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An Epidemiologic Study of Breast Cancer and Benign Breast Neoplasias in Relation to the Oral Contraceptive and Estrogen Use*

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Abstract—*A case-control study was conducted of oral contraceptive and other estrogen use in patients with malignant or benign breast disease of ages less than* 65 yr.

Ever usage of oral contraceptive and estrogens was slightly less common among breast cancer patients up to 49 yr *of age as compared to their controls. No difference in estrogen use was seen in older patients. Significantly lower rates of oral contraceptive ever- and long-term (for* 2 yr *or more) users were found among cystic disease cases; this was not seen in fibroadenoma cases.*

Among patients with cystic disease and fibroadenoma, there was a considerably higher proportion of ever pregnant and ever parous. Menopausal women were less frequent than expected among cystic disease patients. Other factors ordinarily associated with breast cancer were not found to be associated with benign breast neoplasias.

INTRODUCTION

AROUND 1970, large-scale retrospective case-control studies of oral contraceptives as related to the risk of malignant or benign breast diseases were undertaken in Britain and in the United States [1–8]. An informal collaborative project was agreed upon between groups of investigators in the United States which encouraged us to join it and start such a study in Slovenia.

Wider use of oral contraceptives (OCs) in this country began as late as 1964, but the estrogens (Es), administered mainly for post-menopausal replacement therapy, have been in use, of course, much longer. Therefore, we also decided to determine the risk of developing breast neoplasias as a result of exposure to these products. Further, we were interested in investigating the epidemiologic features of benign mastopathies, in light of their potential relationship to breast cancer.

We report here the findings of our study, conducted between 9 May, 1972 and 8 November, 1974. The study was based on interviews of female patients with a malignant or benign breast condition and of control patients not having breast disease. The patients were interviewed for their use of oral contraceptives and other sex hormone preparations, as well as for their social, reproductive, menstrual and medical histories.

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MATERIALS AND METHODS

The study subjects, both cases and controls, were selected from among female patients, residents of Slovenia, admitted during the study period to the Ljubljana Clinical Center. The age limits were 15–64 yr. A total of 2554 patients were interviewed. The interviews were conducted in the hospital (in the ward or outpatient department) by either of two experienced visiting nurses, using a standard questionnaire. In taking the history of OC use, samples of pills were shown to the patients. For identification of other sex hormone preparations received, a list of brands was read to the patients.

Patients with a breast condition who were admitted to the hospital for diagnosis and were subjected to aspiration or excision biopsy were eligible as cases. Patients who had been previously admitted to the hospital for diag-

nosis or treatment of breast disease were not included, because in such cases the use of OCs or other sex hormone preparations might have been contraindicated.

Patients with a breast lesion were interviewed before a biopsy was performed. All but a few were interviewed at the Institute of Oncology, Ljubljana. All microscopic examinations were made as a routine procedure in the Pathology Department of this Institute.

Two controls were selected for each patient with breast cancer, and one for each patient with benign breast disease (BBD). The matching variables were: age (within ± 5 yr) and date of admission (within 2 months). The controls were selected in consecutive order from the patients admitted to Dermatologic, Ophthalmic, Orthopaedic, Otorhinolaryngologic, and Surgical Clinic of the Clinical Center, Ljubljana.

As a separate, non-controlled study group, patients were interviewed who during the same period came for breast examination to the Outpatient Department of our Institute, and in whom a clinical diagnosis of fibrocystic mastopathy was established, based on physical and/or X-ray examination only. They were not subjected to biopsy, mainly because the examining physician did not consider it necessary. Since the number of these patients (hereafter termed simply as "mastopathy" cases) is large, every second patient with this diagnosis was selected. We were interested in this group of patients since they may represent an earlier stage of "cystic disease" than our controlled group of patients with this disease.

The proliferative conditions and tumors of the breast have been classified according to the classification issued by the World Health Organization [9]. For the purpose of the study and comparability with other similar studies, the benign conditions were grouped into three categories: "cystic disease" (simple or papillary cyst, epithelial proliferation in ducts or lobules, duct ectasia, fibrosclerosis and other non-neoplastic proliferative lesions), "fibroadenoma" and "other benign disease" (proliferative and neoplastic lesions, not included in the former two categories, and inflammatory conditions). When cystic dysplasia and fibroadenoma were found in the same specimen the case was included in the cystic disease group. The proliferative conditions, categorized as "cystic disease" ("benign mammary dysplasias" according to WHO classification), together with fibroadenomas will hereafter be termed as "benign breast neoplasias" (BBN).

At the completion of the study, cases were excluded if their interview was rated by the interviewer as "unreliable" (5 with breast cancer, 8 with benign lesion and 5 with mastopathy). In addition, from the series of breast cancer cases there were excluded 2 with other types of malignancy and 1 microscopically unproven case; from the cases with benign disease, 12 were excluded in which microscopically no pathologic tissue was found. From the controls 12 were excluded as "unreliable", but were replaced by the adequate others whose matching cases had been excluded.

The analysis comprised: 374 patients with breast cancer (BC) (mean age 49.8), 318 patients with cystic disease (CD) (mean age 41.3), 109 patients with fibroadenoma (FA) (mean age 33.4), 70 patients with other benign disease (OBD) (mean age 41.8) and 387 patients with "mastopathy" (MP) (mean age 37.0).

When the International Classification of Diseases is used, the diagnoses of the total of 1245 control patients fall into the following categories: musculoskeletal system and connective tissue (25.2%), nervous system and sense organs (18.0%), skin and subcutaneous tissue (11.3%), respiratory system (9.7%), circulatory system (8.6%), others (27.2%).

All relevant data were analysed separately for cases younger than 50 yr of age, and those 50–64 yr old. The younger age group was of main concern, since the OC users appeared almost exclusively within it, and because the occurrence of cystic disease and even more so of fibroadenoma is highly prevalent in ages under 50 yr. Further, with this age grouping a direct comparison with the results of similar studies is possible.

Standardization for confounding variables thought to be related both to the disease and to use of the agent [10], was made by the indirect method [11].

RESULTS

Use of oral contraceptives and estrogens

Among the total of 2503 study subjects there were 371 (14.8%) who have ever used OCs. A small proportion of them, i.e., 16 (4.3%), have used E-containing preparations for another indication as well. Such patients were classified as OC users. Es as medication have been administered altogether to 290 (11.6%) patients, either for relief of menopausal symptoms (50.4%), for regulation of menstruation (34.8%), or for treatment of some other gynaecological condition, for pre-

Table 1. Use of oral contraceptives by patients with breast disease and their matched controls by interval of use

Interval of OC use Age (yr)	Cancer 20–49	Cystic disease 15–49	Fibroadenoma 15–49	Other benign disease 15–49
Current*-up to 24 months:				
Patients	4	5	3	1
Controls	7	5	6	2
Current*-over 24 months:				
Patients	5	6	2	1
Controls	5	10	3	4
Past only:				
Patients	21	38	16	8
Controls	53	54	13	7
Never:				
Patients	160	217†	85	37
%	84.2	81.6	80.2	78.7
Controls	315	197	84	34
%	82.9	74.1	79.3	72.3
Total subjects:				
Patients	190	266	106	47
Controls	380	266	106	47

*Within one month before admission to hospital.
†$P<0.05$ for difference between patients and controls.

Table 2. Use of oral contraceptives by patients with breast disease and their matched controls by total duration of use

Total duration of OC use Age (yr)	Cancer 20–49	Cystic disease 15–49	Fibroadenoma 15–49	Other benign disease 15–49
Less than 24 months:				
Patients	16	32	15	5
Controls	36	33	12	4
24 months or more:				
Patients	14	17*	6	5
Controls	29	35	10	9
Unknown:				
Patients	0	0	0	0
Controls	0	1	0	0
Never used:				
Patients	160	217‡	85	37
%	84.2	81.6	80.2	78.7
Controls	315	197	84	34
%	82.9	74.1	79.2	72.3
Total subjects:				
Patients	190	266	106	47
Controls	380	266	106	47

‡$P<0.05$ for difference between patients and controls.

venting pregnancy loss or even for postpartum drying up the breast (14.8%). There were also 218 patients (8.7%) who at some time received non-estrogenic sex hormones, e.g., progesteron derivate, luteinizing hormone, testosterone. These patients were included accordingly into the OC-, E-, or non-users group, respectively.

Tables 1–4 present data on use of OCs and Es, by interval and total duration of use.

Table 3. Use of estrogens as medication by patients with breast disease and their matched controls by interval of use

Interval of E use	Cancer		Cystic disease		Fibroadenoma		Other benign disease	
Age (yr)	20–49	50–64	15–49	50–64	15–49	50–64	15–49	50–64
Current*-up to 24 months:								
Patients	4	0	6	3	0	0	0	0
Controls	8	3	7	2	0	0	1	0
Current*-over 24 months:								
Patients	0	1	0	0	0	0	0	0
Controls	1	2	2	2	1	0	0	0
Past only:								
Patients	15	20	23	5	5	0	3	4
Controls	37	38	17	5	7	0	3	2
Never:								
Patients	171	163	237	44	101	3	44	19
%	90.0	88.6	89.1	84.6	95.3	100.0	93.6	82.6
Controls	334	325	240	43	98	3	43	21
%	87.9	88.3	90.2	82.7	92.5	100.0	91.5	91.3
Total subjects:								
Patients	190	184	266	52	106	3	47	23
Controls	380	368	266	52	106	3	47	23

*See footnote in Table 1.

Table 4. Use of estrogens as medication by patients with breast disease and their matched controls by total duration of use

Total duration of E use		Cancer		Cystic disease		Fibroadenoma		Other benign disease	
Age (yr)		20–49	50–64	15–49	50–64	15–49	50–64	15–49	50–64
Less than 24 months:									
Patients		16	11	27	7	5	0	2	4
Controls		39	30	23	7	6	0	4	2
24 months or more:									
Patients		2	3	1	0	0	0	0	0
Controls		6	8	2	2	2	0	0	0
Unknown:									
Patients		1	7	1	1	0	0	1	0
Controls		1	5	1	0	0	0	0	0
Never used:									
Patients		171	163	237	44	101	3	44	19
	%	90.0	88.6	89.1	84.6	95.3	100.0	93.6	82.6
Controls		334	325	240	43	98	3	43	21
	%	87.9	88.3	90.2	82.7	92.5	100.0	91.5	91.3
Total subjects:									
Patients		190	184	266	52	106	3	47	23
Controls		380	368	266	52	106	3	47	23

Table 5. Selected characteristics in case subjects and their matched controls. Age of case subjects 20–49 yr

Characteristic	Cancer		Cystic disease		Fibroadenoma		Mastopathy	Other benign disease	
	Cases ($n=190$)	Controls ($n=380$)	Cases ($n=263$)	Controls ($n=263$)	Cases ($n=95$)	Controls ($n=95$)	Cases ($n=312$)	Cases ($n=43$)	Controls ($n=43$)
Residence									
Ljubljana region ..... %	22.6†	46.6	28.9†	47.5	22.1*	36.8	28.2	34.9†	58.1
Occupation—main in life									
Professionals, managers & kindred workers ..... %	12.6	12.9	17.5	15.6	15.8	10.5	17.3	14.0	23.3
Peasants ..... %	15.8*	9.5	8.0*	3.8	5.3	6.3	9.0	7.0	4.7
Schooling-duration									
<8 yr ..... %	42.1	43.7	29.3*	39.5	28.4	29.5	31.1	39.5	27.9
≧12 yr ..... %	17.4	16.6	22.4	20.5	28.4	21.1	26.3	23.3	25.6
Marital status									
Married currently ..... %	78.4	75.5	78.3	74.9	73.7	64.2	81.7	81.4	81.4
Widowed, divorced or separated ..... %	9.5	11.1	8.8	9.9	4.2	8.4	5.8	9.3	7.0
Never married ..... %	12.1	13.4	12.9	15.2	22.1	27.4	12.5	9.3	11.6
Pregnancy									
No.	165	338	237	218	74	69	237	38	36
Ever pregnant ..... %	86.8	89.0	90.1*	82.9	77.9	72.6	87.5	88.3	83.7
No. of pregnancies per ever pregnant woman ..... mean	2.7*	3.0	2.6	2.7	2.4	2.9	2.6	2.5	2.9
Age at 1st pregnancy (yr) ..... mean	25.2†	23.1	22.6	23.0	22.6	21.8	22.3	23.6	23.6
Under age 18 at 1st pregnancy ..... %	2.4	6.8	3.8	3.7	5.4	10.1	3.7	2.6	—

Parity									
No.	158	324	226	212	70	65	267	36	35
Ever parous ..... %	83.2	85.3	85.9	80.6	73.7	68.4	85.6	83.7	81.3
No. of live births per ever pregnant woman .....mean	2.0	2.1	1.9	1.9	1.6*	2.0	1.8	1.8	1.8
Age at 1st birth (yr) .....mean	25.7†	23.8	23.5	23.8	23.0	22.7	23.2	24.7	24.7
Under age 20 at 1st birth..... %	5.7†	15.2	12.4	13.2	17.1	21.5	13.8	5.6	14.3
Menstrual history									
Age at menarche (yr)..... mean	14.4	14.6	14.3	14.2	13.9	14.2	14.1	14.4	14.4
Under age 14 at menarche..... %	32.6	30.8	33.5	40.3	41.1	33.7	38.8	27.9	44.2
Premenopausal ..... %	93.7*	87.1	93.5	89.0	97.9	94.7	95.5	90.7	90.7
Natural menopause ..... %	3.7	10.0	2.7	6.5	1.0	2.1	1.6	4.6	7.0
Artificial menopause ..... %	2.6	2.9	3.8	4.5	1.0	3.2	2.9	4.6	2.3
Breast cancer in mother..... %	3.7	1.6	1.5	0.8	3.2	0.0	1.6	2.3	0.0
Height (cm)..... mean	162.3	163.1	163.2	163.0	163.6	163.5	163.2	163.1	164.5
Weight (kg)..... mean	66.4*	68.3	64.6†	67.4	63.1*	66.1	64.4	67.1	69.2
Visiting the doctor regularly for routine examinations ..... %	70.5†	84.2	82.9	80.6	83.2	80.0	84.3	69.8	81.4

*$P<0.05$ for difference between cases and controls.
†$P<0.01$ for difference between cases and controls.

Noteworthy differences in usage rates for OCs are seen only for CD, where the cases have somewhat fewer past users than controls (Table 1). For the same disease group never users are significantly more common in cases than in controls. In Table 2 it is seen that total duration of OC use of 24 months or more occurs half as often in cases than in controls. Some small differences in OC usage between cases and controls in BC and FA series seen in these two Tables, can be regarded as suggestive, at best.

No significant differences appear in the use of Es in Tables 3 and 4. Never usage was slightly more common in young BC cases, just as it was for OCs. Unlike the data on OCs however, young women with cystic disease seem to be more commonly past users of Es than their controls. In both these series of patients, Es have been administered mostly for menstrual disturbances relief. There was only a small number of Es long-term users, i.e., for 2 yr or more, among our study subjects. These were slightly less frequent among patients with breast neoplasia than among their controls, which may be explained by a higher proportion of menopausal women among the latter (see Table 5).

Characteristics of the groups compared

Table 5 compares the younger group of cases and controls for selected characteristics. These were of interest for two reasons: (a) as potential confounding factors affecting the comparison of cases and controls for hormonal use and (b) as risk factors in the etiology of breast neoplasias, especially for the benigns.

The standardization of the rates in Tables 1–4 for those characteristics that were markedly different in cases and controls, and were also related to hormonal use, in fact, did not essentially change any of the ratios of crude rates.

The proportion of cases whose residence is defined as within Ljubljana region is considerably lower than in their corresponding controls. Ljubljana is the capital of Slovenia, and the socioeconomic status of the residents of this region differs from those of the other regions. This difference in residence distribution among cases and controls is likely to have affected other factors that are related, such as occupation, education and medical care.

The differences seen in the percentage of cases and controls married, are not statistically significant. If any pattern emerges, it is that of cases being less often "never married".

As expected, the proportion of ever pregnant and ever parous women is lower in BC cases, and their age at first pregnancy and first birth is significantly higher than in their controls. The mean number of pregnancies per ever pregnant woman was also lower among BC cases. In CD and FA cases, however, there was a higher proportion of ever pregnant and ever parous women as compared to their controls. The FA cases show the tendency toward a later first pregnancy and first birth than their controls, which is not seen in CD cases. The MP cases compared with other case series in Table 5, are most similar in their pregnancy and parity characteristics to the CD group.

For no disease group was there a marked difference in the mean age at menarche, when compared with controls. Some small differences are seen in the percentage with menarche under 14 yr of age. To the extent that these can be interpreted by this criterion, earlier menarche is seen for BC and FA, but later for CD cases, than for their respective controls.

The percentage of premenopausal women with BC is significantly higher than in their controls. For CD also a noteworthy higher rate of the cases is found to be premenopausal.

Although a very small number of patients have given a history of breast cancer in their mothers, the rates tend to be slightly higher in patients with breast disease than in their controls. It is difficult to be certain that this is not an artifact due to the patient's heightened interest caused by her own breast disease.

We present data on height and weight, which still appear to receive some discussion as "constitutional" factors. The average heights were remarkably similar in every study and control group. On the other hand, mean weight was consistently lower by 2–3 kilos in each of the breast disease groups. This makes one wonder whether these differences are related to an etiologic process in the case groups, or to some factor pertinent to the selection of the controls.

The older group of patients has reasonable sample sizes only for BC and CD cases. For these series the pattern of differences in characteristics between cases and their matched controls is similar to that of the younger patients and therefore the respective data are not presented here.

DISCUSSION

Frequency of oral contraceptive and estrogen usage

The frequency of OC and E usage in our study population was relatively low as compared to that presented in the reports on similar case-control studies carried out in Britain [2, 3] and in the United States [4–8, 12, 13, 14] covering approximately the same time period.

Though lower than in other studies, the rates of OC use were similar in our breast cancer cases and their controls, just as was found in American and British study populations. The suggestion by Fasal and Paffenbarger [8] that the risk of breast cancer might be increased in women using OCs for 2–2 yr, is not in keeping with our data.

Either negative or no association was found between BBD and OC usage in several studies [2, 5–8, 12, 15, 16], as well as a decreased risk with longer duration of use, these results in most studies hold for both cystic disease and fibroadenoma. Our results are compatible with these findings in showing a significantly lower number of OC ever-, and long-term users (for 2 yr or more), among women with CD of ages up to 49 yr than among their matched controls. No significant differences were found for FA, however.

The report of a preliminary study of Arthes *et al.* [4] indicated a somewhat higher rate of E users among older patients with BC, but a significantly lower rate among those under 50 yr of age. Our findings are similar to those of the Boston Collaborative Program [13], i.e., the rates of E users in the older age group are almost equal in cases and controls. A lower rate of E usage in younger BC patients may be explained by a later onset of menopause in these patients. A case-control study by Casagrande *et al.* [14] showed indeed no relationship between BC and E usage after the start of menopausal symptoms in women who had a natural menopause. It is important to remember, however, that interval from use of estrogenic hormones to clinically apparent neoplasia may be many years, as suggested by Hoover *et al.* [17] in their cohort study.

There was essentially no difference in the rate of E users in our patients with CD up to 49 yr of age and in their controls, though there were fewer menopausal women among the former, and thus a lower rate in these patients might have been expected, as was observed by Sartwell *et al.* [5]. However, our patients with CD used Es for menstrual regulation and dysmenorrhea relief more frequently than their controls. Nomura and Comstock [12] in their study of BBN in women 20–49 yr of age, in which there was an equal number of menopausal women among cases and controls, found an even significantly higher rate of E users among the case subjects.

Epidemiologic features

In our BC patients, the characteristics of their pregnancy, parity and menstrual history, as well as of their familial history of breast cancer, appear to be consistent with what is already known about the risk factors of this disease [18]. Our findings on their socioeconomic status as breast cancer risk factor are not conclusive. The disparity in residence between the case and control subjects very likely has biased the apparent differences in their socioeconomic status to a certain extent, as measured by their occupation and duration of schooling.

In contrast to the BC series, almost no significant case-control differences in biological factors appear in our BBN series. Generally, the risk factors that tend to be associated with breast cancer show ambiguous relationship with BBN cases in our study, as has been found in similar case-control studies [2, 5, 7, 8].

A noticeably higher rate of ever pregnant women among CD and FA cases than among their controls, observed in our study, was not seen with BBD cases in studies of Vessey *et al.* [2] and of Fasal and Paffenbarger [8]. No marked differences appeared in mean number of pregnancies between BBN cases and their controls, either in our or in two other studies [5, 8]. The tendency of BBD cases to have their first pregnancy at an older age, observed in previous studies [2, 5], is seen in our data for FA cases, but not for CD cases.

Our results do not agree with those of Kelsey *et al.* [7] who found patients with BBN significantly more likely to be nulliparous and to have given birth to significantly fewer children. We found a higher proportion of ever parous women among BBN cases, and, as in the study of Sartwell *et al.* [5], almost no differences in mean number of live births between cases and controls were observed. In the Boston Collaborative Programme study [6] parity was not found to be significantly associated with BBN, however. Like in two other studies [7, 8], the association of age at first term birth with occurrence of BBN was not striking in our data.

As with previous studies [7, 8], age at menarche was not unusual in our BBN pa-

tients. A lower proportion of these patients than of their controls were menopausal in our data, consistent with the findings of Sartwell *et al.* [5] and Fasal and Paffenbarger [8].

As to the familial history of breast cancer, no noteworthy differences between patients with BBN and their controls were found, either in our or in two other studies [7, 8].

Our observation of lower body weight in case subjects was in agreement with that of Fasal and Paffenbarger [8].

CONCLUSIONS

From the above comparisons it is clear that there are few consistencies in the findings of studies on characteristics of patients with benign mastopathy. The question of whether such patients share epidemiologic features with breast cancer patients remains unsettled. A part of the problem is that "cystic disease" cannot be considered as one disease, and that more attention needs to be paid to specific histological types of benign proliferative breast conditions. MacMahon and associates [18] suggest that only a small proportion of these conditions tends to become malignant, and according to Black [19] only certain types seem to be associated with increased breast cancer risk. Furthermore, they may react differently to endogenous hormonal fluctuation, as well as to exogenous estrogens.

While our findings, like those of most other studies dealt with in this report, indicate a decreased risk of benign breast neoplasias and no relation to breast cancer risk with oral contraceptive usage, the results of some studies suggesting the increased risk of developing benign [12] and malignant [8, 17] breast neoplasias in long-term users of estrogen-containing preparations call for continued monitoring of the effect of these agents on the breast.

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REFERENCES

1. M. P. Vessey, R. Doll and P. M. Sutton, Investigation of the possible relationship between oral contraceptives and benign and malignant breast disease. *Cancer (Philad.)* **28,** 1395 (1971).
2. M. P. Vessey, R. Doll and P. M. Sutton, Oral contraceptives and breast neoplasias: a retrospective study. *Brit. Med. J.* **3,** 719 (1972).
3. M. P. Vessey, R. Doll and K. Jones, Oral contraceptives and breast cancer. Progress report of an epidemiological study. *Lancet* **i,** 941 (1975).
4. F. G. Arthes, P. E. Sartwell and E. F. Lewison, The pill, estrogens and the breast. Epidemiologic aspects. *Cancer (Philad.)* **28,** 1391 (1971).
5. P. E. Sartwell, F. G. Arthes and J. A. Tonascia, Epidemiology of benign breast lesions: lack of association with oral contraceptive use. *New Engl. J. Med.* **288,** 551 (1973).
6. Boston Collaborative Drug Surveillance Programme, Oral contraceptives and venous thromboembolic disease, surgically confirmed gall-bladder disease, and breast tumours. *Lancet* **i,** 1399 (1973).
7. J. L. Kelsey, K. K. Lindfors and C. White, A case-control study of epidemiology of benign breast diseases with reference to oral contraceptive use. *Int. J. Epidemiol.* **3,** 333 (1974).
8. E. Fasal and R. S. Paffenbarger, Oral contraceptives as related to cancer and benign lesions of the breast. *J. nat. Cancer Inst.* **55,** 767 (1975).
9. R. W. Scarff and H. Torloni, *Histological Typing of Breast Tumours*, WHO, Geneva (1968).
10. D. Seigel and S. W. Greenhouse, Validity in estimating relative risk in case-control studies. *J. chron. Dis.* **26,** 219 (1973).

11. A. B. Hill, *Principles of Medical Statistics*. p. 212. The Lancet Ltd., London (1967).
12. A. Nomura and G. W. Comstock, Benign breast tumor and estrogenic hormones: a population-based retrospective study. *Amer. J. Epidemiol.* **103,** 439 (1976).
13. Boston Collaborative Drug Surveillance Program, Surgically confirmed gall-bladder disease, venous thromboembolism, and breast tumors in relation to postmenopausal estrogen therapy. *New Engl. J. Med.* **290,** 15 (1974).
14. J. Casagrande, V. Gerkins, B. E. Henderson, T. Mack and M. C. Pike, Brief communication: exogenous estrogens and breast cancer in women with natural menopause. *J. nat. Cancer Inst.* **56,** 839 (1976).
15. Royal College of General Practitioners, *Oral Contraceptives and Health*. p. 100. Pitman, London (1974).
16. H. Ory, P. Cole, B. MacMahon and R. Hoover, Oral contraceptives and reduced risk of benign breast diseases. *New Engl. J. Med.* **294,** 419 (1976).
17. R. Hoover, L. A. Gray, P. Cole and B. MacMahon, Menopausal estrogens and breast cancer. *New Engl. J. Med.* **295,** 401 (1976).
18. B. MacMahon, P. Cole and J. Brown, Etiology of human breast cancer: a review. *J. nat. Cancer Inst.* **50,** 21 (1973).
19. M. M. Black, T. H. Barlay, S. J. Cutler, B. F. Hankey and A. J. Asire Association of atypical characteristics of benign breast lesions with subsequent risk of breast cancer. *Cancer (Philad.)* **29,** 338 (1972).