Opinion

Estrogens and Increased Endometrial Cancer: Fact or Artifact?

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REPLACEMENT ESTROGENS AND ENDOMETRIAL CANCER

The first case-control studies that demonstrated a strong association between replacement estrogens and endometrial cancer were published in December 1975.\(^1\)\(^2\) Further data supporting the association appeared in June 1976.\(^3\) More recently, Jick et al\(^4\) published the results of a study based on the experience of Group Health Cooperative of Puget Sound (GHC), a health maintenance organization that provides virtually complete prepaid medical coverage for outpatient care, drugs, and hospital services. Carefully documented computerized records of prescriptions filled and of hospital diagnoses have been maintained at GHC since July 1975. From these records, together with interviews with patients who had endometrial cancer and with appropriate controls, it was possible to estimate the risks of developing endometrial cancer for current users and non-users of replacement estrogens over a 24-month period from July 1975 to June 1977. The annual incidence rate among current estrogen users (with intact uteri) was one to three percent. For non-users, it was consistently about 0.1 percent. The vast majority of the cases of endometrial cancer among estrogen users occurred in women who had taken the drug for at least five years. Further evaluation of the data showed that there was a dramatic drop in estrogen use at GHC following the initial reports of an association between this drug and endometrial cancer in 1975.\(^1\)\(^2\) Six months later there was an equally dramatic drop in the incidence of endometrial cancer. These data suggest that the changes induced by long-term estrogen exposure in the development of endometrial cancer are stopped or reversed shortly after the drug is discontinued.

The fall in incidence at GHC came after several years of rising incidence there\(^4\) and is part of a substantial decline that occurred in the United States from 1975 to 1977, especially in the West.\(^4\) Indeed, the fall in incidence of endometrial cancer was estimated to be over 40 percent between 1975 and 1977 in the western United States—an area that previously had had the highest rate of both estrogen use and endometrial cancer in the country.\(^4\) An alternate explanation to that mentioned above is that discontinuation of estrogen postpones the time of diagnosis. Continued monitoring of this population, as well as nationwide statistics, will determine which explanation is correct.
The existence of an extremely strong association between replacement estrogen use and endometrial cancer is virtually certain. Most of the studies estimate the risk to be more than 10 times higher in long-term users than in non-users.2-5

The central remaining question is, "What is the explanation for this strong association?" There are two major possibilities: (1) long-term replacement estrogen use causes endometrial cancer; and (2) long-term replacement estrogen use causes the disease to be diagnosed preferentially in women taking the drug long-term, and there is no real difference in incidence between long-term users and non-users.

The second explanation, repeatedly suggested by Horwitz and Feinstein,6 would require endometrial cancer to be an extremely benign disease that remains undiagnosed in non-users of estrogens in over 90 percent of women who actually have the disease. This explanation is only a remote possibility since there are no documented cancers that I am aware of that remain permanently undiagnosed in over 90 percent of cases. Furthermore, Horwitz and Feinstein6 themselves have cited reports that refute the implication of their hypothesis: they refer to the results of screening efforts that demonstrate that only about one endometrial cancer in five detected by screening is asymptomatic, despite the attempts of one group to screen at annual intervals.7-9 Autopsy data from the Mayo Clinic, showing the rarity of undiagnosed endometrial cancer, confirm that the deductions from their hypothesis are contrary to fact.10 Using the data from the screening reports to which Horwitz and Feinstein refer, Hutchison11 has demonstrated that the maximum detection bias introduced by selective diagnosis among estrogen-takers could account for only a small fraction of the strong overall association that has been observed in many studies in various populations.1-5,10

The untenable argument advanced by Horwitz and Feinstein6 is the primary basis for whatever "controversy" exists over this issue.

The overwhelming evidence indicates that long-term estrogen use causes endometrial cancer. It should be mentioned, however, that taking progesterone seven to 10 days per month may have a protective effect in women with estrogen-induced cancer. This possibility has not been fully explored.

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COMMUNITY SURVEILLANCE BIAS
AND THE ESTROGEN-ENDOMETRIAL
CANCER DISPUTE

A randomized clinical trial, in which post-menopausal women would be assigned to take or not take estrogen replacement therapy, and to receive regular intra-endometrial exams, would be the ideal method to determine whether or not estrogens cause endometrial cancer. This is impossible, however, because most women would not agree to participate in such an experiment.

In the absence of an experimental trial, a longitudinal cohort study would be the next best way to answer this question. Post-menopausal women who have made their own decision to receive or not receive estrogens would be followed for a suitably long period of time thereafter. To determine the rate at which endometrial cancer develops in the two groups, the members of each group would routinely receive intra-endometrial diagnostic examinations.

The latter procedure might be more acceptable to the people under study, although the asymptomatic women in the two groups might have to be strongly persuaded to submit to the endometrial examinations. However, even if the women agreed, the performance of such a study would probably be unacceptable to the investigator, who would have to be prepared to assemble about 20,000 women to achieve satisfactory statistical data since the incidence of endometrial cancer is low. The women would also need follow-up, with suitable examinations, for years. The logistics of such a study are so difficult that it will probably never be conducted.

As a result of these difficulties, investigators have turned to an epidemiologic technique, the case-control study. This type of research is cheap, quick, and easy to perform because it is conducted retrospectively. The investigator begins with a group of cases—women who have already been shown to have endometrial cancer. The investigator then arbitrarily chooses a group of controls from women who have not been shown to have endometrial cancer. The two groups are asked about their previous use of estrogens. From the quantitative data about previous usage, the investigator calculates an "odds ratio." If this odds ratio exceeds 1.00 and is "statistically significant," the investigator concludes that estrogens increase the risk of developing endometrial cancer.

All of the data that have been used to support (or refute) the suspicion that estrogens cause endometrial cancer have come from retrospective case-control studies of the type just described. The current controversy rests on the willingness or unwillingness of investigators to accept conventional case-control studies as a suitable substitute for clinical trials or longitudinal cohort studies. The principal problem is the issue of detection of endometrial cancer. If women who do not receive estrogens do not develop bleeding and also do not receive routine endometrial examinations, they can develop endometrial cancers that may be undetected during life. On the other hand, women who receive estrogens

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commonly develop bleeding as a side effect, resulting in a D&C or other examination that allows an endometrial cancer to be diagnosed. In a clinical trial or longitudinal cohort study conducted with routine endometrial examinations, the problem of differential detection would not occur. In a conventional case-control study, however, the investigator has no way of knowing the magnitude of the problem. The "control" group consists of women who have not been shown to have endometrial cancer, but these women may not have received an endometrial examination. Furthermore, the investigator has no way of knowing the extent to which his case and control groups have been distorted by the community surveillance that would substantially increase the frequency with which estrogen-taking women are referred to medical centers for therapy.

The problem of "community surveillance bias" has been ignored and left unexamined in all of the conventional epidemiologic case-control studies. We believe this bias has led to a spurious overestimation of the association between exogenous estrogens and endometrial cancer. The alleged causal association has been reported in seven recent conventional studies1-7 that conflict with two older investigations8,9 and with subsequent research10 in which the magnitude of the association was substantially lower.

In the six case-control studies1-6 claiming a causal association between estrogens and endometrial cancer, the odds ratio were 7.5, 7.6, 8.0, 4.9, 3.1, and 6.0 respectively. In the two older conflicting studies,8,9 the odds ratios were 1.1 and 0.5. In the most recent study,10 when the cases and controls were stratified into those who presented with or without uterine bleeding complaints, the odds ratios were 1.7 and 1.8 respectively. Our purpose in this report is to demonstrate how "community surveillance bias" has produced the contradictory findings in the cited studies.

Community surveillance refers to medical examinations that occur before a person becomes a case or control in the hospital. A bias in surveillance can arise unless medical attention was sought by the patient and received before hospitalization in a manner allowing the exposed (estrogen-taking) and the non-exposed an equal chance to become classified as cases. Since this bias, if present, has already occurred before the cases and controls are chosen for a case-control study, its distortions cannot be remedied by statistical adjustments of data collected in the conventional manner. Instead, the removal or reduction of the bias requires special procedures for selection of patients and subsequent analysis of data.

In the studies that supported a causal association between estrogens and endometrial cancer, conventional case-control methods were used to select the cases of endometrial cancer from a hospital tumor registry or other diagnostic listing; the control groups were chosen from women with other gynecologic cancer or from general hospital or community groups. The traditional method of selection makes no provision for community surveillance bias and allows for serious distortion in the results because the patients who are collected in the hospital as members of the case-control study start out in the community as exposed cases, non-exposed cases, exposed controls, and non-exposed controls. Each of these four community groups then undergoes various rates of diagnostic surveillance before reaching the hospital to become the components of the case-control study. If the rates of surveillance are similar in each of the four community groups, then the hospitalized cases and controls will properly represent their proportionate numbers in the community. However, if the rates are disparate, so that women who are both exposed and diseased receive an increased diagnostic surveillance in the community, the four case-control groups chosen in a conventional manner will misrepresent the true proportion of persons in the community who are both exposed and diseased.
To demonstrate the importance of community surveillance bias in the relationship of estrogens and endometrial cancer, we performed two different case-control studies simultaneously at the same institution. The first study, performed with conventional case-control selection methods, used a tumor registry to provide cases of endometrial cancer and a separate control group consisting of women with other gynecologic cancers. In the second study, the cases and controls were chosen from women who underwent either dilatation and curettage or hysterectomy. The methodologic purpose in the second study was to equalize the forces of community surveillance by letting cases and controls emerge from a group of women referred to the hospital for the same diagnostic procedure, and by analyzing the results according to the clinical reason for hospital referral. The results of the two comparative studies are presented in the accompanying Table.

In the conventional study, the odds ratio for the unstratified data was 11.98. When the population was stratified according to the reason for hospital referral, the odds ratio was 10.76 for the groups presenting with uterine bleeding and 6.00 for the groups that presented with other, non-bleeding complaints. The results of this conventional study are consistent with the conclusions of the reports that linked estrogens and endometrial uterine cancer.

For the alternative study, with cases and controls selected by the diagnostic-procedure method, the odds ratio for the unstratified data was 2.30. Although this ratio is strikingly smaller than what was obtained by conventional sampling methods, the result continues to reflect the consequence of estrogen-influenced surveillance bias. When this bias was further reduced by stratifying the results according to the reason for hospitalization, the odds ratio was 1.71 for the group presenting with uterine bleeding and was 1.83 for the non-bleeding group. The results of the conventional method of sampling thus agree with those of the six previous reports, whereas the results of the alternative diagnostic-procedure method agree with those of the two older studies.

The disparities can be reconciled in several ways. Two basic assumptions behind the research methods of conventional case-control studies influence the interpretation of the results. The assumptions are: (1) all people with endometrial cancer are overtly symptomatic; and (2) the proportional rates of diagnostic surveillance are similar in the women who are taking or not taking estrogens. When these assumptions are accepted and the odds ratio is significantly greater than 1.0, the conclusion is that estrogens probably cause endometrial cancer. In the alternative hypothesis—which was tested by the new methods—the basic assumptions are that many people with endometrial cancer are asymptomatic, and that the rates of diagnostic surveillance are higher in the estrogen group because estrogens provoke increased bleeding and referral for diagnosis. The alternative conclusion is not that estrogens cause endometrial cancer, but that estrogens cause an increased detection of the cancer.

Of the nine case-control investigations of estrogens and endometrial cancer, community surveillance bias was avoided in the three studies that reported no association between estrogens and endometrial cancer, but not in the six studies that reported a causal association.

The paper by Jick et al gives the impression that about 18,000 women were investigated, although the only active research done by the authors consisted of telephone interviews with 67 patients with endometrial cancer, and a "control" group of 74 other women with intact uteri. In this small case-control study, the authors describe no attempt to deal with problems of community surveillance bias.

The authors' suggestion that 18,000 women were investigated is based on computer statistics of estrogen prescriptions, as well as separately reported diagnoses of endometrial cancer. Except for data in the small group chosen for the
case-control study, none of this information was checked or verified. From what was noted in the statistical trends, the authors concluded that estrogens raise the risk of endometrial cancer for users to higher than 20 times that of non-users. But the authors made no scientific effort to explore the alternative hypothesis, described in this review; this would require assembling data about the occurrence of bleeding and the incidence of diagnostic D&C's in relation to the time trends of estrogen prescriptions.

We have challenged the validity of the causal link between estrogen use and the development of endometrial cancer because the studies performed with conventional methods assembled case groups containing an excessively high proportion of estrogen takers. When this bias was reduced or eliminated by selecting control groups with comparable rates of diagnostic surveillance, the causal association vanished.

Antunes et al disagree with our conclusions because of evidence in their study that the lag-time between the onset of post-menopausal bleeding and contact with a physician was comparable for estrogen users and non-users. This observation is irrelevant to the issue of surveillance bias, however, because the rapidity with which a woman who develops bleeding makes an appointment with her doctor has little to do with what caused the bleeding. The analysis by Antunes et al did not measure the magnitude of surveillance bias, and their analytic procedures did nothing to reduce its effects. We therefore conclude that the association between estrogens and endometrial cancer has been greatly overestimated because of the neglected effects of community surveillance bias. When cases and controls are selected to achieve comparable rates of diagnostic endometrial surveillance, the association between estrogens and endometrial cancer is reduced to non-significant levels.

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