# Some Epidemiological Aspects of Cervical Cancer

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EPIDEMIOLOGY is concerned with study of disease in human populations. In common with other medical sciences, its objective is to determine the factors related to or governing disease occurrence. Unlike other medical sciences, however, its universe of study is the human population or segments of it. Through observations of human experience it attempts to determine the characteristics of those people who develop disease, and of those who escape it. This, in turn, involves the measurement of risk to disease in groups of people with different characteristics.

Epidemiological methods of measuring risk to cancer, and other presumably noninfectious processes, have for the most part been borrowed directly from techniques of proved usefulness in communicable disease study. To a large extent these techniques have been dependent upon the stage of development of other disciplines of medical science. For example, it required relatively simple observations in human experience prior to the birth of the science of bacteriology to demonstrate beyond reasonable doubt that diphtheria was communicable. An understanding of important aspects of its natural history, however, had to await the development of simple and inexpensive laboratory tests which would detect those persons infected but not sick and would evaluate the relative immunity status of the population.

In cancer, observations in human experience were directly responsible for the beginning of what has developed into an enormous amount and variety of experimental research. The first experimental cancers were produced by painting tar on rabbits' ears, an undertaking prompted by the observation in humans that risk to cancer of the scrotum appeared to be excessive in chimney sweeps. Until the development of the Papanicolaou vaginal cytology test (*1*, *2*), however, laboratory research had provided no tools for the epidemiologist to use in extending our present relatively crude descriptive epidemiology of cancer. While it is true that cervical biopsies were introduced as long ago as 1878 by Ruge and Veit (*3*), it is, to say the least, impracticable to attempt cervical biopsies on large numbers of apparently well women. Though the Papanicolaou test does not satisfy all of the requirements desired by the epidemiologist, it is the first simple, acceptable laboratory test which can be applied to large numbers of well women and will select for further diagnostic evaluation most of those with cervical cancer.

Before this test could be used effectively in general epidemiological studies, a number of questions had to be answered. Could it be effectively applied in general population groups of apparently well women? What were its limits of specificity and sensitivity in such groups? What were the practical logistical problems?

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What was the cost in money, equipment, and personnel? Although some of these and other questions have been answered with regard to use of the test as a diagnostic adjunct in clinic and office practice, the only answer to its practicality in general epidemiological study, or as a cancer control measure, lay in an attempt to use it on a communitywide basis. Recognition of this fact led to such a study in Memphis and Shelby County, Tenn. The study was instituted in July 1952 as a joint endeavor of the University of Tennessee, the National Cancer Institute of the Public Health Service, and a host of other individuals and agencies.

Many important facts have already emerged from this study (*4*). Sufficient preliminary data are now available for examining other facets. It is the intent of this presentation to provide a brief background of the disease itself and some descriptive facts and apparent facts of the epidemiology of cervical cancer.

### The Disease Itself

Carcinomas of the uterus may be classed in three groups: epidermoid, or squamous cell, carcinoma of the cervix, endometrial adenocarcinoma of the corpus, and adenocarcinoma of the cervix (*5*). Epidermoid carcinoma of the cervix and adenocarcinoma of the corpus appear to be quite distinct entities in histological structure, clinical behavior, and selective factors associated with their occurrence. Adenocarcinomas of the cervix are less clearly differentiated from the other two groups because of the difficulty in determining the precise point of origin of some adenocarcinomas of the lower part of the uterus.

The relative frequency of the 3 types of uterine carcinoma varies considerably from one reported series of cases to another, but broadly speaking cervical carcinoma is 3 or 4 times as common as endometrial, and cervical epidermoid carcinoma is at least 10 times as common as cervical adenocarcinoma (*5*).

At least some, and conceivably a large part, of the differences in relative frequencies of fundal and cervical carcinoma, as reported in different series of cases, is due to the different composition of each series with respect to age, race, marital status, and other selective factors associated with the occurrence of the two diseases. Most published series do not provide the data on such characteristics, which are necessary to make adequate appraisal of the large differences in recorded relative frequency.

Most epidermoid carcinomas of the cervix arise directly from the stratified epithelium of the external os or the portio vaginalis. Occasionally the origin may be from metaplastic stratified epithelium formed within the cervical canal or glands, or in an endocervical polyp (*5*). The development of the disease in the cervix is not dependent on the presence of the body of the uterus since it occurs after subtotal hysterectomy performed for other uterine disease. While occasional specimens of early cervical carcinoma afford evidence that the growth has arisen, not from a single minute focus, but from a considerable field of epithelium, no clear instances of genuine multicentric origin have been described (*5*).

In addition to frankly invasive malignant lesions of the cervix, histological lesions have been described since 1910 which fulfill all criteria of malignancy except invasion (*6*). As a result of his work with the colposcope, Hinselmann, as quoted by Traut and Benson (*7*), described in 1924 four classes of lesions of abnormal cervical epithelia from dysplasia through anaplasia, and intraepithelial cancer to invasive cancer. The term carcinoma-in-situ was applied to the most definitive of these patterns of abnormal epithelium in 1932 (*8*). Since then, this lesion has been variously labeled surface carcinoma, intraepithelial carcinoma, intramucosal cancer, and carcinoma-in-situ. It is now generally agreed that it may be preinvasive cervical cancer or an early stage of cervical carcinoma. However, there is considerable controversy as to the significance of other epithelial changes, such as dysplasia, hyperplasia, and anaplasia, and their possible relationship to invasive carcinoma.

Since 1932, much literature has appeared concerning the minimum histological criteria necessary for diagnosis of carcinoma-in-situ, as has data on its frequency, incidence, and its significance. Its relation to invasive cancer is inferred because of its histological appearance (*6*) and, according to Schottlaender and Kermauner, because of its occurrence at the pe-

riphery of infiltrating lesions (*9*). The relationship is also inferred because of its demonstrated presence prior to the development of some invasive cancers (*9–12*), and its detection at an earlier average age than usually observed for invasive cancers at this site (*4, 9*). The determination of the relationships of the carcinoma-in-situ lesion to classical cervical carcinoma is of paramount importance. To accomplish this, questions primarily epidemiological in nature must be answered.

Some of the more fundamental questions involved in this relationship are:

1. Do all invasive cervical cancers begin as intraepithelial lesions? If not, what percentage do?
2. Do intraepithelial lesions invariably progress to invasiveness? What percentage do?
3. What is the time required for an intraepithelial lesion to progress to invasiveness?
4. Do some intraepithelial lesions regress and disappear? How often does this occur?
5. Is it possible for an intraepithelial lesion to remain noninvasive indefinitely?
6. What are the age-specific incidence and prevalence rates of carcinoma-in-situ and invasive carcinoma? Are there race-specific variations in such rates?

Whether or not all invasive cancers of the cervix pass through the in-situ stage, and whether this intraepithelial lesion is reversible or always progresses to invasiveness, is not known at the present time. Its recognition, however, besides introducing problems regarding treatment (*13*), has opened new avenues for study of the essential pathogenesis of cervical cancer (*14*).

A large part of the attention now devoted to intraepithelial lesions of the cervix may be attributed to the extensive use of the cytological technique of Papanicolaou. By means of this test definitive diagnostic procedures may be directed to those women who are considered most likely to harbor invasive cancer (*4*). In addition, the test leads to the histological diagnosis of many intraepithelial lesions which otherwise would have remained undetected.

Clinically, the onset of carcinoma of the cervix is generally characterized by an absence of alarming symptoms. Those which would lead to its early discovery may give no concern to the patient during menstrual life. As a result, it frequently progresses into a moderately advanced disease before discovery, and early carcinomas of the cervix (stage I) make up only about 10 percent of the cases seen in many clinics (*15*). In addition, stage for stage, carcinoma of the cervix carries a much poorer prognosis than cancer of the body of the uterus.

The League of Nations' clinical classification of these cancers, adopted first in 1929 and modified in 1937 and in 1950, divides the disease into five stages. Stage 0 is reserved for carcinoma-in-situ and the remaining four stages are reserved for progressively extensive stages of the invasive disease. Patients treated in stage 0 should respond with uniform cure. According to Heyman (*15*), survivorship thereafter becomes progressively worse as treatment is instituted in advanced stages of the disease; there is about 60 percent recovery for stage I and 8 percent recovery for stage IV. Results from treatment in different clinics vary considerably, but factors responsible for such variation cannot be fully assessed. It is clearly evident, however, that the stage of disease at the time treatment starts is of paramount importance in cure. This fact emphasizes the necessity for obtaining a full understanding of the quantitative relationship of carcinoma-in-situ to invasive cancer of the cervix.

## Extent of Uterine Cancer Problem

With the exception of the single year 1914, deaths in the United States attributed to cancer of the uterus were grouped with cancers of all female genital organs until 1930, when the fourth edition of the International List of Causes of Death came into use. Since then, uterine cancer deaths have been tabulated annually by age and race (*16, 17*). Analysis of these data shows a consistent decline in the age adjusted death rates for uterine cancer among white women since 1914 and among the nonwhite since 1930 (unpublished data, A.G.G.).

Death data for cancer of the cervix were first listed separately in 1939, but were not subdivided by age and race until 1949. Such data are of little practical value, however, in assessing the forces of mortality from cervical cancer, since such a high proportion of all

uterine cancer deaths are unspecified as to the portion of the uterus affected. In 1949, 43 percent and in 1955, 34 percent of all uterine cancer deaths were unspecified as to origin in the uterus. It is therefore not possible to determine whether or not cancer of the cervix and cancer of the corpus have participated equally in the decline in mortality attributed to cancer of the uterus as a whole.

During 1955, 15,170 deaths were attributed to cancer of the uterus in the United States (17). Among white women the crude death rate was 17.0 per 100,000 population. This rate was exceeded by only those for cancer of the breast (27.2 per 100,000) and cancer of the large intestine (17.5 per 100,000). Among nonwhite women more deaths were attributed to cancer of the uterus than to any other type of cancer, the crude death rate being 28.7 per 100,000 population. For both races combined, deaths from cancer of the uterus were exceeded by only cancer of the breast. According to unpublished data (A.G.G.), on the basis of rates for deaths from all causes recorded in 1955, 1.8 percent of white and 3.0 percent of nonwhite women would be expected to die eventually of cancer of the uterus.

Of those deaths for which the part of the uterus first affected was recorded on the death certificate, there were, in 1955, 17 times as many cervical as corpus cancer deaths among the nonwhite and 7 times more cervical cancers among the white. As pointed out, however, there was a substantial number of deaths among both races with unspecified origin of the disease in the uterus. In the unlikely event that all of those unspecified had arisen in the corpus, deaths due to cancers of the cervix would still predominate in both races, and the cervix-corpus ratio would still be greater in the nonwhite than in the white.

During this period of decline in mortality, the incidence of the disease has been increasing in at least one State. In New York, between 1942 and 1953, the cervical cancer incidence rate increased 7 percent, and cancer of the corpus, 21 percent (*18*). In Connecticut, on the other hand, the incidence of cervical cancer decreased 8 percent while corpus cancer increased 22 percent between 1935 and 1951 (*19*).

Based on reports from New York State, during 1949–1951, the lifetime probability of developing cervical cancer was 2.2 per 100 women, and cancer of the corpus, 1.5 per 100 women, or a total of 3.7 per 100 women for all uterine cancer (*20*).

### Age Selection

The tendency of cancer of the cervix to occur earlier in life than cancer of the body of the uterus was well known at least as early as 1900. In Williams' series the maximum frequency was in the age group 35 to 45, as compared with the mode in the age group 50 to 60 for cancer of the corpus (*21*). While cases in persons under 20 years of age are uncommon, a few histologically diagnosed cases have been described in such persons (*22–24*), the youngest being an infant of 7 months with a cervical adenocarcinoma (*25*). In 1955, out of 8,804 deaths attributed to cancer of the cervix in the United States, 3 were under 5 years of age and 5 under 20.

Perhaps the most reliable data on age incidence of the disease are those from Denmark and Sweden. These data reflect the annual probability that women of various ages will develop or be diagnosed as having the disease. In Denmark, for the years 1942–44, the incidence rates for cancer of the cervix rose sharply from age 25 to a peak of about 70 per 100,000 in the age group 45–49, and declined fairly regularly thereafter (*26*). In Sweden a similar age selection is evident though the rates, age for age, are lower than observed in Denmark, and the peak of incidence occurs about 5 years later in life (*27*). The Swedish data also show a regular increase in incidence at all ages between the calendar years 1925 and 1945, an increase more marked than that observed in New York State.

In contrast with the type of age selection prevalent in Denmark and in Sweden, risk of the disease in Connecticut increases fairly regularly with age, and instead of declining after 45 or 50 continues to increase, reaching a peak in women 85 and over (*19*). A similar type of age curve is observed among white women in Shelby County, Tenn., but not among the nonwhite (*28*). In New York State the age selection is somewhat different from that observed

in either Denmark or Memphis (*20*). These regional differences in age selection are sufficiently great to warrant the suspicion that they are not artifacts, but no ready explanation is available for them. Further, in each locality, fairly distinct differences exist between the age selection of cancer of the cervix and of cancer of the body of the uterus. The consistently different age selection of cancer in the two parts of the uterus is one reason for suspecting that they represent two disease entities.

### Race Selection

With the exception of limited morbidity data, and fairly extensive mortality figures for the white and nonwhite population of the United States, most of the evidence of racial selection of cervical cancer is derived from relative frequency data. Relative frequencies on some occasions faithfully reflect absolute variations in risk, but on other occasions they do not. In any case, there is probably no other type of cancer in which racial selectivity of the disease, as suggested by relative frequency evidence, offers such intriguing possibilities of better understanding its genesis.

On the basis of relative frequency figures, Williams claimed in 1900 that American Negresses were less prone to uterine cancer than white women (*21*). That the reverse is true is now amply demonstrated not only by mortality figures for a long period of time but by morbidity rates collected in special surveys (*28*, *29*). Many doubt that the clearly excessive risk among the nonwhite women in the United States is due to actual racial susceptibility. Most workers contend that it is due instead to a number of factors which have been loosely classed as social or environmental (*30*, *31*).

While the early relative frequency evidence for the white and the nonwhite women in the United States was not substantiated, evidence of a similar basic nature relating to Jewesses has been established as correctly portraying relative risk (*30*). There appears to be no longer any doubt that Jewesses experience substantially less risk to cancer of the cervix than the non-Jewish (*32*, *33*, *35*). A recent study in Israel has elicited very low incidence rates, and since Jewesses of different "ethnic typology" experience rates of about the same magnitude, the authors believe that it cannot be dependent on a racial factor, but is due instead to circumcision of Jewish males (*35*).

Except for absolute comparisons of risk relating to the white and the nonwhite population in the United States and Jewesses in Israel, most of the other evidence of racial selection involves relative frequency data. For example, Khanolkar's study relating to various classes of Indians attending the Tata Memorial Hospital in Bombay supports the idea that Hindu Decanni and Gujarti, and Moslem women, all experience a different risk to cancer of the cervix (*36*). Since, however, the evidence consists of relative frequencies, not incidence, it does not establish these differences.

Mortality statistics from different countries cannot be easily compared because of the different proportions of deaths in each country which are unspecified as to portion of uterus affected. For cancer of the uterus as a whole, however, the age adjusted death rate in 1950 in Japan was more than twice that recorded in England and Wales; about 40 percent greater than the rate among white American women; and about 40 percent less than that recorded among American nonwhite women (*37*).

Among the American Navajos, if relative frequency comparisons are accepted as evidence, risk of death from all uterine cancer would be twice that observed in American whites and about the same as noted in nonwhites as a whole. Adequate comparisons of absolute risk show, to the contrary however, that the risk for the Navajo is only half that observed for the whites and only a fourth of that noted for the nonwhites (*38*).

### Geographic Distribution

Data on geographic distribution of cervical cancer consist of official mortality statistics, the results of summations of autopsy series, and morbidity surveys conducted in a few localities. While the data from only the latter are reliable as to the absolute probability of developing the disease, official mortality statistics and autopsy studies clearly show that cancer of the cervix has been recorded on every continent, in every large country, and among every important ra-

cial and ethnic group. Furthermore, the frequency of cancer of the cervix relative to all other cancer, as observed in the autopsy series, varies considerably from place to place. Whether or not risk of the disease varies in the same fashion cannot be determined from most such studies.

Within some countries for which pertinent data are available, incidence of the disease varies considerably. In Denmark the highest rates are observed in Copenhagen, and the lowest among the rural population (*39*). This excess risk among urban women also appears to exist in the State of Iowa (*40*). White women in southern cities of the United States appear to experience greater risk than do the northern white women (*29*), and in Copenhagen (*41*) and Pittsburgh (*42*) there is considerable variation in rates within the city. In these latter cities the higher rates are found in the poorer sections.

### Marital and Pregnancy Status

The first clear evidence that cancer of the uterus and cancer of the breast tend to have an opposite selectivity with respect to marital status was presented apparently by Rigoni Stern in 1842. While only 6 percent of the uterine cancer deaths recorded in Verona, 1769 to 1839, were in unmarried women, 29 percent of the breast cancer patients were unmarried (*43*). These differences are the more striking in view of the fact that cancer of the uterus generally occurs at an earlier age when the probability of marriage is less than in later life. These data did not permit the firm conclusion that uterine cancer is more likely to occur among married women than among single, but they did demonstrate the striking difference from breast cancer in terms of selectivity according to marital status.

It has now been established that the annual probability of developing cancer of the cervix is greater in married than in single women (*39*, *44–46*). It would further appear that early age at marriage and instability of marriage are also associated with this disease (*47*, *48*). In addition, there is some reason for believing that other variables associated with instability of marriage are also associated with cancer of the cervix. Thus, there is scattered evidence that illegitimate births (*48*), syphilis (*49*), early sexual relations, multiple sexual partners (*31*), and prostitution (*50*) are all associated with this disease. On the opposite side of the coin, cervical cancer appears to occur very rarely among nuns (*51*).

Another variable associated with marriage, which has been given much consideration, is circumcision of the marital partner. This was due first to the observation that cancer of the cervix is less frequent among Jews, where circumcision is universal. Other races which practice circumcision at varying ages and to a different extent are alleged to have varying risk of cervical cancer. The so-called incidence reported for such races, however, is invariably a relative frequency which may or may not reflect relative risk to this cancer. Reliable data on the incidence of cervical cancer are very badly needed among such groups as the Moslems, Hindus, Bantus, and Fijis. Such rates can now be reliably and relatively inexpensively ascertained through discriminative use of the vaginal cytological technique.

Another variable which has long been associated with cervical cancer is pregnancy. Lane-Claypon's (*52*) data indicated an association between pregnancy, but not number of pregnancies, and cancer of the cervix. Maliphant's series (*44*) suggested the greatest risk in parous women, with each pregnancy adding slightly to the risk; the next greatest risk among childless married women; and a considerably reduced risk among single women. Logan's analysis of British mortality data suggested that marital status alone, apart from childbearing, seemed to be the factor associated with higher mortality (*45*). In Gilliam's series where a precise actuarial method was used in computing age specific pregnancy rates in several types of cancer patients, the difference in fertility between those with breast cancer and those with cervical cancer was limited to the first 30 years of life (*48*). After age 30, pregnancy rates in breast and cervical cancer patients were identical. A further curious finding in this series was the greater difference in pregnancy rates between the cervical cancer patients interviewed in 2 of the cities than was

observed between breast and cervical cancer patients in any 1 of the 3 localities.

It appears clear from the brief considerations mentioned that the role of these various factors associated with cervical cancer still remains to be clarified with additional and perhaps different kinds of systematically collected data.

### Socioeconomic Status

It has been common experience of gynecologists that cancer of the cervix is less frequently encountered in private than in clinic practice. Mortality data for 1930–32 for Great Britain similarly indicated that risk of dying from uterine cancer as a whole increased with the decrease in socioeconomic status (*53*). That this is largely due to cancer of the cervix is now evident from analysis of similar death data for 1950 and 1951 (*46*). These show that when socioeconomic class is judged by occupations of husbands, the rates were lowest in women whose husbands were in the professional class and highest in wives of unskilled laborers, with a fairly regular gradient in the intermediate classes. Stocks concludes from these and other analyses of regional variation in mortality that the disease in Great Britain shows a relationship with overcrowded housing, social class distribution, and predominant industry 20 years before (*46*).

### Infections and Cervical Lacerations

For a considerable period of time, chronic cervical infections and poor obstetrical care were believed to predispose a woman to carcinoma of the cervix. The idea that cervicitis or cervical lacerations might be the cause of this cancer is probably an outgrowth of the general theory of chronic irritation as the cause of all cancer. There appears to be little definitive evidence bearing directly on it one way or the other, however. From the histological standpoint, early cancers at this site are observed with no associated evidence of chronic irritation. Evidence of cervical lacerations, on the other hand, is common in parous women.

Gagnon is of the opinion that the rarity of the disease in nuns is due to the infrequency of cervicitis in this group (*51*). Cashman has noted that fewer cervical cancers than expected occurred in about 5,000 women who could be followed out of 10,000 women whose cervicitis had been treated by deep cauterization (*54*). If, however, there had been a very few cases among those women who were not followed, the results might have been quite different.

With regard to cervical lacerations, Lombard and Potter's case history study indicated an association between history of lacerations and this cancer (*47*). Gilliam's series, on the other hand, at least indicated no undue proportion of instrumental deliveries among cervical cancer patients (*48*). Since both studies depended upon histories as remembered by patients and controls, it is not certain that they correctly portray the actual facts. As for other evidence based on clinical impressions, there is still considerable difference of opinion among gynecologists as to the possible association of these factors and the disease. That even repeated trauma, and by inference cervicitis, is not necessarily involved is suggested by the apparent rarity of the disease in cases of prolapsed uterus (*55*).

### Discussion

It should be clear from this brief account of some of the facts of distribution of cervical cancer among humans that many selective factors bearing on its occurrence have been recognized. There is a common, and perhaps unfortunate, tendency among students of cancer, however, to assign specific causal significance to such factors, often even before the facts themselves are well established. Thus, when it appears that cervical cancer is more common in parous than in nulliparous women, the statement soon after appears in texts, as though it were fact, that the disease is caused by cervical lacerations. When it is evident that Jewesses are less prone than the non-Jewish—then *ergo*, it is caused by intercourse with the uncircumcized. Or, when it appears there is a tendency to select women who marry early in life—it is caused by trauma of immature tissues. Or, when it is shown that risk is greater in syphilitics than in nonsyphilitics—it is caused by chronic irritation. Or, because it selects the lower rather than the higher economic classes,

it is caused by poor hygiene and inadequate general medical care.

All of these factors associated with cervical cancer may well eventually turn out to be causes. On the other hand, an equally tenable hypothesis at the present time is that the disease is caused by some presently unknown factor or patient attribute which is more commonly present in women with these characteristics, but is by no means limited to them. The fact remains that the disease does occur in virgins, in nullipara, in Jewesses, in the nonsyphilitic, and in women of the highest economic classes, to mention only a few of the selective factors. Demonstration of excessive risk in women with certain characteristics does justify a hypothesis. No useful purpose is served, however, by parading hypotheses as fact, a tendency all too commonly encountered among students of cancer in general.

Up to the present we are aware of no weaving together into a coherent and generally satisfying explanation of the disease the threads of facts regarding distribution of cervical cancer in humans. The development of the Papanicolaou test, however, provides a laboratory tool which, if properly exploited epidemiologically, can at least test and either dispose of or extend some hypotheses which have been paraded as fact.

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