<tr>
<td>Jamaica (Kingston &amp; St Andrew)</td>
<td>included</td>
<td>37,9</td>
<td>28,9</td>
<td>75,8</td>
</tr>
<tr>
<td>Columbia (Cali)</td>
<td>excluded</td>
<td>62</td>
<td>35,0</td>
<td>78,5</td>
</tr>
<tr>
<td>England &amp; Wales (South Western region)</td>
<td>excluded</td>
<td>17,3</td>
<td>6,0</td>
<td>31,9</td>
</tr>
<tr>
<td>Denmark</td>
<td>excluded</td>
<td>34,0</td>
<td>11,9</td>
<td>48,5</td>
</tr>
<tr>
<td>U.S.A. (Connecticut)</td>
<td>excluded</td>
<td>16</td>
<td>5,2</td>
<td>29,0</td>
</tr>
<tr>
<td>Israel</td>
<td>excluded</td>
<td>5,5</td>
<td>2,5</td>
<td>19,6</td>
</tr>
</tbody>
</table>

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. 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. 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 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 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. 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. found that true cervical intraepithelial neoplasia (CIN) shows aneuploidy on micro-spectrophotometry whereas other lesions without neoplastic potential show euploidy or polyploidy.

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

Sexually transmitted carcino gens?: Many of the epidemiological features outlined above (smoking being one exception) suggest a sexually-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 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.

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.\textsuperscript{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.\textsuperscript{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\textsuperscript{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:\textsuperscript{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.\textsuperscript{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, 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\textsuperscript{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.

Cytological 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.

REFERENCES

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