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ENVIRONMENTAL FACTORS IN CERVICAL CANCER

AN APPROACH TO ITS PREVENTION*

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Though preventive measures against disease have long been the basic goal of medical research, their possibility has never been fully appreciated in the field of neoplastic disease. This is true in spite of the fact that such an approach has appeared to be practical since Pott's classical observation on scrotal cancer in chimney-sweeps. In a few instances only, involving primarily industrial cancers, have such measures been advanced. Then recent clinical statistical studies on lung cancer, both historical and prospective, demonstrated that environmental factors play a significant part in the production of this major type of cancer. The results of these surveys have led to a continuation of efforts to search for environmental factors that might influence other types of human cancer.

Our initial environmental cancer studies concentrated on those neoplasms whose incidence data suggested significant differences between population groups. We, furthermore, first investigated epidermoid cancers because these types seem particularly dependent on extrinsic factors. Cancer of the cervix belongs to these groups of cancer. It is predominantly an epidermoid cancer and varies significantly among different population groups. Unless such variations can be accounted for by racial factors, they must be explained by differences in environmental patterns. The present communication serves to summarize the findings which may account for the observed rates of cervical cancer recently reported in greater detail (Wynder *et al.*, 1954).

Rates of Cervical Cancer

For statistically significant variables, which epidemiological cancer studies may reveal, to be regarded also as causatively significant, they must at least in part account for such differences in rates. In Table I are shown the relative rates of cervical cancer which have been reported among different population groups. Not all of the data are available as incidence data. Indian data are available only as frequency rates from Indian hospitals. The following rates are of particular interest:

(a) In the United States the incidence of cancer of the cervix among Negroes is 60% higher than among whites, and among the latter it is more common among the lower-income groups (Wynder *et al.*, 1954).

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(b) The rate of cervical cancer among Jews is only one-fifth to one-tenth of that of the non-Jewish women in the United States, and the difference appears to be even greater if one takes the Jewish rate as observed in Israel (A. Symeonidis, personal communication).

(c) A recent report from Denmark by Rojel (1953) shows the rate of cervical cancer among prostitutes to be four times greater than that of non-prostitutes of similar social class.

(d) In most Asiatic and South American countries cancer of the cervix is the most common female cancer.

(e) Gagnon (1950) found no cancer of the cervix among a large group of nuns studied in Canada. A similar finding was recently shown by Schömig (1953) among German nuns.

(f) Cancer of the cervix rarely occurs in women under the age of 20; and in the majority of cases, as reviewed by Pollack and Taylor (1947), before this age, a glandular type of cervical cancer was found.

(g) The relative frequency of cancer of the cervix among Hindu women is about 45%, while it is 29% for the Indian Christians, 18% for the Moslems, and 16% for Parsees as based upon extensive records from the Tata Memorial Hospital in Bombay (Khanolkar, 1950).

These incidence and frequency rates of cervical cancer thus show a marked variation. It has been the purpose

TABLE I.—Relative Frequency Rates of Cervical Cancer Among Some Different Population Groups

Population Group	Relative Rate
Hindus	Very high
Christians (India)	High
Negroes	"
Parsees	Low
Moslems	"
Jews	Very low

TABLE II.—Factors which Previous Groups of Investigators Have Suspected to be of Significance in the Production of Cancer of the Cervix

1. Pregnancy and rate of pregnancy
2. Marriage and age of first marriage
3. Cervical laceration
4. Chronic cervicitis
5. Diet
6. Lack of circumcision (poor penile hygiene)
7. Vaginal discharge
8. Hormonal imbalance
9. Coal-tar douching
10. "Racial" factors

of this investigation to uncover the reason or reasons for these differences. In Table II are listed the factors which previous investigators have suspected to be associated with the production of cervical cancer.

Methodology of Study

The significance of environmental cancer surveys rises and falls with the methodology employed. It is paramount that the study is based upon a representative sample of the types of cancer one wants to study, and it is equally important that a proper comparison group is analysed in identical detail.

The cervical cancer patients were interviewed by specially trained interviewers in nine different hospitals in the United States, with the largest single group being interrogated at the Memorial Center, New York. As controls we selected patients with other pelvic disorders. The control group was age- and hospital-standardized in accord with the cervical cancer group. The analyses were based entirely on epidermoid cancer of the cervix. Microscopical diagnosis was obtained in every case. The Indian cancer cases were interviewed by Dr. P. D. Shroff at the Tata Memorial Hospital in Bombay. The same questionnaire was used for the American and Indian studies. The questionnaire attempted to include all of the factors suggested or suspected of playing a part in the development of cervical cancer that could be determined by clinical interrogation.

In part, the interview attempted to obtain information about rather personal matters. It is realized, of course, that not every patient may have told the truth about the age of her first sexual experience. It is also understood that not every patient was certain about the circumcision status of her partner. However, by careful and private interview we have tried to keep such inherent errors to a minimum. Furthermore, the control patients were questioned in the identical manner. It may thus be assumed that some of the inherent interview errors may be balanced out and that actual differences found between the cancer and control groups studied are of real rather than of apparent significance. Upon completion of the interview, the form was edited to assure complete answers to all of the questions, and then the information was coded and punched on special cards. All of the statistical analyses were carried out by Jerome Cornfield, of the Section of Biometry of the National Institutes of Health. Table III shows the number of patients on which this study is based, divided into the respective population groups studied separately.

TABLE III.—Number of Cervical Cancer and Control Patients Included in Study

	Cervical Cancer	Controls
U.S.A.:		
White (non-Jewish) ..	354	594
.. (Jewish) ..	20	326
Negroes ..	215	391
Total ..	589	1,311
India:		
Hindu ..	255	238
Moslem ..	26	135
Christian ..	22	80
Parsee ..	—	62
Total ..	303	515

If a given variable was found to be significantly different between cancer and control groups, tests were made to determine whether the variable was independently significant or whether it simply depended on some difference in another variable. The pertinent parts of the study are summarized below.

Results

Only along two broad lines did we find significant differences between the cancer and control groups. These referred to the factors of marriage and circumcision. Two negative factors must be stressed because previous investigators had placed much emphasis on these variables. These four factors are discussed in some detail.

Marriage Factor

As in previous studies, we found fewer single women among patients with cancer of the cervix as compared with the controls. Nine per cent. of the controls had never been married, compared with only 2% in the non-Jewish cervix cases. Respective data for the Negro group

FIG. 1.—Percentage of cervix cancer and control groups in American Hospitals having first coitus at age 16 or before.

FIG. 2.—Percentage of control groups at the Tata Memorial Hospital in Bombay, India, having first coitus at age 16 or before.

were 10% and 4%. The single women were of course further questioned for sexual relationship, and in only three instances out of the total white and Negro cases studied was cervical cancer found in a woman who claimed to be virginal.

Cervical cancer patients were found to marry more frequently than control patients. Of the non-Jewish white patients with cervical cancer, 30% had married more than once, in contrast to 14% of the controls. The respective figures for the Negro group were 35% and 23%.

It was a striking fact that the cervical cancer group married significantly earlier than the control group, as has been previously noted by Lombard and Potter (1950). Marriage at the age of 16 or under, for example, for the white cervical cancer group gave 14%, compared with 8% for the controls. The respective data for the Negro group were 32% and 19%, whereas it was 4% for the Jewish controls. Negroes marry at an earlier age than the non-Jewish whites, who in turn do so earlier than Jewish patients. These data are magnified and certainly of greater importance, though perhaps less reliable, if we note the age of first coitus. For the non-Jewish white cervical cancer group it was 19% before the age of 16 and for the controls 10%. Respective data for the Negroes were 55% and 36%, and for the Jewish group 15% and 4% (Fig. 1).

The Indian data showed a significantly earlier onset of first coitus among Hindus and Moslems as compared with Indian Christians and Parsees (Fig. 2). In India the age of first marriage does not necessarily reflect early intercourse, because of childhood marriages. The age of first coitus data among Hindu controls showed 83% to have had intercourse prior to age 16, whereas 76% of Moslems and only 15% of the Indian Christians, and none of the Parsees interviewed, had sexual relations prior to that age.

The data agree with the concept that those population groups with a high incidence or frequency of cervical cancer have uniformly an early onset of first sexual relationship.

Circumcision

In view of the fact that some degree of circumcision has been practised in the United States for the past 60 years and that among non-Jewish males the rate of circumcised men in the age group of 40 to 70 was shown to be 20%, this factor could be studied among the non-Jewish population groups (Wynder *et al.*, 1954). For the white non-Jewish group 5% of the cases reported exposure only to circumcised males, as compared with 14% of the controls. For Negroes the respective percentages were 0.5% and 9%. Among the

FIG. 3.—Percentage of cervix cancer and control groups at American hospitals exposed only to a circumcised sexual partner.

Jewish controls 95% were exposed only to circumcised sexual partners, in contrast to only 55% among 20 Jewish patients with cancer of the cervix (Fig. 3). Among 20 Jewish patients with cervical cancer, three had been married to uncircumcised non-Jews and six admitted to extensive relationships with uncircumcised partners. The age of circumcision does not seem of importance so long as it occurs before marriage. In India only the Moslems practise circumcision. Moslem boys are circumcised between the ages of 6 and 9. The factor of circumcision was cross-analysed and found to be independently significant.

The most desirable way to study the possible effect of penile hygiene would have been to examine the husbands of the patients studied. Because of the obvious difficulty of such a procedure, we examined males from the general hospital population, dividing them into different economic,

TABLE IV.—Percentage Distribution of "Smegma Formation" Among American and Indian Males

	No. of Cases	None	Moderate	Marked
American:				
Non-Jewish white (private)	580	92	7	1
" (clinic)	125	70	24	6
Jewish	980	99.4	0.6	0
Negro	100	44	48	8
India (Bombay):				
Hindu	130	56	28	16
Christian	50	56	30	14
Parsee	50	94	4	2
Moslem	130	100	0	0
India (Madras):				
Hindu	61	16	66	18
Christian	48	27	63	10
Moslem	31	58	42 (slight)	0

racial, and religious groups. The data show that those male groups have the highest degree of poor penile hygiene whose females also have the highest rates of cervical cancer (Table IV). This holds true for the American as well as for the Indian data. It is of interest to note, as judged from the Madras data, that not all circumcisions done on Moslems are complete.

Pregnancy

Several authors have found more pregnancies among patients with cancer of the cervix than among controls, as was indeed also found in this study. For example, in the non-Jewish white group 20% of the cancer group had more than six children, in contrast to 11% among the controls. The respective figures for the Negro cases were 15%

FIG. 4.—Pregnancy rate of cervix cancer and control groups for white non-Jewish women standardized to age of first marriage.

FIG. 5.—Pregnancy rate of cervix cancer and control groups for Negro women standardized to age of first marriage.

and 13%, showing no essential difference. The nulliparous rates for the white non-Jewish group were 9% and 12%, and for the Negroes 11% and 19%. In cross-analysing the data we standardized the number of pregnancies against the age of first marriage, since it was clear from recent studies by the Milbank Foundation that the age of marriage has a significant influence on the number of pregnancies (Kiser and Whelpton, 1944). In Figs. 4 and 5 we present the number of pregnancies standardized to the age of marriage separately for non-Jewish white and Negro cases, and find that there are indeed no significant differences in the rate of pregnancy between cervical cancer and control groups.

Abstinence after Menses

Abstinence from coitus for seven days after the last day of menses, as prescribed by Talmudian law, has often been thought to account for the low rate of cancer of the cervix among Jews (Kennaway, 1948). It was also thought to account for the low rate of cervical cancer among the Parsees. The following points seem to rule out this factor as one of great significance in preventing cervical cancer :

(a) Though the law is practised to some extent in the older Jewish age groups, it is generally not practised at all in the younger age groups. Among Jewish controls 30% reported no abstinence after menses. Among those who abstained, 40% did so for a full seven days. Of those who abstained over the age of 50, 50% abstained for seven days. The comparative figure for those under 50 was 28%. Very few Jewish women under 40 abstained for the seven-day period. Thus, cervical cancer should begin to increase in frequency in Jewish women if this factor were indeed of great significance.

(b) Twenty Jewish cervical cancer cases do not suffice for statistical comparison, but they seem to be in line with the controls. Five of the 20 patients in this group did not abstain after menses.

(c) None of the Parsees studied abstained for one week after menses.

Miscellaneous Factors

Other negative factors included douching, hormone therapy, and vaginal discharge. Negative factors found also include onset and regularity of menses, and number of miscarriages and abortions.

There was some difference in the rate of syphilis; however, the data indicated this to be a result of the earlier age of first intercourse among the patients with cancer of the cervix. The role of contraception remains questionable because no reliable data could be obtained on the frequency of the use of contraceptives, though the data suggested that the use of condoms was somewhat greater among the control group. We did question our patients on the frequency of sexual relations in the early part of their sexual lives. We felt, however, that the patient's memory in respect to these data was too hazy to give information which would be useful for statistical analysis.

The presence of cervical laceration could not be studied with any degree of reliability by personal interview, but, in view of the fact that there was no difference in the number of pregnancies, some doubt must be placed on the role of this factor. Chronic cervicitis was as often diagnosed among the Jewish patients as among the non-Jewish patients studied.

The study also included 32 cases of adenocarcinoma and 34 cases of carcinoma *in situ*. These are not sufficient to afford statistical analysis. In general the *in situ* cancer cases tended to be in line with the epidermoid cancer cases, while the adenocarcinoma cases went in the direction of the controls.

Discussion

For statistical association to have also causative significance the association must at least in part explain differences in incidence and frequency patterns. Table V presents

TABLE V

Population Group	Rate of Cervical Cancer	Age of First Coitus	Circumcision State and Penile Hygiene
Hindus (India)	Very high	Very early	Very poor
Negroes (U.S.A.)	High	Early	Poor
Christians (India)	Low	Very early	Good
Moslems (India)	Low	late	Good
Parsees (India)	Very low	Late	Very good
Jews (U.S.A.)	Very low	Late	Very good

evidence suggesting that the factors of age at first coitus and lack of circumcision may account for the differences in rates of cervical cancer. In respect to circumcision, it may well be that good penile hygiene may achieve the same end.

The data suggest that virgins have the least risk of developing cancer of the cervix, whereas those groups practising early relationships and whose males have poor penile hygiene have the highest risks of cervical cancer. These two factors can, in our opinion, account for the observed differences in frequency rates. For example, Negroes tend to have early sexual relations and relatively poor penile

hygiene, and have a high rate of cervical cancer. Hindus have an even earlier rate of first intercourse and more extensive bad hygiene, and have the highest rate of cervical cancer. Jewish women have a relatively late age of first marriage, the males practise excellent penile hygiene due to circumcision, and have a low incidence of cervical cancer. Moslems marry quite early yet have only one-third of the rate of cervical cancer as compared with the Hindus. No other differences could be determined between the Hindu and Moslem data except for the circumcision variable. Parsees, with a relatively low incidence of cervical cancer, marry late, and, though they do not practise circumcision, have good penile hygiene. Cancer of the cervix is rare among women without sexual relations, and is quite frequent among prostitutes.

It does not lie within the confines of this communication to speculate upon the mechanisms by which lack of circumcision and early sexual relationships may influence the development of cervical cancer. It may be theorized that under the male foreskin exists a carcinogenic agent. This hypothesis is emphasized by the infrequency of penile cancer among circumcised males and by the fact that horse smegma has been found to be carcinogenic to mouse skin (Plaut and Kohn-Speyer, 1947). Recently, H. R. Pratt-Thomas (personal communication) induced a significant number of cervical cancers in mice with human smegma. It is of interest, too, in this respect that population groups with a high rate of penile cancer also have a high rate of cervical cancer. The fact that the latter is more common than the former may be due to the much greater tissue susceptibility of cervical epithelium to cancer formation.

The earlier onset of intercourse among patients with cancer of the cervix could be explained on the basis of special hormonal patterns or merely as a result of the socio-economic mores of a given population group. We believe it to be primarily due to the latter factor, since early coitus seems to be a consequence of socio-economic and conventional standards rather than due to a special hormonal status. It can only be speculated why early intercourse leads to more cervical cancer. It may be due to greater susceptibility of young cervical tissue. It may be because of a more active sexual life in women who marry early. It may be due to a greater variety of sexual partners in women who marry early—a factor which we were not able to study in detail. The fact that cancer of the cervix occurs more frequently, for example, in women who have been married more than once might be on the basis that these women have had two active sex lives, or on the basis that such a woman is more likely to be exposed to a "carcinogenic" male than one who has had only one marriage.

The lack of correlation of pregnancy with the development of cervical cancer is of academic as well as of statistical interest. It demonstrates the importance of properly controlled and analysed environmental studies. It is suggested that if previous investigators had standardized their data to age of first marriage the pregnancy rate of their controls would also have been similar to those of the cervical cancer patients.

Since pregnancy rate, including that of miscarriage and abortion, was demonstrated to be a negative variable, it may be proposed that factors associated with pregnancy, such as cervical laceration and poor prenatal care, may also not be significant in the development of cervical cancer.

Epidermoid Carcinogenesis

The results of this study re-emphasize the data of Pott, other industrial cancer investigators, and recent lung cancer surveys that epidermoid cancer but rarely arises in sites not exposed to extrinsic factors of irritation. The human evidence in this respect is supported by animal data. Spontaneous epidermoid cancers in laboratory animals are quite uncommon. In a large necropsy series (Wells, Slye, and Holmes, 1941) they could find only a few epidermoid lung cancers. Spontaneous skin cancer in mice is very uncommon, though this area is quite susceptible to carcinogens.

From the point of view of practical significance it makes little difference what concept one holds regarding the mechanism which transforms a normal cell into a neoplastic one. It might well be, as Warburg (1954) suggests, that extrinsic factors interfere with the oxidation mechanism of the cells and thus initiate neoplasia. Perhaps at some future date we may uncover the specific mechanism by which certain extrinsic factors may initiate cancer. From the present point of view, however, it is most important to recognize that in the absence of these factors the incidence of some cancers is greatly reduced, and that by their control we are advancing an effective means of cancer prevention.

Epidemiological Considerations

Recent epidemiological surveys on cancer have re-emphasized the significance of properly controlled and conducted clinical studies which, we believe, can add more information about the effect of environmental factors on human cancer than could be obtained from any laboratory experiment. It is a method which requires a close co-operation of qualified statisticians, clinicians, and trained interviewers. Such a team can establish data which can be regarded as experimental as any laboratory work, and thus do not represent "just some statistics." If the data obtained by such an investigation are compatible with the incidence pattern of the cancer, with its geographic distribution, and with its time trends, then, it seems, we are dealing with factors that are not only of statistical but also of causative significance.

Practical Considerations

In environmental cancer work we have to separate data into those of academic and those of practical importance. The factor of age of first intercourse is primarily of the former, whereas those referring to circumcision and penile hygiene are of the latter. The data suggest, though they do not prove, that good penile hygiene may be as effective as circumcision and that this may account for the relatively low frequency of cervical cancer among the high-income groups, a fact which of course may also be influenced by the later onset of marriage as compared with the low-income group (Wynder *et al.*, 1954). The best and most practical measure for obtaining good penile hygiene is universal circumcision. For the past ten years a high degree of circumcision has indeed been practised in the United States. In a recent study based upon reports from 84 hospitals throughout the United States, 85% of all non-Jewish male babies born in the semi-private or private class were circumcised at birth (E. L. Wynder, unpublished data). The circumcision rate was equally high among Protestant and Catholic births. Thus, if it is indeed true that circumcision acts as a preventive measure against cancer of the cervix, a marked lowering should be noted in this type of cancer in the coming generation.

In summary, this study again showed that in the development of epidermoid cancer extrinsic factors are of significance. It was demonstrated that clinical-statistical investigation, provided that it considers all of the environmental factors, can separate those that are independently and those that are only dependently significant. It was shown that factors can thus be determined which can account for marked differences in frequency patterns found among different population groups which previously had been supposed to be on the basis of racial factors. The two most important factors were those of the age of first sexual relations and the lack of circumcision, or the associated poor penile hygiene. Of these two factors, the latter has the greatest practical significance. Even these two factors, of course, represent only a link in the total chain of cancer development, and undoubtedly other factors must be present, though so far they remain unknown to us. However, if by removing a link we can interrupt a chain of development we have succeeded in preventing the chain from undergoing completion. It is along this line that environmental cancer research has its greatest purpose.

Summary and Conclusions

A study of the role of environmental factors in cervical cancer indicates that differences in age of first coitus and circumcision status or lack of good penile hygiene can explain variant incidence data of cervical cancer among different population groups.

There is no statistical evidence that pregnancy rate plays a part in the production of cervical cancer. The data on pregnancy demonstrate the significance of careful statistical analysis in separating the dependent from the independent variables. They clearly emphasize the importance of trained statistical aid in these investigations.

The abstinence period practised by orthodox Jewish women after the end of menses is not believed to be the basic factor accounting for the low incidence of cervical cancer among Jewish women.

The data emphasize that exogenous factors play a major part in the development of epidermoid cancer.

The results underline the importance of international co-operation, which can achieve more conclusive results than can be obtained from any one country alone.

The findings suggest that universal circumcision may be a practical preventive step, significantly reducing the incidence of cervical cancer.

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The downward trend in the total volume of crime in England and Wales, first noted in 1952, continued throughout 1953, according to statistics in the *Report of Her Majesty's Inspectors of Constabulary for the Year ended September 30, 1954*. Offences against property without violence decreased by 8.9%, and offences with violence by 9.5%, including 6,512 fewer crimes of shopbreaking and 1,619 fewer of housebreaking. An encouraging decrease was also shown in the number of boys under 14 and youths under 17 found guilty of indictable offences. Though the figures are still high, 20,774 and 14,549 respectively, compared with those for 1938, it is believed that the post-war wave of juvenile delinquency has at last been checked. The most disquieting feature of the report was the record of continued increase in sexual crimes; sexual offences increased by 9% and offences of violence against the person by 1½% over the previous year. The public's response to the police drive to make them "crime prevention conscious" is one of the main reasons given for the reduction in the total. It is also thought that the building-up of the uniformed branches of the police, the advantage of basic training for young officers, and the still increasing assistance given by the forensic laboratories have proved a deterrent. The preliminary figures for the first nine months of 1954 show that the improvement continues. Of the non-indictable offences, traffic offences decreased by 6%, but gaming and betting offences increased by 7%. There was little change in the number of persons found guilty of drunkenness.