The New England
Journal of Medicine

Volume 299 NOVEMBER 16, 1978 Number 20

ALTERNATIVE ANALYTIC METHODS FOR CASE-CONTROL STUDIES OF ESTROGENS AND ENDOMETRIAL CANCER

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Abstract In a case-control study of estrogens and endometrial cancer, alternative sampling methods were used to eliminate the detection bias that arises from the increased diagnostic attention received by women with uterine bleeding after estrogen exposure. In a set of cases and controls chosen by conventional procedures the odds ratio was 11.98. In an alternative set of cases and controls at the same institution, consisting of patients who had all received dilatation and curettage or hysterectomy because of uterine bleeding, the odds ratio was 1.7.

A methodologic analysis demonstrates detection bias arising from the pattern of hospital referral and shows the way in which the bias is neglected or increased by conventional sampling procedures, but reduced by the alternative procedure. The magnitude of the association between estrogens and endometrial cancer has been greatly overestimated because of detection bias; when an appropriate compensation for the bias is introduced, the odds ratio approaches a value much closer to 1. (N Engl J Med 299:1089-1094, 1978)

AN association between exogenous estrogens and endometrial cancer has been reported for postmenopausal women in five recent investigations[1-5] that all employed the conventional methods of the "retrospective case-control" study.

In a case-control study the investigator works in a hospital or other medical setting and follows people backward from the effect toward the cause. In that setting he collects a group of the diseased people called "cases," and from the available nondiseased people he chooses a separate group called "controls." He then finds out which people were exposed or not exposed to the alleged causal agent. With this information, the patients are divided into four groups, whose numbers are counted as a, b, c and d, as shown in Figure 1.

The odds ratio used to express the results of a case-control study is obtained from these numbers as a ratio of two ratios: the exposure ratio in the cases, divided by the exposure ratio in the controls ($a/c \div b/d$). The *odds ratio* is used as a substitute for the *risk ratio,* which is the rate with which the disease occurs in exposed people, divided by the rate of the disease's occurrence in nonexposed people. If these two rates of occurrence are very small and if no distortions have occurred in the four groups that comprise the case-control study, the odds ratio will be approximately equal to the risk ratio. If the odds ratio exceeds 1 and is statistically significant, either in a direct test of significance or by demonstration that the value of 1 is not contained in the associated confidence interval, the investigator concludes that a causal relation may exist between the agent and the disease.

With the conventional methods, the results of the five recent case-control investigations of estrogens and endometrial cancer produced odds ratios of 7.5, 7.6, 8.0, 4.9 and 3.1, respectively. These data were in conflict with two older case-control studies[6,7] in which the respective odds ratios were 1.1 and 0.5. The two older studies had been performed with a different method of patient selection in which the population under investigation consisted of women with postmenopausal bleeding receiving dilatation and curettage. The cases and controls were determined according to the results of that procedure.

In contemplating the discrepancy in results between the older and the more recent studies, we wondered about the role of estrogens in provoking bleeding as an adverse side effect. With an asymptomatic endometrial cancer, women who did not take estrogen might not have any symptoms that would provoke an intra-endometrial diagnostic examination, but the use of estrogens might cause the bleeding that would lead to referral for the diagnostic test whose results detect a cancer that might otherwise be undiscovered. The increase in detection might take place at two separate phases of a patient's medical itinerary. For a patient in the community, the bleeding might

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Supported in part by a grant (HS 00408) from the National Center for Health Services Research and Development, U.S. Public Health Service, and by a grant from Ayerst Laboratories.

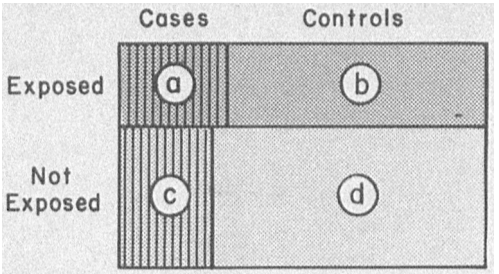

Figure 1. Assembly of the Case-Control Groups.

evoke increased medical surveillance, followed by the doctor's decision to seek the diagnostic test. For a patient hospitalized for whatever reason, the bleeding might evoke a direct ordering of the test. These two sources of an increased detection rate, rather than the pathogenetic effect of estrogens, might thus be responsible for the elevated odds ratio.

To test this possibility, we decided to perform two separate case-control studies at the same institution. In the first study, we would select cases and controls by the same conventional process used in one of the five recent investigations. In the second study, we would use an alternative method of sampling, by letting the cases and controls emerge from the results found in a group of women referred to the hospital for the same intra-endometrial diagnostic procedure. The purpose of the alternative approach was to try to equalize the forces of "diagnostic surveillance" that might otherwise create major "detection bias" in the conventional data of cases and controls.

In this paper, we report the results of those two studies.

Patient Selection and Research Methods

For both studies the starting population was postmenopausal women hospitalized at the Yale-New Haven Medical Center. In the conventional study, which duplicated the case-control groups chosen by Smith et al.,[1] the source of the selected patients was 561 women with gynecologic cancer listed in the Yale Tumor Registry between July 1, 1974, and June 30, 1976. Of these women, 119 had a diagnosis of endometrial cancer and became the case group. From the remaining women, 119 were matched for age (within four years) and race to become the controls. Among the 119 controls, 60 had carcinoma of the cervix, 43 had carcinoma of the ovary, 15 had carcinoma of the vulva, and one had carcinoma of the vagina.

In the alternative study, the source of the population was 6869 consecutive women who underwent dilatation and curettage or hysterectomy between January 1, 1974, and June 30, 1976. Of these women, 149 were diagnosed as having endometrial cancer and became the case group. The women with diagnoses other than uterine cancer were the comparative patients, from whom the controls were randomly selected among those previously matched for age (within four years) and race with each member of the case group. The diverse histologic diagnoses received by these 149 controls included: uterine polyps and leiomyomas, 49; atrophic endometrium, 36; proliferative endometrium, 14; hyperplastic endometrium, 12; secretory endometrium, two; and basal or resting endometrium, 46. (More than 149 diagnoses are listed because more than one histologic diagnosis may have been made on a single specimen of endometrial tissue.)

To be accepted as a case in either study, a patient was required to have endometrial carcinoma of Grade 1 or higher. Patients with Stage 0 "in situ" carcinoma of the endometrium were not accepted as either cases or controls.

In all previous studies of this topic, the investigators have rarely stipulated what was meant by "exposure to estrogens." Before the current research began, a decision was made, after consultation with gynecologic authorities, that estrogen exposure would be defined as at least 0.3 mg of conjugated estrogens per day for at least six months at any time before hospitalization. For both studies, the data about pharmacologic exposure to estrogens were collected, from the patients' hospital charts and from office records of the appropriate physicians, by data abstractors who were kept "blind" to the research hypothesis.

For each study, the data were collected in the form of a two-by-two table relating estrogen exposure or nonexposure to the patients' status as a case or control. Because of the role of uterine bleeding as a stimulus to hospitalization, each two-by-two table was further subdivided according to the presence or absence of such bleeding. Since the control patients were chosen by a matching procedure, each set of results could be analyzed with either a matched or unmatched form of analysis. Because the results of the matched and unmatched analyses were essentially identical, we shall present the results of the unmatched analyses, which are conceptually simpler and easier to understand.

For each of the original two-by-two tables, we calculated the odds ratio, in the conventional manner, as an estimate of the overall relative risk. The "statistical significance" was calculated by the use of the Fisher exact test; the 95 per cent confidence interval around the odds ratio was calculated according to the method described by Thomas.[8] When the original two-by-two tables were stratified according to the presence or absence of bleeding, each of the subsequent tables could have its own odds ratio, Fisher exact test and confidence intervals calculated in a similar manner.

Results

Table 1 shows the pertinent clinical features of the cases and controls in both studies. The mean age of the patients at the time of diagnosis and at the time of menopause was similar in all four groups. In both studies, the case groups had significantly more patients with nulliparity and obesity — factors that have previously been noted in relation to endometrial cancer.[9] However, there was no difference between the two studies in the prevalence of these factors in the two case groups or in the two control groups. Hypertension and diabetes occurred with similar rates of frequency among the cases and controls of both studies.

The relation of estrogen to endometrial cancer as found by the conventional sampling method is shown in Tables 2 and 3. In Table 2, 29 per cent of the cases

Table 1. Clinical Characteristics of the Case and Control Groups.

Characteristic	Case Group		Control Group	
	Conventional Method	Alternative Method	Conventional Method	Alternative Method
No. of patients	119	149	119	149
Mean age of patient (yr)	61±9*	62±9	62±9	61±9
Mean age at menopause (yr)	50±4	50±4	48±7	50±5
% Nulliparous	26	27	18	13
% Obese	30	33	22	21
% Hypertensive	33	40	28	36
% Diabetic	10	11	8	8

*± SD.

Table 2. Relation of Estrogen to Endometrial Cancer in the Conventional Study.

GROUP	CASES	CONTROLS
Estrogen takers	35	4
Non-estrogen takers	84	115
Totals	119	119
Odds ratio	11.98	
95% confidence interval	4.02–47.73	
Fisher's exact test	P = 0.001.	

but only 3 per cent of the controls were estrogen takers. The odds ratio (calculated as [35 times 115] divided by [4 times 84]) is 11.98. The 95 per cent confidence interval excludes 1, and the Fisher exact test yields P = 0.001. Table 3 shows the same results, but with the patients stratified for bleeding. Among the women with uterine bleeding, 30 per cent (34 of 113) were estrogen takers, as compared with 4 per cent (one of 26) of the controls. Among the women with nonbleeding complaints, 17 per cent (one of six) of the case group were exposed to estrogens, as compared with three per cent (three of 93) of the controls.

Table 3. Results of Table 2, Stratified for Bleeding.

GROUP	PRESENTING COMPLAINT			
	UTERINE BLEEDING		NO BLEEDING	
	case	*control*	*case*	*control*
Estrogen takers	34	1	1	3
Non-estrogen takers	79	25	5	90
Totals	113	26	6	93
Odds ratio	10.76		6.00	
95% confidence interval	1.60–454.57		0.09–89.81	
Fisher's exact test	P = 0.005		P = 0.224	

For the group with uterine bleeding, the odds ratio is 10.76, and the 95 per cent confidence interval excludes 1. For the group with complaints other than uterine bleeding, the odds ratio is 6.00, and the 95 per cent confidence interval includes 1.

The results of the alternative sampling method are presented in Tables 4 and 5. The unstratified data, shown in Table 4, indicate that 30 per cent of the cases were estrogen takers (44 of 149), as compared with 15 per cent of the controls (23 of 149). The odds ratio is 2.3, with a 95 per cent confidence interval that excludes 1 and a Fisher exact test with P = 0.005. This ratio, although strikingly smaller than what was obtained by conventional sampling methods, may continue to reflect the consequence of estrogen-influenced detection bias.

To adjust for this important source of bias, the results are stratified according to the reason for hospitalization. As demonstrated in Table 5, among the women with uterine bleeding, 30 per cent (43 of 142) of the case group were estrogen takers, as compared with 20 per cent (18 of 89) of the controls. Among those without bleeding 14 per cent (one of seven) of the case group were estrogen takers, as compared with 8 per cent (five of 60) of the controls. The individual odds ratios are 1.71 for the group with uterine bleeding and 1.83 for the group with nonbleeding complaints. The similarity of the values obtained in the bleeding and nonbleeding groups suggests that the risk ratio is being accurately appraised.

Table 4. Relation of Estrogen to Endometrial Cancer, Studied by the Alternative Sampling Method.

GROUP	CASES	CONTROLS
Estrogen takers	44	23
Non-estrogen takers	105	126
Totals	149	149
Odds ratio	2.30	
95% confidence interval	1.26–4.25	
Fisher's exact test	P = 0.005	

In both groups, the 95 per cent confidence interval around the odds ratio includes 1.

Table 6 shows the results for the alternative sampling method after exclusion of controls with histologic diagnoses that are possibly related to estrogens (patients with proliferative or hyperplastic endometrium). The unstratified data indicate that 30 per cent of the case group (44 of 149) were estrogen takers, as compared with 13 per cent of the controls (17 of 126). The odds ratio is 2.69, with a 95 per cent confidence interval that excludes 1 (1.46 to 4.94). In the patients who had uterine bleeding, 43 of the 142 case group were estrogen takers (30 per cent), as compared with 13 of the 73 controls (18 per cent). The odds ratio decreases to 2.0, with a 95 per cent confidence interval that excludes 1 (1.01 to 4.14).

Table 5. Results of Table 4, Stratified for Bleeding.

GROUP	PRESENTING COMPLAINT			
	UTERINE BLEEDING		NO BLEEDING	
	case	*control*	*case*	*control*
Estrogen takers	43	18	1	5
Non-estrogen takers	99	71	6	55
Totals	142	89	7	60
Odds ratio	1.71		1.83	
95% confidence interval	0.88–3.42		0.03–20.97	
Fisher's exact test	P = 0.123		P = 0.498	

Table 6. Results for Alternative Sampling Method: Controls with Estrogen-Related Disorders Excluded.

Group	Case	Control
Unstratified for presenting complaint:		
Estrogen takers	44	17
Non-estrogen takers	105	109
Totals	149	126
Odds ratio	2.69	
95% confidence interval	1.46–4.94	
Fisher's exact test	P = 0.002	
Stratified for uterine bleeding as presenting complaint:		
Estrogen takers	43	13
Non-estrogen takers	99	60
Totals	142	73
Odds ratio	2.00	
95% confidence interval	1.01–4.14	
Fisher's exact test	P = 0.034	

Discussion

With a conventional procedure to select cases and controls, our results are similar to those of the five previous studies that reported an association between estrogens and endometrial cancer.[1-5] With the alternative method of selecting cases and controls, however, the results are quite different, resembling those of the two older studies,[6,7] with individual odds ratios that did not significantly differ from 1.

The alternative method tests a hypothesis that depends on two assumptions: that many cases of 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. With these assumptions, estrogens may lead to an increased detection of the cancer but need not be a causal agent.

The assumptions are supported by at least two types of evidence. One set of evidence is the high proportion (≥20 per cent) of uterine cancer that was found to be asymptomatic in three different investigations. In 1964, Hofmeister and Barbo,[10] performing routine endometrial sampling for more than 19,000 women in private gynecologic practice, found 66 women with uterine cancer, of whom 13, or 20 per cent, were symptom-free at the time of diagnosis. In 1966, Abramson and Driscoll,[11] after routine endometrial sampling for 1540 patients, reported five cases of uterine cancer, of which three, or 60 per cent, were asymptomatic. In 1970, Ng and Reagan,[12] working in the gynecology clinic of the Case-Western Reserve Medical Center, found 363 cases of endometrial cancer among patients who were routinely advised to have endometrial aspiration. Of those patients, 20 per cent were asymptomatic.

A second set of supporting evidence, found during our study, appears in Table 7. Consistent with the assumption that women with low-grade (Grade 1) cancer exposed to estrogens are likely to have uterine bleeding and to be referred to the hospital, the results show that Grade 1 cancer occurred in 63 per cent of the nonexposed bleeding women but in 88 per cent of those who bled and were exposed to estrogens (chi-square = 9.5; $P<0.005$). Among women without bleeding, the numbers are consistent with the assumption, but are too small to allow any meaningful statistical conclusions.

The Validity of the Control-Group Selection

As noted earlier, the odds ratio will approximate the risk ratio only if the four constituent groups of the case-control study are selected without distortion. These four groups are referred to the hospital from among the people in the community who are exposed and diseased, exposed and nondiseased, nonexposed and diseased, and nonexposed and nondiseased. If these four community groups have been referred to the hospital at similar rates, the four hospital groups will suitably represent the exposure ratios that exist in the community. If the rates of referral are disparate, the exposure ratios found in the hospital groups may be distorted.

A source of such disparity is the uterine bleeding that commonly occurs as a side effect of exposure to estrogens. Since women with uterine cancer who take estrogens are more likely than non-estrogen takers to bleed and to be referred to the hospital for diagnostic testing, the value of a in the exposed and diseased hospital case group will be elevated to a value, a', that exceeds its corresponding value in the community. The exposure ratio for cases will be calculated as a'/c and will thus be higher than the correct proportion, a/c. Consequently, since the odds ratio will be calculated as $a'/c \div b/d$, it will be falsely elevated because of the inevitable bias in the selection of the case group.

This bias will be incorporated into any case-control study that is conducted in the conventional manner, making no provision for the "detection bias" in the case group. An important role for the control group, therefore, is to counteract the effects of this bias.

A control group consisting of "other uterine dis-

Table 7. Rate of Occurrence of Grade 1 Endometrial Cancer in Relation to Estrogen Exposure and Uterine Bleeding.

Group	No. of Women*
Bleeders: Estrogen takers	38/43 (88%)
Bleeders: Non-estrogen takers	62/99 (63%)
Non-bleeders: Estrogen takers	1/1 (100%)
Non-bleeders: Non-estrogen takers	3/6 (50%)
Subtotal: Bleeders	100/142 (70%)
Subtotal: Non-bleeders	4/7 (57%)
Subtotal: Estrogen takers	39/44 (89%)
Subtotal: Non-estrogen takers	65/105 (62%)
Totals	104/149 (70%)

*Denominators represent all women in this category with endometrial cancer, & numerators women with Grade 1 endometrial cancer.

ease" will include many women who were also referred to the hospital for the diagnostic evaluation of uterine bleeding that may have been produced by estrogens. The value of b in the exposed and nondiseased members of this control group will thus be raised upward to a value of b′. When the odds ratio is calculated as $a'/c \div b'/d$, the effects of the elevated a′ and b′ will counteract each other, so that the result will more closely approximate the correct value of $a/c \div b/d$.

In a control group of women with other gynecologic cancers, uterine bleeding is not a common symptom, and the diverse clinical phenomena that lead to hospital referral are unaffected by estrogen usage. In this situation, the value of b/d, which is the exposure ratio for the controls, will be unaffected, and the odds ratio will be falsely elevated when calculated as $a'/c \div b/d$.

A control group of "all others," consisting of people without gynecologic cancer or other uterine disease, will include women in the community or women referred to the hospital for all other reasons. Since the proportionate composition of this group will also be unaffected by estrogen usage, the value of b/d as the exposure ratio of controls will again be unaffected, and the odds ratio will continue to be falsely elevated when calculated as $a'/c \div b/d$.

The true risk ratio will thus be inflated if the controls emerge either from a community group of "all others" or from patients with other gynecologic cancer. Consequently, the best chance of minimizing the influence of hospital referral bias, and of getting an undistorted value for the odds ratio, is to choose controls from among women with "other uterine disease." Even here, however, the exact effects of bleeding will be uncertain and best compensated for by stratification of the odds ratio according to the presence or absence of bleeding as a stimulus for hospital referral.

In the five recent studies[1-5] reporting a causal association between estrogens and endometrial cancer, the control groups were selected either from women with gynecologic cancer or from general-hospital or community groups. Since these control groups do not compensate for estrogen-influenced hospital referral bias in the case group, the high odds ratios found in those studies are artificially elevated. Similarly, in the study in which we replicated conventional methods (using women with other gynecologic cancers as controls), we also found an extremely high odds ratio. When the controls were selected from women with other uterine disease, as in our second sampling procedure, the elevation of the exposure ratio in the control group compensated for the elevation in the case group, and the odds ratio was more likely to approximate the true value of the risk ratio.

Our alternative sampling procedure was actually used, inadvertently, in two previous investigations. Dunn and Bradbury,[6] selecting their cases from among women with untreated endometrial cancer and their controls from women with postmenopausal bleeding, found an odds ratio of 1.1. Pacheco and Kempers,[7] after choosing cases and controls from among all patients seen for postmenopausal bleeding who underwent dilatation and curettage, found an odds ratio of 0.5. In both studies the selection of women with uterine bleeding as a comparative group led to greater similarity of diagnostic surveillance between cases and controls.

Believers in the customary sampling procedure for case-control studies would argue that our alternative method of selecting controls is improper because estrogen usage leads both to postmenopausal bleeding and subsequent dilatation and curettage. Rather than representing a weakness in patient selection, our alternative approach has the important scientific merit of compensating for the estrogen-induced detection bias that is irremediable in the case group when sampling is performed with the customary methods. If no such compensation is made in the control group, the major bias that exists in the case group will be neglected and will grossly distort the results.

A second counterargument is that our alternative-method control group should not contain patients with such possibly estrogen-related histologic diagnoses as hyperplastic or proliferative endometrium. This argument is answered by a comparison of the results shown in Tables 5 and 6. Regardless of whether such patients were included or excluded from the control group, the alternative sampling method produces odds ratios that are substantially lower than what is found with conventional procedures.

Except for noting this distinction, we are reluctant to draw any conclusions from Table 6, which was prepared to answer critics who believe that "estrogen-related disorders" should not be permitted in the control group. We believe that this table contains an unfair comparison. Since uterine bleeding attributable to estrogen-related endometrial hyperplasia and proliferation is largely responsible for the bias in the case group, the exclusion of such disorders from the control group removes a major mechanism that compensates for the bias. If these disorders do not belong in the control group, carcinomas accompanied by hyperplasia or proliferation do not belong in the cases.

The fact that the five recent case-control studies all "confirmed" one another does not constitute scientific proof that their conclusion is correct. The late Harold Dorn, in writing about case-control research, once said that "reproducibility does not establish validity, since the same mistake can be made repeatedly."[13]

Epidemiologic authorities have often stated that estimates[4] of the odds ratio could be distorted by the influence of exposure on the composition of the case and control groups. McMahon and Pugh, in their standard textbook, *Epidemiology: Principles and methods,* assert "...computation of relative risk involves two assumptions: (1) that the disease under study is relatively infrequent in both exposed and unexposed persons; and (2) that neither cases nor controls are selected in favor of either exposed or non-exposed

individuals...."[14] This statement does not indicate what should be done when "detection bias" produces a case group that is distorted in favor of exposed individuals. Our alternative method of selecting controls provides a compensation for this bias, by allowing the control group an opportunity to have received the same type of selection.

Regardless of the method used to adjust for bias in the case group, no such adjustments were performed in studies reporting a high risk ratio between estrogens and endometrial cancer. Because the ratios were greatly overestimated in those studies and because the ratios are much closer to 1 when a compensating control group is used, we conclude that the strength of the much publicized association between estrogens and endometrial cancer has doubtlessly been exaggerated and needs re-evaluation.

The type of problem we have cited is particularly disturbing because it is not unique to the case-control relation of estrogens and endometrial cancer. The absence of suitable attention to detection bias casts doubt on the odds ratios found for many other etiologic associations that have been explored with case-control studies. The detection-bias problem will arise whenever a target disease that can occur in asymptomatic or other subclinical forms is likely to be preferentially diagnosed in persons exposed to the alleged etiologic agent. Finding an effective solution to this problem offers a major scientific challenge to case-control investigators. We believe the alternative method proposed here offers one such solution.

We are indebted to research assistants Jane Stremlau, Kristie Sonnek and Luci White, to John McL. Morris, M.D., for making available his files of women with endometrial cancer and to the many practicing gynecologists in the New Haven region who made their office records freely available to us.

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