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Breast Cancer and Hormonal Contraceptives: Further Results

Collaborative Group on Hormonal Factors in Breast Cancer

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The Collaborative Group on Hormonal Factors in Breast Cancer has brought together and reanalysed the worldwide epidemiological evidence on breast cancer risk and use of hormonal contraceptives. Original data from 54 studies, representing about 90% of the information available on the topic, were collected, checked and analysed centrally. The 54 studies were performed in 26 countries and include a total of 53,297 women with breast cancer and 100,239 women without breast cancer. The studies were varied in their design, setting and timing. Most information came from case-control studies with controls chosen from the general population; most women resided in Europe or North America and most cancers were diagnosed during the 1980s. Overall 41% of the women with breast cancer and 40% of the women without breast cancer had used oral contraceptives at some time; the median age at first use was 26 years, the median duration of use was 3 years, the median year of first use was 1968, the median time since first use was 16 years, and the median time since last use was 9 years.

The main findings, summarised elsewhere,[1] are that there is a small increase in the risk of having breast cancer diagnosed in current users of combined oral contraceptives and in women who had stopped use in the past 10 years but that there is no evidence of an increase in the risk more than 10 years after stopping use. In addition, the cancers diagnosed in women who had used oral contraceptives tended to be less advanced clinically than the cancers diagnosed in women who had not used them.

Despite the large number of possibilities investigated, few factors appeared to modify the main findings either in recent or in past users. For recent users who began use before age 20 the relative risks are higher than for recent users who began at older ages. For women whose use of oral contraceptives ceased more than 10 years before there was some suggestion of a reduction in breast cancer risk in certain subgroups, with a deficit of tumors that had spread beyond the breast, especially among women who had used preparations containing the highest doses of oestrogen and progestogen. These findings are unexpected and need to be confirmed.

Although these data represent most of the epidemiological evidence on the topic to date, there is still insufficient information to comment reliably about the effects of specific types of oestrogen or of progestogen. What evidence there is suggests, however, no major differences in the effects for specific types of oestrogen or of progestogen and that the pattern of risk associated with use of hormonal contraceptives containing progestogens alone may be similar to that observed for preparations containing both oestrogens and progestogens.

On the basis of these results, there is little difference between women who have and have not used combined oral contraceptives in terms of the estimated cumulative number of breast cancers diagnosed during the period from starting use up to 20 years after stopping. The cancers diagnosed in women who have used oral contraceptives are, however, less advanced clinically than the cancers diagnosed in never users.

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Further research is needed to establish whether the associations described here are due to earlier diagnosis of breast cancer in women who have used oral contraceptives, to the biological effects of the hormonal contraceptives or to a combination of both. Little information is as yet available about the effects on breast cancer risk of oral contraceptive use that ceased more than 20 years before and as such data accumulate it will be necessary to re-examine the worldwide evidence. CONTRACEPTION 1996; 54:1S–000S

Introduction

The Collaborative Group on Hormonal Factors in Breast Cancer was set up in 1992 with the aim of bringing together, reanalysing and publishing the worldwide epidemiological evidence on breast cancer risk in relation to hormonal factors including hormonal contraceptives, hormone replacement therapy and reproductive factors. Principal investigators of epidemiological studies of hormonal factors in breast cancer were identified from review articles, computer searches and discussions with colleagues, and were invited to collaborate. Preliminary results were discussed at meetings of collaborators in Oxford in September 1993 and in March 1995.

The findings for use of hormonal contraceptives have been summarised elsewhere.[1] The main findings are: first, there is a small increase in the risk of having breast cancer diagnosed in women currently using oral contraceptives or who had stopped use in the preceding 10 years; and second, there is no evidence of an increase in the risk of breast cancer 10 years or more after stopping use. In addition, the cancers diagnosed in women who have used oral contraceptives are less advanced clinically than the cancers diagnosed in women who have never used oral contraceptives.[1] This article describes the studies and women included in the collaboration and presents further results on breast cancer risk in relation to hormonal contraceptive use.

Materials

Collection of Data

Epidemiological studies that included at least 100 women with breast cancer and with information on the use of hormonal contraceptives and on reproductive history were eligible for this review. Of the eligible studies identified,[2–65] 54 (including two studies that have not published results) were available for this analysis.[2–53] Original data could not be retrieved for 11 studies[54–64] and only one group of researchers declined to participate in the collaboration.[65] From each case-control study, data for individual women were sought on socio-demographic factors, family history of breast cancer, height, weight, age at menarche, reproductive history, use of hormonal contraceptives and of hormone replacement therapy, menopausal status, age at menopause, gynecological surgery, previous biopsies for benign breast disease, previous mammographic examinations, and consumption of tobacco and alcohol. Where possible, information on tumour characteristics was obtained for women with breast cancer. From prospective studies, similar information was sought using a nested case-control design in which four randomly selected controls were matched to each eligible case by exact year of birth, exact year of entry into the study and broad geographical region. Individuals were eligible to serve as controls only if they had never been diagnosed with breast cancer but had been at risk of developing cancer as long as the corresponding case. As far as possible women could not serve as controls for more than one case. The availability of data on individual women permitted a wide range of consistency checks to be performed. Apparent inconsistencies, implausibilities or omissions were clarified and, where possible, rectified by correspondence. Investigators were then supplied with summary tables and listings of the variables that were to be used in the analysis for checking. This process was repeated until no further corrections were required.

Definitions and Comparability of Variables Used in These Analyses

"Cases" are women with invasive breast cancer and "controls" are women without breast cancer. The outcome variable in these analyses is breast cancer, and where information was available, the tumours were further subdivided according to whether they were localised to the breast or had spread beyond it. The variables relating to exposure to combined oral contraceptives and to progestogen-only contraceptives were: ever use; age at first use; years since first use; years since last use; total duration of use; use in relation to childbearing; and specific brands used first, last and for the longest period of time. Sequential and phasic oral contraceptives were included with the "combined" type. Other variables that were used to stratify data within studies were: age at diagnosis for cases (or age at pseudodiagnosis for controls); total parity (number of live and stillbirths); age when the first child was born (live or stillbirth); history of and age at tubal ligation; menopausal status; age at which menstruation ceased and reason for its cessation (natural menopause, hysterectomy, bilateral oophorectomy or irradiation of the ovaries).

Information on most variables had been collected in fairly comparable ways in most studies, or could be derived simply, so that it was generally straightfor-

ward to use the same definitions across all studies. Where definitions of variables were similar, but not identical, it was often still possible to derive comparable groups. For example, in some studies information had been collected about use of all types of oral contraceptives without distinguishing between the combined and progestogen-only types and for those studies the data on "oral contraceptives" were taken to relate to the combined type. In other studies, details of past births had included information on livebirths but not on stillbirths and for those studies information on livebirths was taken to relate to live and stillbirths. These conventions should not materially alter the overall results because in studies where these distinctions were made, around 99% of oral contraceptive use was of the combined type, and about 99% of all births were livebirths.

In cohort studies certain conventions had to be adopted to allow the contraceptive history at the time of diagnosis (or pseudodiagnosis) to be estimated from the information last recorded. If less than two years had elapsed between the last time that information was collected and the date of diagnosis (or pseudodiagnosis) or if the woman was aged over 40 and not currently using hormonal contraceptives at that time, it was assumed that her use continued as had been last recorded; otherwise her use was defined as unknown.

In 27 studies, including 2 unpublished studies, information was available about the specific hormonal preparations used by each woman.[3,4,9,10,12,13,15,18,24–26,28,30,33,34,37,38,40,41,48–53] For each of those studies, details of the specific type and dose of oestrogen and progestogen in each contraceptive preparation were compiled centrally and cross-checked against drug compendia and other listings of the hormonal content of specific hormonal contraceptives. This information was used to construct a summary of the dose and type of oestrogen and of progestogen that each woman had first used, had last used and had used for the longest period of time. For sequential and phasic preparations the dose of oestrogen and of progestogen was estimated as the average daily dose of oestrogen and of progestogen. For some analyses preparations were grouped into three broad categories of dose: low, medium and high (containing <50μg, 50μg and 50μg+ oestrogen, respectively).

Information on tumour size, stage or spread was available for 24 studies,[2,4,8,16,20–23,25,30–35,37,43,48–50,52,53] of which 2 are unpublished, and this was used to classify the tumours as "localised to the breast" or "spread beyond the breast." Direct information on whether the tumour was localised or not was available for 19 studies; in 3 studies[22,23,25] the classification could be based only on whether regional lymph nodes were involved; and in 2 studies[20,48] it could be based only on TNM stage,[66] with stage I tumours classified as "localised" and stage II, III and IV tumours classified as having "spread." Information on distant metastases was available for all but one study.[22]

Characteristics of the Studies and the Women

The Studies

The 54 studies that contributed to the collaboration are listed in Appendix I, together with details of their design, the country or countries in which they were performed, the method of obtaining information about use of hormonal contraceptives, the median age of the women when their breast cancer was diagnosed, the median year when the cancers were diagnosed, the number of cases and controls, the percent in each group that had ever used combined oral contraceptives and the percent in each group of recent users, i.e., women currently using oral contraceptives or who had stopped using them within the last 5 years. The studies are grouped according to three main types of design: prospective studies, case-control studies with population controls and case-control studies with hospital controls. Within each of the three categories of study design, individual studies are listed in chronological order, according to the median year when the cancers were diagnosed.

It can be seen in Appendix 1 that there is considerable variability in study design, in the countries where the studies were performed, in the way that information on oral contraceptive use was obtained, in the ages of the women included, in the years when the cancers were diagnosed and in the prevalence of use of combined contraceptives. The studies were conducted in 25 countries and most were case-control studies with controls chosen from the general population. Information about hormonal contraceptive use was mostly obtained by interviewing subjects, but in some studies, especially those of prospective design, information was obtained from self-completed questionnaires and in a few studies medical records were used. Sometimes more than one source was consulted to obtain information about hormonal contraceptive use.

The median year of diagnosis of breast cancer ranged from 1974 to 1992 in the different studies (Appendix 1). The overall median year of diagnosis was 1984 and the overall distribution of the year when the cancers were diagnosed is shown in Table 1. Three-quarters of the cancers (74%) were diagnosed during the 1980s; 3% were diagnosed before 1975 and 13% in 1990 or later.

Table 1. Distribution of year of diagnosis of breast cancer in cases

Year	Cases
<1975	3%
1975–79	10%
1980–84	38%
1985–89	36%
1990–94	13%
Total	100%

The Women

Altogether data were available on 53,297 cases and 100,239 controls. The overall median age of the cases and of the controls was 49. Table 2 shows the overall age distribution of the cases and controls and it can be seen that most women were aged between 35 and 64 (78% cases and 76% controls, respectively). Even though the percentages of young women appear small, the actual numbers are substantial. For example, 4148 women with breast cancer were younger than 35 and 1118 were younger than 30. The median age at diagnosis for the women with breast cancer in the different studies ranged from 32 to 69, indicative of the different eligibility criteria with respect to age of the individual studies. Appendix 2 shows the age distribution of the cases and controls included in each study.

The overall distribution of the year of birth of the cases and the controls is shown in Table 3. Most women (69% cases and 68% controls) were born between 1920 and 1944. Although only 8% of the women with breast cancer were born in 1950 or later, this represents 4579 women. The distribution of year of birth of the cases and of the controls in each study are given in Appendix 3.

In the entire study population, the proportion of women who had ever used combined oral contraceptives was 41% in the cases and 40% in the controls. Ever use of oral contraceptives was classified here as unknown for 353 (1%) cases and 1109 (1%) controls,

Table 2. Distribution of age of women with invasive breast cancer (cases) and of controls

Age	Cases	Controls
<25	1%	2%
25–34	8%	10%
35–44	25%	24%
45–54	33%	32%
55–64	20%	20%
65–74	12%	10%
75+	1%	2%
Total	100%	100%

Table 3. Distribution of year of birth of women with invasive breast cancer (cases) and of controls

Year of Birth	Cases	Controls
<1915	5%	5%
1915–	7%	5%
1920–	11%	10%
1925–	14%	14%
1930–	16%	17%
1935–	15%	15%
1940–	13%	12%
1945–	11%	10%
1950+	8%	12%
Total	100%	100%

but this does not generally represent defective data. Most of the "unknown" values were from prospective studies, and according to the convention adopted for these analyses (described in the *Materials* section), certain women, if had been followed for more than two years since the last date of known oral contraceptive use, their use was defined as unknown.

In the individual studies, the prevalence of ever use of combined oral contraceptives ranged from 2% to 92% among cases and from 4% to 91% among controls (Appendix 1). This large variation in the prevalence of ever use from one study to another reflects the range of ages and of years of birth of the women and the different patterns of oral contraceptive use between countries (Appendices 4 and 5). In Northern Europe, North America, Australia and New Zealand few women born before 1920 had ever used oral contraceptives; thereafter, the prevalence of ever use increased rapidly for successive birth cohorts, such that 80% or more of the women born in 1945 or later had used combined oral contraceptives at some time. In many Southern European, Asian, Central and Southern American and African countries, there was little oral contraceptive use by women who were born before 1930, and the prevalence of use increased in subsequent birth cohorts with about half the women born after 1945 having ever used oral contraceptives (Appendix 5).

The prevalence of recent use of oral contraceptives also varied markedly from one study to another, largely reflecting the ages of the women included and the overall prevalence of use in the country in which the study was performed. Appendix 6 lists separately for each study the age-specific prevalence of current use or of use in the last 5 years among cases and controls. For women aged under 35 in Northern Europe, North America, Australia and New Zealand around a third to a half were recent users. For women aged under 35 in other countries the percentages were generally lower, reflecting the lower prevalence of

ever use in those populations. At ages 35 and older the prevalence of recent use was considerably lower than at younger ages; and, as expected, almost none of the women aged 55 or older had used oral contraceptives in the preceding 5 years. Information on time since last use of oral contraceptives was not available for 11 studies (see Appendix 6).

Pattern and Timing of Use of Combined Oral Contraceptives

This section describes the pattern and timing of use of combined oral contraceptives in the 22,000 women with breast cancer and 40,000 controls who had ever used them.

Distribution of Indices of the Timing of Use

Table 4 shows the overall distribution of the reported total duration of use of combined oral contraceptives in the cases and controls. About one-quarter of the cases and of the controls who had used oral contraceptives had done so for a total of less than a year and the median duration of use among ever users was 3.5 years in cases and 3 years in controls. The distribution of the total duration of use reported among women who had ever used combined oral contraceptives is shown for each study separately in Appendix 7. The entries in Appendix 7 are calculated separately for cases and for controls, excluding women with missing data.

Appendix 8 shows the distribution of total duration of use, measured in months, up to 75 months. Both in cases and controls there are sharp peaks at multiples of a year, i.e., at 12, 24, 36, 48, 60 and 72 months. In some studies total duration of use was recorded only to the nearest year, but even where use was recorded in months, there was a tendency to round to multiples of 12 months, presumably because it is difficult for women to remember the exact number of months that they had used oral contraceptives, especially if use had ceased many years ago. Among women whose total duration of use was reported to be less than a year, half (50% of cases and 50% of controls) had reported durations of use of 3 months or less.

Another feature of the distribution of the reported duration of use of oral contraceptives is the substantial variation between studies in the frequency of use lasting for short periods of time. For example, the proportion of ever users whose reported total duration of use was less than a year ranged from 2% to 73% in cases and from 4% to 53% in controls, although within studies the proportions were roughly similar for cases and controls (Appendix 7). This wide range of values is largely a consequence of differing definitions of "ever use" between studies: in some studies women were classified as an "ever user" if they had ever taken oral contraceptive tablets regardless of their duration of use, whereas in other studies women were defined as an "ever user" only if they had taken oral contraceptives for a minimum period of time, such as 3 months. Where total duration of use was recorded only to the nearest year it is not always clear how women with very short durations of use were classified. The implications for the main findings of this lack of consistency between studies in the definition of ever use are discussed later.

Women began using oral contraceptives at a median age of 26 for both cases and controls. Table 5 shows the overall distribution of age at first use among cases and controls who had ever used oral contraceptives and Appendix 9 shows the distribution of age at first use separately for the cases and the controls in each study. Overall, half the ever users began use in their 20s (52% of cases and of controls), but again the distribution varied markedly between studies, reflecting the age groups of the women included and the years when the cancers were diagnosed. Among women with breast cancer 2967 had begun oral contraceptive use before age 20. Just over a quarter of the cases and of the controls who had used oral contraceptives had begun use while they were nulliparous (30% of the cases and 26% of the controls).

The median time since first use of oral contraceptives was 16 years in cases and 15 years in controls. Table 6 shows the overall distribution of time since

Table 4. Distribution of total duration of use of combined oral contraceptives in cases and controls who had used oral contraceptives

Total Duration of Use	Cases	Controls
<1 year	23%	25%
1–4 years	36%	37%
5–9 years	26%	24%
10–14 years	12%	11%
15+ years	3%	3%
Total	100%	100%

Table 5. Distribution of age at first use in cases and controls who had used combined oral contraceptives

Age at First Use	Cases	Controls
<20	15%	14%
20–24	30%	29%
25–29	22%	23%
30–34	16%	17%
35+	17%	17%
Total	100%	100%

Table 6. Distribution of time since first use in cases and contols who had used combined oral contraceptives

Time Since First Use	Cases	Controls
<5 years	4%	7%
5–9 years	12%	14%
10–14 years	25%	24%
15–19 years	32%	29%
20–24 years	20%	19%
25+ years	7%	7%
Total	100%	100%

first use in cases and controls and Appendix 10 shows the distributions separately for cases and controls in each study. About a quarter of the cases and controls (27% and 26%, respectively) had begun use 20 or more years ago. Again these percentages varied by study, and, as expected, the studies conducted most recently tended to include comparatively more women who had begun use relatively long ago.

The median time since last use of oral contraceptives was 9 years for both cases and controls. Table 7 shows the overall distribution of time since last use in cases and controls and Appendix 11 shows the distribution within individual studies. Overall 13% of the cases and 13% of the controls who had ever used oral contraceptives were current users and 28% of the cases and 27% of the controls had used them in the last 5 years, but again the percentages varied between the studies, depending on the ages of the women involved.

Two-thirds of the women had begun use before 1970 and just over a quarter last used them before 1970 (Tables 8 and 9). Relatively few women had begun oral contraceptive use after 1980 and about one-fifth had last used them after 1980 (Tables 8 and 9). The median year of first use was 1968 for both cases and controls, while the median year of last use was 1974 for cases and 1973 for controls.

Table 7. Distribution of time since last use in cases and controls who had used combined oral contraceptives

Time Since Last Use	Cases	Controls
Current*	13%	13%
1–4 years	15%	14%
5–9 years	23%	23%
10–14 years	24%	24%
15–19 years	16%	17%
20+ years	9%	9%
Total	100%	100%

*Includes use < months ago.

Table 8. Distribution of year of first use in cases and controls who had used combined oral contraceptives

Year of First Use	Cases	Controls
<1965	26%	26%
1965–69	39%	36%
1970–74	24%	23%
1975–79	8%	10%
1980+	3%	5%
Total	100%	100%

Relationships Between Indices of the Timing of Use

Variables that describe the timing of oral contraceptive use are highly correlated. This section describes the relationships between four main indices of the timing of use (duration of use, age at first use, time since first use and time since last use) and illustrates the potential for the association between breast cancer risk and each of these factors to be confounded by the effects of the other factors.

Some indices of oral contraceptive use must, by definition, be related. For example, time since last use must necessarily be shorter than time since first use. The fact that oral contraceptives have been available only for a relatively short period of time and are used only during a particular period in a woman's life induces further relationships between indices of the timing of use. For example, women who had stopped use long ago would not have had the opportunity to have taken oral contraceptives for long durations. Also, since oral contraceptives are typically used during the reproductive years, women who started use as teenagers or in their early 20s would have a greater potential for long durations of use than women who started use in their 30s or 40s.

Tables 10–13 summarise, for cases and controls combined, the overall relationships between duration of use, age at first use, time since first use and time since last use. The chi-squared statistic of association gives a measure of the magnitude of the correlations, and since all are based on 4 degrees of freedom, the

Table 9. Distribution of year of last use in cases and controls who had used combined oral contraceptives

Year of Last Use	Cases	Controls
<1965	7%	7%
1965–69	20%	21%
1970–74	27%	27%
1975–79	25%	25%
1980+	21%	20%
Total	100%	100%

Table 10. Association of duration of use of combined oral contraceptives with other indices of use

Duration of Use	Proportion in Each Duration of Use Category With: First Use Before Age 20	First Use 20+ Years Ago	Last Use <5 Years Ago
<1 year	9%	23%	15%
1–4 years	13%	24%	20%
5–9 years	19%	27%	35%
10–14 years	17%	36%	50%
15+ years	16%	60%	66%
χ^2 for association (4 d.f.)	584	1396	4406

values can be compared directly. The strongest association, i.e., the largest chi-squared values, are between time since first use and time since last use. After this, the strongest associations are between duration of use and the times since first and last use. Age at first use, although significantly correlated with all the other three factors, showed the weakest relationships with other indices. These results show that in the overall data there is considerable scope for confounding between time since first and last use and also between duration of use and time since first and last use and, to a lesser extent, between age at first use, duration of use and time since first and last use.

When tabulations of the type shown in Tables 10–13 are restricted to certain subgroups of women, the potential for confounding can be even more extreme than indicated in the tables for all women. For example, if analyses are restricted to current users of oral contraceptives, time since first use and duration of use are even more strongly correlated than in general, and for current users whose use has been virtually continuous, time since first use and duration of use are essentially the same.

Table 11. Association of age at first use of combined oral contraceptives with other indices of use

Age at First Use	Proportion in Each Age at First Use Category With: Total Duration of Use of 5+ Years	First Use 20+ Years Ago	Last Use <5 Years Ago
<20	50%	26%	41%
20–24	41%	28%	29%
25–29	38%	30%	25%
30–34	38%	27%	26%
35+	31%	21%	27%
χ^2 for association (4 d.f.)	715	243	587

Table 12. Association of time since first use of combined oral contraceptives with other indices of use

Time Since First Use	Proportion in Each Time Since First Use Category With: Total Duration of Use of 5+ Years	First Use Before Age 20	Last Use <5 Years Ago
<10 years	20%	12%	69%
10–14 years	40%	15%	34%
15–19 years	45%	15%	18%
20–24 years	46%	15%	7%
25+ years	50%	13%	2%
χ^2 for association (4 d.f.)	2186	49	11623

Patterns of Use by Age

The distribution of ever use of oral contraceptives, and the distributions of the four main indices of timing of use, vary markedly by age (Table 14). The most striking differences by age are in the proportion of women who began use before age 20, and in the proportion of recent users, both of which decrease rapidly with age.

An additional consideration is that within certain age groups the distribution of some indices of use is severely restricted, partly due to the limited period of availability of oral contraceptives and partly due to the fixed age interval during which a woman is likely to use them. This effect is most evident for age at first use and time since last use. For example, most women aged 45 and older could not have started using

Table 13. Association of time since last use of combined oral contraceptives with other indices of use

Time Since Last Use	Proportion in Each Time Since Last Use Category With: Total Duration of Use of 5+ Years	First Use Before Age 20	First Use 20+ Years Ago
Current†	64%	23%	4%
1–4 years	57%	18%	6%
5–9 years	48%	14%	12%
10–14 years	34%	12%	23%
15+ years	16%	11%	64%
χ^2 for association (4 d.f.)	6191	628	13513

†Includes use ≤12 months ago.

Table 14. Age-specific distributions of ever use, duration of use, age at first use, time since first use and time since last use of oral contraceptives

	Age			
	<35	35–44	45–54	55+
Ever use	62%	63%	41%	15%
Duration of use				
<1 years	23%	22%	27%	26%
1–4 years	43%	38%	34%	34%
5–9 years	27%	26%	23%	21%
10–14 years	7%	11%	12%	14%
15+ years	0%	3%	4%	5%
Total	100%	100%	100%	100%
Age at first use				
<20	42%	16%	1%	0%
20–24	43%	42%	15%	1%
25–29	13%	25%	29%	7%
30–34	2%	12%	28%	24%
35+	0%	5%	26%	68%
Total	100%	100%	100%	100%
Time since first use				
<10 years	52%	15%	10%	3%
10–14 years	39%	27%	18%	9%
15–19 years	9%	40%	31%	22%
20–24 years	0%	17%	29%	36%
25+ years	0%	1%	12%	30%
Total	100%	100%	100%	100%
Time since last use				
Current	35%	13%	5%	1%
1–4 years	28%	15%	10%	3%
5–9 years	26%	26%	21%	15%
10–14 years	10%	27%	28%	26%
15+ years	1%	19%	36%	55%
Total	100%	100%	100%	100%

oral contraceptives before age 25. Time since last use is also restricted both for young and for old women, as women aged under 35 are unlikely to have completed their use of oral contraceptives more than 15 years ago and women aged over 45 are unlikely to be current users.

The restrictions in the patterns of use by age, illustrated in Table 14, have two main consequences. First, certain patterns of use will be associated with certain age groups, and in some extreme cases, there will be limited scope for comparing the effect of a given pattern of use across age groups. For example, the effect of durations of use of 15 years or longer or of use that stopped more than 15 years ago cannot be assessed in women aged under 35. Second, within age groups, the degree of confounding between the indices of use can be even stronger than in general. The data in Table 15 illustrate this effect, taking as an example the correlation between duration of use and the two indices of use described elsewhere as being related to breast cancer risk, namely time since last use and age at first use.[1]

Table 15 shows the association of total duration of use with age at first use and time since last use in women of two age groups: under 35 and 35 and older. For women aged under 35, duration of use is highly correlated both with age at first use and with recency of use, the relationship being even stronger for the joint distribution of age at first use and recency of use. Among women aged 35 and over there is still some confounding between duration of use and recency of use, but the relationship between duration of use and age at first use is much weaker than at younger ages. Thus, for women aged under 35 there is scope for substantial confounding in analyses of the effects of duration of use unless the effects of recency of use and age at first use are taken into account. For women aged 35 and over the potential for confounding is less severe.

In conclusion, not only is there more scope for confounding between the various indices of the timing of use of oral contraceptives within specific age groups than in the overall data, but analyses within specific age groups can restrict the comparisons that are possible. In order to establish which aspects of hormonal contraceptive use are directly related to breast cancer risk, the approach in these analyses has been initially to examine the relation between risk and various in-

Table 15. Association of duration of use of combined oral contraceptives with age at first use and time since last use, in women aged <35 and 35+

	Proportion in Each Age and Duration of Use Category With:					
	First Use Before Age 20		Last Use <5 Years Ago		First Use Before Age 20 and Last Use <5 Years Ago	
Duration of Use	Age <35	Age 35+	Age <35	Age 35+	Age <35	Age 35+
<1 year	28%	5%	45%	8%	8%	0%
1–4 years	36%	7%	56%	11%	16%	0%
5–9 years	53%	10%	81%	24%	39%	1%
10–14 years	71%	11%	97%	45%	68%	5%
15+ years	95%	15%	100%	65%	100%	12%

dices of use in all age groups combined. Once the main determinants of risk were identified, residual effects for other aspects of use were sought and the consistency of the results were examined in various subgroups of women, including women of different ages.

Statistical Analyses

Data from different studies are combined by the "Mantel-Haenszel" stratification technique.[67] To ensure that women in one study are compared directly only with similar women in the same study, all analyses are stratified by study, as well as by other factors, as described below. The stratum-specific quantities that are calculated are the standard "Observed minus Expected" (O-E) numbers of women with breast cancer, together with their variances and covariances.[68,69] Use of these simple stratified O-E values in preference to more mathematical models may sacrifice some statistical power, but has the advantage of avoiding assumptions about the precise forms of any relationships in the data.

The stratified O-E values, together with their variances and covariances, yield both statistical tests (p-values) and statistical descriptions (odds ratios, subsequently referred to as relative risks). To obtain relative risk estimates from O-E values the "one-step" method is used and, in analyses involving comparisons of more than two groups, the confidence intervals associated with these relative risks are estimated by treating the relative risks as "floating absolute risks."[70] The use of floating absolute risks does not alter the relative risks but does reduce the variances attributed to those relative risks that are not defined as one, and should greatly reduce unwanted covariances between them. A more detailed description of these methods is given below.

The "One-Step Method"

As the name suggests, the one-step method involves taking only the first step of the iterative procedure that is normally used in conditional logistic regression. In the case of risk factors with only moderate effects, that is, with associated relative risks of less than about 2, this approximation yields results almost identical to those from the iterative method. The advantage of the one-step estimate of the relative risk is that it is related in a reasonably direct way to the observed and expected numbers of cases. The following describes the method, and its application to various types of analysis.

Two exposure groups. Consider the simplest case of unstratified data with just two exposure groups, A and B. Let O denote the number of cases in group A, and let E denote the "expected" number of cases in group A, i.e., the size of group A times the average risk in both groups together. The one-step estimate of the log of the relative risk for A versus B is log RR = (O-E)/var(O-E), and the variance of this estimate is V, where V is 1/var(O-E). Significance tests are based on the ratio of the log relative risk to its standard error, i.e., z = (log RR)/se(log RR), and tables of the standard normal distribution are used to determine the corresponding significance level. Appendix 12 shows an example of these calculations using hypothetical data on ever and never use of oral contraceptives from within a single study.

Stratified data. In these analyses the data are divided into several strata with separate values of (O-E) and of its variance, var(O-E), calculated for each stratum. In this case an overall stratified estimate of the relative risk can be obtained by simply applying the procedure described above to the sum of the individual (O-E) values and the sum of their variances. Note that within each stratum, the var(O-E) is the reciprocal of the variance of the log relative risk and hence represents the amount of "information" in that stratum about that log relative risk. The overall estimate of the log relative risk is, therefore, a weighted average of the individual log relative risks with individual weights proportional to var(O-E), the information content of the stratum. This "additive" property of the (O-E) quantities and of their variances makes it easy to see exactly how a particular stratum or study contributes to the overall result and provides the reader with the opportunity of examining the sensitivity of the overall results by subtracting whatever results they wish from the total. Appendix 13 illustrates how to use the method for combining data from different strata and shows how to examine the sensitivity of the overall result to the contribution from a particular study or stratum.

More than two exposure groups. In most analyses, the exposure of interest has more than two categories. For example, time since last use of oral contraceptives is grouped into five categories: current use, 1–4 years, 5–9 years, 10–14 years and 15+ years. In this situation the method must be applied in vector form. Suppose that, apart from the baseline group, there are K other groups. Let **(O-E)** denote the vector of their K observed minus expected values and let **V** denote the inverse of the corresponding K × K variance-covariance matrix. The one-step estimator of the K log relative risks is then obtained by multiplying **(O-E)** by **V** and the variance of the vector of log relative risk estimates is simply **V**. When the number of exposure groups is greater than two a further re-

finement can be made to the variance-covariance matrix, **V**, and this is described below.

Refinement of Variance Estimates Using Floating Absolute Risks

To explain the use of floating absolute risks in the analysis of case-control data, it is helpful to consider first the analysis of prospective data. Consider a cohort with one baseline group and K exposure groups. In this case it is straightforward to estimate the log of the probability of disease, α_i $(i = 0, 1, \ldots, K)$ for each of the K + 1 exposure groups and, because each α_i is estimated from a separate group of individuals, these estimates will be completely independent with estimated variances V_i $(i = 0, \ldots, K)$.

With case-control data, however, it is not possible to estimate the absolute probability of disease because of the way in which the data have been sampled. Instead, the usual convention is to present estimates of the risk in each exposure group relative to some arbitrary "reference" group which, by definition, has a relative risk of one. This results in estimates of the log *relative* risks $\beta_1, \beta_2, \ldots, \beta_K$, relative to the baseline group. Thus if the group with subscript zero is chosen as the reference group then $\beta_i = \alpha_i - \alpha_0$, $i = 1, 2, \ldots, K$, and their estimates will be mutually correlated because they all involve α_0. The conventional estimate of the variance of β_i is approximately equal to $V_0 + V_i$ $(i = 1,2, \ldots, K)$ which means that if the chosen baseline group is very small, each of the log relative risk parameters will have a large component of variability due to V_0.

The main reason for adopting this relative risk approach is because the baseline probability of disease, α_0, cannot be estimated from case-control data. However, even though the log absolute risks themselves cannot be estimated, it is possible to estimate what variances, V_i, should be, including that for the baseline group. The floating absolute risks approach still sets the log of the baseline probability of disease, α_0, to zero, as in the conventional approach, but regards the log relative risk estimates $\{\beta_i\}$ as approximately independent "floating log absolute risks" $\{\alpha_i\}$, with variances $\{V_i\}$. In other words, the log relative risk estimates can be thought of as log absolute risks measured not from zero but from the unknown value of α_0. This modification does not alter the value of the relative risk estimates, but it does reduce the variances attributed to them and allows them to be treated as approximately independent estimates of relative risk in tests of heterogeneity and trend. Of course, if the baseline group is large enough then V_0 will be negligible and this modification will have very little effect on the final standard errors. An example of how to apply this method to the variances of relative risks associated with various categories of time since last use of oral contraceptives is given in Appendix 14.

Stratification Procedure

Among the 54 studies that contributed to the collaboration, there is considerable variability in the prevalence and pattern of oral contraceptive use (Appendices 4–7, 9–11). While much of this variability is due to differences in the distribution of age, nationality and calendar period of diagnosis of the women in the studies, some of it may well reflect less tangible differences among the study populations both in the women themselves and in the way in which the studies were conducted. For this reason, women from one study were only ever compared with similar women from the same study and this was achieved by stratifying all analyses by study, and for multicentre studies by centre within study.

There are of course many other variables that could conceivably confound the relationship between breast cancer risk and hormonal contraceptive use and that therefore need to be considered as possible stratification factors. The most important of these is age at diagnosis. Breast cancer risk increases rapidly with age, the steepest increase occurring during a woman's reproductive years, the period during which she is most likely to use oral contraceptives. Data were therefore stratified by single year of age up to age 65 and by 5-year groupings thereafter: 16, 17, ... 63, 64, 65–69, 70–74, 75–79, 80–84 and 85–89, cases and controls below the age of 16 or above the age of 89 being excluded.

Of the other known risk factors for breast cancer, variables relating to reproductive history are the ones most strongly associated with pattern of oral contraceptive use. Table 16 shows the overall distribution of parity and Table 17 shows the distribution of the age women were when their first child was born. The distribution of these factors also varies according to country of residence and year of birth (Appendices 15–17). The effect of a woman's age when her first

Table 16. Distribution of parity in cases and controls

Parity	Cases	Controls
0	16%	14%
1	15%	13%
2	31%	27%
3	20%	20%
4+	18%	26%
Total	100%	100%

Table 17. Distribution of women's age when their first child was born in cases and controls (parous women only)

Age at First Birth	Cases	Controls
<20	12%	16%
20–	42%	46%
25–	32%	28%
30–	11%	8%
35+	3%	2%
Total	100%	100%

child was born and of her subsequent parity on breast cancer risk is shown in Appendix 18 for never users of oral contraceptives. The results illustrate the strong protective effect afforded to women who have their first child at an early age and, within a given age at first birth, the additional protection associated with increasing parity. The corresponding association between reproductive history and ever use of oral contraceptives is also shown among controls. Overall, parous women are more likely to have used oral contraceptives than nulliparous women and the probability of ever use increases with increasing parity (Appendix 18).

The relative risk of breast cancer is also reduced once a woman is no longer at risk of conception (i.e., is menopausal, has had a hysterectomy, bilateral oophorectomy, or tubal ligation), and the relative reduction in risk tends to be greater the younger women are when this occurs (Appendix 18). The likelihood of ever having used oral contraceptives is also related to the age at which a woman's risk of conception ceases: the older she is when this occurs, the more likely she is to have used oral contraceptives (Appendix 18).

The results in Appendix 18 demonstrate the associations between reproductive variables both with breast cancer risk and with various aspects of oral contraceptive use. Some relationships are particularly strong. For example, recency of use is more strongly related to whether or not a woman is still at risk of conception than is ever use (Appendix 18). Thus, confounding caused by reproductive variables may be more extreme when examining risk associated with specific indices of use than with ever use. Because age at first birth, parity and the age at which a woman ceases to be at risk of conception are closely related to breast cancer risk and to various aspects of oral contraceptive use, all main analyses were routinely stratified by these variables, according to the divisions shown in Appendix 18.

Excessive stratification by factors that are not actually confounders for the association of interest can lead to an appreciable decrease in the precision of the estimated effects, i.e., to a substantial loss of information. Having established that time since last use is the variable that most strongly relates oral contraceptive use to breast cancer risk, the effect of other potential confounders on this main finding is examined in detail in Appendix 19. This has been done using an exact conditional logistic regression model in which study, age at diagnosis, parity, age at first birth and age at which risk of conception ceased were used to define the strata, and additional adjustment for each variable of interest was made by incorporating an appropriate term in the model. This approach was used because the data were already so finely stratified that further stratification would have led to the loss of a considerable amount of information. The results, which when adjusted for only the routine stratification variables are virtually identical to those obtained using the one-step method, show that none of the variables examined appeared to confound the relationship between breast cancer risk and time since last use, so no additional adjustments were deemed necessary.

Presentation of Results

Results are for the relative risk of breast cancer are given as adjusted relative risks, the precise stratification used being specified in each case. Due to the large number of estimates involved, 99% confidence limits are used. In general, the results are presented as plots, with each relative risk plotted as a black square whose area is inversely proportional to the variance of the logarithm of the estimate, and hence is an indication of the amount of statistical information available for that particular estimate, i.e., the information content. There are two main types of plot.

One type of plot describes a two-way comparison, such as ever use versus never use, and gives O-E, var(O-E) and the corresponding relative risk separately for each of the studies with substantial amounts of statistical information. The studies with smaller amounts of statistical information are included in the appropriate "other" category according to their design. In this case the overall estimate is calculated by using the sum of the study-specific values for O-E and var(O-E).

Another type of plot describes the results of categorical analyses involving more than two groups and represents the aggregated results from all relevant studies. This type of plot shows the relative risks for each exposure category relative to the baseline category together with the appropriate 99% confidence interval using variance estimates based on the floating absolute risk approach.[70] Each point is accompanied by two statistics: log RR/var(log RR), and 1/var-

(log RR). The latter is the information content with respect to the particular relative risk estimate and the former is simply the log relative risk estimate weighted by the inverse of its variance. Where the confidence interval associated with the relative risk estimate extends beyond the scale of the plot, this is indicated by an arrow and where the confidence interval is too wide there is sometimes insufficient space to print the relative risk estimate and its standard error: in these cases, however, both the relative risk and the standard error can be calculated directly from the information given, i.e., for two-way plots from the relevant O-E and var(O-E), as described in Appendix 12, or if the analysis involves more than two exposure groups, from the relevant log RR/var (log RR) and 1/var (log RR). Heterogeneity between relative risk estimates and, where appropriate, linear trends in relative risks are assessed by the usual "chi-squared" statistics. Appendix 20 shows an example of this type of presentation based on the results in Appendix 14, together with an illustration of some ways in which the statistics presented can be used.

Where results are presented in tabular form, only summary information is given and the relative risk estimates and their standard error are based on conventional methods rather than the floating absolute risks approach. Where 1/var (log RR), i.e., the "information content," for a particular estimate is less than 20.0, the result is considered to be based on "insufficient data" for the point estimate to be presented.

Breast Cancer Risk and Use of Combined Oral Contraceptives

This section describes the results relating to various aspects of oral contraceptive use and examines the consistency of the main findings within women of different characteristics. Patterns of risk are also presented separately for cancers localised to the breast and for more extensive disease. The analyses include 52,925 women with breast cancer and 99,018 controls (22 cases and 125 controls having been excluded because they were aged under 16 or 90 or older and a further 350 cases and 1096 controls having been excluded because their use of oral contraceptives was classified as unknown).

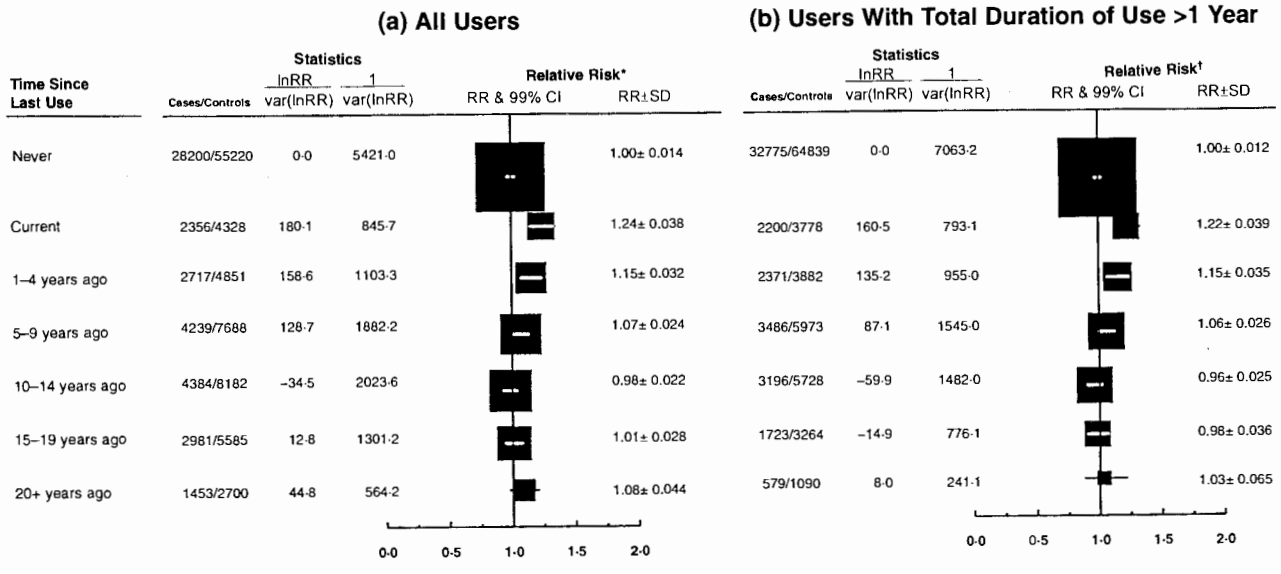
An important consideration in these analyses is what the definition of an "ever user" is and how that definition might affect the conclusions. Many women have used oral contraceptives for only a few months or even less, and there are differences between studies in whether such women are actually defined as "ever users." This is reflected in the substantial variation between studies in the proportion of women reported to have used oral contraceptives for less than a year (Appendix 7) and the fact that among such women, 50% had reported durations of use of 3 months or less (Appendix 8). Reporting of use for short durations is common, especially among women whose last use of oral contraceptives was long ago: the proportion of users whose total duration of use was reported to be 12 months or less was 17% for women who stopped use less than 10 years ago, 35% for women who stopped use 10–19 years ago, and 62% for women who stopped use more than 20 years ago. Given the large proportion of women who stopped use long ago whose reported duration of oral contraceptive use is less than a year and the fact that such use is likely to have been very brief, even a slight tendency for cases to recall such use more often than controls could potentially bias the results.

Although there is no way of knowing whether the different definitions of ever use between studies or the differential recall of short durations of use by cases and controls have biased the results, their possible effects on the main findings have been examined here by performing sensitivity analyses in which ever users are defined firstly as women with any reported use of oral contraceptives and secondly as women with durations of use of more than 12 months (in which case women with durations of use of 12 months or less are reclassified as never users). Results that are comparatively unaffected by the reclassification of short duration users are considered more trustworthy than results that vary according to the approach used. Such sensitivity analyses are designed to explore the possible biases within the data, not to investigate the effects on breast cancer risk of oral contraceptive use that lasted more than a year.

Recency of Use

Recency of use is the aspect of oral contraceptive use most strongly related to breast cancer risk.[1] That relationship is illustrated in Appendix 21 which shows, for single years of time since last use up to 20 years, the number of cases and controls and the associated relative risk of breast cancer. It can be seen that the relative risk is significantly elevated in current users and remains above 1.0 until about 10 years after cessation of use.

Figure 1 contrasts the results according to time since last use of oral contraceptives, using two different definitions of ever-use: in Figure 1a women with durations of use of 12 months or less are included among the ever users and in Figure 1b they are included among the never users. The overall pattern of risk with time since last use is virtually unchanged by the reclassification, as is the information content of



*Relative to never users, stratified by study, age at diagnosis, parity, age at first birth and age at which risk of conception ceased.
† Relative to never users and users with a total duration of use ≤12 months, stratified by study, age at diagnosis, parity, age at first birth and age at which risk of conception ceased.

Figure 1. Relative risk of breast cancer by time since last use of combined oral contraceptives.

the data, i.e., 1/var (log RR) (see *Statistical Analysis* section) for women who stopped use up to about 10 years before. For use that stopped 10 or more years before, however, the numbers of cases and controls and the information content of the data is substantially reduced when women with short durations of use are classified as never users. It can be seen that the results for use that ceased 20 or more years ago are particularly sensitive to how short duration users are classified, and the paucity of information in that category for women with reported use of more than a year is evident. The relative risk estimate at all but one level of time since last use is very slightly lower when women with short durations of use are classified as never users than when they are classified as ever users. Therefore, the different definitions of ever use between studies and the possible differential reporting of short durations of use by cases and controls does not appear to have affected the main conclusions, i.e., of an increased risk in recent users but no elevation of risk in past users, but they may have inflated the relative risk estimates very slightly at each level of time since last use. In addition, results that pertain to use that stopped many years ago are especially sensitive to the way in which ever-use is defined.

Appendices 22 and 23 show for individual studies the relative risks associated with recent use of oral contraceptives and use that ceased 5 or more years ago, respectively. Reclassification of short duration users as never users made little difference to the heterogeneity between studies or study designs, but slightly reduced the relative risk estimate associated with use that ceased 5 or more years ago (Appendix 23). Appendix 24 shows age-specific results for time since last use, using the two definitions of ever-use. Again, the results are little affected by how ever-use is defined.

Duration of Use

Appendix 25 shows the distribution of single years of total duration of use of combined oral contraceptives, up to 15 years, and the associated relative risks. Most relative risks tend to be slightly above 1.0. There is a weak trend of increasing risk with increasing duration of use, but once time since last use is taken into account there is no evidence of a residual effect of total duration of use.[1] Because breast cancer risk is related to recency of oral contraceptive use, it is possible that only durations of continuous, or fairly continuous, recent use are relevant. Breast cancer risk was therefore examined in relation to duration of use among women whose entire use of oral contraceptives was continuous or interrupted by only 24 months or less, excluding pregnancies (Appendix 26). Within each level of time since last use there was no significant heterogeneity or trend in the risks associated with different durations of continuous use. Furthermore, among current or recent users, it is difficult to distinguish the effect of long durations of continuous use from that of beginning use at a very early age.

Age at First Use

The overall distribution of age at starting use of combined oral contraceptives and the associated relative

risks of breast cancer are shown in Appendix 27 for single years of age at starting. Women began use at a wide range of ages and there is a considerable amount of information available for use starting at age 16 or younger up to age 40 or older. The most commonly reported age at starting is 20, and this in part reflects the tendency for women to round up or down to that age. The relative risk of having breast cancer diagnosed tends to be slightly greater than 1.0 for all ages at starting, and to be somewhat larger for women who started use as teenagers.

Appendix 28 shows detailed results for use beginning at single years of age from 17 up to 21, according to time since last use of oral contraceptives. In current users and women who stopped use 1–4 years ago, the relative risks of having breast cancer diagnosed increase significantly the younger women were at first use, and these trends are not materially affected by the way short duration users are classified. By contrast, for women who stopped use 5 or more years ago, the trend with age at first use is not statistically significant and any apparent increased risk associated with use beginning at young ages is diminished when short duration users are classified as never users. It can be seen in Appendices 27 and 28 that overall, and within most levels of time since last use, there is an apparent step down in the relative risk of breast cancer between first use at age 19 and age 20 which is more marked than the differences in risk between first use at other adjacent young ages. The step down in the relative risk between ages 19 and 20 is less likely to be due to biological differences which exist only between ages 19 and 20 than to slight differential reporting of age at first use between cases and controls. To investigate whether such biases might effect the results, analyses were performed grouping age at first use as <21, 21–25, 26–30, and 31+ and the results are contrasted with those in which age at first use was grouped as <20, 20–24, 25–29 and 30+ (Appendix 29). These analyses were also repeated classifying ever users as women with a reported duration of use of more than 12 months. It can be seen in Appendix 29 that no matter what grouping of age at first use or whatever definition of ever use is applied, among current users and those whose last use was 1–4 years ago, the relative risk of breast cancer associated with use at early ages, i.e., at ages <20 or <21, is elevated although the relative excess is not as marked for the group aged <21 as for the group aged <20. By contrast, for women whose last use was 5 or more years ago, the results are sensitive to the way both early use and ever use is defined. For example, for women whose last use was 15+ years ago the relative risk estimate for use beginning at young ages ranged from 1.14 (SD 0.08) to 0.89 (SD 0.07), depending on the definitions used. The apparently high relative risk of breast cancer for women in this subgroup with short durations of use beginning at an early age may well be due to differential reporting by cases and controls of brief use at early ages that ceased long ago, especially since there is no excess risk associated with use of longer durations (Appendix 30).

Appendix 31 shows that among women who began use at early ages the relative risk of breast cancer associated with use in the last 5 years tends to be higher the younger the women are when their cancer is diagnosed, regardless of the definition of early use or of ever use. Where use stopped 10 or more years ago, however, the results are sensitive to the way in which early use and ever use is defined and overall there is no consistent evidence of an elevated risk of diagnosis of breast cancer at any age for women who began use at young ages, although there is only a limited amount of information available for women aged 45 and older.

Within each time since last use category there is no statistically significant trend in the risk of having breast cancer diagnosed according to duration of use in women who started use either before age 20 or at older ages, irrespective of the way in which ever use is defined (Appendix 32). Nor is there any statistically significant trend with duration of use within specific age groups, either for women who began use before age 20 or at older ages (Appendix 33). The restrictions of the available age-specific information according to age at first use and duration of use can be seen in Appendix 33.

Age at first use of oral contraceptives is closely related to the time between menarche and first use. Appendix 34 shows the relationship between the risk of having breast cancer diagnosed and time between menarche and first use of combined oral contraceptives. Among current and recent users, women who started use within 5 years of their menarche have the highest relative risk of breast cancer, but the magnitude of the excess is not as large as that attributed to teenage use shown in Appendices 28 and 29 and there is no significant heterogeneity in the results. For women who had stopped use five or more years before, there is no evidence of an excess risk of having breast cancer diagnosed among women who had started use soon after their menarche.

In summary, among current and recent users the relative risk of having breast cancer diagnosed is greater among women who began use at young ages, i.e., as teenagers, than among women who began use at later ages. Although the magnitude of this excess is sensitive to the way use at young ages is defined, with the results being most extreme when it is defined as "use beginning before the age of 20," the association

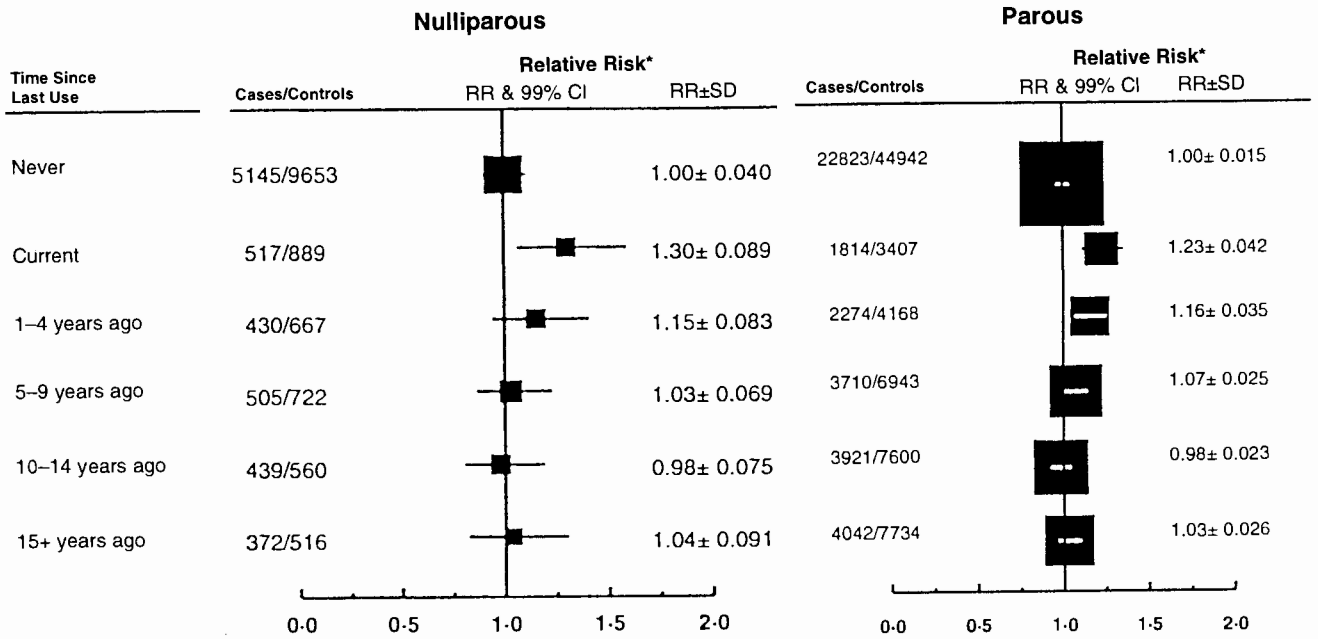
persists regardless of how early use or ever use is defined. By contrast, among women whose use ceased many years ago the relative risk of breast cancer associated with use beginning at young ages is sensitive to the way both early use and ever use are defined, and there appears to be some differential reporting between cases and controls of short durations of use beginning at young ages. Overall, however, 10 or more years after cessation of use there is no consistent evidence of an increased risk of breast cancer in women who began use at young ages. Most information about women who began use at young ages is derived from women aged under 45 when their cancer was diagnosed. For women aged over 45 the limited available information does not suggest an increased risk of breast cancer associated with use beginning at young ages, but as more data for women aged over 45 accumulate in the future, it will be necessary to re-examine the worldwide evidence. When this is done it will be important to bear in mind that there might be differential reporting of brief use at young ages, especially where use is reported to have ceased many years ago.

Use in Relation to Childbearing

It is known that breast cancer risk is affected by a woman's reproductive history (Appendix 18). While stratification for various aspects of reproductive history should eliminate confounding due to those variables, it is of interest to examine whether the results relating to oral contraceptive use are consistent among women with different patterns of childbearing.

Nulliparous women have a higher risk of breast cancer than parous women (Appendix 18). They also constitute a special group in that there is no opportunity for the effects of their oral contraceptive use to be modified or confounded by their pattern of childbearing. It is worth noting, therefore, that when nulliparous women are examined separately, their pattern of risk in relation to time since last use of oral contraceptives is similar to that observed for parous women (Figure 2).

Parous women have lower risks of breast cancer than nulliparous women and their risk declines with decreasing age at first birth and with increasing parity (Appendix 18). The decline in breast cancer risk with time since last use of oral contraceptives is evident for all parous women (Figure 2) and for women who had their first child at different ages and for women who had different numbers of children (Appendix 35). Although there is some evidence of heterogeneity in the relative risks by parity among women who stopped use 5–9 years ago, this could well be due to chance since similar patterns were not seen for the relative risks associated with other periods since last use.



*Relative to never users, stratified by study, age at diagnosis, parity, age at first birth and age at which risk of conception ceased.

Figure 2. Relative risk of breast cancer by time since last use of combined oral contraceptives in nulliparous and parous women.

The pattern of risk by time since last use of oral contraceptives is similar for women who began use before the birth of their first child and for women who began use after the birth of their first child, both patterns being similar to that seen for nulliparous women.[1] In addition, breast cancer risk is not related to the duration or timing of use of oral contraceptives while a woman is nulliparous. Appendix 36 shows the relative risk of breast cancer according to time since last use and duration of use of oral contraceptives while nulliparous, the data for nulliparous and parous women having been combined because there were no differences between the patterns of risk between the groups. Even where 5 years of nulliparous use had been completed 15 or more years before the diagnosis of breast cancer, there is no evidence of an increase in breast cancer risk (Appendix 37). Nor were the findings according to age at first use explained by use while nulliparous: Appendix 38 shows detailed analyses of breast cancer risk according to time since last use of oral contraceptives, age at first use, parity at first use and total duration of use.

There was, however, some suggestion that the timing of childbearing might modify the risks associated with recent oral contraceptive use, with the relative risk of breast cancer being greater for women whose last birth was within the last 15 years than for women whose last birth was more than 15 years ago (Figure 3). Similar patterns were also seen with time since first birth, but the trends in relation to the first birth were not as strong as in relation to the last birth (Appendix 39). The effects of the timing of childbearing on the relative risks associated with recent use appeared to be independent of a woman's age when her cancer was diagnosed (Appendix 40).

Appendix 41 shows an analysis of the relative risk of breast cancer by age at first use and time since last use of oral contraceptives in nulliparous women and in parous women who had a birth <15 years and 15+ years before. In recent users who began use before age 20 there is considerable heterogeneity in the risk according to the timing of childbearing (X^2 on 2 d.f. = 9.6; p = 0.008), but for women who began use after age 20 or older, the heterogeneity is less marked (X^2 on 2 d.f. = 5.0; NS). It can be seen, however, that very few recent users who began oral contraceptive use before age 20 had their last birth more than 15 years ago.

In summary, these results suggest that childbearing patterns and the timing of use of oral contraceptives in relation to childbearing do not have a major effect on the relative risks associated with recent or past oral contraceptive use. Timing of the last birth is the only factor that appeared to modify the magnitude of the relative increase in breast cancer risk among recent users, with the relative risk of breast cancer associated with recent use of oral contraceptives being higher for nulliparous women and women whose last birth was less than 15 years ago, especially where use began before age 20. However, even with the large amount of information available here, it is impossible to disentangle the exact nature of the effects of age at first use, age at diagnosis and timing of childbearing on the relative risk of breast cancer in recent users. Nor is it possible to rule out the possibility that these findings are due to chance.

Age at Last Use

The distribution of age at last use of combined oral contraceptives in cases and in controls and the corre-

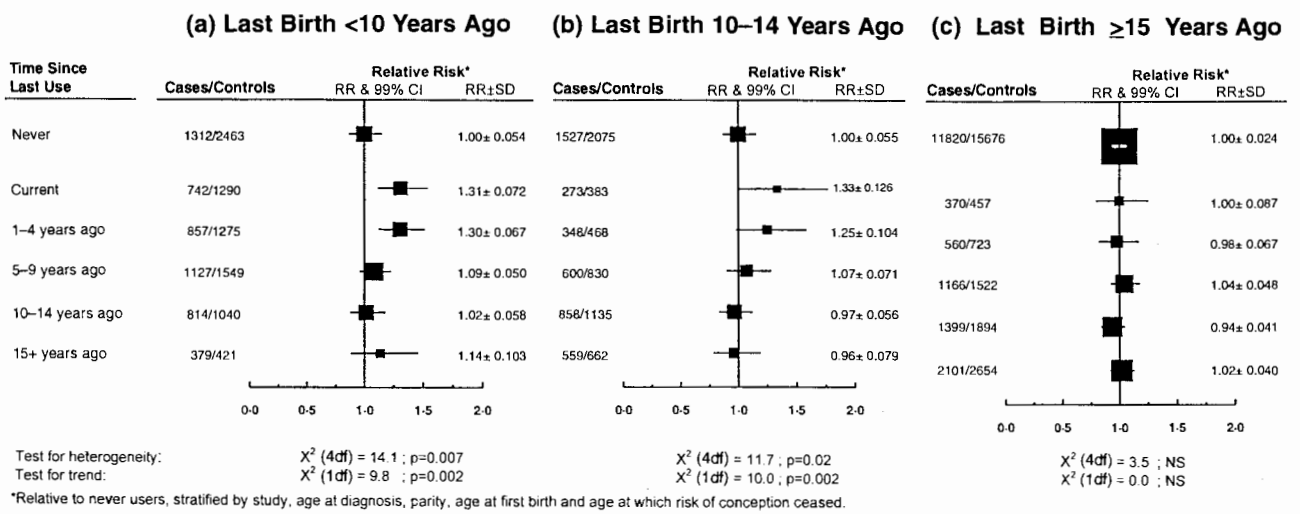


Figure 3. Relative risk of breast cancer by time since last use of combined oral contraceptives in parous women, according to time since last birth.

sponding relative risks are shown in Appendix 42. Overall, the older women were when they stopped using oral contraceptives, the greater the relative risk. Once time since last use is taken into account, however, there is no significant variation in risk by age at last use (Appendix 43). It can be seen in Appendix 43 that two thirds of the information about current use is for women aged 35 or older at last use and one third is for women aged 40 or older at last use. In recent users who started use before age 20, the relative risks tended to be greater the younger the women were when use stopped (Appendix 44). In recent users, age at last use is closely correlated with age at diagnosis and the findings in Appendix 44 are indicative of the effects already described, namely, that among recent users who began use at early ages, the relative risk tends to be higher while women are young (Appendix 24) and to decline with time since last birth (results are summarized in Table 18). For women who stopped use 5 or more years ago, there is no clear pattern of risk with age at stopping use.

Time Since First Use

The distribution of time since first use in cases and controls and the associated relative risks are shown in Appendix 45. Most relative risks were greater than 1.0, and they tend to be highest of all around 10 years after starting use. Thereafter the relative risks fall, returning to around 1.0 at about 20 years after first use. When the data are subdivided by time since last use and, in recent users, by age at first use there is little residual effect of time since first use, except perhaps in recent users who began use before age 20 (Appendix 46). The decline in risk with time since first use in recent users who began use before age 20 is a reflection of the declining risk with age at diagnosis, with age at last use and with time since last birth (Table 18).

Year of First and Last Use

Most women included in these analyses had begun taking oral contraceptives before 1970 and had ceased use before 1980. There was some heterogeneity of risk by year of first use (Appendix 47) and a strong trend of increasing risk with increasing year of last use (Appendix 48). The trend with year of last use is largely explained by the fact that women who stopped use in recent years are likely to be recent users (Appendix 49). Once account is taken of time since last use,

Table 18. Relative risk of breast cancer in recent users of combined oral contraceptives by age at first use and other factors

	RR* ± SD Associated with Recent Use† of Oral Contraceptives in Women Who Began Use Before Age 20	RR* ± SD Associated with Recent Use† of Oral Contraceptives in Women Who Began Use at Age 20 or Older
Age at diagnosis		
<30	1.95 ± 0.217	1.14 ± 0.160
30–34	1.54 ± 0.132	1.13 ± 0.092
35–39	1.27 ± 0.128	1.16 ± 0.074
40+	insufficient data	1.16 ± 0.042
Test for trend	χ^2 (1 d.f.) = 5.1; p = 0.02	χ^2 (1 d.f.) = 0.0: NS
Age at last use		
<25	2.00 ± 0.284	1.19 ± 0.229
25–34	1.58 ± 0.088	1.16 ± 0.056
35+	1.42 ± 0.134	1.14 ± 0.047
Test for trend	χ^2 (1 d.f.) = 5.5; p = 0.02	χ^2 (1 d.f.) = 0.1; NS
Time since first use		
<10 years	1.85 ± 0.198	1.16 ± 0.044
10–14 years	1.66 ± 0.116	1.22 ± 0.052
15+ years	1.40 ± 0.097	1.08 ± 0.056
Test for trend	χ^2 (1 d.f.) = 3.7: p = 0.06	χ^2 (1 d.f.) = 0.6; NS
Childbearing history		
nulliparous	1.76 ± 0.150	1.08 ± 0.080
last birth <15 years ago	1.46 ± 0.098	1.21 ± 0.061
last birth 15+ years ago	0.71 ± 0.233	1.00 ± 0.063
Test for heterogeneity between all women	χ^2 (2 d.f.) = 9.6; p = 0.008	χ^2 (2 d.f.) = 5.0; NS
Test for heterogeneity between parous women	χ^2 (1 d.f.) = 6.4: p = 0.01	χ^2 (1 d.f.) = 4.9; p = 0.03

*Relative to never users of combined oral contraceptives, stratified by study, age at diagnosis, parity, age at first birth, and age at which risk of conception ceased.

†Recent use denotes current use or use which ceased <5 years ago.

there are no statistically significant residual trends with year of last use.

Women with Different Characteristics

Various factors, such as a family history of breast cancer, are known to affect breast cancer risk, and although not confounded with oral contraceptive use, they need to be considered as potential modifiers of the effects of oral contraceptive use. Appendix 50 shows the relative risk of breast cancer associated with recent and past oral contraceptive use for various subgroups of women. There is little evidence of variation in the relative risks associated with any pattern of oral contraceptive use according to the woman's characteristics, with none of the 43 tests for trend or heterogeneity shown in Appendix 50 being statistically significant. A global test for heterogeneity for all the results in Appendix 50 yields a non-significant chi-square statistic of 59.4 on 63 degrees of freedom, which is in line with what would be expected if there were no heterogeneity in the effects of oral contraceptives on the relative risk of breast cancer by any of these characteristics.

Tumour Spread

The pattern of an excess risk of breast cancer in current users, with the relative risk declining with time since stopping use, is seen both for cancers that are localised to the breast and for cancers that have spread beyond it (Figures 4 and 5). At each level of time since last use the relative risk is, however, larger for women with localised disease than for women with more extensive disease. When women with localised disease and women with extended disease are compared directly, a relative deficit of disease which had spread beyond the breast among ever users is found at each level of time since use and the magnitude of the deficit does not vary significantly with time since last use of oral contraceptives (χ^2 for heterogeneity on 4 d.f. = 6.2; NS). Overall, the relative risk of disease that had spread beyond the breast compared to localised disease in ever versus never users is 0.88 (2p = 0.002).

Similar results with respect to tumour spread were found when the analyses were repeated with users of durations of 12 months or less classified as never users (Appendix 51). The excess risk of breast cancer in recent users who began use before age 20 is evident both for localised and more extensive disease, regardless of how short duration users are classified (Appendix 52) and within each category of time since last use there is no significant trend with duration of use either for localised disease or for disease which had spread beyond the breast (Appendix 53).

The question of whether the relative excess of localised disease and the relative deficit of more extensive disease is a consequence of earlier diagnosis of breast cancer in women who have used oral contraceptives cannot be answered directly from these data. Increased surveillance for breast cancer while women are currently using oral contraceptives is unlikely to be the sole explanation for the findings because the relative excess of localised cancers is no greater in current users than in past users (Figure 4c). Furthermore, indirect evidence based on the reporting of past mammographic examinations among controls does not suggest that mammographic screening is more frequent among current or recent users than never users (Appendix 54). Information on whether women

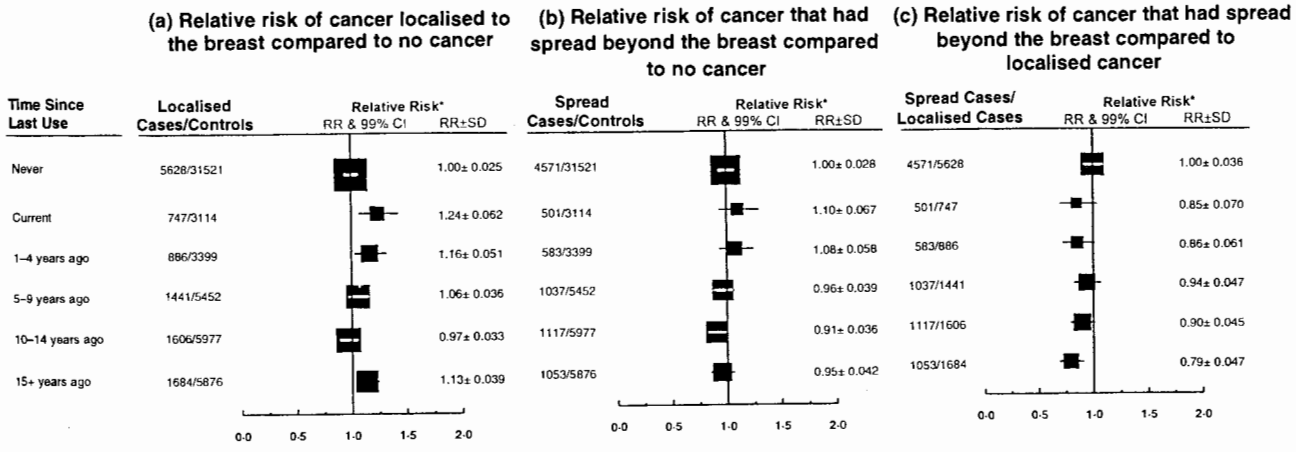
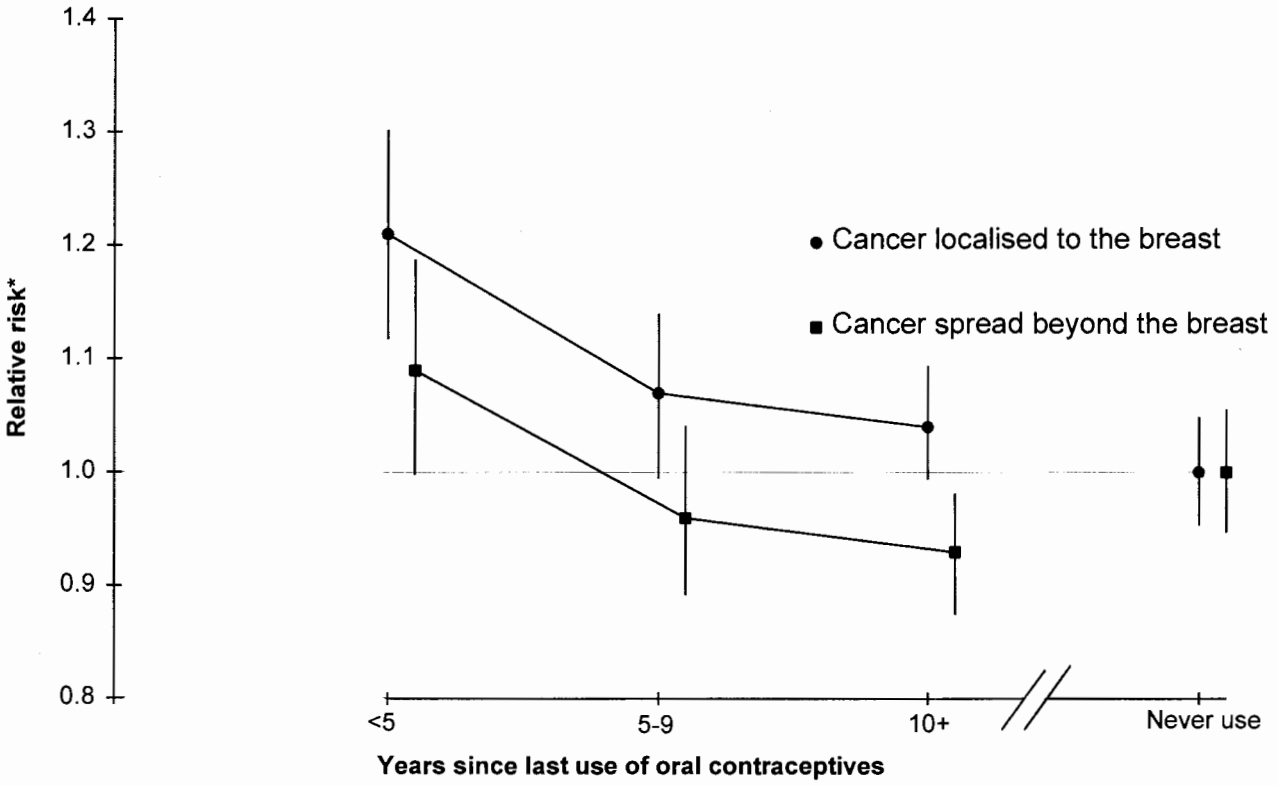


Figure 4. Relative risk of localised cancer and cancer that had spread beyond the breast by time since last use of combined oral contraceptives.



*Relative risk (given with 95%CI) relative to never use, stratified by study, age at diagnosis, parity, age at first birth, and age at which risk of conception ceased.

Figure 5. Relative risk of breast cancer by time since last use of oral contraceptives, according to the extent of tumour spread.

had a mammogram in the past was available for 19 studies,[2,3,8,20,31,32,37,40,42,43,45,47–50,52,53] of which 2 are unpublished, and Appendix 54 shows the relationship among controls between this variable and time since last use of oral contraceptives. There is significant heterogeneity in the proportion of women who reported having had a mammogram by recency of use, with higher proportions of past users of oral contraceptives having had a mammogram. The results in Appendix 54 offer only indirect evidence about the possible effects of different surveillance patterns, and merit further investigation. They do not, however, provide an explanation for the elevated risk of breast cancer among recent users.

Another consideration is that women with higher levels of education may have their breast cancers diagnosed earlier, and that the results are in some way confounded by educational level. Appendix 55 shows results for the relative risk of both localised and more extensive disease by time since last use of oral contraceptives and by years of schooling. Among never users it can be seen that high educational level is associated with an increased risk of diagnosis of localised disease which is consistent with the idea that women of higher educational level have their cancers diagnosed earlier. However, the fact that the patterns of risk of localised and more extensive disease with time since last use were apparent in women with both high and low education level seem to indicate that those effects are not a result of confounding between oral contraceptive use and education level.

In conclusion, the relative deficit of disease that had spread beyond the breast in women who had taken oral contraceptives is statistically strong, is consistently found in various subgroups, and is not substantially affected by the way in which short duration users are classified. This finding differs from the others described thus far in that it relates to the effect of oral contraceptives many years after stopping use and suggests that in the long-term there might be a relative deficit of advanced breast cancer in women who have used oral contraceptives.

Hormonal Constituents

Information on the specific type and dose of oestrogen and progestogen in the combined oral contraceptive preparations that individual women had first used,

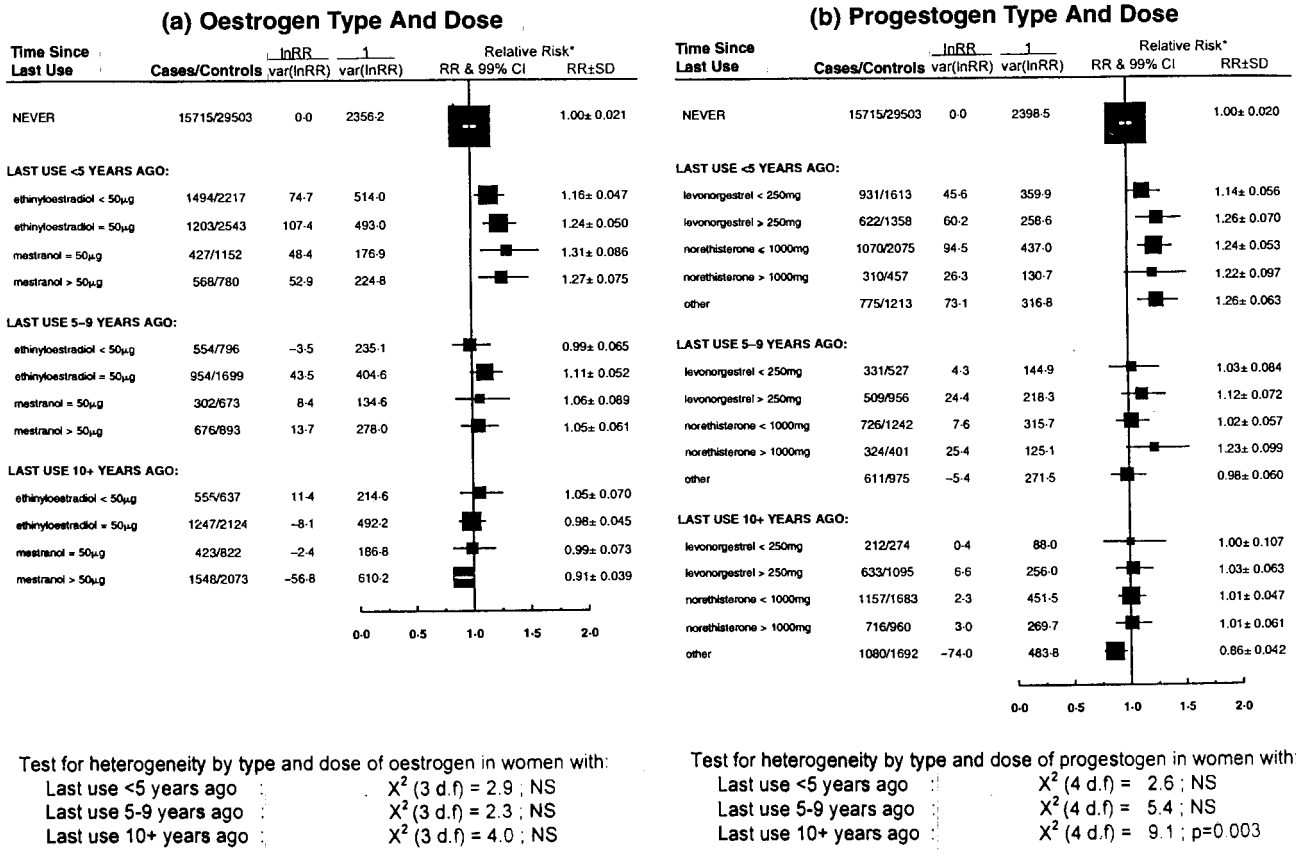


Figure 6. Relative risk of breast cancer by time since last use and oestrogena nd progestogen type and dose of combined oral contraceptives last used.

had last used and had used for the longest period of time was available for 27 studies (see *Materials* section). Most ever users had used the standard type of combined oral contraceptives in which each pill contains a fixed dose of an oestrogen and a progestogen, and relatively few women had used sequential or phasic preparations, where the dose of progestogen and/or oestrogen varies during the cycle. There is no evidence of heterogeneity in the risk of breast cancer according to whether the preparations were sequential, phasic or standard (Appendix 56) and so sequential and phasic preparations have been grouped with the standard type in all other analyses.

Overall women had used 18 unique combinations of specific types of oestrogen and progestogen (Appendix 57). The proportion of women who had first used and last used each combination was broadly similar although over time there was a tendency for women to change from use of the oestrogen, mestranol, to ethinyloestradiol, and to change to using the progestogen, levonorgestrel (norgestrel). By far, the most commonly used combinations were: ethinyloestradiol with levonorgestrel (norgestrel); ethinyloestradiol with norethisterone or norethisterone acetate; and mestranol with norethisterone. Appendix 58 shows, for the most frequently used combinations, the number of cases and controls that had first used, last used and mostly used each combination and the associated relative risks, by time since last use of oral contraceptives. Within each time since last use category, there is no significant heterogeneity in breast cancer risk associated with use of the various specific combinations.

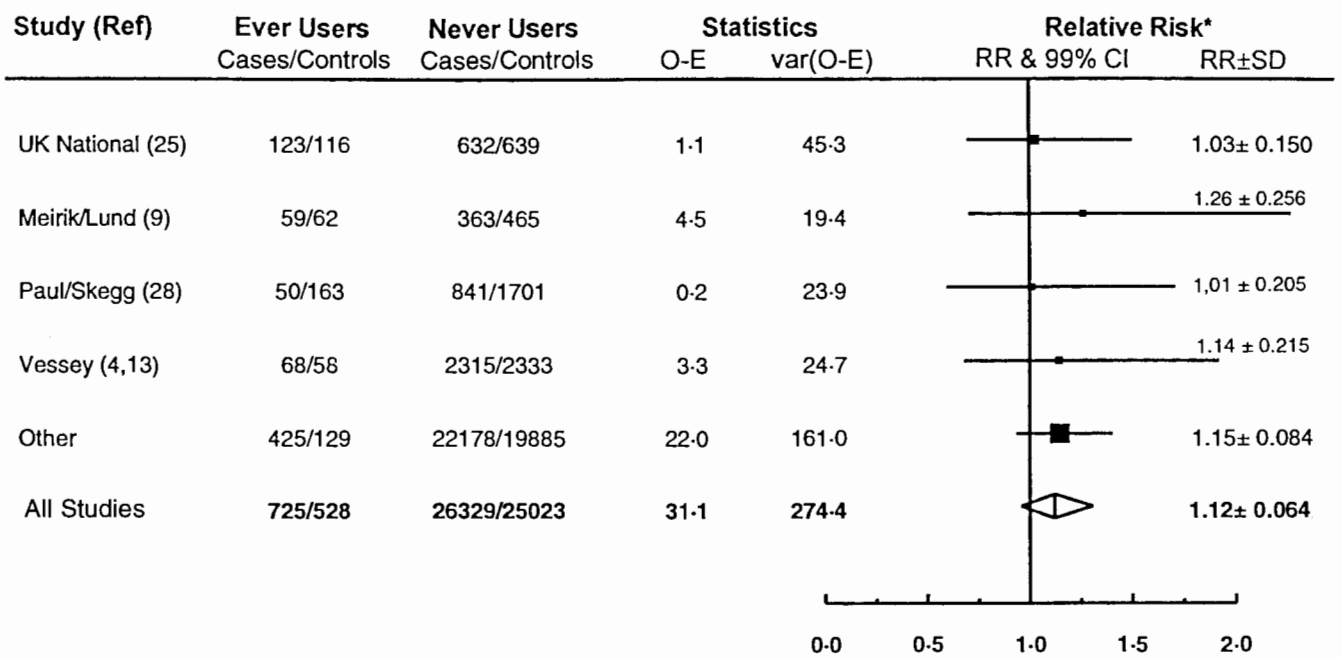
There is a tendency for specific types and doses of oestrogen and progestogen to be used together (Appendix 59). For example, the progestogens norethynodrel and chlormadinone acetate have been used only with the higher doses of the oestrogen, mestranol, whereas the progestogens desogestrol and gestodene have been used only with lower doses of the oestrogen, ethinyloestradiol. Combinations of ethinyloestradiol or mestranol with norethisterone (or norethisterone acetate) or ethinyloestradiol with levonorgestrel are the only ones that were sufficiently frequent to permit analyses of the possible effects of variations in dose within specific hormone combina-

tions. Appendix 60 shows results grouped according to oestrogen dose and type and Appendix 61 shows the results grouped according to progestogen dose and type, and those results are summarised in Figure 6. It can be seen that in general there is no strong evidence of heterogeneity of risk between specific doses or specific types of oestrogen or of progestogen. The only statistically significant heterogeneity is for progestogen type in women who stopped use 10 or more years ago, with women who had used "other" types of progestogens showing a significantly lower risk than for the specified types (Figure 5b). With so many comparisons made, however, this could be due to chance.

The preparations were grouped broadly into low, medium and high dose, based on oestrogen dose (<50 μg, = 50 μg and >50 μg, respectively, which, as can be seen from Appendix 59, also reflects progestogen dose). Most women (73%) remained in the same dose category during their entire period of hormonal contraceptive use. There is no statistically significant association between overall breast cancer risk and hormonal dose among recent users or among women who stopped use 5–9 years before (Appendix 62). In women who had stopped use 10 or more years ago, however, there was some evidence of a decrease in risk with increasing dose of the preparation most used and last used. This trend remains statistically significant when short duration users are classified as never users (χ^2 on 1 d.f. = 5.1; p = 0.02). There is no significant trend with dose in recent users who began use either before 20 or at older ages (Appendix 63), nor is there any significant trend with durations of use in each dose category either overall or separately for women aged under 35 or 35 and older (Appendix 64).

When analyses with respect to time since last use and dose were repeated separately for women with localised disease and more extensive disease, the trend of decreasing risk with increasing dose among past users was strongest for disease that had spread beyond the breast. This trend remained when short duration users were classified as never users (Appendix 65). The trend with dose in past users was statistically significant not only for the dose of the preparation last used, but also for dose of the preparation first used and dose of the preparation used for the longest period of time (Appendix 66).

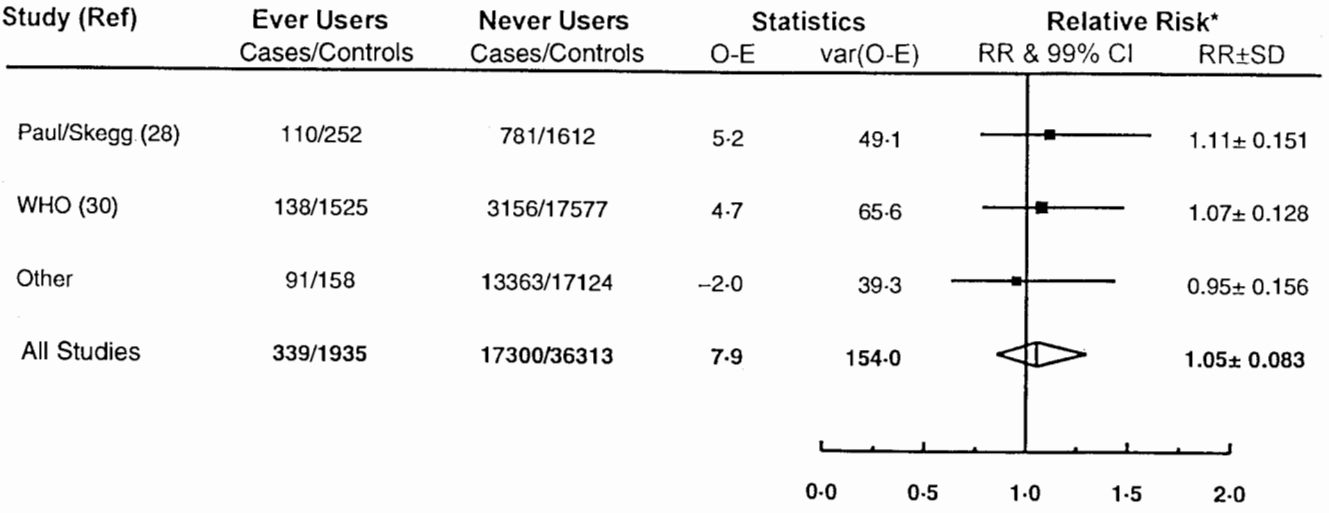
In summary, although there is insufficient information to comment reliably on the effects of specific hormonal constituents of the combined contraceptive, what evidence there is suggests that there are no major differences in the effects of specific types of oestrogen or of progestogen on breast cancer risk. However, when preparations are grouped into three broad dose groups, there is some evidence of a de-



Test for heterogeneity between studies: X^2 (4 d.f) = 1.0 ; NS

*Relative to never users, stratified by study, age at diagnosis, parity, age at first birth and age at which risk of conception ceased.

Figure 7. Relative risk of breast cancer in ever versus never users of progestogen-only oral contraceptives.



Test for heterogeneity between studies: X^2 (2 d.f) = 0.6 ; NS.

*Relative to never users, stratified by study, age at diagnosis, parity, age at first birth and age at which risk of conception ceased.

Figure 8. Relative risk of breast cancer in ever versus never users of depo-progestogens.

creasing risk with increasing dose among women whose use ceased 10 or more years ago; this trend is principally due to a significant deficit of disease that had spread beyond the breast among women who last used high dose preparations.

Breast Cancer Risk and Use of Contraceptives Containing Only Progestogens

Oral Preparations

Use of progestogen-only oral contraceptives was reported by only 1253 (0.8%) women, mostly from the UK, Scandinavia or New Zealand and, overall, there was a slight but not significant increase in risk associated with ever use (Figure 7). Most use was for relatively short durations (67% for less than a total of 2 years) and breast cancer risk was not significantly related to duration of use (Appendix 67). Most women began use after age 25 and there was no clear difference in risk by age at first use (Appendix 68). Risk appeared to be increased in women who had begun or ceased use in the last 10 years, although none of the relative risk estimates or trends was statistically significant (Appendices 69 and 70).

Injectable Preparations

Use of injectable progestogens was also infrequent, reported by 2,274 (1.5%) women, mostly from Thailand and New Zealand and there was no evidence of an increased risk in ever users (Figure 7). As with oral progestogen-only preparations, use was for relatively short durations (64% for less than a total of 2 years), and breast cancer risk did not appear to be related to duration of use (Appendix 71) or to age at first use (Appendix 72). Risk did appear to be increased in women who had begun or ceased use recently, decreasing with time since first and last use (Appendices 73 and 74) and the trend for time since first use was statistically significant. Time since starting and time since stopping use are highly correlated and stratification of one factor by the other had the effect of widening the respective confidence intervals substantially, making it difficult to determine which was of more fundamental relevance.

In summary, hormonal contraceptives containing progestogen-only have not been widely used, but the pattern of risk with time since last use is similar to that found for combined oral contraceptives (Appendix 75). The same pattern of risk is also observed when the analysis is confined to women who had not used combined oral contraceptives in the last 5 years (Appendix 76).

Cumulative Risk of Breast Cancer

Since recent users of oral contraceptives are more likely to have breast cancers diagnosed than never users and there are differences in the extent of tumour spread between women who have and have not used oral contraceptives, it is of interest to explore what these results imply in terms of the incidence of and

Table 19. Estimated number of breast cancers diagnosed in Europe or North America in 10,000 women who never used combined oral contraceptives and in 10,000 women who used them from ages 25 to 29

Breast Cancers Diagnosed in 10,000 Women Who Never Used Combined Oral Contraceptives			Breast Cancers Diagnosed in 10,000 Women Who Used Combined Oral Contraceptive From Ages 25 to 29			
Age at Diagnosis of Breast Cancer	5 year Incidence[a] During Period	Cumulative Incidence Up to End of Period	Relative Risk	5 Year Incidence During Period	Cumulative Incidence up to End of Period	Excess Cumulative Incidence ± SD
Using Estimates of Relative Risk for All Users†						
20 to 24	0.5	0.5	1	0.5	0.5	0
25 to 29	3.5	4	1.24	4.3	4.8	0.8 ± 0.1
30 to 34	12	16	1.15	13.9	18.7	2.7 ± 0.5
35 to 39	28	44	1.07	30.0	48.7	4.7 ± 1.0
40 to 44	56	100	0.98	55.1	103.7	3.7 ± 2.0
45 to 49	80	180	1.01	80.8	184.5	4.5 ± 3.6
Using Estimates of Relative Risk for Users With Total Duration of Use of >1 Year†						
20 to 24	0.5	0.5	1	0.5	0.5	0
25 to 29	3.5	4	1.22	4.3	4.8	0.8 ± 0.1
30 to 34	12	16	1.15	13.8	18.6	2.6 ± 0.5
35 to 39	28	44	1.06	29.6	48.2	4.2 ± 1.0
40 to 44	56	100	0.96	53.8	102.0	2.0 ± 2.0
45 to 49	80	180	0.98	78.5	180.5	0.5 ± 3.9

[a]Annual incidence rates per 100,000 never users were taken to be 160 at ages 45 to 49 and 0.007 (age −17)^3 at ages 20 to 44, which are intermediate between UK and USA rates in the mid-1980s.
†From Figure 1.

mortality from breast cancer. Although there is a definite increase in the relative risk of having breast cancer diagnosed in recent users of oral contraceptives, the strong effect of a woman's age on the incidence of breast cancer complicates the way in which relative risks according to time since last use translate into cumulative risks of having cancer diagnosed. In this section, data on the age-specific incidence of breast cancer in various populations and estimates of the relative risk of having breast cancer diagnosed by time since last use are combined to calculate how the expected number of breast cancers diagnosed in women who have taken oral contraceptives at various ages would differ from the expected number in never users. Since the relative risks associated with use that stopped more than 20 years ago cannot yet be reliably estimated, the cumulative risks presented here have not been calculated beyond 20 years after cessation of use.

Cumulative Incidence

The results for the entire study population may not be representative of all subgroups but probably apply most closely to women in Europe or North America who used oral contraceptives from about age 25 to 29, since this was the most common pattern of use. Even though it is not clear whether the associations observed are due to earlier diagnosis of breast cancer in women taking oral contraceptives or to the biological effects of hormonal contraceptives, the implications of these findings in terms of the incidence of breast cancer in such women are illustrated using estimates of the cumulative number of cancers diagnosed in never users and in women who used oral contraceptives from age 25 to age 29. Details of the calculations are shown in Table 19. The incidence in women who had never used oral contraceptives is based on estimated age-specific incidence rates that are midway between rates in Europe and North America; these rates, and the expected number of breast cancers diagnosed in 10,000 women who had never taken the pill, are shown in Table 19 for each 5-year age interval. The corresponding number of breast cancers which would be expected to be diagnosed in 10,000 women who had taken oral contraceptives from age 25 to 29 is calculated by applying estimates of the relative risk according to time since last use, taken from Figure 1, to these numbers of expected cancers in never users. It has already been shown that relative risk estimates relating to use which ceased many years ago are sensitive to the way in which women with short durations of use are classified. For this reason, cumulative incidence estimates are also calculated using relative risk estimates for users with a total duration of use of greater than a year and these are also given in Table 19.

Based on these calculations, 3.5 cancers would be expected to be diagnosed among 10,000 never users aged 25 to 29, compared with an estimated 4.3 can-

cers among 10,000 women currently using oral contraceptives at ages 25 to 29—a statistically significant excess of 0.8 (SD 0.1) cancers. After women stop taking oral contraceptives the relative risk of having breast cancer diagnosed declines, but the incidence of breast cancer increases. Thus, during the next 5 years, i.e., the age interval 30 to 34, 12.0 cancers would be diagnosed among the never users and 13.9 would be diagnosed among the women who stopped use, giving a statistically significant cumulative excess of 2.7 (SD 0.5) cancers per 10,000 women diagnosed before age 35. Before age 40, i.e., up to 10 years after stopping, the estimated cumulative excess is similar regardless of whether the relative risks were based on results for all users (cumulative excess 4.7 SD 1.0) or for users with a total duration of use of greater than a year (4.2 SD 1.0). Between ages 40 and 50, i.e., between 10 and 20 years after stopping use, the relative risk of having breast cancer diagnosed is no longer elevated. The estimated cumulative excess number of cancers diagnosed by age 50 differed somewhat depending on whether the relative risk estimates were taken for all users (cumulative excess 4.5 SD 3.6) or for users with a total duration of use of greater than a year (0.5 SD 3.9), but neither estimate was significantly greater than zero. Therefore, on the basis of these calculations, there is a clear and statistically significant excess in the cumulative number of cancers diagnosed up to 10 years after stopping use. Over the next 10 years, estimates of how many cancers could be expected to be diagnosed depend somewhat on the choice of relative risk estimates; in this example, however, there is no significant excess in the estimated cumulative number of cancers diagnosed up to 20 years after stopping use, regardless of the choice of relative risk estimates.

To examine how the excess cumulative number of cancers diagnosed might vary with the different patterns of use, the same background incidence rates and relative risk estimates as in Table 19 were used to calculate the cumulative excess incidence in women beginning oral contraceptive use at ages 20, 25, 30, 35, and 40 respectively, and stopping at ages 24, 29, 34, 39, and 44. The results are shown in Appendix 77 for durations of use of 5, 10 and 15 years. It can be seen that up to 10 years after stopping use, the cumulative excess number of cancers diagnosed is roughly similar for women who stopped use at a given age regardless of the age at which use started, but that for women who began use at a given age the excess is smaller the younger women were when they stopped use. Thus, the estimated cumulative excess is largely determined by the age women are when they last used oral contraceptives and is little affected by the age they were when use started, or, therefore, by their total duration of use. The same conclusion is reached up to 10 years after stopping use regardless of whether relative risk estimates for all users or users with a total duration of use of greater than a year are used. By contrast, up to 20 years after stopping use the estimates of cumulative incidence are somewhat sensitive to which relative risk estimates are used, and it is possible that some of the excess cancers diagnosed in the first 10 years after stopping use are offset by a slight deficit in the number of cancers diagnosed 10–20 years after stopping use.

The relative risk of having breast cancer diagnosed in relation to recency of use does not differ significantly between women from developed or developing countries (Appendix 50). However, in developing countries breast cancer incidence rates are lower than in Europe or North America, and so the estimated excess cumulative incidence for women from developing countries is correspondingly lower at each age (Appendix 78).

In current and recent users, women who began use as teenagers have higher relative risks of having breast cancer diagnosed than women who began use at older ages, but more than five years after stopping use, there is no heterogeneity in the relative risks according to the age at which women began use (Appendix 29). Calculations of the cumulative excess incidence associated with use beginning at age 16 and ending at ages 19 and 24, respectively, were made using the risk estimates from Appendix 29 for recent users who began use before age 20 (Appendix 79). The estimated cumulative excess up to 10 years after stopping use in 10,000 women who used oral contraceptives from age 16 to 19 and from age 16 to 24 compared to never users is 0.5 (SD 0.1) and 2.0 (SD 0.3), respectively. These estimated excesses are of a similar order of magnitude to the estimated excess for use from age 20 to 24 or from age 25 to 29. Thus, although the relative risks of having breast cancer diagnosed associated with current and recent use beginning at age 16 are greater than for use beginning at, say, age 25, they act during an age interval when breast cancer risk is extremely low and therefore have comparatively little effect on the estimated cumulative incidence of breast cancer.

Cancers diagnosed in women who had used oral contraceptives are less likely to have spread beyond the breast than the cancers diagnosed in never users (Figure 4). Using methods similar to those described in Table 19, estimates of cumulative incidence were calculated separately for localised disease and for more extensive disease and the results are given in Appendix 80. Among 10,000 women who used oral contraceptives from ages 25 to 29, it is estimated that for localised disease 107 cancers would be diagnosed

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by age 50, compared to 100 such cancers in 10,000 never users, an excess of 7.2 (SD 3.3) cancers; the estimated excess based on analyses in which short duration users are classified as never users is 6.5 (SD 3.6). For disease that had spread beyond the breast there is a small deficit by age 50 of 4.0 (SD 2.9) using relative risk estimates for all users and a deficit of 5.6 (SD 3.1) using relative risk estimates for users with a duration of greater than a year.

In summary, because breast cancer incidence rises steeply with age, the age-interval during which a woman's use occurs is critical in determining the excess number of cancers diagnosed. In effect, it is a woman's age at last use which is the main determinant of the excess, which increases with increasing age at last use. The excess cancers diagnosed in the period from starting use up to 10 years after stopping are mainly cancers that are localised to the breast. Up to 20 years after cessation of use, the estimated cumulative number of cancers diagnosed is somewhat sensitive to the choice of relative risk estimates but it is possible that some of the excess cancers diagnosed in the first 10 years after stopping use are offset by a slight deficit in the number of cancers diagnosed 10 to 20 years after stopping use. There is, however, a clear difference in clinical presentation between the cancers diagnosed in women who have and have not used oral contraceptives in that the cancers diagnosed in ever users tend to be less advanced clinically than the cancers diagnosed in never users. There is insufficient information in these data to estimate the number of cancers that would be diagnosed in women who ceased using oral contraceptives 20 or more years ago and as new data on such women emerge it will be important to revise these estimates accordingly.

Cumulative Mortality

Tumours that are localised to the breast are associated with a better survival than tumours that have spread beyond it, but without follow-up information on the women with breast cancer it is not possible to be sure whether oral contraceptives use increases, decreases, or has no effect on cumulative mortality from breast cancer. It is of importance, therefore, to obtain direct information about the survival of women who have and have not used oral contraceptives.

Conclusion

Breast cancer is the most common cancer among women worldwide and oral contraceptives have already been used by more than 200 million women. Even if oral contraceptive use produced small changes in the relative risk of breast cancer this would affect large numbers of women, particularly effects that persist long after cessation of use. This international collaboration involves data from 54 studies and includes more than 53,000 women with breast cancer from 25 countries. The studies contributing to this review are varied in their setting and design. Likewise, the individual women included in the analyses are of varied backgrounds and have different baseline risks of breast cancer. Despite the heterogeneity of the study designs and of the subjects, the results are remarkably consistent across the various studies and for women with different characteristics.

Recency of oral contraceptive use appears to explain most of the variation in breast cancer risk associated with oral contraceptive use and the data presented here demonstrate that once this factor is taken into account, few other aspects of oral contraceptive use have an additional effect on the relative risks of breast cancer. Among recent users, there is a small increase in the relative risk of having breast cancer diagnosed, and the excess is largely due to cancers that are localised to the breast. The relative risk among recent users was greater in women who began use before age 20 than in women who began after that age. It is not clear whether these findings are the consequence of cancers being diagnosed earlier in women who have used oral contraceptives, whether they are due to biological effects of the hormones, or whether they are due to a combination of both. Further research may clarify the mechanisms.

This collaboration demonstrates that there is little evidence for a persistent increase in breast cancer risk 10 to 20 years after cessation of use of oral contraceptives; indeed for certain groups of past users there may, if anything, be a reduction in the risk of breast cancer. In particular, there is a reduction in the risk of tumours that have spread beyond the breast, associated with use of oral contraceptive preparations containing high doses of hormones. These unexpected findings need to be confirmed.

There is still little information about the effects of oral contraceptive use that ceased more than 20 years ago. The collection of new data should provide further information about the effects of oral contraceptives more than 20 years after stopping use, particularly about women who began use as teenagers and are now reaching an age when breast cancer is common. Such data should become available in the next decade, and it will then be necessary to re-evaluate the worldwide evidence on the long-term effects of hormonal contraceptives on breast cancer risk.

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List of Appendices