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Oral Contraceptives and Breast Cancer

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A case-control interview study, conducted among participants in the Breast Cancer Detection Demonstration Project and involving 963 breast cancer cases and 858 controls, allowed evaluation of the risk of breast cancer associated with use of oral contraceptives. Overall, there was no association between use and risk of disease (RR = 1.1). In addition, there was no indication of increasing risk with years of use or years since initial use, despite slight excess risks observed among users of high-dose preparations. Premenopausal women who used the pill after the age of 40 demonstrated approximately a 50% increased risk, possibly as a result of artificial prolongation of a premenopausal rate of disease incidence. Non-significant excess risks associated with pill use were also seen among premenopausal women who reported a family history of breast cancer in a sister (RR = 3.6) or previous biopsies for benign breast disease (RR = 3.2). The latter excess was limited to women whose use of the pill preceded a first biopsy, suggesting that the types of lesions requiring biopsy among current long-term pill users may be those that predispose to breast cancer.

The relationship between use of oral contraceptives and risk of breast cancer has received widespread interest. This has been stimulated by the recognition that endogenous hormones are involved with the onset[1,2] and course[3] of the disease. Recent reports that oestrogens prescribed for the menopause may increase the risk of breast cancer[4–8] have increased concern that oral contraceptives may exert a similar effect.

To date, most studies have failed to find an association between oral contraceptive use and breast cancer; these include both cohort[9–13] and case-control[14–19] studies. However, the interpretation of these findings is limited by the fact that the latent period necessary for cancer induction may not have been realized and the numbers of women with certain patterns of use may have been limited. This would be particularly true if, as recent evidence indicates, excess risks are confined to specific subsets of users, including women who have used the pill to delay a first pregnancy,[20,21] those who have had a breast biopsy,[20] those with a family history of breast cancer[22] and those whose use began later in their reproductive lives.[23,24]

The present study, conducted within the context of a nationwide breast cancer screening programme, offered a unique opportunity to evaluate the relationship between oral contraceptive use and risk of disease. Unlike many of the previous investigations, the subjects in this study were generally older, most pill users had begun use in the distant past, and many had used them in association with other breast cancer risk factors or at later periods in their reproductive lives.

A previous mailed questionnaire study among 405 breast cancer cases and 1156 normal 'screenees' identified through the same screening programme showed non-significant elevations in risk of breast cancer among menopausal women who had used oral contraceptives in the presence of other risk factors, eg history of previous breast biopsy, family history of breast cancer, and late age when first child was born.[17] The present study attempted to evaluate these associations more extensively by obtaining home interview data on an expanded series of breast cancer cases and a newly selected sample of normal screenees.

METHODS

The study population was chosen from participants in the Breast Cancer Detection Demonstration Project (BCDDP), a nationwide screening project supported jointly by the National Cancer Institute and the American Cancer Society. This programme recruited over 280 000 asymptomatic women to 29 widely dispersed screening centres for annual breast screening. Screening began at the various centres between 1973 and 1975, and employed combined modalities of clinical examination, mammography and thermography.

For this study, we identified all women with breast cancer detected during the period July 1973 to May 1977 at 28 of the centres. These women were individually matched with another Project participant whose screens did not result in a recommendation for biopsy. The matching factors were centre, race (White, Black, Oriental, other), age (same five-year age group),

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time of entry to the Project (same six-month interval), and length of continuation in the Project (a control subject had to have completed as many years of screening as her matched cancer case).

All study subjects were interviewed in their homes by uniformly trained nurse-interviewers. Completed interviews were obtained from 86.1% of eligible cases (n = 1552) and 74.2% of control subjects (n = 1375). The lower response rate for controls than for cases was primarily due to the controls being more difficult to locate (7.6% controls versus 2.2% cases unavailable) and to their refusing more frequently to be interviewed (10.5% versus 4.6%). Women who were interviewed did not differ significantly from those not interviewed with regard to a number of factors determined for each woman at entry to the Project—including age, race, family income, and history of benign breast surgery.

The majority of cases (74%) were interviewed within three years after diagnosis. However, in the analyses, various exposure information was considered only until the date of diagnosis for cases, or the equivalent period for matched controls. A number of women (60 cases, 11 controls) reported a history of breast cancer prior to entering the screening Project; these women were not included in the current analysis.

Previous analyses from this study have shown a possible association between menopausal oestrogen use and risk of breast cancer, particularly among women who received oestrogens following a bilateral oophorectomy.[7] Because of the high correlation between oral contraceptive use and oestrogen use and the extensiveness of oestrogen exposure among women with a surgical menopause, we eliminated from the present analysis women with a history of an artificial menopause (418 cases, 424 controls) and those with missing information on menopause status (24 cases, 11 controls). The present analysis is further restricted to white study subjects (91% of the women interviewed), and thus consists of 963 breast cancer cases and 858 control subjects.

The measure of association between pill use and risk of breast cancer was the relative risk (RR), as estimated by the odds ratio. When necessary, effects of confounding variables, such as menopause status, were taken into account by stratification; maximum likelihood estimates of the overall risk and corresponding 95% confidence intervals (CI) were derived.[25] For multiple levels of exposure, significance was assessed using the linear trend test given by Mantel.[26] The measure of trend is a chi statistic, with positive or negative values, indicating the direction of trend. Probability values are based on a one-tailed test, since primary interest was in testing whether there was an increased risk of breast cancer associated with oral contraceptive usage.

RESULTS

Rates of 'ever use' (for one month or longer) of oral contraceptives among the breast cancer cases and controls are presented in Table 1. The highest rates of usage were reported by the youngest women, with approximately 65% of women less than 40 years of age indicating any use of oral contraceptives. Use declined with increasing age; only 1% of the women over the age of 60 reported having used birth control pills. No significant association between use of the pill and risk of breast cancer was observed in any of the five-year age groups. The relative risks ranged from a low of 0.8 in women less than 40 years of age at breast cancer diagnosis to 1.3 among women aged 45–49. The overall age-adjusted relative risk was 1.1 (95% CI 0.8–1.4).

Table 2 presents information regarding use of oral contraceptives by menopause status. The risks associated with ever use were similar for premenopausal (RR = 1.1) and naturally menopausal (1.0) women. In neither group was there any linear relationship of risk with years of use of oral contraceptives or years since initial use. Among the premenopausal women, the highest risk was observed among users of 7–9 years, whereas users of 10 or more years demonstrated no elevation in risk. A similar pattern of risk among premenopausal women was seen with years since initial use of oral contraceptives, with the risk among women whose use began 7–12 years prior to diagnosis exceeding that of women whose use began earlier. Analysis of data on years since last use revealed no distinctive trends. Current users had approximately the same risk as those who had discontinued the pill more than one year prior to diagnosis. There was, however, an excess risk for those who had stopped taking the pill in the year before diagnosis.

When effects were examined according to age at first use of oral contraceptives, no excess risks prevailed for the menopausal women in any of the 'age at first use'

TABLE 1 *Rates of use of oral contraceptives among cases and controls by age at breast cancer diagnosis*

Age at diagnosis	Cases N	Cases % Users	Controls N	Controls % Users	RR	(95% C.I.)
<40	37	62.2	37	67.6	0.79	(0.3–2.1)
40–44	103	54.4	97	52.6	1.08	(0.6–1.9)
45–49	195	34.9	161	29.8	1.26	(0.8–2.0)
50–54	221	23.5	187	22.5	1.06	(0.7–1.7)
55–59	150	14.7	131	15.3	0.95	(0.5–1.8)
60+	256	1.2	245	1.2	0.96	(0.2–4.8)
Total	962	23.3	858	22.0	1.08	(0.8–1.4)

N.B. Total relative risk adjusted for age.
Women with unknowns regarding ever-use of oral contraceptives excluded from analysis.

TABLE 2 *Relative risks of breast cancer by selected measures of use of oral contraceptives, by menopause status*

	Premenopausal	Menopausal	Total
Never used	1.00 (284, 237)	1.00 (454, 432)	1.00 (738, 669)
Ever used	1.11 (174, 142)	1.02 (50, 47)	1.08 (224, 189)
95% C.I.	(0.8–1.5)	(0.6–1.6)	(0.8–1.4)
Years of use			
<4	0.88 (81, 82)	0.96 (32, 33)	0.91 (113, 115)
4–6	1.31 (30, 20)	1.00 (6, 6)	1.23 (36, 26)
7–9	1.61 (29, 16)	1.22 (6, 5)	1.52 (35, 21)
10+	1.05 (26, 21)	1.01 (3, 3)	1.04 (29, 24)
χ_1 for linear trend	1.10 (p = 0.14)	0.11 (p = 0.46)	1.04 (p = 0.15)
Years since initial use			
<7	0.95 (26, 24)	0.79 (7, 9)	0.90 (33, 33)
7–12	1.28 (98, 69)	1.15 (26, 23)	1.24 (124, 92)
13+	0.78 (42, 47)	0.88 (14, 16)	0.81 (56, 63)
χ_1 for linear trend	0.09 (p = 0.46)	−0.04 (p = 0.48)	0.05 (p = 0.48)
Years since last use			
Current user	1.06 (32, 26)	–	1.06 (32, 26)
<1	6.20 (14, 2)	∞ (1, 0)	6.74 (15, 2)
1	1.19 (11, 8)	1.02 (3, 3)	1.15 (14, 11)
2–4	0.84 (25, 27)	1.45 (10, 7)	0.97 (35, 34)
5+	1.00 (86, 77)	0.89 (33, 37)	0.96 (119, 114)

N.B. Numbers in parentheses represent numbers of cases, numbers of controls.
Relative risks adjusted for age; risks in total column adjusted additionally for menopause status.
Unknowns excluded from analysis.

categories. The numbers of users in most categories, however, were limited. Among the premenopausal women, non-significant elevations in risk were seen among those whose use began at ages 35–39 (1.4), ages 45–49 (1.3) and beyond these ages (1.3). These associations were pursued further by examining duration of use according to age at first use among the premenopausal women. This analysis generally showed a pattern of increased risk for women who continued using the pill after approximately age 40. For example, women who began taking oral contraceptives at age 35–39 and who used them for seven or more years showed a relative risk of 2.3. The risk was 2.0 for shorter term users (4–6 years) among women who started taking the pill at ages 40–44, and (1.7) for users of less than four years among those who began taking the pill at 45 years or later.

Further analysis examined duration of use before and after the age of 40 in both premenopausal and menopausal women (Table 3). No consistent pattern of risk was observed with years of use before age 40. After age

TABLE 3 *Relative risks of breast cancer by years of use of oral contraceptives before and after the age of 40*

	Premenopausal women		Menopausal women	
	Use before age 40	Use after age 40	Use before age 40	Use after age 40
Years of use within age categories				
<2	0.81 (57)	0.86 (30)	0.95 (13)	0.99 (28)
2–3	1.25 (30)	1.67 (14)		
4–5	1.14 (15)	1.39 (15)	—	0.95 (13)
6+	1.02 (27)	1.60 (25)		

N.B. Numbers in parentheses represent number of cases.
All risks relative to women who have never used oral contraceptives.
Observations pertaining to years of use before and after age 40 are not necessarily independent, ie women could be included in both categories if use occurred before as well as after age 40.
Women with unknown ages at first use of oral contraceptives or years of use within age categories excluded from analysis.

40, however, risk was slightly, but not significantly, elevated following two or more years of use among the premenopausal women. This elevation was of the order of 40–70%, with no apparent trends according to duration of use. Among the menopausal women, there was no evidence of elevated risk for use before or after the age of 40.

Information on the types of oral contraceptives used was also analysed. No excess risk was observed with any one type of pill, but the numbers of users for any particular pill were usually limited. When pills were grouped by amount of oestrogen, there was some increase in risk for users of high-dose (100+μg) preparations (Table 4). This was true for the dose of the first oral contraceptive and for the dose of the oral contraceptive used for the longest period of time. In the menopausal women, users of the high-dose preparations showed twofold excess risks. However, risk did not increase with dose among users of the lower dose preparations. For the high-dose users, risks were examined according to years of use, with no apparent trends revealed. The relationship of risk to dose and duration of use was further evaluated by calculating a cumulative lifetime oestrogen dose. This failed to reveal any distinct trend. However, since the analysis required knowing the name and duration of use of each oral contraceptive used, many women (including more cases than controls) were classified with an unknown value for this summary parameter.

Analyses were also performed to examine the possible confounding effects on pill use of other breast cancer risk factors. These factors included age at birth of the first child, parity, family history of breast cancer, history of a breast biopsy, age at menarche, weight, use of non-contraceptive hormones, and among the menopausal women, age at cessation of menses. Control for these variables did not substantially alter any of the estimates associated with various measures of pill usage, including ever use of the pill, years of use, years since initial use or age at first use.

Several modifications of pill effects were noted, however, by the presence of certain other risk factors (Table 5). These effects were most evident among the premenopausal women. The most striking interaction was seen for women whose sisters also had breast cancer. These women exhibited a threefold excess risk of breast cancer associated with use of the pill, with the effect seen among both premenopausal and menopausal women. Among the premenopausal women, use of the pill was also associated with an increased risk among those with a history of benign breast biopsy, particularly when two or more biopsies were reported (RR = 3.2). In this group, the elevated risk was restricted to women who began use of the pill before the occurrence of breast surgery. The relative risk for pill use, adjusted for number of breast biopsies, was 2.5 (95% CI 0.8–8.0) for those whose use began prior to surgery, as opposed to 0.7 (0.3–1.7) for those whose use began afterwards. There was also some indication that the effects of pill use were less for parous than for nulliparous women, but the extent of increased risk among nulliparous women was considerably less than for the other identified effect modifiers. In contrast to the premenopausal women, no interactions of pill use with prior breast surgery or parity were seen among the menopausal women. However, only four of the menopausal breast cancer cases reported use of the pill prior to the occurrence of a first breast biopsy. No distinct patterns of risk for pill usage

TABLE 4 *Relative risks of breast cancer by oestrogen dose of first and longest used oral contraceptive*

	Premenopausal	Menopausal	Total
Oestrogen dose of first oral contraceptive used			
Non-user	1.00 (284, 237)	1.00 (454, 432)	1.00 (738, 669)
<60 μg.	0.77 (32, 36)	0.68 (8, 12)	0.75 (40, 48)
60–80 μg.	1.01 (22, 19)	0.32 (4, 13)	0.73 (26, 32)
100+ μg.	1.27 (65, 47)	2.23 (18, 8)	1.43 (83, 55)
Unknown	1.20 (55, 40)	1.41 (20, 14)	1.26 (75, 54)
Oestrogen dose of oral contraceptive used longest			
Non-user	1.00 (284, 237)	1.00 (454, 432)	1.00 (738, 669)
<60 μg.	0.89 (40, 39)	0.60 (7, 12)	0.82 (47, 51)
60–80 μg.	1.36 (25, 16)	0.24 (3, 13)	0.86 (28, 29)
100+ μg.	1.20 (59, 45)	2.23 (18, 8)	1.38 (77, 53)
Unknown	1.05 (50, 42)	1.56 (22, 14)	1.19 (72, 56)

N.B. Numbers in parentheses represent number of cases, number of controls.
Relative risks adjusted for age; risks in total column adjusted additionally for menopause status.

TABLE 5 *Relative risks of breast cancer associated with use of oral contraceptives, by selected risk factors and menopausal status*

	Premenopausal women			Menopausal women		
	Exposed cases	Exposed controls	RR (95% CI)	Exposed cases	Exposed controls	RR (95% CI)
Family history—mother						
No	147	126	1.15 (0.8–1.6)	45	43	1.06 (0.6–1.7)
Yes	24	15	0.93 (0.4–2.3)	4	4	0.65 (0.1–5.2)
Family history—sister						
No	161	140	1.13 (0.8–1.5)	42	46	0.94 (0.6–1.5)
Yes	12	1	3.63 (0.4–31.6)	8	1	3.38 (0.4–78.8)
Breast biopsy						
No	139	125	1.11 (0.8–1.6)	40	39	1.05 (0.6–1.8)
Yes	35	17	1.24 (0.6–2.7)	10	8	0.93 (0.3–2.9)
1	20	15	0.92 (0.4–2.4)	8	5	1.27 (0.3–5.1)
2+	15	2	3.17 (0.5–24.5)	2	3	0.52 (0.1–5.0)
Parity						
0	13	8	1.46 (0.4–5.1)	4	6	0.69 (0.1–3.2)
1–2	84	63	1.28 (0.8–2.1)	24	21	1.03 (0.5–2.1)
3+	77	71	1.02 (0.6–1.6)	22	20	1.26 (0.6–2.7)
Age at first livebirth						
<20	10	22	0.48 (0.2–1.4)	3	1	3.94 (0.4–34.6)
20–24	76	69	1.22 (0.8–2.0)	16	22	0.88 (0.4–1.9)
25–29	59	32	1.59 (0.9–2.9)	17	13	1.04 (0.4–2.7)
30+	16	11	0.98 (0.3–3.1)	10	5	1.58 (0.4–6.5)

N.B. Relative risks represent risk of ever use of oral contraceptives versus no use within each risk factor category. Risks adjusted for age. Unknowns excluded from analysis.

were associated with a family history of breast cancer in the mother or with age at first childbirth among either the premenopausal or menopausal study subjects.

Attempts were made to test findings from the stratified analyses using standard matched techniques[27] as well as multivariate procedures for unmatched[28] and matched[29] data. The multivariate models took into account the simultaneous influence of several potentially confounding variables. All analyses showed estimates similar to those derived by the unmatched stratified technique.

DISCUSSION

The results of this study are, for the most part, reassuring. In the total series of women, use of the pill was not associated with an increased risk of breast cancer (RR = 1.1) nor was there any indication of an increase in risk with duration of use or with time since initial use. Some increase was seen for recent users of the pill. However, this was predominantly for women who had discontinued using the pill in the year prior to diagnosis, suggesting selective discontinuation by cases because of suspected breast abnormalities.

There were, however, several subgroups where elevated risks prevailed. All of our findings in subgroups were based on small numbers of users, requiring cautious interpretation. Most of these elevated risks were not statistically significant, but their consistency with previous observations and with other knowledge regarding the biology of breast cancer suggests that the associations may be real.

One subgroup for whom pill usage seemed to exert an adverse effect were women with a family history of breast cancer, a finding consistent with that of Black *et al.*[22] In our study, the elevation in risk derived primarily from women who had a sister with breast cancer. No excess risk was observed for pill usage among women whose mothers had breast cancer, a finding not in accord with a previous study among BCDDP participants.[17] We attempted to determine in the present study if the elevated risk associated with pill use among women with affected sisters might be due to these women developing their breast cancer at an early age or to their having more than one affected relative. However, neither of these factors seemed to explain why these women might be particularly susceptible to the effects of the pill. It is unclear as to why use of the pill would enhance risk among women whose sisters had breast cancer, but not among women whose mothers had breast cancer. The difference may reflect a chance finding in one subgroup, and requires further study.

Our finding of an increased risk for pill users who had a history of benign breast disease is consistent with previous reports.[17,20] This may appear initially to be at variance with the protective effect of oral contraceptives on the occurrence of benign breast disease.[20,30]

Thus, it is noteworthy that the elevation in risk associated with pill use was restricted to women who began taking the pill prior to biopsy for benign disease, and that the majority of these women were long-term users of the pill at the time of their biopsy. Since long-term current users of the pill are less likely than other women to have breast lumps biopsied,[31] our finding suggests that those women who receive a biopsy while using the pill may have a distinctive form of mastopathy that predisposes to breast cancer. This notion would be consistent with the study of LiVolsi *et al*[32] who found no protective effect of pill usage for benign lesions with marked epithelial proliferation.

By nature of this study population, we had a special opportunity to examine a subgroup of women who used the pill at later periods in their reproductive lives, ie after the age of 40. Although this subgroup has not received much attention in the past, several studies have in fact reported elevated risks among women whose use of the pill occurred later in life. For example, Vessey *et al.*[18] found a positive association between pill use and breast cancer risk among women aged 46–50, but dismissed the effect since trends in those aged 41–45 were mainly in the opposite direction. Stavraky and Emmons[24] noted a similar effect of age at first use, with women who began taking the pill at age 40 or later having a threefold excess risk. A recent study by Jick *et al.*[23] showed an increased risk of breast cancer for older women currently using the pill, with risk ratios of 4.0 in women aged 46–50 years and 15.5 in women aged 51–55.

Although our findings are in line with these other studies, the strength of association in our study was considerably less than that previously observed, particularly as compared with the estimates derived by Jick *et al.*[23] In our study, among premenopausal women, use of the pill for more than two years after the age of 40 was associated with approximately a 50% increased risk. This excess risk was not consistent with a dose-response relationship according to years of use, nor did it apply to the menopausal women. However, the absence of an effect in menopausal women may reflect the fact that only 13 breast cancer patients in our study reported extended durations of use after the age of 40.

If the elevated risk associated with use of the pill after the age of 40 is real, it would be consistent with other observations regarding changing patterns of risk with age. Although the incidence of breast cancer increases with age, it has long been recognized that the slope of the increase is greater in younger women and changes around the age of 45–50 to a more gradual trend.[1] This phenomenon at the time of menopause has been attributed to a decrease in the production of ovarian hormones, and is consistent with the hypothesis that endogenous ovarian oestrogens 'promote' the rate of breast cancer in initiated cells. Thus, it is not surprising that women who use oestrogens in their late 40s, including those oestrogens contained in oral contraceptives, might continue to experience a risk of breast cancer which increases at the same rate as that among premenopausal women. In fact, the 50% increased risk that we observed among women who used the pill after the age of 40 is the order of risk that would be expected if the premenopausal rate of increase in breast cancer incidence were to prevail.

In interpreting the lack of an overall association between oral contraceptive use and risk of breast cancer, it must be cautioned that our cases had breast cancer as detected through intensive screening efforts. Many of the cancers included in this study were identified at an initial screen, and may not be true incident cases. Also they may be unrepresentative of breast cancer cases in terms of histology, size or stage. Although it would have been desirable to study oral contraceptive effects by restricting analyses to lesions detected on a second or later screen and/or by using varied definitions of disease, we were limited by the size of our exposed population and are continuing the study. While there does not currently appear to be an overall relationship between oral contraceptives and breast cancer, our analyses suggest that certain subsets of users are at a slightly increased risk. Further studies are needed that include large numbers of women with particular patterns of use, including women who have taken the pill at a late age, those with a family history of breast cancer and those with a history of benign breast disease.

REFERENCES

[1] Kelsey J L. A review of the epidemiology of human breast cancer. *Epidemiol Rev* 1979; **1**: 74–109.

[2] MacMahon B, Cole P. The ovarian etiology of human breast cancer. *Recent Res Cancer Res* 1972; **39**: 185–92.

[3] McGuire W L, Horwitz K B, Pearson O H, Segaloff A. Current status of estrogen and progesterone receptors in breast cancer. *Cancer* 1977; **39**: 2934–47.

[4] Hoover R, Gray L A, Cole P, MacMahon B. Menopausal estrogens and breast cancer. *New Engl J Med* 1976; **295**: 401–5.

[5] Jick H, Walker A M, Watkins R N, *et al.* Replacement estrogens and breast cancer. *Am J Epidemiol* 1980; **112**: 586–94.

[6] Ross R K, Paganini-Hill A, Gerkins V R, Mack T M, Pfeffer R, Arthur M, Henderson B E. A case-control study of menopausal estrogen therapy and breast cancer. *JAMA* 1980; **243**: 1635–9.

[7] Brinton L A, Hoover R N, Szklo M, Fraumeni J F Jr. Menopausal estrogen use and risk of breast cancer. *Cancer* 1981; **47**: 2517–22.

[8] Hoover R, Glass A, Finkle W D, Azevedo D, Milne K. Conjugated estrogens and breast cancer risk in women. *JNCI* 1981; **67**: 815–20.

[9] Ory H, Cole P, MacMahon B, Hoover R. Oral contraceptives and reduced risk of benign breast diseases. *New Engl J Med* 1976; **294**: 419–22.

[10] Royal College of General Practitioners. Breast cancer and oral contraceptives: findings in Royal College of General Practitioners' study. *Br Med J* 1981; **282:** 2089–93.

[11] Vessey M P, McPherson K, Doll R. Breast cancer and oral contraceptives: findings in Oxford–Family Planning Association contraceptive study. *Br Med J* 1981; **282:** 2093–4.

[12] Trapido E J. A prospective study of oral contraceptives and breast cancer. *JNCI* 1981; **67:** 1011–15.

[13] Ramcharan S, Pellegrin F A, Ray R, Hsu J, Brown W. The Walnut Creek Contraceptive Drug Study. A Prospective Study of the Side Effects of Oral Contraceptives. Vol. III. U.S. Govt. Printing Office, 1981.

[14] Boston Collaborative Drug Surveillance Programme: Oral contraceptives and venous thromboembolic disease, surgically confirmed gallbladder disease, and breast tumours. *Lancet* 1973; **1:** 1399–1404.

[15] Henderson B E, Powell D, Rosario I *et al.* An epidemiologic study of breast cancer. *JNCI* 1974; **53:** 609–14.

[16] Sartwell P E, Arthes F G, Tonascia J A. Exogenous hormones, reproductive history and breast cancer. *JNCI* 1977; **59:** 1589–92.

[17] Brinton L A, Williams R R, Hoover R N, Stegens N L, Feinleib M, Fraumeni J F Jr. Breast cancer risk factors among screening program participants. *JNCI* 1979; **62:** 37–44.

[18] Vessey M P, Doll R, Jones K, McPherson K, Yeates D. An epidemiological study of oral contraceptives and breast cancer. *Br Med J* 1979; **1:** 1757–60.

[19] Kelsey J L, Fischer D B, Holford T R *et al.* Exogenous estrogens and other factors in the epidemiology of breast cancer. *JNCI* 1981; **67:** 327–33.

[20] Fasal E, Paffenbarger R S. Oral contraceptives as related to cancer and benign lesions of the breast. *JNCI* 1975; **55:** 767–73.

[21] Pike M C, Henderson B E, Casagrande J T, Rosario I, Gray G E. Oral contraceptive use and early abortion as risk factors for breast cancer in young women. *Br J Cancer* 1981; **43:** 72–6.

[22] Black M M, Kwon C S, Leis H P Jr, Barclay T H C. Family history and oral contraceptives. Unique relationships in breast cancer patients. *Cancer* 1980; **46:** 2747–51.

[23] Jick H, Walker A M, Watkins R N *et al.* Oral contraceptives and breast cancer. *Am J Epidemiol* 1980; **112:** 577–85.

[24] Stavraky K, Emmons S. Breast cancer in premenopausal and postmenopausal women. *JNCI* 1974; **53:** 647–54.

[25] Gart J J. Point and interval estimation of the common odds ratio in the combination of 2×2 tables with fixed marginals. *Biometrika* 1970; **57:** 471–5.

[26] Mantel N. Chi-squared tests with one degree of freedom, extensions of the Mantel-Hansezel procedure. *J Am Stat Ass* 1963; **58:** 690–700.

[27] Fleiss J. Statistical methods for rates and proportions. New York, John Wiley & Sons, 1973.

[28] Anderson J A. Separate sample logistic discrimination. *Biometrika* 1972; **59:** 19–35.

[29] Breslow N E, Day N E, Halvorsen K T, Prentice R L, Sabai C. Estimation of multiple relative risk functions in matched case-control studies. *Am J Epidemiol* 1978; **108:** 299–307.

[30] Vessey M P, Doll R, Sutton P M. Oral contraceptives and breast neoplasia: A retrospective study. *Br Med J* 1972; **3:** 719–24.

[31] Brinton L A, Vessey M P, Flavel R, Yeates D. Risk factors for benign breast disease. *Am J Epidemiol* 1981; **113:** 203–14.

[32] LiVolsi V A, Stadel B V, Kelsey J L, Holford T R, White C. Fibrocystic breast disease in oral contraceptive users. A histopathological evaluation of epithelial atypia. *New Engl J Med* 1978; **299:** 381–5.

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