

Oral contraceptives and breast cancer in Northern Italy. Final report from a case-control study

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Summary To assess the relation between oral contraceptive (OC) use and breast cancer, we analysed data from a case-control study conducted in Northern Italy between 1983 and 1991 on 2,309 cases below age 60 and 1,928 controls admitted to hospital for acute diseases unrelated to OC use and to any of the known or potential risk factors for breast cancer. OC use was reported by 16% of cases and 14% of controls. The multivariate relative risk (RR) for ever vs never use of combination OC was 1.2 (95% confidence interval (CI) 1.0–1.4). However, there was no trend in risk with duration. The RR was elevated for very short use, but declined to 0.8 (95% CI = 0.5–1.0) for five or more years' use. No noteworthy relationship was found for other major measures of OC use, although RR estimates were above unity for women who had stopped use less than 5 years before (RR = 1.5, 95% CI = 1.1–2.0), started use less than 10 years before (RR = 1.3, 95% CI = 1.0–1.9), started when 25 or more years old (RR = 1.4, 95% CI = 1.1–1.7), or after first birth (RR = 1.2, 95% CI = 1.0–1.5). No interaction was observed between OC use and family history of breast cancer, parity and age at first birth. A separate analysis of 373 cases and 456 control below age 40 showed no association with ever use (RR = 0.9, 95% CI = 0.6–1.2).

Although a substantial amount of epidemiological data has been published on the oral contraceptive (OC)/breast cancer issue, the topic is still open and of interest on account of its major public health relevance (Doll, 1990; Mann, 1990). The global evidence on the influence of OC use on the breast in all age groups is largely reassuring (Prentice & Thomas, 1987; Thomas, 1988; Doll, 1990; Mann, 1990; Olsson, 1989; Delgado-Rodriguez *et al.*, 1991; La Vecchia, 1992), and in a formal overview based on 16 studies and over 12,000 cases, an overall relative risk (RR) for over use of 1.0 (95% confidence interval (CI) = 0.9–1.1) was found (Thomas, 1988).

A positive association between OC and breast cancer has been reported in several subgroups of women, but not always consistently. There is convincing evidence that long-term pill use increases the risk of breast cancer in women before age 35 or 45 (Lubin *et al.*, 1982; Meirik *et al.*, 1986; Miller *et al.*, 1989; Olsson *et al.*, 1989; Peto, 1989; UK National Case-Control Study Group, 1989; Delgado-Rodriguez *et al.*, 1991; Rushton & Jones, 1992; Ursin *et al.*, 1992), also in the absence of any evidence of an association in older women (Romieu *et al.*, 1990; McPherson *et al.*, 1987; Kay & Hannaford, 1988; Rosenberg *et al.*, 1984; Weinstein *et al.*, 1991). Increased risks have also been reported for use before first term pregnancy (Pike *et al.*, 1981; Meirik *et al.*, 1986; McPherson *et al.*, 1987), but these results are not consistent (Vessey *et al.*, 1982; Stadel *et al.*, 1985; Paul *et al.*, 1986).

OC use may become a risk factor only after a long 'latent period', so that now we may be observing only the start of a pill-induced breast cancer epidemic (McPherson *et al.*, 1987). However, this is not borne out by several studies which found no relationship between time since first use and subsequent breast cancer risk (Brinton *et al.*, 1982; Schesselman *et al.*, 1988; Vessey *et al.*, 1989; Ewertz, 1992).

To provide further information on this issue, we report here the final update of a case-control study conducted in Northern Italy (La Vecchia *et al.*, 1986a, 1989), in a population with a frequency of OC use considerably lower than that in North Europe and America, where most epidemiological studies have been conducted.

Subjects and methods

Data were derived from a case-control study of breast cancer, based on women admitted between January 1983 and December 1991 to a network of teaching and general hospitals in the greater Milan area, Northern Italy. On average, less than 2% of the eligible cases and 3% of controls refused to be interviewed. The general design of this investigation has already been described (La Vecchia *et al.*, 1986a,b; La Vecchia *et al.*, 1989).

Trained interviewers identified and questioned cases and controls using a structured questionnaire, including information on personal characteristics and habits, education and socio-economic factors, gynaecological and obstetrical data, related medical history and history of lifetime use of OC and female hormones for other indications, including time and duration of each episode of use and the brand name, whenever available.

Cases were women with histologically confirmed breast cancer, admitted to the Obstetric and Gynecology Clinics of the University of Milan, the National Cancer Institute and the Ospedale Maggiore (which includes the four largest teaching and general hospitals in the greater Milan area). There were 2,309 incident cases below the age of 60 (median age 48 years, range 22–59) diagnosed within the year preceding the interview.

Controls were women residing in a comparable geographical area and admitted for acute conditions to the same network of hospitals where cases had been identified. Women were not included if they had been admitted for gynaecological, hormonal or neoplastic diseases. A total of 1,928 controls below age 60 (median age 48 years, range 18–59) was interviewed. They were admitted to hospital for a wide spectrum of acute diseases (37% traumas, 13% other orthopedic disorders, 40% acute surgical conditions, 10% miscellaneous other diseases).

Data analysis Relative risks (RR) of breast cancer and the corresponding 95% confidence intervals (CI) in relation to OC use were estimated, after adjustment for age, by the method described by Mantel and Haenszel (1959); for multiple levels of exposure, the significance of the linear trend in risk was assessed by the Mantel test. Unconditional multiple logistic regression, fitted by the method of maximum likelihood, was used to allow for several possible confounding factors (Breslow & Day, 1980). The regression model included terms for age, education, marital status, family history of

breast cancer, age at first birth, age at menarche, age at menopause, and, in turn, various measures of OC use.

Results

The distribution of cases and controls according to age and major identified breast cancer risk factors is reported in Table I. Cases were more educated, more frequently married and less frequently multiparous. There was a direct relation between breast cancer and younger age at menarche, older age at first birth and at menopause, and history of breast cancer in a first-degree relative.

Table II shows the distribution of cases and controls according to various aspects of OC use. Ever use was reported by 16% of cases and 14% of controls; the corresponding age-adjusted relative risk (RR) estimate was 1.3 (95% Confidence Interval (CI) = 1.1-1.6). After simultaneous allowance for major identified potential confounding factors by multiple logistic regression, the increase in risk was of borderline statistical significance (RR = 1.2, 95% CI = 1.0-1.4). There was no direct relation with duration of use and short-term users (<24 months) had the highest risk (multivariate RR = 1.5); the RR declined (0.8, 95% CI = 0.5-1.0) for use lasting 5 years or longer.

In relation to time since first or last OC use, the risk was highest among women with the shortest intervals since first use (RR = 1.5, 95% CI = 1.1-2.0) and last use (RR = 1.3, 95% CI = 1.0-1.9). The RR estimate was of borderline statistical significance compared to never users also after simultaneous allowance for major identified potential confounding factors. The risk of breast cancer was higher in women who had first used OC when older than 25 (RR = 1.4, 95% CI = 1.1-1.7) and after their first birth (RR = 1.2, 95% CI = 1.0-1.5). In women below 40 years, ever OC use was reported by 35% of cases and 33% of controls, giving an age-adjusted RR estimate of 1.1 (95% CI = 0.7-1.3) and a multivariate RR of 0.9 (95% CI = 0.6-1.2) for ever use. The

Table I Distribution of 2,309 cases of breast cancer and 1,928 controls^a in women younger than 60 years according to selected variables. Milan, Italy, 1983-1991

	Breast cancer		Controls	
	No.	%	No.	%
<i>Age (yrs)</i>				
<35	139	6.0	245	12.7
35-39	234	10.1	213	11.1
40-44	422	18.3	279	14.5
45-49	514	22.3	369	19.1
50-54	522	22.6	421	21.8
55-59	478	20.7	401	20.8
<i>Education (yrs)</i>				
0-6	1003	43.4	973	50.5
7-11	703	30.5	559	29.0
≥12	603	26.1	396	20.5
<i>Marital status</i>				
Ever married	2087	90.4	1638	85.0
Never married	222	9.6	290	15.0
<i>Family history of breast cancer</i>				
No	2061	89.4	1851	96.1
Yes	245	10.6	75	3.9
<i>Parity</i>				
0	402	17.4	410	21.2
1-3	1762	76.4	1329	69.0
≥4	144	6.2	188	9.8
<i>Age at first birth (yrs)</i>				
<25	732	38.4	764	50.4
25-29	793	41.6	525	34.6
≥30	380	20.0	227	15.0
<i>Age at menarche (yrs)</i>				
≤12	996	43.2	802	41.6
13-14	1015	44.1	820	42.6
≥15	292	12.7	305	15.8
<i>Age at menopause (yrs)</i>				
Premenopause	1426	61.8	1085	56.3
<45	181	7.8	237	12.3
45-49	302	13.1	279	14.5
≥50	399	17.3	326	16.9

^aFor some variables the sum of strata does not add up to the total because of missing values.

Table II Distribution of breast cancer cases and controls^a and relative risk estimates (95% confidence interval, CI) in women younger than 60 years according to oral contraceptive (OC) use. Milan, Italy, 1983-1991

	Breast cancer	Controls	Relative risk estimates (95% CI)	
			M-H ^b	Multivariate ^c
<i>Ever use</i>				
No	1938	1663	1 ^d	1 ^d
Yes	371	265	1.3 (1.1-1.6)	1.2 (1.0-1.4)
<i>Duration of use (months)</i>				
<24	185	109	1.7 (1.3-2.2)	1.5 (1.2-2.0)
24-59	103	70	1.4 (1.0-2.0)	1.3 (0.9-1.8)
≥60	82	84	0.8 (0.6-1.2)	0.8 (0.5-1.0)
χ ² , trend (significance)			1.48 (P = 0.22)	0.0024 (P = 0.96)
<i>Time since first use (years)</i>				
<10	125	95	1.6 (1.2-2.1)	1.5 (1.1-2.0)
10-14	106	84	1.1 (0.8-1.5)	1.0 (0.7-1.4)
≥15	140	85	1.3 (1.0-1.8)	1.2 (0.9-1.6)
<i>Time since last use (years)</i>				
<5	97	82	1.4 (1.0-2.0)	1.3 (1.0-1.9)
5-9	105	75	1.3 (0.9-1.7)	1.1 (0.8-1.6)
≥10	166	103	1.3 (1.0-1.7)	1.2 (0.9-1.5)
<i>Age at first use (years)</i>				
<25	67	101	0.8 (0.6-1.1)	0.7 (0.5-1.1)
≥25	304	164	1.6 (1.3-1.9)	1.4 (1.1-1.7)
<i>First use in relation to first birth</i>				
Before	56	44	1.1 (0.7-1.7)	0.9 (0.6-1.3)
After	258	168	1.3 (1.0-1.6)	1.2 (1.0-1.5)
<i>Ever used for women aged <40 years</i>				
No	243	307	1 ^d	1 ^d
Yes	130	151	1.1 (0.7-1.3)	0.9 (0.6-1.2)
<i>Duration of use for women aged <40 years (months)</i>				
<24	67	61	1.4 (0.9-2.1)	1.2 (0.8-1.9)
≥24	63	89	0.9 (0.6-1.3)	0.9 (0.6-1.3)

^aFor some variables the sum of strata does not add up to the total because of missing values. ^bMantel-Haenszel estimates adjusted for age. ^cEstimates from multiple logistic regression; allowance was made for age, education, marital status, family history of breast cancer, age at menarche and menopause, parity, age at first birth, and, in turn, OC use, duration of use, time since first and last use, age at first use and first use in relation to birth. ^dReference category.

Table III Interaction between oral contraceptive (OC) use with family history of breast cancer, parity and age at first birth on the risk of breast cancer. Milan, Italy, 1983–1991

	Relative risk estimates (95% CI) ^a	
	Never ^b	Ever
<i>Family history of breast cancer</i>		
No	1 [1728:1595]	1.3 (1.1–1.6) [333:256]
Yes	1 [210:68]	1.6 (0.7–3.5) [38:9]
<i>Parity</i>		
Nulliparae	1 [338:347]	1.5 (1.0–2.4) [64:62]
Parae	1 [1600:1316]	1.3 (1.1–1.6) [307:203]
<i>Age at first birth</i>		
<25	1 [618:648]	1.1 (0.8–1.5) [114:116]
≥25	1 [982:668]	1.5 (1.1–2.0) [193:86]

^aNumber in square brackets are the case:controls in each category.

^bReference category.

risk estimate was not elevated also for two or more years of use (RR = 0.9, 95% CI = 0.6–1.3). The interaction between OC use and parity, age at first birth and family history of breast cancer is considered in Table III. The risk estimates were similar in various strata of covariates considered, and no significant interaction was observed.

Discussion

The final results of this study indicate that in women below 60 years there was no relationship between duration of OC use and breast cancer risk and, indeed, the risk tended to decrease with longer exposure. In women below 40 years, who had a higher prevalence of use than those aged 40 to 59, the RR estimates for ever use were not significant. However, although large, this study included only 56 cases and 44 controls who used OC before first pregnancy, 67 cases and 101 controls before age 25, 140 cases and 85 controls starting use 15 or more years before diagnosis, and 166 cases and 103 controls stopping use 10 or more years before diagnosis; thus it provides only limited information to several questions currently causing concern (Mann, 1990).

Allowance for major identified confounding factors led to a small, but systematic decrease in the RR estimates, suggesting that some residual confounding by social class or other covariates may still be present and might explain the increase in risk observed for shorter duration of use, for starting use after 25 years and after first birth. A potential residual confounding factor may be the presence of benign breast disease, which is inversely related to OC use, but directly associated with breast cancer risk (La Vecchia, 1984). Benign breast disease could also at least in part, underlie the inconsistency observed in the relationship between breast cancer risk and duration, latency and recency of OC use.

Information or recall bias may also be a plausible explanation of the increased risk for short duration of use: short-term or use a long time ago might have been reported more carefully by cases than controls (Skegg, 1988). Thus, the apparently elevated risk estimates in these subgroups should be viewed with extreme caution.

The RR estimates slightly above unity for short time since

first and last OC use may be explained within the framework of a multistage process of breast carcinogenesis, in terms of a late stage (promotional) effect (Day & Brown, 1980). This resembles the transient increase in the risk of breast cancer found after a full-term pregnancy (Bruzzi *et al.*, 1988; La Vecchia *et al.*, 1990).

These findings are not in agreement with most previous evidence referring to the pattern of risk in younger women (<40 years) (Lubin *et al.*, 1982; Meirik *et al.*, 1986; McPherson *et al.*, 1987; Kay & Hannaford, 1988; Miller *et al.*, 1989; Olsson *et al.*, 1989; Peto, 1989; UK National Case-Control Study Group, 1989; Romieu *et al.*, 1990; Delgado-Rodriguez *et al.*, 1991; Weinstein *et al.*, 1991; Rushton & Jones, 1992; Ursin *et al.*, 1992), and in those who used OC at a younger age or before first birth (Pike *et al.*, 1981; Meirik *et al.*, 1986; McPherson *et al.*, 1987). Since the confidence intervals of these estimates are wide, chance by itself is a plausible interpretation.

The possibility of bias must also be considered. Possibly the results of this study reflect the different pattern of OC use among Italian women, characterised by extremely infrequent (and probably highly selective) use in the older generations (i.e. among women above age 30 in the 1970s and 1980s) (La Vecchia *et al.*, 1986b). Although the low prevalence of OC use causes major difficulties in relation to study power and possibly also to selective mechanisms, the sample size of this study, based on over 2,300 cases and 1,900 controls, provides reasonably stable risk estimates in a population whose patterns of pill use differ substantially from Northern Europe or the USA (Thomas, 1988; Romieu *et al.*, 1990).

Another potential limitation of this study is its hospital-based design, with all the consequent implications, such as the use of hospital controls, which can be open to debate (Mantel & Haenszel, 1959). The results, however, could not be explained in terms of selection or confounding bias, since the catchment areas of cases and controls were well comparable, participation was almost complete, and allowance for several confounding factors only slightly modified the relative risk estimates. Further, the hospital setting may well improve recall of past drug use, particularly in controls, although this cannot totally eliminate a potential better recall by breast cancer cases, particularly for short term use in the distant past (Skegg, 1988).

In conclusion, the low prevalence of OC use in this Italian population seriously hampered analysis, and particularly any inference on subgroups, time factors, dose or type of preparation. Nevertheless, the large size of the dataset, the originality of the population, in terms of baseline breast cancer incidence and patterns of hormone use (La Vecchia *et al.*, 1986b), and the consistency of its results with the overall evidence from other studies (Mann, 1990) add useful information to a debate of major public health relevance. The indications emerging from this study for the use of OC and the risk of breast cancer are reassuring and should help in assessing the pattern of breast cancer risk better for various time-related factors of OC use in a Southern European population.

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