

## AETIOLOGICAL FACTORS IN CARCINOMA OF THE UTERINE CERVIX

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Standard textbooks on pathology<sup>1, 4</sup> have very little to say on the aetiology of cervical carcinoma. Anderson does not mention the subject. Boyd discusses the carcinogenic properties of smegma and oestrogens very briefly, the latter when not opposed by the influence of cyclical progesterone. Novak and Woodruff<sup>24</sup> give a brief summary of the more important publications. Most British textbooks on gynaecology<sup>3, 15</sup> do little more than summarize some of the recent work.

## I. SURVEY OF THE LITERATURE

*Age Incidence*

According to Novak and Woodruff<sup>24</sup> cervical cancer appears, on an average, 10 years earlier than cancer of the endometrium, and women between 40 and 65 years are more likely to be affected. After the age of 65 years the risk diminishes. Diddle and Watts<sup>8</sup> state that cancer of the cervix also affects the relatively young, 6% of all such cancers appearing before the age of 30.

Rewell,<sup>29</sup> in comparing the incidence of cancer of the cervix in India and Britain, found that carcinoma appeared 10 years earlier in India. He ascribes this to the fact that, on the average, Indian women marry 10 years earlier than British women, concluding that earlier marriage causes earlier appearance of carcinoma of the cervix. This conclusion may be criticized on the basis that childbirth in Indian women occurs 5 years earlier than in British women. As a result, a 5-year shift in the appearance of cancer could swing the balance from the 45-55 year age group to the 35-45 year age group. Thus a shift of 5 years would really appear as a 10-year shift in his data.

*Marital State, Parity and Sexual Habits*

For years marital state and parity have aroused interest, but it is only lately that sexual habits have been studied intensively. The low incidence of cervical cancer in nuns and the high incidence in prostitutes is common knowledge. In the USA Pereyra,<sup>27</sup> in a study of female prisoners, found that carcinoma of the cervix appeared 6 times more often among prisoners than among a mixed civilian population. He ascribed this to low moral behaviour.

Recent publications draw attention to a specific sexual pattern, i.e. regular intercourse starting at an early age, early marriage, extra-marital coitus, increased frequency of coitus and the absence of contraceptive appliances and media.<sup>30-32, 34</sup>

Terris,<sup>33</sup> in a later publication states that early coitus might be a contributing factor to carcinoma of the cervix but that at present there is no such proof. Rotkin,<sup>31</sup> in his control group which had not developed cancer, found that intercourse started at a later age, and that the partners were sexually more active than in a group with cervical carcinoma.

Cummins<sup>7</sup> could not confirm this sexual pattern and could find no evidence that an early first pregnancy con-

tributed to the incidence of cancer of the cervix. Duration of marital state seemed to be of no statistical significance.<sup>16</sup>

Rewell,<sup>29</sup> in India, equalizing age at first confinement with fertility, compared the age of first confinement in a group of patients with carcinoma of the cervix and in a group of patients undergoing hysterectomy. Age of first confinement was the same in both groups. He therefore concluded that fertility did not influence the frequency of carcinoma of the cervix. Coitus from an early age seemed to be a common factor in both groups.

Maliphant stated that high parity predisposed to cancer of the cervix. His work was criticized<sup>3, 33</sup> because his control group was chosen from a different socio-economic sphere. Rotkin and King<sup>31</sup> and others<sup>16</sup> concluded that parity *per se* had no influence on the incidence of the development of cervical cancer. Dunham<sup>9</sup> found that multiparity, as an aetiological factor in the frequency of carcinoma of the cervix, was statistically of slight significance.

Cummins<sup>7</sup> states that cervical cancer is the end result of an unknown but specific carcinogenic stimulus that may come into play during any pregnancy. Multiparity increase the risk of cervical cancer because it increases the number of exposures to this specific stimulus.

Masturbation is not considered a factor of aetiological importance.<sup>31</sup>

*Circumcision and the Possible Carcinogenic Influence of Smegma*

Circumcision in the male has been given as a reason why Jewesses rarely develop carcinoma of the cervix. Smegma was incriminated when the search for the carcinogen started in the male. In experiments by Heins,<sup>33</sup> human smegma was applied to uterine cervixes of mice. Carcinoma developed in 50% of cases but in repeating the experiment only 1 carcinoma developed in 25 mice.

Yagi<sup>36</sup> tried to find collateral evidence as to the influence of smegma. In Japan there is a high incidence of cervical carcinoma. He reasoned that if carcinoma of the cervix was due to the carcinogenic factor in smegma, it was probable that conditions which gave rise to an accumulation of smegma, for instance phimosis and paraphimosis, would be more common in Japan than elsewhere. He found a low incidence of phimosis and paraphimosis and therefore concluded that smegma probably did not influence the incidence of carcinoma of the cervix.

In the Sudan, Lynch *et al.*<sup>21</sup> found a low incidence of cervical cancer which they ascribed to the practice of circumcision among Mohammedan tribesmen. They found that the incidence of carcinoma of the cervix among Sudanese women was still higher than among Jewesses. This they ascribed to additional factors such as early coitus, multiple pregnancies and poor socio-economic conditions.

Rewell<sup>29</sup> found that in Indian women there was no significant statistical difference in the incidence of cancer

of the cervix between Hindu women and a small group of Mohammedan women whose male partners were all circumcised.

Some publications<sup>9, 32</sup> indicate that there is a slight correlation between carcinoma of the uterine cervix and circumcision; others found no such correlation.<sup>25</sup> Jones *et al.*<sup>16</sup> and Terris<sup>33</sup> found no correlation with circumcision at all once the Jews were excluded. In the Bantu in South Africa there was no close correlation between carcinoma of the cervix and the state of circumcision of the husband.<sup>14</sup>

The validity of many of these conclusions was questioned when it was found that a large number of females could not accurately state whether the male cohabitant was circumcised or not.<sup>14, 31-33</sup>

Contraceptive appliances and media keep the cervix sheltered from direct contact with smegma. Some authors found that less contraceptives were used by patients with carcinoma<sup>33</sup> while others<sup>31</sup> found no difference.

#### Racial Incidence

From the discussion above it is clear that there could be racial differences despite certain common practices. Dunham<sup>9</sup> is of the opinion that ethnic factors are important.

#### The Influence of the Ductless Glands and Oestrogens

Experimental oestrogenic stimulation in mice gave rise to all stages of dysplasia, carcinoma *in situ* and infiltrating carcinoma of the cervix.<sup>11</sup> The influence on the endometrium could not be assessed because pyometra invariably developed.

Since socio-economic factors are so important, Terris<sup>33</sup> rejects endocrine influence as a material factor. In this he is supported by Rotkin,<sup>30</sup> who found no menstrual disturbances among groups suffering from carcinoma and control groups. Jones *et al.*<sup>16</sup> also found no difference in oestrogenic excretion, the menarche, the menstrual cycle or the menopause in groups studied. A further point of interest will be discussed in relation to dysplasia.

#### Vaginal Discharge

The rarity of cervical cancer in patients with uterine prolapse was thought to be due to the fact that the cervix was not continuously exposed to the vaginal discharge. Cancer in patients with the cervix completely outside the vulva, though rare, does occur. Mossetti<sup>22</sup> found 4 among 41 cases of procidentia. It is thought that carcinoma in these cases developed after external irritation (clothes, etc.).

Certain cellular changes could explain the relative resistance to neoplastic change. In the exposed vagina and cervix of patients with prolapse, a low intranuclear desoxyribonucleic acid (DNA) content is found.<sup>2</sup> These changes persist for years after operations for vaginal repair. In contrast, of course, is the high DNA content that is found in tissues with a high rate of cellular growth.

#### Diverse Aetiological Factors

(a) *Infections of the cervix.* Rotkin<sup>30</sup> found that venereal disease, cervicitis and cervical pathology<sup>16, 31</sup> are not decisive aetiological factors in carcinoma of the cervix. Bilharziasis has been stressed as an important factor in South Africa,<sup>5</sup> but Crichton<sup>6</sup> recently found no significant incidence of bilharziasis in his series of cervical cancer.

Trichomonas causes certain cellular changes<sup>26</sup> which could be confusing, but in the human being these are neither dyskariosis nor malignant changes.<sup>35</sup> Pelvic infections<sup>27</sup> and syphilis<sup>32</sup> are considered aetiological factors of minor importance.

(b) *Trauma.* Previous curettage<sup>31</sup> and forceps delivery<sup>16</sup> did not show any causal relationship to cervical carcinoma. It has been suggested that criminal abortion should be further investigated.<sup>31</sup>

(c) *Diet.* Diet and vitamin deficiencies<sup>16</sup> had no influence on the incidence of carcinoma of the cervix. Obesity might be of importance.<sup>31</sup>

(d) *Viruses.* Intra-cytoplasmic inclusion bodies, which probably cause conjunctivitis in neonatal infants, have been found in the cervix.<sup>18</sup> Other viruses found in the cervix are known to cause condylomata acuminata and cytomegalic inclusion disease (salivary gland virus).<sup>17</sup>

The formation of a neoplasm by viruses is not excluded. Therefore the presence of such viruses may be an aetiological factor in carcinoma of the cervix.

(e) *Cancer of the cervical stump.* After subtotal hysterectomy, the risk of developing cancer in the cervical stump is probably no greater than the risk of other women of the same age.<sup>10</sup>

#### Dysplasia and Carcinoma in situ

One aspect which is of great interest is the incidence and aetiological relationship between erosions, dysplasia, carcinoma *in situ* and infiltrating carcinoma. Certain authors<sup>12, 28</sup> have already correlated the known facts. Unfortunately they do not state whether all biopsy specimens were derived from one racial group only and whether any Jews were included.

Reagan and Patten<sup>28</sup> found that certain epithelial reactions appeared in relation to the junctional zone or transitional area of the cervix and in this critical area a high proportion of epithelial reactions are found. The reactions are: squamous metaplasia, reserve cell hyperplasia, dysplasia and carcinoma *in situ*.

Dysplasia in the majority of cases involves both mature squamous epithelium and immature metaplastic squamous epithelium, but at times may be restricted to any one type of squamous epithelium.<sup>28</sup> Dysplasia is not solely related to squamous epithelial cancers but has been observed in association with adenocarcinoma of the cervix.

Dysplasia most often originates in the area of the mature squamous epithelium and it increases with increasing age of the patient. It is in this area that keratinizing squamous carcinoma is found most frequently and it is probable that this type of carcinoma arises from the mature type of squamous epithelium.

Squamous metaplasia, reserve cell hyperplasia, dysplasia in areas of metaplasia and carcinoma *in situ* all appear in relation to endocervical cylindrical epithelium in the junctional zone. Large cell metaplastic squamous epithelium is the probable origin of the large cell carcinoma whether of carcinoma *in situ* or of the infiltrating type. In the same way the small cell type of carcinoma (*in situ* or infiltrating) probably derives from the small reserve cells.<sup>28</sup>

Dysplasia increases with advancing age. Dysplasia in metaplastic cells appears maximally at 35 years of age

(5.5 years earlier than in carcinoma *in situ*) and decreases with advancing age as did the extent of immature squamous metaplasia. In a small series of cancers of the uterine cervix this general pattern was confirmed.<sup>28</sup>

Nieburg<sup>23</sup> expressed the opinion that the early stages of dysplasia (stages 1 and 2: benign dysplasia) are reversible lesions. These lesions do not have a definite preneoplastic significance and if they do become neoplastic it will probably only be after the 8-year follow-up period. The later stage of dysplasia (stage 3: atypical dysplasia) is thought to be potentially malignant and carcinoma may develop within 4-5 years.

Stromal atypia is often found with carcinoma *in situ*.<sup>23</sup> Geschickter and Fernandez<sup>12</sup> also postulated that reserve cell hyperplasia may develop from stromal metaplasia after certain injurious influences have damaged the stroma.

As regards the influence of hormones, Geschickter and Fernandez<sup>12</sup> are of the opinion that oestrogenic stimulation may cause hyperplasia and metaplasia. On the other hand, it is only when additional factors come into play that dysplasia develops. Dysplasia is more prevalent during pregnancy and increases in frequency in relation to parity.<sup>28</sup>

### Discussion

The literature on aetiology of cancer of the cervix is rather confusing. Dunham<sup>9</sup> writes: 'It might be indicated to study environmental factors in the same race with and without the groups of questioned factors in order to separate environmental and genetic influences.'

Therefore it was decided to compare parity in different age groups in the Bantu in a group with carcinoma of the cervix and a group without carcinoma to establish whether multiparity is an aetiological factor in carcinoma of the cervix.

### II. COMPARISON OF PARITY IN DIFFERENT AGE GROUPS IN A GROUP OF BANTU WOMEN WITH CARCINOMA OF THE CERVIX AND A CONTROL GROUP WITHOUT CARCINOMA

#### Materials and Methods

The groups studied were chosen from among the adult female Bantu patients attending the Pretoria General Hospital. These patients must of necessity be representative of the Bantu population of Pretoria, because there is no other hospital in this area which they can attend.

The Bantu patients attending the Pretoria General Hospital are a comparatively well-fed, well-dressed community with adequate housing facilities. Socio-economic condi-

tions, however, are lower than those prevalent in advanced Western countries.

The groups studied were chosen as follows: All cases treated for carcinoma of the cervix during 1962 were included in this study and tabulated according to age group and parity. As a control sample all adult Bantu were included, who on one day attended the Outpatient Department or were being treated in any female ward, except gynaecological and obstetrical wards.

The cases of carcinoma of the cervix and the control group were subjected to statistical analysis and testing procedures (Table I).<sup>19,20</sup>

The cases of carcinoma of the cervix were also tabulated according to age, stage and parity (Tables II, III).

As null hypothesis was taken the statement that patients with carcinoma of the cervix had given birth to the same number of children as the control group of women of representative age groups.

TABLE II. PARITY AND STAGE IN 100 BANTU FEMALES WITH CARCINOMA OF THE CERVIX

Stage	Parity 0	1-2	3-5	6+
0	0	0	0	1
I	0	0	3	2
II	0	5	4	9
III	0	10	19	17
IV	0	2	11	17

TABLE III. AGE INCIDENCE AND STAGE IN 100 BANTU FEMALES WITH CARCINOMA OF THE CERVIX

Age group	Stage 0	I	II	III	IV
20-30	0	0	0	5	4
30-40	0	2	6	9	6
40-50	1	2	6	13	4
50-60	0	0	4	10	5
60+	0	1	2	9	11

#### Results

The G-values calculated and tabulated above (Table I) for each cell is smaller than the critical G-value excluding the age group 20-30 years; the reason for this is not apparent. However, for all 5 age groups put together, under the null hypothesis,  $G=20.3433$  approximately distributed with a chi square with 12 degrees of freedom, which is not meaningful at a 5% level of significance.

#### Conclusion

The null hypothesis could not be rejected. Therefore

TABLE I. 100 CASES OF CARCINOMA OF THE CERVIX AND A CONTROL OF 172 CASES ABOVE THE AGE OF 19 YEARS\*

Number of children	0		1-2		3-5		6+		Calculated G-value	Critical G-value
	Patient	Control	Patient	Control	Patient	Control	Patient	Control		
Age groups										
20-30	0	7	0	24	7	19	2	4	11.7469	7.815
30-40	0	4	7	10	7	17	9	11	3.9384	7.815
40-50	0	0	4	10	7	9	15	11	3.2391	5.991
50-60	0	0	3	5	6	5	10	16	0.9002	5.991
60+	0	0	3	4	10	7	10	9	0.5187	5.991

\*A combined table of age, parity and G-values in 100 cases of carcinoma of the cervix and 172 control cases above the age of 19 years. A 5% level of significance was adopted throughout. For all age groups put together, under the null hypothesis,  $G=20.3433$  approximately distributed with a chi square with 12 degrees of freedom, which is not meaningful at a 5% level of significance.

as a result of the above investigation, it would appear that multiparity is not an aetiological factor in the incidence of carcinoma of the cervix.

### Discussion

In the group studied it was found that all patients under 30 years of age (9%) had advanced carcinoma. This differed from Helbing's<sup>13</sup> findings where advanced cervical carcinoma was found in patients of advanced age.

In Western countries delay in seeking treatment is probably due to multiparity and multiple household duties.

In the Pretoria group the delay in seeking treatment was attributed to ignorance and lack of campaigns enlightening the Bantu on early signs and symptoms of carcinoma of the cervix.

The Bantu patients of high parity do not seem to have a preponderance of stages III and IV carcinoma of the cervix (Table II) when compared to patients of lesser parity.

### SUMMARY

1. A survey of the literature on the aetiology of carcinoma of the cervix is presented.

2. A group of Bantu patients suffering from carcinoma of the cervix and a control group from the Bantu population of the same hospital were subjected to statistical analysis and testing procedures with the following results:

Patients with carcinoma of the cervix had given birth to the same number of children as the control group of representative age groups, excluding the 20-30 year groups who statistically had significantly more children than the hospital population.

All age groups put together had also given birth to the same number of children.

3. Results of the test conducted are discussed. It is concluded that multiparity would not appear to be an aetiological factor in the incidence of carcinoma of the cervix.

### OPSOMMING

1. 'n Oorsig oor die literatuur i.v.m. die etiologie van servikale karsinoom word aangebied.

2. 'n Groep Bantoe-vroue met servikale karsinoom en 'n kontrole groep Bantoe-vroue van dieselfde hospitaal is aan 'n statistiese analise en toetsing onderwerp. Die volgende resultate is verkry:

Pasiënte met servikale karsinoom het, behalwe in die 20-30 jaar groep, aan dieselfde aantal kinders geboorte geskenk as die kontrole groep in die onderskeie ouderdomme. In die 20-30 jaar ouderdomsgroep van pasiënte met karsinoom was

daar statisties betekenisvol meer geboortes as in die kontrole groep.

Alle ouderdomsgroepe tesame gevat, het in beide karsinoom en kontrole groepe eweveel geboortes gehad.

3. Die resultaat van die toets is bespreek en die gevolgtrekking is dat multipariteit waarskynlik nie 'n etiologiese faktor in die insidensie van karsinoom van die serviks is nie.

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