

Hormonal, Infectious, and Nutritional Aspects of Cancer of the Female Reproductive Tract

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Two malignancies of the female reproductive tract, endometrial cancer and cancer of the uterine cervix, seem to be ideal candidates for intensive interdisciplinary collaboration between epidemiologists and laboratory scientists. Epidemiologic, clinical, and laboratory research on endometrial cancer have led to a relatively unified theory of how a variety of risk factors might operate to influence the risk of this disease. While this "estrogenic-etiology" theory has been extensively developed, a number of questions about key biological mechanisms remain unanswered. The level of development of epidemiologic methods and laboratory adjuncts relevant to these questions suggests that interdisciplinary studies targeted on some of these issues might advance substantially our understanding of hormonal and nutritional aspects of carcinogenesis. Recent epidemiologic research on cervical cancer has produced a number of often interrelated leads (sexual, hormonal, chemical, and nutritional) to etiologic factors. At the same time, technological advances have permitted laboratory investigators to suggest specific testable hypotheses for the biochemical and/or molecular basis of these factors. The epidemiologic and pathological complexities of cervical cancer and the sophistication of the laboratory assays would seem to require close collaboration between epidemiologists and laboratory scientists for these hypotheses to be explored adequately.

Key words: endometrial cancer, cervical cancer, epidemiology, hormones, nutrition, viruses

The term *biochemical epidemiology* is rapidly becoming one of the more frequently used and abused phrases in the area of etiologic research on cancer. As a concept, it engenders almost universal enthusiasm among those considering it. Curiously enough, however, given the stature of those who discuss it, this enthusiasm is infrequently focused and rarely critical. Part of this stems from a lack of any consistent definition of what biochemical epidemiology is and is not. It often means different things to laboratory scientists, clinicians, and epidemiologists and is often defined differently by the same individual depending the topic under discussion and with whom it is being discussed.

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In general, I believe it is incumbent upon epidemiologists to perceive of biochemical epidemiology in one of its more restrictive definitions. Under these definitions, biochemical epidemiology would not include simply a series of laboratory measurements (no matter how elegant) on groups of humans, some of whom may have or may be at high risk of malignancy and others who may not. Rather, under the more restrictive definition, biochemical epidemiology is the incorporation of laboratory measurements into traditional, rigorous epidemiologic designs to enhance the value of both the epidemiologic investigation and the interpretation of the laboratory results. By this definition then, besides the usual criteria for good laboratory and epidemiologic research, there would be at least four additional requirements (two laboratory and two epidemiologic) to conduct a high-quality interdisciplinary investigation. First of all, the laboratory test would have to be adequately developed and standardized. Much of the current enthusiasm for interdisciplinary studies relates to avant-garde laboratory assays that are on the cutting edge of laboratory research and are neither well developed nor standardized when they are suggested for incorporation into human studies. Second, the laboratory assays suggested need to be applicable to the practical demands of epidemiologic investigations. With the rapid advances in technology, this is becoming less of a problem than it has been in the past. However, it is still the case that for a laboratory adjunct to be useful in epidemiologic investigations the material required needs to be obtainable relatively simply in field situations, and the assays themselves need to be relatively simple and inexpensive so that they can be performed on large numbers of subjects. A requirement on the epidemiologic side is the ability to identify, target, and focus on a population that will be relevant for a study of the risk factor or biologic process on which the laboratory assays are focused. In addition, the investigation needs to ensure that there is adequate control for all sources of bias and confounding of the laboratory assays as well as those for the more traditional epidemiologic risk factors.

For all of these reasons, under this working definition of "biochemical epidemiology," to conduct a high-quality investigation is a challenging enterprise that can be very difficult both scientifically and in a practical sense, and it is often expensive. Because of this, there is a need to be selective and to focus resources (both scientific and monetary) on those issues and hypotheses that are developed enough to test robustly and for which the likelihood of a high scientific yield exists no matter what the results of the investigation.

Fortunately, for many reasons there are a substantial number of such opportunities in the area of malignancies of the reproductive tract. For the purpose of this discussion I will focus on two sites that offer a variety of such possibilities, endometrial cancer and cancer of the uterine cervix. I have chosen endometrial cancer because it is a site for which we have detailed insights into possible mechanisms of carcinogenesis based on a substantial amount of epidemiologic and clinical/laboratory research. While these disciplines have focused on some of the same issues, they have usually done so separately and, thus, there is also an apparent opportunity for major advances in our understanding of several key issues in carcinogenesis (including hormones and diet) by judiciously combining disciplines and working together on these issues. Cancer of the uterine cervix is particularly important in this area because of the number of epidemiologic leads to etiologic factors for which there has recently been both more specific hypotheses formulated and for which the technology exists to address these questions in an interdisciplinary manner.

ENDOMETRIAL CANCER

A number of independent risk factors have been well established epidemiologically for endometrial cancer. Several medical conditions are related to increased risk of endometrial cancer. Included are functional (estrogen secreting) ovarian tumors [1], the Stein-Leventhal syndrome [2], diabetes, and hypertension [3]. In addition, several reproductive risk factors are related to increased risk, most notably nulliparity and a late age at natural menopause [4]. Dietary-related factors seem also to be important. Obesity is a well-recognized risk factor for the development of endometrial cancer [5]. In addition, vegetarians experience a decreased risk of endometrial cancer, which may or may not be independent of weight [6,7]. Exogenous hormones have also been related to the risk of endometrial cancer. The use of menopausal estrogens [8] and sequential oral contraceptives [9,10] increases the risk of endometrial cancer, while the use of combination oral contraceptives results in a diminished risk [10-14]. Finally, age-related influences on endometrial cancer risk are somewhat different than for a number of other tumors, even a number of other hormonally related tumors. Specifically, endometrial cancer is extremely rare under age 45, but the risk rises precipitously among women in their late 40s and 50s in a much more dramatic fashion than for other tumors (Fig. 1) [15].

While epidemiologists were defining and quantifying these risk factors for the disease, clinical and laboratory investigations were being focused on these same conditions, resulting in a fairly unified theory of how these risk factors were influencing the risk of endometrial cancer (Fig. 2) [16,17]. Over half of these risk factors are associated either directly or through some as yet undetermined mechanism with increased levels of circulating estrogens, particularly so-called free or not protein-bound estrogens. Both the age effect and the use of combination oral contraceptives are felt to modify in some manner the increased risk associated with increased estrogen level through the modulating effects of progestogens. Finally, while nulliparity, diabetes, hypertension, and race have not been directly related to increased levels of circulating estrogens when controlled for the other factors, or for differences in

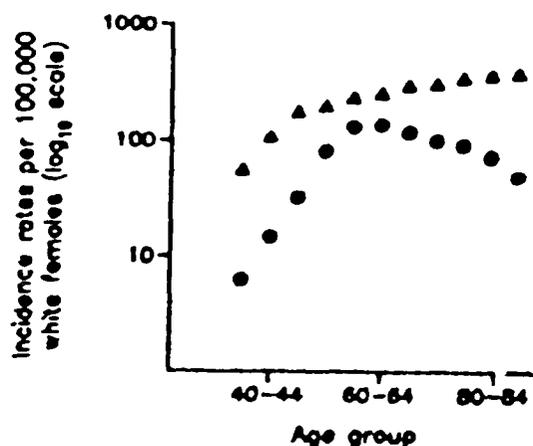


Fig. 1. Average annual breast cancer (▲) and endometrial cancer (●) incidence rates for white females (SEER data, 1973-1977).

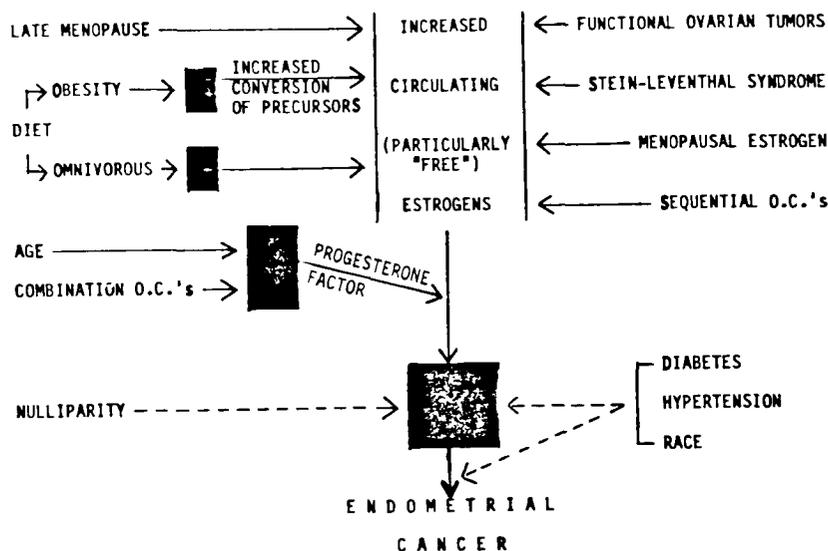


Fig. 2. Risk factors for endometrial cancer and their possible modes of action.

progesterone levels, it is quite possible that these risk factors operate through a basic hormonal mechanism that has yet to be defined.

Given our knowledge of most human malignancy, the amount of information we have on this tumor concerning risk factors and the intermediate steps between these factors and endometrial cancer is substantial. However, this also serves to point up more specifically what we do not know and to whet one's appetite for the ability to unlock these unknown areas. Some issues that need to be resolved are strictly epidemiologic or strictly laboratory. Examples on the epidemiologic side are: How truly independent are some of these risk factors, particularly diabetes, hypertension, and obesity? How much of the racial effect is artifact caused by differential hysterectomy rates or ascertainment bias, and how much is "real"? How is the risk of endometrial cancer associated with menopausal estrogen use altered by the addition of a progestational drug to the regimen? How much of the disease in a defined population is accounted for by the aggregate of all of these risk factors?

However, most of the issues with respect to endometrial carcinogenesis can seemingly only be addressed adequately by truly interdisciplinary studies incorporating features of epidemiologic design along with appropriate laboratory adjuncts. These efforts could be directed specifically toward the black boxes on Figure 2 relating to the mechanisms by which certain risk factors operate.

Obesity is a well-established risk factor for endometrial cancer. It is also well established that obesity is related to increased peripheral conversion of precursors to circulating estrogens [18]. However, the manner in which this occurs is still unclear. There are very few data to address the issue of when in a woman's life the development of obesity is most important. In one preliminary effort with small numbers of observations, weight reduction from teenage obesity levels did not seem to have a large impact on adult endometrial cancer risk [19]. Laboratory observations in this general area have also shown that while weight reduction is associated with some decrease in total circulating estrogens, the increased conversion of precursors is

apparently not much altered by such weight reduction [20]. This is bolstered by *in vitro* assays demonstrating increased conversion of precursors by fat samples from endometrial cancer cases compared to the fat samples from controls [21]. All of this raises the question of exactly how peripheral conversion of precursors to free estrogens is influenced by the numbers of adipocytes, their content in terms of type of fat, or some other factor. The observation that vegetarians experience a lower risk of endometrial cancer and have lower levels of free estrogens, even after control for indices of body fat, raises similar questions about possible mechanisms [22].

It has been speculated that the relative protection associated with being premenopausal and with the use of a combination of oral contraceptives operates through some type of progesterone mechanism that interferes with the estrogen etiology of endometrial cancer. The mechanism involved, however, remains unclear, although several have been proposed [16]. A key to an understanding of the mechanism will certainly involve a clarification of the currently conflicting epidemiologic evidence on the effect of cessation of use of combination oral contraceptives [12,13]. Two studies [12,13] noted that the "protection" was more substantial among current users and subsided somewhat with cessation. However, one study implied that the protection in fact was transitory [12], while the other still noted substantial protection a number of years after stopping [13].

Perhaps the most important of the black boxes in Figure 2 is the precise mechanism by which increased circulating estrogens produce endometrial cancer. To date, several possible mechanisms have been proposed. These include the possibility that estrogens are complete carcinogens themselves, that estrogens act as promoters in the classical laboratory sense of promotion, or that the increased risk of malignancy is simply due to the growth stimulation produced by estrogens that offers a greater opportunity for abnormal cells to arise or for carcinogens to act on vulnerable genetic material. The current epidemiologic evidence by itself does not allow the distinction of promotion from growth stimulation. However, the evidence can at least partially address the issue of distinguishing an early stage from a relatively late stage effect. Most notably, the increased risk associated with menopausal estrogen use shows up approximately 2 years after the onset of such use [23,24], and the risk declines progressively with each passing year after cessation of use [23,25]. As noted previously, the protective effect associated with combination oral contraceptives shows a similar pattern. The abrupt onset of risk with menopausal age can also be construed as a very rapid effect. Together these observations would argue fairly persuasively that estrogens act at a relatively late stage in the process of carcinogenesis.

If one chooses to embrace the tumor promotion model for estrogens and endometrial cancer, one has to deal with the dilemma of speculating about what the initiator could be. Thus far, no risk factors that would fall into this category are readily apparent, although admittedly they have not been well pursued by epidemiologic investigations.

Pursuit of these general issues translates to pursuit of a number of more specific questions, such as: How much of the effect of the epidemiologic risk factors is accounted for by the estrogen effect? Is there a dose effect for circulating estrogens that is similar regardless of source? How much of the increased circulating estrogen effect is due to free versus bound estrogen, and is there any difference in effect between major estrogens? How lasting is the exogenous estrogen effect on both disease and hormonal metabolism? What is the mechanism of action on hormonal

status and endometrial cancer risk of the oral contraceptives? Are the few risk factors not yet related to a hormonal etiology actually related to hormonal metabolism in some way? How much of the obesity effect is simply calories and how much is source of calories, and, further, how much of the effect is related to the number of fat cells versus their content or type of fat? What is the mechanism of action of the increased circulating estrogen levels? If the mechanism is that of promotion, what are the initiating agents?

As I noted, addressing these issues in a high-quality manner would seem to require a combination of formal epidemiologic approaches with the incorporation of a number of laboratory adjuncts. Specifically, what would seem to be desirable would be a study of a large series of incident cases from a defined population, along with a large sample of controls who were representative of this same population. The study would involve extensive assessments of dietary patterns including major lifetime changes, anthropometric data throughout life, reproductive and medicinal risk factors, and probing for other relevant exposures. The laboratory adjuncts to such a study would include serum and urinary hormones, fat biopsies, and a variety of assays on fresh tumor material. It would seem that both the epidemiologic capabilities and the appropriate laboratory assays are developed enough to support such an investigation.

CANCERS OF THE UTERINE CERVIX

Our level of insight into mechanisms of carcinogenesis for the uterine cervix is certainly a long way from that of endometrial cancer. However, for some time a diverse number of risk factors have been repeatedly demonstrated for cancers of the uterine cervix. More recently, many more specific hypotheses have been proffered to explain the basis for these risk factors. In addition, recent advances in technology enable a number of these more specific hypotheses to be addressed directly in the context of epidemiologic investigations. Two noteworthy features of this disease make the interdisciplinary approach particularly attractive. First of all, most cervical cancer risk factors, and the hypotheses proffered concerning their mechanisms, are highly interrelated. Second, the disease presents some very complex problems in the areas of pathology and epidemiology. These two features of cervical cancer seem to insure that further advances toward more specific etiologic factors and mechanisms can probably only be made through interdisciplinary studies. On the other hand, these same features make such investigations very difficult to do well and to interpret appropriately.

Historically, several risk factors for this disease have been well known for some time. From the first observations relating to the frequency of this disease among married women and its absence among nuns [26] it has been suspected that this could be a sexually transmitted disease. Two of the more powerful risk factors that are routinely identified for this disease are an increased risk with increased numbers of sexual partners and an increased risk with earlier ages at first coitus [27,28]. Recently, these findings have been augmented by demonstration of the so-called male factor for this disease. Specifically, among women who have had only one sex partner, the risk of cervical cancer is directly related to various indicators of sexual promiscuity for this male partner [29]. Another long-recognized risk factor for this disease is socioeconomic status. Those in the lowest social classes experience approximately

twice the risk of disease as those in the highest. A substantial portion of this relationship appears to be independent of the sexual factors previously mentioned.

More recently, three new risk factors for this disease have been proposed along with supporting data. High-quality epidemiologic investigations of oral contraception have produced a remarkably consistent impression that risk of cervical cancer increased with increased use of oral contraceptives [28,30-34]. This has been true whether the endpoint was dysplasia, carcinoma in situ, or invasive carcinoma. It was also true that a twofold excess risk has been noted for long-term use in both case-control studies and cohort investigations. Also recently, suggestions were made from descriptive, correlational studies that cigarette smoking might be a risk factor for cancers of the uterine cervix [35]. While there was some initial concern that this was only an apparent relationship because of the confounding influences of socioeconomic status and sexual factors, several analytic studies focused on this issue have indicated an excess risk of cervical cancer associated with cigarette smoking that is apparently independent of these other risk factors [28,36-38]. There is, however, a fair amount of inconsistency, including some lack of persuasive dose-response relationships, making a causal interpretation somewhat speculative at this time. Last among the more recent candidates for cervical cancer risk factors has been various micronutrient deficiencies. Since the malignancies of the uterine cervix are primarily squamous cell carcinomas of epithelial tissue, the theoretical speculation about a protective role for vitamin A and/or carotene seems to be applicable to these malignancies. Indeed, several studies have found that indices of vitamin A and carotene intake in the diet or serum were inversely related to the risk of cervical cancer [39-41]. Another study has suggested that vitamin C might also be relatively more common among the controls rather than the cases and, therefore, might be a biologically important protective factor against this malignancy [42].

As our knowledge of cervical cancer risk factors has evolved, more specific hypotheses have been suggested to explain the mechanisms through which some of these factors might operate. With the advent of these more specific hypotheses has also come the realization of how interrelated a number of these issues really are. In the area of infectious agents, infections with a variety of sexually transmitted agents have been related to elevated risks of cervical neoplasia. This is not surprising, since this is what one would expect simply on the basis of a relationship between promiscuity and risk of this tumor. The salient question is whether any one or several of these infectious agents are responsible for the associations of risk with the sexual factors, or are they merely a reflection of these risk factors. Much epidemiologic and laboratory effort has been directed toward evaluating this question. Historically, most of the interest has been in herpesvirus type II [43]. A number of early results suggested a relationship, while several failed to find such. Much of the early work was severely hampered by difficulties in the assays used to detect antibodies and a resulting wide variation in prevalence rates from study to study. A major concern was also whether these infections actually preceded the neoplastic process or whether neoplastic tissue was simply a more receptive host for this virus. To address these questions, a large prospective study was initiated in Czechoslovakia over 9 years ago [44]. Sera were obtained from women, who were followed for various conditions over this 9-year period. A case-control study within this cohort was reported last year [45]. Controls were matched to the cases of cervical neoplasia on the basis of age, age at first intercourse, number of sexual partners, smoking habits, and therapeutic

procedures. No difference was found between the cases and controls in the level of antibody to herpes simplex virus type II by either of two laboratory assays. Another prospective study that started about the same time to follow women who were exposed in utero to DES also provided the opportunity to collect serum in a prospective manner [46]. Recent results from this study also indicate no difference in the levels of antibody to herpes simplex virus type II in either the sera collected at entry or that obtained at time of diagnosis [47]. Curiously enough, there was a difference in antibodies to herpes simplex virus type I between cases and controls in the sera collected at both times.

The candidate virus that has generated the most recent enthusiasm for an etiologic role in cervical neoplasia is the papilloma virus [48]. Adequate assessments have been made more difficult by the lack of antibody assays for the appropriate strains. However, a substantial amount of biochemical and molecular evidence has pointed toward a role for this virus. Since this is a topic of another paper in this session I will not go extensively into the evidence. It may be of some interest, however, to note that one of the hypothesized roles for this virus is that of a tumor promoter, perhaps promoting the effects of other infectious agents [49]. The recent results from the follow-up of the DES-exposed cohort indicate a 17-fold increased risk of cervical neoplasia for women with histological evidence of papilloma infection at the time of diagnosis [47]. None of these histological changes were present in the biopsy material obtained from a subset of these cases prior to diagnosis. This may indicate that if this virus has a role, it is likely to be involved at the latter stages of the carcinogenesis process. It also emphasizes the need to document whether the infection preceded the tumor, or whether neoplastic tissue is somehow more receptive to viral infection.

Possible mechanisms for the association with cigarette smoking have also recently been suggested. In a study from the American Health Foundation, it was noted that cervical mucus among smokers reflected the levels of cotinine seen in the serum and that the levels of nicotine were in fact more concentrated than those seen in the serum [50]. A logical next step would be to look for tobacco carcinogen-DNA adducts in cervical cancer specimens.

A number of the micronutrient hypotheses have also become more specific and more focused, some taking into account the apparent interrelationships between a number of these risk factors. One of the more provocative findings has been the observation that oral contraceptive users have lower serum and red blood cell folate levels than nonusers and that contraceptive users who also have cervical dysplasia have even lower levels [51]. These low levels are also accompanied by megaloblastic changes in the cervical epithelium. In a placebo-controlled trial of folic acid supplements in women with varying degrees of cervical dysplasia the dysplasia progressively improved among the group receiving folic acid and remained approximately the same among the placebo group [51]. A number of interesting questions are raised by these observations. Is risk of neoplasia associated with oral contraceptives caused by an accompanying folic acid deficiency, or are these independent or perhaps interactive risk factors? Is folic acid a factor in neoplasia among women who are not oral contraceptive users? The recent findings of diminished induced chromosomal breaks at fragile sites near oncogenes following supplementation with folic acid makes these observations even more provocative for their etiologic and mechanistic possibilities [52].

In summary, we certainly do not have the depth of knowledge of possible mechanisms of carcinogenesis for cancers of the uterine cervix that we have for endometrial cancer. However, a substantial number of risk factors are known for cervical cancer. Recently, a number of more specific, mechanistically oriented hypotheses have been suggested to explain these risk factors. In addition, recent advances in technology have enabled a number of these more specific hypotheses to be addressed in epidemiologic studies.

It is appropriate for an epidemiologist to conclude a discussion of cervical cancer with a comment on the complexities of studying this disease. The neoplastic state itself is a complex one, which offers many intermediate endpoints between mild dysplasia and invasive malignancy. Many studies focus on early neoplastic states without recognizing that the progressive transition from one stage to another is not universal, and the diagnosis of many of these entities themselves is dependent on participation in screening programs. In addition, the majority of the risk factors and the hypotheses proposed to explain them are highly interrelated, offering numerous possibilities for spurious associations if other variables are not adequately controlled. An illustration of this latter point comes from preliminary analyses of a five-center study of invasive cancers of the uterine cervix (Table I) (L. Brinton, personal communication). In the crude data there appeared to be little or no association of risk with use of oral contraceptives. However, after introducing appropriate control for seven separate risk factors for cervical cancer, a significant trend of increasing risk with increasing duration of oral contraceptive use emerged. Indeed a substantial amount of this dramatic change was brought about by control for a distinctly nonbiological risk factor, that is, interval from diagnosis to last pap smear. Patients who have developed invasive cervical cancer tend not to have been participants in active screening. Therefore, the disease is related to relatively long intervals to last pap smear. Conversely, oral contraceptive users tend to be screened by pap smear relatively frequently because of their frequent contacts with the medical care system. Thus, there is a distinct possibility for negative confounding, and the failure to find a true association because of the confounding by this medical-care variable. This is apparently what happened in this instance.

Thus, because of the complexity of the disease and virtually all aspects of studies designed to address its risks factors, it appears that further advances toward specific etiologic factors and mechanisms will only be possible through interdisciplinary studies. It is just as clear that for the same reasons such investigations will be very difficult to do well and to interpret appropriately.

TABLE I. Relative Risks for Invasive Cervical Cancer by Years of Oral Contraceptive Use: Preliminary Results From a Case-Control Study in Five Geographic US Areas

Years of pill use	Age-adjusted RR	Adjusted ^a RR ¹
None	1.00	1.00
< 5	0.78	1.29
5-9	1.16	2.00
10+	1.26	1.84

^aAdjusted for age, race, number of sexual partners, age at first intercourse, interval since last pap smear, years smoked, history of a nonspecific genital infection or sore, and education.

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