Eur J Cancer Clin Oncol, Vol. 25, No. 11, pp. 1613–1618, 1989.
Printed in Great Britain

0277–5379/89$3.00 + 0.00

Breast Cancer and Combined Oral Contraceptives: An Italian Case-control Study

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Abstract—*The risk of breast cancer in relation to use of oral contraceptives was evaluated using data from a hospital-based case-control study from Northern Italy on* 1517 *cases below age* 60 *and* 1351 *controls admitted for acute diseases unrelated to any of the known or potential risk factors for breast cancer. The multivariate relative risk for ever vs. never users was* 1.3 (95% *confidence interval* = 1.0–1.7). *However, the risk was not related to duration of use: indeed the highest risk was observed among short-term users* (<2 *years*), *and the point estimate was* 0.9 *among users for* 5 *years or more. The elevated risk among short-term users, if not due to residual confounding or selection mechanisms, is probably explainable in terms of recall bias (i.e. more careful report of short or very short use by cases). No definite pattern was observed in relation to latency or recency of use, and the point estimates were* 0.8 *for women who had ever used the pill before age* 25 *and* 0.8 *for those who had ever used the pill before first full-term pregnancy. Thus, the study presents further reassuring information on the oral contraceptive/breast cancer debate. Its major limitation lies in the low prevalence of oral contraceptive users in Italy, with a consequently reduced statistical power, although, with the number of cases involved, it was possible to exclude a relative risk of* 1.4 *for long-term use or for ever use before first birth.*

INTRODUCTION

THE ASSOCIATION between oral contraceptives and breast cancer has been studied extensively, and the overall evidence for ever use, based on 16 studies and over 12,000 cases (as summarized by Prentice and Thomas [1]) is reassuring: the estimated summary relative risk was 1.0, with of course very narrow confidence limits and there was no evidence of heterogeneity between studies.

Nonetheless, there is still concern about the possible association between oral contraceptives and breast cancer risk in selected populations or subgroups of women. Most of the positive results in specific subgroups (i.e. women with family history of breast cancer [2], nulliparity or late age at first birth [2, 3]) are probably due to chance, while others (e.g. in women with history of benign breast disease [3–5]) can be explained in terms of selection mechanisms, since oral contraceptives have a beneficial impact on less severe forms of benign breast disease [6].

Accepted 5 July 1989.
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However, chance or bias alone can hardly account for the elevated breast cancer risk observed in various studies among young women who had used the pill for long periods at younger ages and/or prior to first full term pregnancy [7–9]. This has led to the suggestion that we are now observing the beginning of a rise in breast cancer risk in countries where the pill was widely utilized earlier by young women, and that a similar rise may become evident in other populations after an adequate latent period [10].

Studies from the United States [11], Britain [12], Scandinavia [9] and New Zealand [13], however, are not totally consistent with this hypothesis and, in general, there remains a need for data from different populations with different patterns of oral contraceptive usage. Our case-control study of breast cancer in Northern Italy [14, 15] now provides a quantity of information on a population with patterns of pill use substantially different from Northern European or American countries [16]. The large number of cases (over 1500 below age 60) permitted meaningful analysis of subgroups even in a situation of low overall prevalence of pill use [16].

SUBJECTS AND METHODS

The design of this investigation has already been described [14, 15]. Briefly, since January 1983 trained interviewers have identified and questioned women admitted for breast cancer and for a wide spectrum of other conditions to university and general hospitals in the greater Milan area. Overall participation rate was over 97% for both case and control subjects.

Cases

The cases were women with histologically confirmed breast cancer, diagnosed within the year prior to interview, admitted to the National Cancer Institute and the Ospedale Maggiore, which includes the four largest teaching and general hospitals in the greater Milan area. A total of 1517 cases, aged 24–59 (median age = 47 years) were considered in the present analysis.

Controls

The comparison group consisted of women admitted for non-neoplastic acute conditions other than breast, gynaecological or hormone-related diseases to the same network of hospitals where cases had been identified, i.e. the Ospedale Maggiore of Milan and a few specialized university clinics. A total of 1351 controls aged 21–59 (median age = 48 years) was considered. Of these, 31% were admitted for traumatic conditions, 18% had non-traumatic orthopaedic disorders, 21% acute surgical conditions, and 30% other miscellaneous illnesses, such as skin, eye, ear, nose and throat or dental disorders.

A structured questionnaire was used to obtain information on socio-demographic factors and general characteristics and habits, frequency of use of a few selected dietary items including the major sources of alcohol, fats and vitamin A; a problem-oriented medical history, and history of use of selected drugs, including oral contraceptives, non-contraceptive oestrogens for menopausal replacement treatment, and female hormones for other indications. The time and duration of each episode of drug use were recorded as well as the brand name, whenever available.

The present analysis is based on data collected before June 1988.

Data analysis

The relative risks (RR) of breast cancer, together with their 95% approximate confidence intervals (CI) [17], according to various measures of oral contraceptive use were first derived from data stratified for age in decades by the usual Mantel–Haenszel procedure [18]. Further, to allow simultaneously for other potential confounding variables, unconditional multiple logistic regression was used [17], fitted by the method of maximum likelihood [19]. Included in the regression equations were terms for age, education, age at menarche, parity, age at first birth, menopausal status, history of benign breast disease and family history of breast cancer. Inclusion of other variables, such as marital status, area of residence, smoking or alcohol did not modify the pill-related risks: therefore they were not included in the final models.

RESULTS

The distribution of cases and controls according to age and major identified breast cancer risk factors is given in Table 1. As expected, cases were more educated, less frequently reported later menarche (at age 15 or over), and were less frequently multiparous (five or more births). There was a direct relation between breast cancer risk and age at first birth, pre-menopausal status, history of benign breast disease and of breast cancer in first-degree relatives.

The risk of breast cancer in relation to various measures of oral contraceptive use is considered in Table 2. As compared to never users, the age-adjusted relative risk was significantly elevated (RR = 1.5, 95% CI = 1.2–1.8) in women who had ever used the pill, and still of borderline statistical significance (RR = 1.3, 95% CI = 1.0–1.7) after simultaneous allowance for major identified potential confounding factors by multiple logistic regression.

However, there was no direct relation with duration of use: indeed, the highest risk was observed among short-term users (<2 years), and the point estimate was below unity among users for 5 or more years.

No definite pattern was evident in relation to latency or recency of use, although the point estimates tended to be somewhat higher for shorter intervals since first or last use (but not for current use, restricted to 21 cases and 17 controls).

In this population, only small numbers of women had used the pill before age 25 or before first full-term pregnancy. Still, for both subgroups the point estimates were below unity, and the upper 95% confidence limits below 1.5.

Table 3 gives the age-adjusted risk of breast cancer according to separate strata of duration and time since last use. The only significant estimate was for short duration ten or more years since last use, while no consistent pattern was observed in other strata.

The risk of breast cancer in short- (<24 months) and medium-long- (≥24 months) term users was further examined in strata of age and other selected covariates (Table 4). There was no apparent interaction with any of the variables considered, the variations observed being largely within the limits of random fluctuation.

*Table 1. Characteristics of 1517 breast cancer cases and 1351 controls; Milan, Italy, 1983–1988**

	Breast cancer		Controls	
	Number	%	Number	%
Age (years)				
<35	91	6.0	152	11.3
35–39	161	10.6	166	12.3
40–44	302	19.9	200	14.8
45–49	341	22.5	261	19.3
50–54	313	20.6	301	22.3
55–59	309	20.4	271	20.1
Marital status				
Never married	189	12.5	202	15.0
Ever married	1328	87.5	1149	85.0
Education (years)				
<7	702	46.3	713	52.8
7–11	445	29.3	385	28.5
≥12	370	24.4	253	18.7
Age at menarche				
<15	1314	86.8	1124	83.2
≥15	200	13.2	227	16.8
Parity				
0	272	17.9	270	20.0
1–2	947	62.4	774	57.3
3–4	262	17.3	247	18.3
≥5	36	2.4	60	4.4
Age at first birth				
<20	42	3.4	106	9.8
20–24	440	35.3	424	39.3
25–29	499	40.1	381	35.3
≥30	264	21.2	167	15.5
Age at menopause				
Pre-menopause	922	60.8	737	54.6
<45	131	8.6	166	12.3
45–49	198	13.1	215	15.9
≥50	266	17.5	231	17.1
History of breast cancer in first degree relatives				
No	1357	89.5	1296	95.9
Yes	160	10.5	55	4.1
History of benign breast disease				
No	1293	85.2	1238	91.6
Yes	224	14.8	113	8.4

*For some variables, the sum of strata does not add up to the total because of missing values; the distribution of all variables, except marital status, was statistically significant ($P < 0.01$), after allowance for age.

DISCUSSION

This study provides further information [1, 11, 13, 20–23] on the oral contraceptive/breast cancer debate. Its results are reassuring as regards the effect of oral contraceptives in women who had not used the pill for a large proportion of their fertile life. In fact, although the point estimate for ever use was above unity, there was no consistent duration/risk relationship (and, indeed, the relative risk tended to decrease with longer duration). Further, none of the other time factors considered provided consistent evidence for a causative association, nor did the two subgroups (women who had used the pill before age 25 or before their first full-term pregnancy) identified *a priori* on the basis of indications from previous studies [7–9, 12].

A major limitation of this study lies, obviously, in the low prevalence of oral contraceptive users in Italy (particularly of very long-term users), with a consequently reduced statistical power. Still the study, based on over 2800 subjects, included 400 ever users and 86 long-term (≥5 years) users. With this sample size, it was possible to exclude a relative risk of 1.4 for long-term users, or for ever users before first birth at the conventional 95% confidence limit.

In this study, breast cancer risk was significantly elevated among short-term oral contraceptive users. Possibly, even the multivariate estimate was somewhat inflated by residual confounding by social class or other covariates, since the point estimate declined from 1.80 to 1.57 after adjustment for major identified confounding factors. Other potential confounding factors may selectively influence duration of OC use. Benign breast disease, for instance, is inversely related to OC use but directly associated with breast cancer risk and (through a complex combination of side-effects of the pill and of selection mechanisms [6]), may therefore contribute to the inconsistent duration-risk relationship observed. The simplest explanation for this inconsistent pattern with duration is however, in our opinion, recall bias: it is in fact plausible that short- or even very short-term use was reported more carefully by breast cancer cases than by women admitted for diseases unrelated to female hormones. This hypothesis is somewhat supported by the observation that the excess risk for short-term use was greater after longer periods since last use, i.e. when recall bias is more likely.

Other possible sources of bias are unlikely to have considerably influenced any of these estimates, although the use of hospital controls for the study of oral contraceptives and disease may lead to an underestimation of the true risk [24]. Cases and controls were drawn from comparable catchment areas, participation rate was practically total, and the well-established risk factors for breast cancer were apparent in the data.

The results of this study are thus in agreement with most published evidence on oral contraceptives and breast cancer [1]: indeed, no previous study found a consistently elevated risk among middle aged women (i.e. above age 40 or 45), who contributed most of the information for this study.

There is now, in contrast, consistent evidence of a positive association between oral contraceptives

Table 2. Relative risk of breast cancer in relation to various measures of oral contraceptive use; Milan, Italy 1983–1988

	Breast cancer	Controls	Relative risk estimate (95% CI) M-H*	MLR†
Ever use				
No	1281	1188	1‡	1‡
Yes	236	163	1.48 (1.18–1.85)	1.32 (1.05–1.68)
Duration of use (months)				
<24	128	75	1.80 (1.32–2.45)	1.57 (1.14–2.15)
24–59	65	45	1.56 (1.04–2.34)	1.36 (0.90–2.06)
≥60	43	43	0.96 (0.62–1.49)	0.89 (0.57–1.39)
χ^2_1 (*trend*)			3.91 ($P = 0.05$)	1.28 (n.s.)
Time since first use (years)§				
<10	87	60	1.65 (1.14–2.39)	1.60 (1.11–2.32)
10–14	74	53	1.42 (0.97–2.07)	1.22 (0.83–1.78)
≥14	74	48	1.44 (0.99–2.09)	1.17 (0.80–1.72)
Time since last use (years)§				
<5	60	42	1.74 (1.12–2.69)	1.78 (1.13–2.80)
5–9	75	57	1.40 (0.97–2.03)	1.18 (0.81–1.73)
≥10	101	63	1.47 (1.06–2.04)	1.23 (0.83–1.72)
OC use before age 25				
Ever	36	51	0.87 (0.55–1.38)	0.93 (0.53–1.47)
OC use before first birth				
Ever	29	26	1.08 (0.63–1.86)	0.80 (0.45–1.40)

*Mantel–Haenszel estimates adjusted for age.
†Estimates for multiple logistic regression equations including terms for age, education, age at menarche, parity, age at first birth, menopausal status, history of benign breast disease and family history of breast cancer.
‡Reference category.
§The sum of strata does not add up to the total because of some missing values.

Table 3. Relative risk of breast cancer in separate strata of duration and time since last oral contraceptive use*

	Duration of use (months) <24	24–59	≥60
Time since last use (years)			
<5	1.71 (0.90–3.26)	1.13 (0.54–2.35)	1.40 (0.66–2.96)
5–9	1.58 (0.92–2.70)	1.60 (0.70–3.65)	0.57 (0.21–1.55)
≥10	2.78 (1.48–5.24)	1.11 (0.46–2.69)	1.82 (0.69–4.80)

*Mantel–Haenszel estimates adjusted for age. Reference category: never OC users.

Table 4. Relative risk of breast cancer in relation to oral contraceptive (OC) use in separate strata of selected covariates; Milan, Italy, 1983–1988

	Relative risk estimates* according to duration of OC use		
	Never	<24 months	≥24 months
Age (years)			
<45	1†	1.39	1.16
≥45	1†	2.19	1.30
Parity			
0	1†	1.84	1.08
≥1	1†	1.59	1.21
Age at first birth (years)			
<25	1†	1.31	1.20
≥25	1†	1.84	1.18
Menopausal status			
Pre-menopausal	1†	1.55	1.28
Post-menopausal		2.17	0.84
Family history of breast cancer			
No	1†	1.56	1.14
Yes	1†	3.79	0.89
History of benign breast disease			
No	1†	1.50	1.13
Yes	1†	2.43	1.24

*Estimates for multiple logistic regression equations including terms for age, age at menarche, parity, age at first birth, menopausal status, history of benign breast disease and family history of breast cancer.
†Reference category.

and breast cancer in young women. This was originally suggested by a Californian study of women under 37 [7]. This age group showed elevated risk in a national study from New Zealand, too [13], although the estimate was not significant. Further, the only subgroup showing a significantly elevated risk of 2.7 in a Canadian study [2] were younger (<45 years) recent pill users, and in a large British study [12] there were elevated risks among long-term users aged less than 45 at diagnosis (and significantly so for users before first full-term pregnancy), but not among older women. In the Royal College of General Practitioners oral contraception cohort study [25] the relative risk was 2.4, of borderline statistical significance, in women below age 35, but no association was evident above age 35. A significant association with long-term oral contraceptives use was found in the U.K. National case-control study [26], or in the most recent data from a large American hospital-based case-control study [27], and in a re-analysis of the Cancer and Steroid Hormone Group Study [28].

Although our data add little information on the specific issue of long-term use in young women, in the present study, too, significantly elevated risk estimates were observed in the short latency and recency subgroups only.

Thus, any critical review of the evidence from various studies should consider not only chance or bias [29], but also the possible different age- and time-effects of hormonal factors on breast carcinogenesis [30, 31]. For instance, the effect of a full-term pregnancy on breast cancer risk differs in terms of age at pregnancy [32] but also in time since pregnancy, with a short-term increase in risk followed by a long-term protection [33]. Similar complex interactions with age and other temporal factors in breast carcinogenesis should be considered in order to put forward hypotheses which could help explain some of the contradictory results from various studies.

Acknowledgements—This work was conducted within the framework of the CNR (Italian National Research Council) Applied Project 'Oncology' (Contract No. 87.01544.44). The contribution of the Italian League Against Tumours, and of the Italian Association for Cancer Research, Milan, Italy are gratefully acknowledged. We wish to thank Ms. Judy Baggott, Ms. Ivana Garimoldi and the G.A. Pfeiffer Memorial Library Staff for editorial assistance.

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