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Original Contributions

BENIGN BREAST TUMOR AND ESTROGENIC HORMONES: A POPULATION-BASED RETROSPECTIVE STUDY

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Nomura, A. and G. W. Comstock (Training Center for Public Health Research, Box 2067, Hagerstown, MD 21740). Benign breast tumor and estrogenic hormones: a population-based retrospective study. *Am J Epidemiol* 103:439–444, 1976.

Histories of the usage of oral contraceptives and other estrogens were obtained from 320 women 20–49 years of age who had pathologically confirmed diagnoses of benign breast disease made at Washington County Hospital in Hagerstown, Maryland, during the period 1968 through 1972. Similar histories were obtained from 320 controls matched for race, sex, age, residence in county, and willingness to participate in a health survey. No association could be found between oral contraceptive usage and benign breast tumor. The use of other estrogens, notably diethylstilbestrol, was significantly related to the presence of benign breast disease.

breast diseases; contraceptives, oral; diethylstilbestrol; estrogens

Ever since Lacassagne demonstrated in 1932 that exogenous estrogen induced mammary tumors in mice (1), investigators have debated whether or not estrogen usage can also cause breast neoplasms in humans. Although most interest has been focused on the relationship of estrogens to breast cancer, two recent hospital-based retrospective studies have suggested that benign breast tumor is not related to the use of estrogenic hormones (2, 3).

The widespread use of oral contraceptives has added urgency and a new dimension to this debate. While estrogenic hormone use is largely restricted to menopausal ovarian replacement therapy, estrogen-progestogen oral contraceptive preparations are being used by large numbers of young women. Four hospital-based studies have looked at the association of oral contraceptives and benign breast disease. One study found no conclusive evidence of an association (2); the other three found a possible protective effect, as proportionally fewer cases than controls had a history of oral contraceptive use (4–6).

Because of the potential importance of the question, it seemed desirable to replicate these studies in still another population using a somewhat different experimental design and analysis. Major assumptions of case-control studies are that diagnosed cases and their controls come from the same population and that they

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are, respectively, representative samples of persons with and without the disease in question. It is obviously difficult to be certain that these assumptions are correct when applied to cases and controls drawn from many hospitals. Do women with benign breast disease come from the same population as women hospitalized for other purposes? Are women with other diseases representative of all women without benign breast disease?

The present study was undertaken to examine the associations of estrogens (defined as non-contraceptive estrogens in this study) and oral contraceptives with benign breast disease on a community-wide basis. Special efforts were made to insure that cases and controls came from the same designated population.

Materials and methods

The setting for this study was Washington County, Maryland, which has a relatively stable and homogeneous population of about 100,000 residents, most of whom are white Protestants. Patients who had a benign breast tumor removed from 1968 through 1972 were identified in the file of pathology reports from Washington County Hospital, which is a 500-bed institution serving the entire county and neighboring regions. Cases in the present study were limited to white females, who were 20–49 years of age when their diagnostic breast biopsy procedure was done and who had participated in the 1963 private census of the county. This census, which was conducted by the Johns Hopkins School of Hygiene and Public Health, the Washington County Health Department and the National Cancer Institute, obtained information from more than 98 per cent of the households (7).

Because cases were limited to participants of the 1963 private census, the census list was used as the sampling frame for the selection of population controls. For each case, the next person of the same sex, race, and age in the census lists was chosen as a control after a random start. Whenever a potential control was not interviewed, another was chosen in the same manner. In this way, cases and their population controls were also matched for continued residence in the county and for their willingness to participate in a health survey.

The interviews were conducted in the summer of 1973 by five trained female lay interviewers. To minimize possible interviewer bias, approximately equal numbers of cases and controls were assigned to each interviewer. In addition, the interview form was designed to resemble a general health survey with special reference to the use of various hormone preparations. Great care was taken to keep the interviewers from knowing who was a case and who was a control. All potential participants who still lived in the county were contacted; 4.5 per cent of cases and 7.5 per cent of controls declined the interviews, a difference that is not statistically significant.

The interview form requested the usual identification and demographic information, pregnancy and menstrual histories, and information about medications taken for a variety of conditions such as thyroid disease, diabetes mellitus, hypertension, and migraine headaches. An inquiry was also made into past history of estrogen and oral contraceptive use to ascertain the dates and duration of use of the hormones. To assist in the identification of the preparations, the respondents were shown samples of the various estrogenic hormones and color photographs of forty-six different packets of oral contraceptives.

The date of biopsy was the reference date for each case, and the control matched to that case was given the same reference date. For both cases and controls, information on certain important predisposing factors was limited to their occurrences prior to the reference date. These factors included the pregnancy history, menstrual history, and history of estrogen use. The rest of the information from the study questionnaire was recorded according to

TABLE 1

Age distribution of benign breast tumor cases by type of pathologic diagnosis

Age group (years)	Cystic disease*		Fibroadenoma	
	No	%	No	%
20–24	16	5.8	15	33.3
25–29	19	6.9	10	22.2
30–34	37	13.5	7	15.6
35–39	51	18.5	4	8 9
40–44	80	29.1	5	11.1
45–49	72	26.2	4	8.9
Total	275	100.0	45	100.0

* Includes fibrocystic disease, chronic cystic mastitis, sclerosing adenosis and papillomatosis

TABLE 2

Estrogen and oral contraceptive use of matched pairs of cases and controls, and relative risk of benign breast tumor associated with use of these preparations

	Cases	Controls	
		User	Non-user
Estrogen			
User		2	40
Non-user		16	259
Relative risk = 40/16 = 2.50			
$p < .005$ (McNemar test, reference 8)			
Oral contraceptive			
User		29	48
Non-user		42	199
Relative risk = 48/42 = 1 14			
$p = 0.28$ (McNemar test, reference 8)			

the responses given at the time of interview. In addition, the 1963 census provided other personal and environmental information on the study population.

The hospital records showed that 53 cases and only four controls had a history of a benign mammary tumor which occurred prior to the reference date of the study. Because the analysis showed that a history of an earlier benign lesion was not related to the subsequent pattern of estrogen use, these cases and controls were not excluded from the study population.

RESULTS

Interviews were completed on 320 cases and their matched controls. Among the cases, 275 had a diagnosis of cystic disease and 45 had fibroadenoma. Their age distributions are given in table 1. As expected, cystic disease was more common in the older age groups and more cases of fibroadenoma occurred in the younger age groups.

The association between estrogen usage and benign mammary tumor was calculated by the matched-pair method of analysis (8). The results in table 2 show that the use of estrogenic hormones was significantly associated with an increased risk for benign breast tumor, while use of oral contraceptives was not related to any appreciable risk. The findings were similar for both cystic disease and fibroadenoma cases.

When benign cases and controls were compared in table 3 by the specific hormone preparation used, it was noted that only diethylstilbestrol was significantly different between the two groups. Nine cases and none of the controls had taken diethylstilbestrol, the only non-steroidal synthetic estrogen listed in the table.

Cases and controls were also compared by the duration of use of estrogenic hor-

TABLE 3

Specific types of estrogens and oral contraceptives used by cases and controls

	Cases	Controls
Type of estrogenic hormone*		
Diethylstilbestrol†	9	0
Estrogen injection	11	3
Conjugated estrogen	12	7
Other	1	2
Type unknown	12	7
Type of oral contraceptive*		
Ethinyl estradiol-norethindrone	24	23
Mestranol-norethindrone	16	14
Mestranol-norethynodrel	16	13
Mestranol-chlormadinone acetate	12	9
Mestranol-ethynodiol diacetate	12	9
Ethinyl estradiol-norgestrel	7	10
Other	9	12
Type unknown	11	11

* Not mutually exclusive
† Significant at $p < 01$

mones and of oral contraceptives prior to the reference date. The median duration of use was similar for both groups: for estrogens, 48.5 and 50.0 months, and for oral contraceptives, 6.0 and 7.0 months, respectively, for cases and controls.

In calculating the interval period, defined as the interval from initial hormone use to the reference date (date of biopsy for the case of each pair), the 56 matched pairs in which either the case or the control had had a previous benign breast lesion were excluded. By restricting the analysis to cases with only a single diagnosis of benign breast disease, the problem of multiple interval periods is avoided. If there were no association of estrogenic hormone use with benign tumor, the distributions of cases and controls by interval periods should be similar. However, as is shown in table 4, this is not the case. Cases and controls were similar in numbers only in the group that had used estrogens less than 4 years prior to the reference date. There was a clear excess of cases ($p < .01$) among women whose estrogen usage had begun more than 4 years prior to the reference date.

TABLE 4

Comparison of interval periods of estrogenic hormone users among 264 cases with only one operation for benign breast disease and their matched controls*

History	Cases	Controls
Non-users	232	250
Interval period of estrogenic hormone users (years)		
0–3	9	8
4–7	8	1
8+	11	3
Unknown	4	2
Total	264	264

* Interval period refers to the interval from initial estrogen use to the reference date (date of biopsy for the case of each pair)

TABLE 5

Crude and adjusted percentage of estrogenic hormone users and oral contraceptive users among cases and controls

	Estrogenic hormone users		Oral contraceptive users	
	Crude %	Adjusted %*	Crude %	Adjusted %*
Cases	13.4†	13.0†	23.7	22 2
Controls	5.4	5.8	22.2	23.7

* Adjusted by Feldstein's method of binary multiple regression for the following independent variables educational history, family income, age at first term pregnancy, number of term pregnancies, residential status in 1963, smoking history in 1963, age at time of reference date, frequency of pap smears, and use of seat belts (9).

† Percentage of cases was significantly greater than controls at $p < .01$.

Because the association between use of estrogen preparations and the occurrence of a benign breast tumor can be confounded or concealed by possibly correlated variables, simultaneous adjustment for a number of these variables was done by a binary multiple regression method (9). In the application of this regression model to retrospective information, use of estrogenic hormones or of oral contraceptives was the dependent variable and case-control status was one of the independent variables. The results are shown in table 5. The adjusted percentages of estrogen hormone and oral contraceptive users did not differ appreciably from the unadjusted percentages. The significant excess of estrogen hormone users among cases persisted after adjustment, as did the similarity in the proportion of oral contraceptive users among cases and controls.

DISCUSSION

In estimating relative risk from retrospective (case-control) studies, one assumption is that diagnosed cases and their controls come from the same defined population. It is usually impossible to be certain that this assumption is correct in hospital-based studies. A major advantage of the present study is that cases and controls are known to have come from the same population, namely persons who were enumerated in the 1963 census of Washington County, Maryland, and who were currently residing in the county and willing to be interviewed.

It is also necessary to assume that the study cases and controls are representative samples of all diagnosed cases and all non-cases, respectively, in the population. There is no question that the controls in this study meet this requirement—they are a random sample of the target population, stratified by race, sex, and age.

It is less certain that the cases are a random sample of all diagnosed cases in the population. However, because Washington County Hospital is the largest and best-equipped hospital within a 50-mile radius, it seems unlikely that more than a few breast tumor cases would be referred elsewhere for biopsy. Data from the Maryland Regional Medical Program revealed that 93.9 per cent of Washington County residents, who were hospitalized in Maryland for any cause in 1967 were admitted to Washington County Hospital (L. Gordis, unpublished data from the 1967 Regional Medical Program Inpatient Survey of Maryland). Although there is no reason to believe that the study cases are not a representative sample of all diagnosed cases in the defined population, the advantage of the present study over earlier studies in this respect lies in the somewhat greater confidence that can be placed in this assertion.

Although cases by definition sought physician care for their health needs, the controls may not have had the same level of medical care because they were not selected from the hospital file. This difference could lead to excess estrogen use among the cases, because the use of estrogenic preparations is also dependent on the use of physician services. Data from the National Center for Health Statistics showed that people with lower income and less education had fewer physician visits a year than their more educated and well-to-do counterparts (10). Therefore, simultaneous adjustment was done for income, education, residence, as well as for pap smear frequency and frequency of seat belt use (both of which reflect preventive health behavior), as shown in table 5. After this adjustment, there was little change in the percentage of estrogen users among cases and controls. This suggests that the effects of differential health care utilization on estrogen or oral contraceptive use among cases and controls were probably not important.

The finding that non-contraceptive estrogen use was significantly associated with increased risk for benign breast disease was not surprising in view of the findings from animal experimentation. Guinea pigs (11), mice (12), and various strains of rats (13–15) were shown to develop benign mammary lesions with estrogen stimulation.

The discrepancies between the relative risks of estrogen use from this study and two earlier studies are not inexplicable, even without calling upon differences in experimental design. The Boston Collaborative Drug Surveillance Program, which dealt primarily with postmenopausal cases, defined a woman as an estrogen user if she took the hormone within the 3-month period prior to hospitalization (3). This restriction probably excluded many women whose use of these preparations was confined to the past. In the present study, significant differences between cases and controls were demonstrated only among women who had first used estrogens more than 4 years prior to biopsy.

In the study by Sartwell and his colleagues (2), a history of estrogen use was limited to a 10-year period preceding diagnosis. In addition, more controls than cases had experienced menopause and were therefore at increased risk of being given estrogens. In the present study, the same number (50) of cases and controls had undergone menopause, either natural or artificial, prior to the reference date.

Even though the results of the present study showed a positive association of estrogen use with benign mammary neoplasm, it is difficult to rule out the possibil-

ity that the development of the tumor was connected with the reason for which the cases received the estrogenic hormones, and not to the hormones per se. Direct evidence on this possibility is not available. However, a finding supporting the importance of the estrogen hormone itself in the development of benign breast tumor was the marked excess of cases among women whose estrogen usage was begun more than 4 years prior to the reference date. This is compatible with the observation that considerable time usually elapses between the initial exposure to a tumor-inducing agent and the resulting tumor (16). Furthermore, of the 42 cases and 38 controls who had artificial menopause prior to the reference date, 40.5 per cent of the cases and only 26.5 per cent of the controls took these preparations after their surgical or radiation-induced menopause.

With respect to oral contraceptives, the present study found no meaningful association between the use of these preparations and benign mammary tumors. Although this finding did not agree with the results of other studies (4–6) which suggested a protective effect of oral contraceptives, it is reassuring to note that there is as yet no evidence that estrogen-progestogen contraceptive preparations cause benign breast lesions. Because these contraceptives were not licensed for sale until the recent past, it will probably be years before the question of a relationship between oral contraceptives and benign breast disease is settled.

References

1. Lacassagne A: Appertion de cancers de la namelle chez la souris male, sourmis ades injections de folliculine. Compt Rend Acad Sci 195.630–632, 1932
2. Sartwell PE, Arthes FG, Tonascia JA: Epidemiology of benign breast lesions. Lack of association with oral contraceptive use. N Engl J Med 288:551-554, 1973
3. Boston Collaborative Drug Surveillance Program: Surgically confirmed gallbladder disease, venous thromboembolism, and breast tumors in relation to postmenopausal estrogen therapy. N Engl J Med 290:15–19, 1974
4. Vessey MP, Doll R, Sutton PM: Oral contraceptives and breast neoplasia. A retrospective study. Br Med J 3:719–724, 1972
5. Boston Collaborative Drug Surveillance Program: Oral contraceptives and venous thromboembolic disease, surgically confirmed gallbladder disease and breast tumors Lancet 1:1399–1404, 1973
6. Kelsey JL, Lindfors KK, White C: A case-control study of the epidemiology of benign breast diseases with reference to oral contraceptive use. Intl J Epidemiol 3:333–340, 1974
7. Comstock GW, Abbey H, Lundin FE: The unofficial census as a basic tool for epidemiological observations in Washington County, Maryland. The Community as an Epidemiological Laboratory Edited by II Kessler and ML Levin. Baltimore, The Johns Hopkins Press, 1970, pp 73–97
8. Siegel S. Nonparametric Statistics for the Behavioral Sciences New York, McGraw-Hill Book Company, 1956
9. Feldstein MS. A binary variable multiple regression method of analyzing factors affecting perinatal mortality and other outcomes of pregnancy J Roy Stat Soc 129 (Series A, Part I):61–73, 1966
10. Bice TW, Eichhorn RL, Fox PD· Socioeconomic status and use of physician services. A reconsideration. Med Care 10.261–271, 1972
11. Pincus G, Thimann KV, Astwood EF: The Hormones, Vol. 5 New York, Academic Press, 1965
12. Blair PB, Blair SM, Lyons WR· Effect of hormones and of parity on the occurrence of hyperplastic alveolar nodules and tumors in the mammary gland of female A/crgl mice. Cancer Res 20·1640–1645, 1960
13. Astwood EB. Development of the mammary gland of the rat. Am J Anat 61:363–375, 1937
14. Eisen MJ: The occurrence of benign and malignant mammary lesions in rats treated with crystalline estrogens. Cancer Res 2:632–644, 1942
15. Heiman J: Comparative effects of estrogen, testosterone and progesterone in benign mammary tumors of the rat. Cancer Res 3:65–67, 1943
16. Hueper WC: Age aspects of environmental and occupational cancer. Public Health Rep 67:773–779, 1952