Brief Communication: Exogenous Estrogens and Breast Cancer in Women With Natural Menopause [1, 2]

J. Casagrande,[3, 4] V. Gerkins,[5] B. E. Henderson,[5] T. Mack,[3, 5] *and* M. C. Pike [3]

SUMMARY—Age, age at menopause, and calendar year at menopause were controlled as factors related to estrogen use. Data on 90 breast cancer patients and 83 controls—all of whom had a natural menopause—showed no relationship between breast cancer and estrogen usage after the start of menopause symptoms.—J Natl Cancer Inst 56: 839–841, 1976.

In the rat, two of the three estrogen fractions (estradiol and estrone) produce mammary tumors, whereas the third (estriol) does not (*1–3*). Wynder and Schneiderman (*4*) recently discussed the existing epidemiologic evidence concerning breast cancer and exogenous estrogens. In none of the seven prospective studies they listed did the number of breast cancers observed exceed the number expected. However, in none of these studies were any of the known risk factors controlled; moreover, selection biases may have been operating, since mortality in the cohorts, when provided as data, was suspiciously low. The use of oral contraceptives has not appeared thus far to affect the risk of breast cancer, though it still might be too early to see an effect (*5, 6*). In sum, these data suggest that, at worst, exogenous estrogens are harmless and that they might even protect women from breast cancer.

We reported previously a case–control study showing a decreased risk of breast cancer in women taking exogenous estrogens after natural menopause (*7*). We have now studied a further group of breast cancer patients and controls. This second study appears to show the opposite effect, namely an increased risk of breast cancer in women given exogenous estrogens at natural menopause. Thus we examined both sets of data in greater detail. We concluded that the protective effect previously reported can be explained by a rather subtle relationship between the timing of menopause and diagnosis.

MATERIALS AND METHODS

Information on exogenous estrogen use was obtained from two series of breast cancer cases and matched controls.

1) Group I consisted of those 100 case–control pairs from our previous study (*7*), who were between 50 and 64 years of age at diagnosis. These patients, whose cancers were diagnosed in 1969–72, were white residents of Los Angeles County. A matched control was selected from the outpatient rosters of each index case's referring physician. The control was matched by date of birth (within 5 yr) and by socioeconomic status with the use of the two-factor Hollingshead index (*8*).

2) Group II consisted of those 47 white patients without previous cancer, whose cancers were diagnosed in 1972–73, who were between ages 50 and 59 at disease diagnosis, lived in six middle-class white health districts of eastern Los Angeles County, and could be matched with a healthy control by the interview in sequence of the three nearest neighbors 50–59 years old. Controls for 64% of the 47 cases were obtained from the nearest neighbor; the second and third neighbors approached were willing to cooperate as controls for 30 and 6%, respectively. Sixteen patients could not be matched within three tries. A socioeconomic class was assigned to each pair, with the use of the mean income and education of their census tract of residence, in a modification of the two-factor Hollingshead index (*8, 9*).

Interviews of patient and control were conducted in the same format and usually by the same nurse–epidemiologist. We obtained information on estrogen use, gynecologic operations, and age at menopause.

We tried to verify all information on estrogen use and hysterectomy/oophorectomy with the attending physicians of the group II women. This proved difficult for two reasons: The length of time from menopause to diagnosis was often so long that the records were not available or traceable, and many women could not recall when and by whom they were treated. When the information obtained from a woman was at odds with her physician's report, we recontacted both of them to reconcile the difference.

Many women took estrogens intermittently throughout the climacteric period. We coded the total duration of continuous estrogen use after menopause symptoms. For example, if a woman took estrogens for 18 months, discontinued use for a year, and then resumed use again for 6 months, she was coded as using estrogens for 24 months.

The data were analyzed by standard contingency table techniques (*10, 11*). Duration of usage was analyzed by the Wilcoxon 2-sample rank test (*12*).

RESULTS

Little correlation (group I, $r=0.09$; group II, $r=-0.01$) was found between the use of estrogen by patient and control pairs, and the matching was therefore ignored (*13*). Individuals with frankly artificial menopause or who claimed menopause symptoms some period after

TABLE 1.—*Crude (unadjusted) analysis of the relative risk of breast cancer related to the use of estrogens at any time after natural menopause*

Group	Patients [a] (%)	Controls [a] (%)	Relative risk
I	34/60 (57)	39/53 (74)	0.47
II	25/33 (76)	16/27 (59)	2.15

[a] Number of women given estrogens at natural menopause/total No. of women with natural menopause.

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[3] Department of Community Medicine, University of Southern California School of Medicine, Los Angeles, Calif. 90032.

[4] *Address reprint requests to* J. Casagrande, Cancer Research Project, Edmondson Research Bldg., 1840 North Soto St., Los Angeles, Calif. 90033.

[5] Department of Pathology, University of Southern California School of Medicine.

TABLE 2.—*Estrogen use in study group I: Allowance made for age at diagnosis and age at menopause*

Age at diagnosis of breast cancer (yr)	Age at natural menopause (yr) [a]									
	<40		40–44		45–49		50–54		Total	
	Patients	Controls	Patients	Controls	Patients	Controls	Patients	Controls	Patients	Controls
50–54	1/1	3/3	4/7	2/5	3/4	10/10	2/13	2/3	10/25	17/21
55–59	1/1	1/1	6/7	4/6	7/9	10/13	6/11	5/8	20/28	20/28
60–64	1/1	—	2/2	1/1	1/1	1/1	0/3	0/2	4/7	2/4
Total	3/3	4/4	12/16	7/12	11/14	21/24	8/27	7/13	34/60	39/53

[a] Number of women given hormones at natural menopause/total No. of women with natural menopause.

hysterectomy and/or oophorectomy were excluded (group I exclusions: 40 patients, 47 controls; group II exclusions: 14 patients, 20 controls).

Table 1 shows the proportion of cases and controls who ever used exogenous estrogens after menopause. A "crude" calculation from group I gave an estimated relative risk of 0.5 for exogenous estrogen use, whereas group II yielded an estimated relative risk of 2.2.

In this study, estrogen use was related to two determinants of breast cancer: age at menopause and age. Of group I controls who started menopause before age 50, 80% (32/40) took estrogens, compared with 54% (7/13) of those with later menopause (table 2). Similarly, 81% (17/21) of controls interviewed before age 55 had taken estrogens, compared with 69% (22/32) of older women (table 2). Estrogen use may also be presumed to be related to calendar year at menopause, since there has been a twofold to threefold increase in estrogen use since the early 1960's (*14*). Since diagnosis in the two studies took place at about the same time, we can control all three factors by subdividing the data into narrow categories defined by age at disease diagnosis and age at menopause.

Table 2 shows that patients and controls were well matched with respect to age, as expected, but the patients were considerably older at menopause. This had the effect that, when these factors were controlled, the protective effect of estrogens seen in group I was reduced from an estimated summary risk ratio of 0.47 to 0.75. The remaining effect in group I was concentrated entirely in those 50- to 54-year-old women who had menopause after age 45 (5/17 cases vs. 12/13 controls; relative risk = 0.03; $P \approx 0.002$). Despite the stratification, this highly significant result was still consistent with confounding by an interaction of age at menopause and age at disease diagnosis. Table 3 shows that the patients in this category had, on average, a shorter interval between menopause and diagnosis–interview than did the controls. If those with a difference of less than 2 years between menopause and diagnosis were excluded, the apparent protection by estrogen use disappeared. Almost all the remaining women took estrogens (5/6 cases vs. 10/10 controls); under such conditions of nigh universal usage, this subgroup became uninformative with respect to the function of exogenous estrogens in breast cancer etiology. Among those excluded, 0 of 11 cases compared to 2 of 3 controls took exogenous estrogens [P(1 sided) = 0.033]. Although this difference may be regarded as just statistically significant, any biologic explanation for a true difference would necessarily include the unlikely provision that exogenous estrogens exert an immediate but transient protective effect. A noncausal relationship between incipient breast cancer and factors determining the initiation of menopause therapy would seem a plausable alternative explanation.

TABLE 3.—*Analysis of estrogen use and years at risk in study group I for women age 50–54 years or years at diagnosis/interview and with menopause at 45 years or older*

Years from natural menopause to diagnosis–interview	Patients [a]	Controls [a]
0	0/4	2/2
1	0/7	0/1
2	1/2	4/4
3	1/1	2/2
4	1/1	—
5	1/1	—
6+	1/1	4/4

[a] Number of women given estrogens at natural menopause/total No. of women with natural menopause.

Duration of estrogen use in group I was not different in the cases compared to the controls, when allowance was made for the above artifacts. The credibility of a protective association between exogenous estrogens and breast cancer is thus further lessened.

When age at menopause and age at diagnosis/interview were controlled in group II (data shown in table 4), the estimated summary relative risk was also increased from 2.2 to 3.1; the latter was not significant, however. When the two studies were pooled (*10*), the estimated risk ratio was 1.2 ($P \approx 0.40$). Moreover, mean duration of estrogen use was the same in the combined cases as in the combined controls.

Stratification by socioeconomic class did not affect these conclusions.

TABLE 4.—*Estrogen use in study group II: Allowance made for age at diagnosis and at menopause*

Age at diagnosis of breast cancer (yr)	Age at natural menopause (yr) [a]									
	<40		40–44		45–49		50–54		Total	
	Patients	Controls	Patients	Controls	Patients	Controls	Patients	Controls	Patients	Controls
50–54	2/2	3/4	5/5	3/3	2/3	5/9	3/6	0/2	12/16	11/18
55–59	6/6	0/1	1/2	2/2	3/3	1/3	3/6	2/3	13/17	5/9
Total	8/8	3/5	6/7	5/5	5/6	6/12	6/12	2/5	25/33	16/27

[a] Number of women given hormones at natural menopause/total No. of women with natural menopause.

DISCUSSION

Adjusting for age and age at menopause essentially negates our previously reported (*7*) results indicating a protective effect against breast cancer from use of exogenous estrogens at natural menopause. Our second study group shows a possibly harmful effect of these drugs, but by combining all our data, we find no evidence of any effect. The controls in our first study group were, however, women attended by the physicians of the patients and were thus possibly not representative of the population from which the breast cancer patients were drawn. It is therefore still possible that there is some increased risk of breast cancer associated with exogenous estrogen use, and further study is required.

Several trends, including the increasing incidence of breast cancer, will soon demand that we understand the role, if any, of exogenous estrogens in its etiology. The clear utility of estrogens has promoted increasingly widespread use, partly because suggestions of a protective action against cancer have allayed theoretic fears. If, as has recently been suggested (*15–17*), these drugs have become important causes of endometrial adenocarcinoma, the question of breast cancer will inevitably arise. People who must make medical decisions are sure to be placed in a very difficult dilemma and will need all pertinent information.

We believe that reliable information is not likely to be obtained from further studies, such as ours, in the usual settings. This is true because of attributes of the disease, estrogen usage, and several confounding factors. Breast cancer is linked to reproductive events, socioeconomic status, and the demand for medical care (*18*). Estrogen use is also related to these factors, whereas the symptoms of natural menopause and the indications for surgical menopause vary greatly.

Most importantly, our ability to measure these things in restrospect is poor. Interview questions concerning estrogen use, menopause, or surgery often provoke responses colored by the respondent's personal views of femininity, as well as her personal views of health. The answers are highly dependent, in terms of content, on intelligence, birth cohort, and past doctor–patient relationships. Medical records also tend to be unreliable with respect to such items. Continuity of gynecologic care is often imperfect, and gynecologic events are often thought not pertinent to the other illnesses of postmenopausal women.

We believe that these facts have seriously impaired studies to date, including our own. At present, there is no convincing evidence of an increased risk of breast cancer attributable to exogenous estrogens. Little more, save controversy, can be expected from additional case–control or cohort studies in conventional settings. Randomized trials will probably not be feasible.

We believe that the most promising available means of providing useful information would be a case–control study conducted in the setting of a large, prepaid medical care system. This would tend to eliminate cases from both socioeconomic extremes and to permit the selection of multiple controls who are comparable with respect to socioeconomic class and access to care. Standardized records could be used to document a relatively complete history, with chronologic drug notes and unbiased documentation of intervening reproductive and surgical events. Verification of the drug history by pharmacy records might be feasible. We hope that such a study will be initiated soon.

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