2. Studies of Cancer in Humans

2.1 Breast cancer

The relationship between the use of combined oral contraceptives and the risk for breast cancer was reviewed by a working group convened by IARC in 1979 (IARC, 1979). At the time, the results from several follow-up (Royal College of General Practitioners, 1974; Ory *et al*., 1976; Vessey *et al*., 1976) and case–control studies (Vessey *et al*., 1972, 1975; Paffenbarger *et al*., 1977; Sartwell *et al*., 1977; Kelsey *et al*., 1978; Lees *et al*., 1978) had been published. The data were sparse even for the analysis of use. The Group concluded that there was no clear evidence that use of combined oral contraceptives influences the risk for breast cancer.

In the two decades since the 1979 report, oral contraceptive formulations have been changed: The doses of oestrogen and progestogen have been lowered, the components used have changed, cyclic preparations with different doses at different times during the menstrual cycle have been introduced, and progestogen-only formulations have become available.

Various aspects of the use of combined oral contraceptives in relation to the incidence of breast cancer have been assessed in numerous epidemiological studies conducted since 1979. Several detailed reviews of the epidemiological evidence have been published (Prentice & Thomas, 1987; Olsson, 1989; Romieu *et al*., 1990; Malone, 1991; Thomas, 1991a; WHO, 1992; Malone *et al*., 1993; Schlesselman, 1995). In addition, a pooled analysis of the individual data from 54 studies was reported (Collaborative Group on Hormonal Factors in Breast Cancer, 1996a,b); the analyses covered an estimated 90% of the data available at that time.

Studies in which cases of breast cancer occurring before 1980 were analysed provide limited information on many aspects of the use of combined oral contraceptives that are of interest, notably use at a young age, long duration of use, recent use and use followed by a long latent period (Ravnihar *et al*., 1979; Jick *et al*., 1980; Brinton *et al*., 1982; Harris *et al*., 1982; Vessey *et al*., 1982; Janerich *et al*., 1983; Hennekens *et al*., 1984; Schildkraut *et al*., 1990; Morabia *et al*., 1993). The early studies have been reviewed in detail (Thomas, 1991a). The studies considered here are based on data collected since 1979 and are limited to those reported in English.

The follow-up studies are summarized in Table 4, the case–control studies in which hospitalized controls were used are summarized in Table 5 and the case–control studies in which controls from other sources were used are summarized in Table 6. When several reports are available on the same study, all are listed; however, the data shown are taken from the report (marked with an asterisk) that was based on the largest numbers. The studies are listed in order of the year of the first publication of results. Thus, follow-up data have been published from the Nurses' Health Study (Colditz *et al*., 1994), in which data on the use of combined oral contraceptives and risk factors were collected by postal questionnaire and the diagnoses were verified from hospital records.

A variety of methods was used in the case–control studies. The data on use of combined oral contraceptives and other risk factors for breast cancer were obtained almost exclusively by personal interview; the diagnoses of breast cancer were generally verified from hospital or cancer registry records. In virtually all of the studies, relative risks were estimated after control for important potential confounding factors, such as reproductive variables and socioeconomic status. The Collaborative Group on Hormonal Factors in Breast Cancer (1996a,b) analysed all of the published and unpublished studies available to them, for a combined total of some 53 000 cases and 100 000 controls. Individual data from each of the studies were analysed centrally; combined relative risk estimates were obtained by a modification of the Mantel-Haenszel procedure, with stratification on study, age at diagnosis, parity and age at the birth of the first child.

Comparisons of any use of combined oral contraceptives ('ever use') with no use ('never use') yielded overall relative risk estimates close to 1.0 in most studies. In the analysis of the Collaborative Group on Hormonal Factors in Breast Cancer (1996a,b), the relative risk estimate was 1.17 [95% confidence interval [CI], 1.1–1.24] on the basis of data from hospital-based case–control studies, 1.0 [95% CI, 0.97–1.1] from case–control studies with population controls and 1.07 [95% CI, 1.00–1.14] from follow-up studies. These estimates were not significantly different. The characteristics of women who had ever used oral contraceptives varied, however, from study to study and changed over time: there was a tendency to use combined oral contraceptives at younger ages and for longer.

In the early and mid-1980s, a number of associations between the use of combined oral contraceptives and an increased risk for breast cancer were observed in subgroups of some epidemiological studies, and hypotheses were raised (and later refuted) to explain those observations. In 1981, Pike *et al*. observed that the risk for breast cancer more strongly tended to increase with increasing duration of use of combined oral contraceptives before the first full-term pregnancy than after, raising the hypothesis that use of these contraceptives before the first full-term pregnancy is more harmful. A few subsequent studies provided some support for this hypothesis (McPherson *et al*., 1987; Rohan & McMichael, 1988; Olsson *et al*., 1989, 1991a), but most studies did not (Meirik *et al*., 1986, 1989; Romieu *et al*., 1989; Stanford *et al*., 1989; UK National Case–Control Study Group, 1989; Paul *et al*., 1990; WHO Collaborative Study of Neoplasia and Steroid Contraceptives, 1990; Weinstein *et al*., 1991; Wingo *et al*., 1991; Ewertz, 1992;

Table 4. Follow-up studies of breast cancer associated with use of combined oral contraceptives

Reference	Country	Age at recruitment (years)	Size of cohort	Period of follow-up	No. of cases	Loss to follow-up (%)	Any use (%)	RR (95% CI), any versus none	RR (95% CI) for longest duration
Lipnick *et al.* (1986); Romieu *et al*. (1989); Colditz *et al.* (1994)[*] (Nurses' Health Study)	United States	30–55	118 273	1976–86	1 799	5	48	1.1 (0.97–1.2)	Not reported
Kay & Hannaford (1988)[a] (incidence)	United Kingdom	Not reported	47 000	1968–85	239	[61]	Not reported	Former use (99 cases in 134 079 person–years), 1.2 (0.9–1.6) Current use (44 cases in 104 505 person–years), 1.2 (0.84–1.9)	≥ 10 years, 1.4 (0.91–2.3)
Mills *et al*. (1989)	United States	≥ 25	20 341	1976–82	215	1	27	1.5 (0.94–2.5) based on 29 cases in 31 188 person–years among women ≤ 45 years of age in 1960	≥ 10 years, 1.4 (0.34–6.0) based on 2 cases in 1660 person–years among women ≤ 45 years of age in 1960
Vessey *et al*. (1989a)	United Kingdom	25–39	17 032	1968–87	189	0.3 per year	Not reported	Not reported	Ages 25–44, ≥ 10 years, 0.65/1000 person–years (14 cases) versus 0.62/1000 person–years for no use (49 cases) [RR, 1.0] Ages ≥ 45, ≥ 10 years, 1/1000 person–years versus (8 cases) 2.2/1000 person–years for no use (50 cases) [RR, 0.48]

Table 4 (contd)

Reference	Country	Age at recruitment (years)	Size of cohort	Period of follow-up	No. of cases	Loss to follow-up (%)	Any use (%)	RR (95% CI), any versus none	RR (95% CI) for longest duration
Beral *et al.* (1999)[a]	United Kingdom	Not reported	46 000	1968–93	259 (deaths[b])	25	63	1.1 (0.82–1.4)	≥ 10 years, 1.4 (0.86–2.1) (26 deaths)
Collaborative Group (1996b)	–	–	–	–	6 806	–	[38]	1.07 [1.00–1.14]	≥ 15 years, 1.1 [0.96–1.2]

RR, relative risk; CI, confidence interval
* Report from which data are taken
[a] Data from Royal College of General Pracitioners (1974)
[b] 154 deaths for any use, 105 deaths for no use

Table 5. Case–control studies of use of combined oral contraceptives and breast cancer with hospital controls

Reference	Country	Years of case diagnosis	Age (years)	No. of cases	No. of controls	Participation rate (%)	Any use (%)	RR (95% CI), ever versus never	RR (95% CI), longest duration
						Cases/Controls	Cases/Controls		
Vessey *et al*. (1983)	United Kingdom	1968–80	16–50	1 176	1 176	Not reported	46/47	0.98 (0.81–1.2)	≥ 97 months versus never 0.99 (0.67–1.4)
Rosenberg *et al*. (1984); Miller *et al*. (1986, 1989); Rosenberg *et al*. (1996)* (surveillance study)	United States	1977–92	25–59	3 540 (white women)	4 488	95	≥ 1 year of use [29/30]	≥ 1 year versus < 1 year 1.1 (1.0–1.3)	≥ 10 years versus < 1 year 0.9 (0.7–1.1)
Talamini *et al*. (1985)	Italy	1980–83	26–79	368	373	99	4/6	0.7 (0.4–1.4)	Not reported
Ellery et *al*. (1986)	Australia	1980–82	25–64	141	279	Not reported	[48/42]	0.9 (0.6–1.5)	≥ 6 years 1.3 (0.7–2.7)
La Vecchia *et al*. (1986, 1989); Tavani *et al*. (1993a)*	Italy	1983–91	< 60	2 309	1 928	98/97	16/14	1.2 (1.0–1.4)	≥ 60 months versus never 0.8 (0.5–1.0)
McPherson *et al*. (1987)	United Kingdom	1980–84	16–44	351	351	Not reported	68/65	Not reported	≥ 12 years versus never 1.8 (0.82–3.9)
			≥ 45	774	774	Not reported	24/27	Not reported	≥ 12 years versus never 0.84 (0.39–1.8)
Ravnihar *et al*. (1988)	Slovenia	1980–83	25–54	534	1 989	Not reported	30/24	1.6 (1.3–2.1)	> 7 years versus never 2.4 (1.5–3.8)
Harris *et al*. (1990)	United States	1979–81	All	401	519	Not reported	19/23	0.8 (0.6–1.2)	≥ 5 years (age < 50) 0.4 (0.2–0.8)

Table 5 (contd)

Reference	Country	Years of case diagnosis	Age (years)	No. of cases	No. of controls	Participation rate (%)	Any use (%)	RR (95% CI), ever versus never	RR (95% CI), longest duration
						Cases/Controls	Cases/Controls		
WHO Collaborative Study (1990)*; Ebeling *et al*. (1991); Thomas (1991b); Thomas *et al*. (1991, 1992, 1994)	10 countries: 3 developed, 7 developing	1979–86	< 62	2 116	13 072	Not reported	34/34	1.2 (1.0–1.3)	> 8 years 1.6 (1.2–2.0)
Clavel *et al*. (1991)	France	1983–87	25–56	464	542	99/99	[51/44]	1.5 (1.1–2.1)	≥ 21 years versus never 1.2 (0.4–3.9)
Bustan *et al*. (1993)	Indonesia	1990–91	25–55	119	258	90	32/21	1.8 (1.1–3.0)	> 5 years 1.1 (0.6–2.1)
Gomes *et al*. (1995)	Brazil	1978–87	25–75	300	600	Not reported	21/15	1.8 (1.2–2.9)	Not reported
La Vecchia *et al*. (1995)	Italy	1991–94	< 65	1 991	1 899	96/96	18/14	1.1 (0.9–1.4)	> 8 years versus never 1.2 (0.7–1.9)
Lipworth *et al*. (1995)	Greece	1989–91	All	820	795	95/93	4/4	≤ 45 years of age 1.1 (0.60–2.0) > 45 years of age 1.6 (0.82–3.3)	≤ 45 years of age, ≥ 3 years 0.47 (0.13–1.70) 45 years of age, ≥ 3 years 1.2 (0.32–4.2)
Palmer *et al*. (1995) (surveillance)	United States	1977–92	25–59	524 (black women)	1 021	95	[31/27]	≥ 1 year versus < 1 year 1.6 (1.2–2.1)	≥ 10 years versus < 1 year 1.1 (0.6–2.0)
Levi *et al*. (1996)	Switzerland	1990–95	< 70	206	424	85	37/32	1.5 (1.1–2.3)	≥ 10 years versus never 2.4 (1.4–4.2)

Table 5 (contd)

Reference	Country	Years of case diagnosis	Age (years)	No. of cases	No. of controls	Participation rate (%)	Any use (%)	RR (95% CI), ever versus never	RR (95% CI), longest duration
						Cases/Controls	Cases/Controls		
Tomasson & Tomasson (1996)	Iceland	1965–89	25–69	1 062	5 622 (cancer detection clinic)	Not reported	Not reported	Not reported	> 8 years 0.96 (0.69–1.3)
Tryggvadóttir *et al.* (1997)	Iceland	1975–95	18–43	204	1 183 (cancer detection clinic)	Not reported	79/81	Not reported	> 8 years 1.3 (p = 0.55)
Collaborative Group (1996a)[a]	–	–	–	15 030	34 565	–	26/31	1.17 [1.1–1.24]	≥ 15 years versus never 1.1 [0.96–1.2]

RR, relative risk; CI, confidence interval
* Report from which data are taken
[a] Includes all studies mentioned above

Table 6. Case–control studies of use of combined oral contraceptives and breast cancer with controls other than hospitalized patients

Reference	Country	Years of case diagnosis	Age (years)	No. of cases	No. of controls	Participation rate (%)	Any use (%)	RR (95% CI), ever versus never	RR (95% CI), longest duration
						Cases/Controls	Cases/Controls		
Pike *et al*. (1981, 1983); Bernstein *et al*. (1990)*	United States	1972–83	< 37	439 (population-based)	439 (neighbours)	68/not reported	85/85	Not reported	> 8 years versus never 1.7 ($p_{trend} < 0.01$)
Centers for Disease Control Cancer and Steroid Hormone Study (1983a); Stadel *et al*. (1985); Cancer and Steroid Study (1986)*; Schlesselmann *et al*. (1987, 1988); Stadel *et al*. (1988); Wingo *et al*. (1991); Mayberry & Stoddard-Wright (1992) (CASH Study)	United States	1980–82	20–54	4 711 (population-based)	4 676 (random-digit dialling)	80/83	[63/64]	1.0 (0.9–1.1)	≥ 15 years versus never 0.9 (0.8–1.1)
Meirik *et al*. (1986)*; Lund *et al*. (1989); Meirik *et al*. (1989); Holmberg *et al*. (1994) (Sweden–Norway Joint National Study)	Sweden, Norway	1984–85	< 45	422	722 (population-based)	89/81	77/78	Not reported	≥ 12 years versus never 2.2 (1.2–4.0)
Paul *et al*. (1986, 1990*, 1995) (New Zealand National Study)	New Zealand	1983–87	25–54	891 (population-based)	1 864 (electoral rolls)	95/90	77/83	1.0 (0.82–1.3)	≥ 14 years versus never 1.1 (0.78–1.7)

Table 6 (contd)

Reference	Country	Years of case diagnosis	Age (years)	No. of cases	No. of controls	Participation rate (%)	Any use (%)	RR (95% CI), ever versus never	RR (95% CI), longest duration
						Cases/Controls	Cases/Controls		
Rohan & McMichael (1988)	Australia	1982–84	20–69	395 (population-based)	386 (electoral rolls)	[81/72]	49/49	1.1 (0.70–1.6)	> 7 years versus never 0.67 (0.38–1.2)
Yuan *et al*. (1988)	China	1984–85	20–69	534	534 (population-based)	94/99	[19/18]	1.1 (0.74–1.5)	≥ 10 years versus never 1.4 (0.62–3.2)
Jick *et al*. (1989)	United States	1975–83	< 43	127 (health plan)	174 (health plan)	Not reported	61/71	0.9 (0.4–1.9)	≥ 10 years 1.4 (0.4–4.6)
Olsson *et al*. (1989*, 1991a)	Sweden	1979–80 1982–85	≤ 46	174 (hospital)	459 (population-based)	100/92	82/72	[1.8]	Not reported
Stanford *et al*. (1989)	United States	1973–80	All	2 022	2 183 (screening programme)	78/83	24/24	1.0 (0.9–1.2)	≥ 15 years versus never 0.65 (0.3–1.6)
UK National Case–Control Study Group (1989*, 1990); Chilvers *et al*. (1994) (United Kingdom National Study)	United Kingdom	1980–85	< 36	755 (population-based)	755 (general practice)	72/89	[91/89]	Not reported	> 8 years versus never 1.7 (p_{trend} < 0.001)
Weinstein *et al*. (1991)	United States	1984–86	20–70	1 067 (population-based)	1 066 (drivers' license files)	66/41	26/23	1.2 (0.98–1.5)	≥ 4 years versus never 1.2 (0.82–1.6)

Table 6 (contd)

Reference	Country	Years of case diagnosis	Age (years)	No. of cases	No. of controls	Participation rate (%)	Any use (%)	RR (95% CI), ever versus never	RR (95% CI), longest duration
						Cases/Controls	Cases/Controls		
Ewertz (1992)	Denmark	1983–84	< 40	203	212	90/88	[81/79]	1.2 (0.73–1.9)	≥ 12 years versus
			40–59	856	778	89/80	36/37	Not reported	< 4 years 1.3 (0.82–2.0)
				(population-based)					
Rosenberg *et al*. (1992)	Canada	1982–86	< 70	607 (cancer hospital)	1 214 (neighbourhood)	79/65	43/45	Not reported	≥ 15 years versus never 0.9 (0.4–1.7)
Ursin *et al*. (1992)	United States and Canada	1935–89	< 50	149 (2 registries)	243 (sisters)	Not reported	[42/30]	1.7 (1.0–2.9)	≥ 7 years 2.0 (0.93–4.2)
Rookus *et al*. (1994)	Netherlands	1986–89	20–54	918	918	60/72	85/85	1.1 (0.8–1.4)	≥ 12 years versus never 1.3 (0.9–1.9)
				(population-based)					
White *et al*. (1994)	United States	1983–90	21–45	747 (population-based)	961 (random-digit dialling)	83/78	78 (≥ 1 year)/ 76 (≥ 1 year)	1.0 (0.71–1.5)	≥ 10 years versus never 1.3 (0.92–1.9)
Brinton *et al*. (1995)	United States	1990–92	20–45	1 648 (population-based)	1 505 (random-digit dialling)	86/78	76/71 (≥ 6 months)	Not reported ≥ 6 months to < 5 years versus < 6 months 1.3 (1.1–1.5)	≥ 10 years versus < 6 months 1.3 (1.0–1.6)

Table 6 (contd)

Reference	Country	Years of case diagnosis	Age (years)	No. of cases	No. of controls	Participation rate (%)	Any use (%)	RR (95% CI), ever versus never	RR (95% CI), longest duration
						Cases/Controls	Cases/Controls		
Primic- akelj *et al*. (1995)	Slovenia	1988–90	25–54	624 (hospital)	624 (population-based)	94/83	48/48	1.1 (0.85–1.4)	> 8 years versus never 1.2 (0.76–1.7)
Newcomb *et al*. (1996)	United States	1988–91	< 75	6 751 (population-based)	9 311 (drivers' licenses or Medicare)	81/84	38/39	1.1 (1.0–1.2)	≥ 15 years versus never 1.0 (0.8–1.4)
Rossing *et al*. (1996)	United States	1988–90	50–64	537 (population-based)	545 (random-digit dialling)	81/73	[47/41]	1.1 (0.8–1.4)	> 10 years versus never 0.8 (0.5–1.3)
Collaborative Group (1996b)[a]	–	–	–	31 089	37 676	–	[48/49]	1.0 [0.97–1.1]	≥ 15 years 1.1 (0.96–1.2)

RR, relative risk; CI, confidence interval
* Reports from which data are taken
[a] Includes all studies

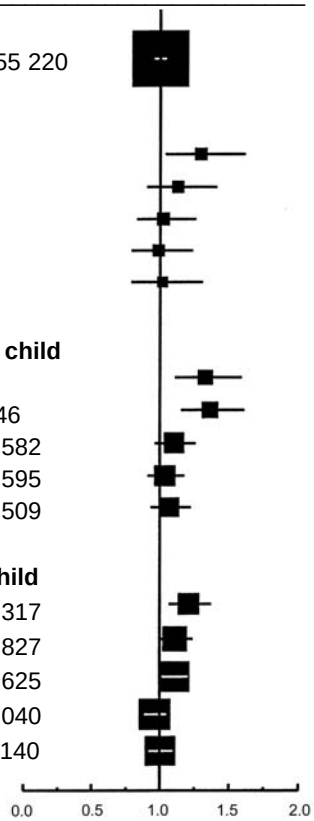
Tavani *et al*., 1993a; White *et al*., 1994; Brinton *et al*., 1995; Palmer *et al*., 1995; Primic- akelj *et al*., 1995; Collaborative Group on Hormonal Factors in Breast Cancer, 1996b; Levi *et al*., 1996; Newcomb *et al*., 1996; Rosenberg *et al*., 1996). When the study from which the hypothesis arose was completed, with larger numbers, the effect was no longer seen (Bernstein *et al*., 1990). Rather, the data now suggested that the increase in risk was related to use before the age of 25. Some subsequent evidence has suggested that the risk is greater the younger the woman is when she first uses combined oral contraceptives (White *et al*., 1994), but most studies have not supported this idea (Meirik *et al*., 1986; Ravnihar *et al*., 1988; Rohan & McMichael, 1988; Stanford *et al*., 1989; UK National Case–Control Study Group, 1989; Paul *et al*., 1990; WHO Collaborative Study of Neoplasia and Steroid Contraceptives, 1990; Clavel *et al*., 1991; Weinstein *et al*., 1991; Wingo *et al*., 1991; Ewertz, 1992; Rosenberg *et al*., 1992; Tavani *et al*., 1993a; Brinton *et al*., 1995; Palmer *et al*., 1995; Primic- akelj *et al*., 1995; Levi *et al*., 1996; Newcomb *et al*., 1996; Rosenberg *et al*., 1996; Rossing *et al*., 1996). The study of Rookus *et al*. (1994) suggested an increased risk for breast cancer before the age of 35 for women who started to use combined oral contraceptives at an early age but no increased risk between the ages of 36 and 45. The Collaborative Group on Hormonal Factors in Breast Cancer (1996a,b) provided little support for the idea that the effect of combined oral contraceptives is modified by the timing in relation to the first pregnancy (Figure 2) or the age at first use, except perhaps that the relative risks were somewhat higher in current or recent users who began use before the age of 20 (Figure 3). There is, however, no evidence of any persistent excess risk many years after use has ceased for women who began use before the age of 20.

Data on the use of combined oral contraceptives in relation to age at the time of diagnosis of breast cancer are shown in Table 7. As evidence has accumulated, a relatively consistent finding has been an increased risk for breast cancer occurring before the age of 45, and particularly before 35, among users of combined oral contraceptives (Meirik *et al*., 1986; McPherson *et al*., 1987; Stanford *et al*., 1989; UK National Case–Control Study Group, 1989; Bernstein *et al*., 1990; Paul *et al*., 1990; WHO Collaborative Study of Neoplasia and Steroid Contraceptives, 1990; Weinstein *et al*., 1991; Wingo *et al*., 1991; Rookus *et al*., 1994; Brinton *et al*., 1995; Palmer *et al*., 1995; La Vecchia *et al*., 1995; Newcomb *et al*., 1996; Rosenberg *et al*., 1996). Some studies have not shown such an increase, however (Vessey *et al*., 1983; Ravnihar *et al*., 1988; Ewertz, 1992; Rosenberg *et al*., 1992; Tavani *et al*., 1993a; White *et al*., 1994; Primic- akelj *et al*., 1995). Most of the studies show no overall increase in risk for older women, although the relative risk estimates were increased for older women in some studies (Vessey *et al*., 1983; Ravnihar *et al*., 1988; Rookus *et al*., 1994). The Collaborative Group on Hormonal Factors in Breast Cancer (1996a,b) found little difference in risk according to the age at diagnosis of breast cancer once recency of use had been taken into account (Figure 4).

Data on the recency of use of combined oral contraceptives are shown in Table 8. A relatively consistent finding is that the risk for breast cancer is increased among women who have used these oral contraceptives recently, within the previous five to 10 years

Figure 2. Relative risk for breast cancer by time since last use of combined oral contraceptives and in relation to childbearing

Use of combined oral contraceptives in relation to childbearing	RR[a] ± SD	Cases/controls
Never used	1.00 ± 0.018	28 200/55 220
Nulliparous women		
Current user	1.30 ± 0.098	516/883
Last use 1–4 years previously	1.13 ± 0.092	418/639
5–9 years previously	1.02 ± 0.082	472/610
10–14 years previously	0.99 ± 0.086	411/477
≥ 15 years previously	1.02 ± 0.099	338/432
Parous women who began use before the birth of their first child		
Current user	1.33 ± 0.081	605/862
Last use 1–4 years previously	1.36 ± 0.076	744/1 046
5–9 years previously	1.10 ± 0.054	1 072/1 582
10–14 years previously	1.04 ± 0.051	1 159/1 595
≥ 15 years previously	1.07 ± 0.055	1 106/1 509
Parous women who began use after the birth of their first child		
Current user	1.21 ± 0.054	1 142/2 317
Last use 1–4 years previously	1.11 ± 0.045	1 448/2 827
5–9 years previously	1.11 ± 0.036	2 473/4 625
10–14 years previously	0.97 ± 0.032	2 514/5 040
≥ 15 years previously	1.00 ± 0.034	2 611/5 140



Adapted from Collaborative Group on Hormonal Factors in Breast Cancer (1996a,b)

[a] Relative risk (RR) given with 99% confidence interval (CI) relative to no use, stratified by study, age at diagnosis, parity and, where appropriate, age when first child was born and age when the risk for conceiving ceased

Size of square indicates the number of cases

Figure 3. Relative risk for breast cancer for various indices of the timing of combined oral contraceptive use within categories of time since last use

(a) Relative risk for breast cancer by duration of use and time since last use of combined oral contraceptives

	RR[a] ± SD	Cases/controls
Never used	1.00 ± 0.014	28 200/55 220
Current user		
Duration ≤ 12 months	1.18 ± 0.122	176/621
1–4 years	1.27 ± 0.079	489/1 158
5–9 years	1.21 ± 0.061	794/1 338
≥ 10 years	1.29 ± 0.060	882/1 156
Last use 1–4 years previously		
Duration ≤ 12 months	1.05 ± 0.080	359/1 021
1–4 years	1.12 ± 0.064	649/1 240
5–9 years	1.26 ± 0.059	908/1 369
≥ 10 years	1.14 ± 0.060	746/1 045
Last use 5–9 years previously		
Duration ≤ 12 months	1.05 ± 0.056	757/1 712
1–4 years	1.05 ± 0.043	1 280/2 186
5–9 years	1.13 ± 0.044	1 340/2 067
≥ 10 years	1.14 ± 0.062	714/1 060
Last use 10–14 years previously		
Duration ≤ 12 months	1.00 ± 0.044	1 160/2 337
1–4 years	0.97 ± 0.037	1 581/2 639
5–9 years	0.99 ± 0.046	1 075/1 681
≥ 10 years	1.01 ± 0.083	332/598
Last use ≥ 15 years previously		
Duration ≤ 12 months	1.05 ± 0.036	1 999/3 470
1–4 years	1.04 ± 0.041	1 533/2 574
5–9 years	0.87 ± 0.064	483/946
≥ 10 years	0.90 ± 0.146	83/196

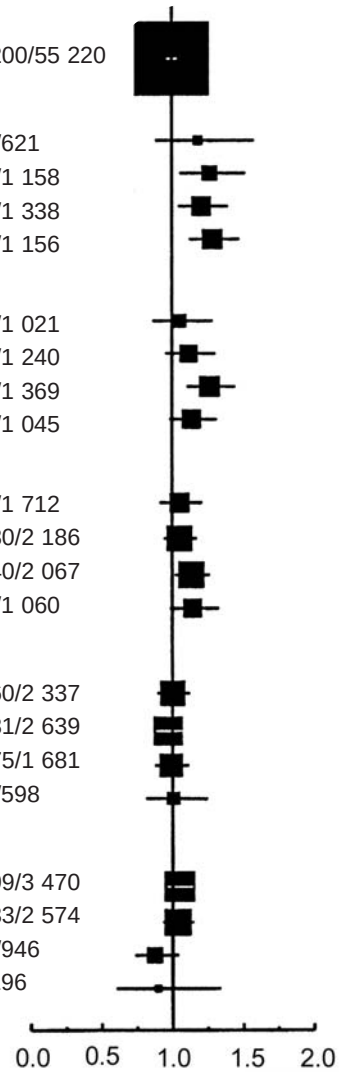


Figure 3 (contd)

(b) Relative risk for breast cancer by age at first use and time since last use of combined oral contraceptives

	RR[a] ± SD	Cases/controls
Never used	1.00 ± 0.018	28 200/55 220
Current user		
Age at first use < 20 years	1.59 ± 0.093	565/945
20–24 years	1.17 ± 0.065	679/1 336
25–29 years	1.16 ± 0.077	421/895
≥ 30 years	1.25 ± 0.069	676/1 097
Last use 1–4 years previously		
Age at first use < 20 years	1.49 ± 0.093	503/794
20–24 years	1.15 ± 0.060	768/1 379
25–29 years	1.09 ± 0.072	483/906
≥ 30 years	1.11 ± 0.055	908/1 596
Last use 5–9 years previously		
Age at first use < 20 years	1.07 ± 0.070	560/938
20–24 years	1.09 ± 0.046	1 224/2 039
25–29 years	1.01 ± 0.052	803/1 551
≥ 30 years	1.18 ± 0.046	1 504/2 497
Last use 10–14 years previously		
Age at first use < 20 years	1.13 ± 0.072	555/771
20–24 years	0.93 ± 0.041	1 249/2 088
25–29 years	1.06 ± 0.051	1 001/1 705
≥ 30 years	0.95 ± 0.042	1 343/2 691
Last use ≥ 15 years previously		
Age at first use < 20 years	1.14 ± 0.077	524/714
20–24 years	1.01 ± 0.045	1 305/1 988
25–29 years	1.01 ± 0.051	1 035/1 854
≥ 30 years	0.99 ± 0.046	1 234/2 630

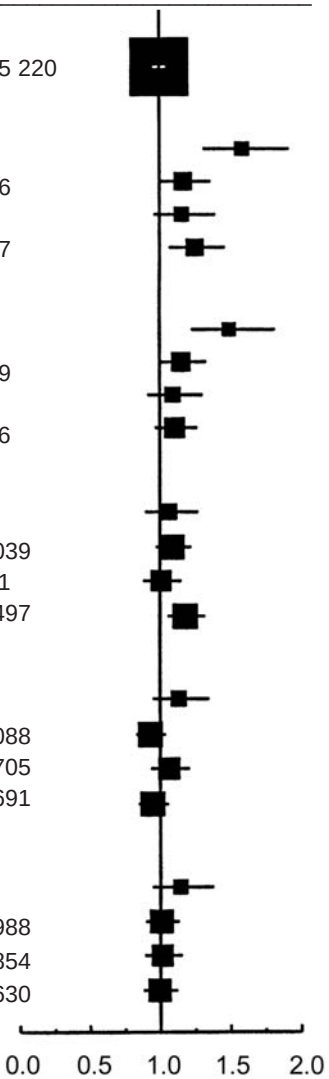
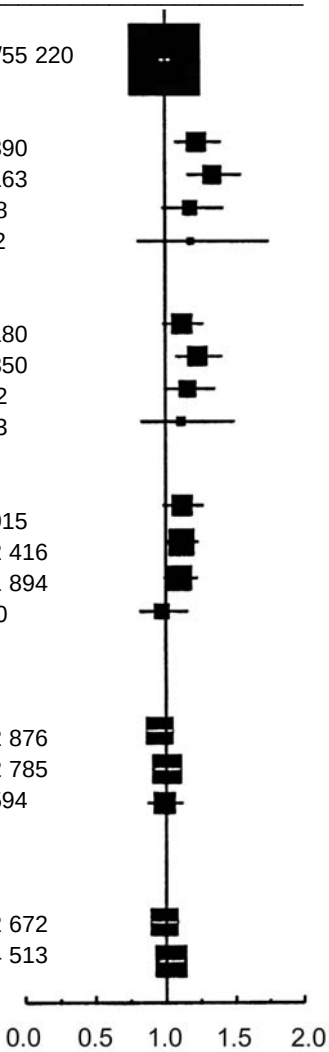


Figure 3 (contd)

(c) Relative risk for breast cancer by time since first use and time since last use of combined oral contraceptives

	RR[a] ± SD	Cases/controls
Never used	1.00 ± 0.015	28 200/55 220
Current user		
First use < 10 years previously	1.22 ± 0.058	947/2 390
10–14 years previously	1.34 ± 0.065	823/1 163
15–19 years previously	1.18 ± 0.079	461/588
≥ 20 years previously	1.18 ± 0.165	110/132
Last use 1–4 years previously		
First use < 10 years previously	1.12 ± 0.054	967/2 180
10–14 years previously	1.23 ± 0.059	869/1 350
15–19 years previously	1.16 ± 0.066	650/902
≥ 20 years previously	1.11 ± 0.121	176/243
Last use 5–9 years previously		
First use < 10 years previously	1.12 ± 0.053	941/1 915
10–14 years previously	1.11 ± 0.043	1 424/2 416
15–19 years previously	1.10 ± 0.045	1 246/1 894
≥ 20 years previously	0.97 ± 0.068	480/800
Last use 10–14 years previously		
First use < 10 years previously	Not applicable	
10–14 years previously	0.95 ± 0.038	1 433/2 876
15–19 years previously	1.01 ± 0.036	1 739/2 785
≥ 20 years previously	0.99 ± 0.049	976/1 594
Last use ≥ 15 years previously		
First use < 15 years previously	Not applicable	
15–19 years previously	0.98 ± 0.038	1 523/2 672
≥ 20 years previously	1.03 ± 0.034	2 575/4 513



Adapted from Collaborative Group on Hormonal Factors in Breast Cancer (1996a,b)

Of 15 tests for heterogeneity, one within each time since last use category, two are statistically significant: age at first use in current users ($\chi^2 = 12.7$, degrees of freedom (d.f.) = 3, $p = 0.005$) and age at first use by women whose last use was 1–4 years previously ($\chi^2 = 12.6$, d.f. = 3, $p = 0.006$).

[a] Relative risk (given with 99% confidence interval) relative to no use, stratified by study, age at diagnosis, parity, and, where appropriate, the age when first child was born and age when risk for conceiving ceased.

Table 7. Use of combined oral contraceptives and risk for breast cancer risk according to age at diagnosis

Reference	Years of diagnosis	Comparison	Age at diagnosis (years)	Users		RR	95% CI
				No. of cases	No. of controls or person–years		
Vessey *et al*. (1983)	1968–80	Ever versus never	< 36	210	210	0.94	0.57–1.5
			36–40	257	257	0.86	0.56–1.3
			41–45	388	388	0.72	0.51–1.0
			46–50	321	321	1.5	1.0–2.2
Meirik *et al*. (1986)	1984–85	≥ 12 years versus never	< 45	39	23	2.2	1.2–4.0
McPherson *et al*. (1987)	1980–84	≥ 12 years versus never	< 45	21	20	1.8	0.82–3.9
			≥ 45	13	23	0.84	0.39–1.8
Ravnihar *et al*. (1988)	1980–83	Ever versus never	< 35	31	96	1.5	0.68–3.4
			35–44	84	249	1.7	1.2–2.4
			45–54	57	122	1.5	1.0–2.3
Romieu *et al*. (1989)	1976–86	Current versus never	30–34	3	8 090[a]	0.71	0.19–2.6
		Past versus never		18	51 417[a]	0.67	0.3–1.4
		Current versus never	35–39	6	6 674[a]	1.0	0.43–2.4
		Past versus never		100	114 278[a]	1.0	0.74–1.5
		Current versus never	40–44	13	4 369[a]	2.7	1.5–4.6
		Past versus never		153	119 882[a]	1.1	0.89–1.5
		Current versus never	45–49	8	2 635[a]	1.6	0.81–3.3
		Past versus never		196	91 394[a]	1.2	0.95–1.4
		Current versus never	50–54	2	777[a]	1.1	0.28–4.4
		Past versus never		133	61 657[a]	1.1	0.90–1.4
		Current versus never	55–59	0	72[a]	–	
		Past versus never		69	29 144[a]	1.0	0.80–1.4
		Current versus never	60–64	0	5[a]	–	
		Past versus never		16	5 056[a]	1.2	0.72–2.1

Table 7 (contd)

Reference	Years of diagnosis	Comparison	Age at diagnosis (years)	Users		RR	95% CI
				No. of cases	No. of controls or person–years		
Stanford *et al.* (1989)	1973–80	Ever versus never	< 40	76	92	1.0	0.5–1.9
			40–44	208	235	1.4	0.9–1.9
			45–49	385	377	1.1	0.8–1.4
			50–54	425	448	0.8	0.6–1.1
			55–59	331	366	0.99	0.6–1.5
			≥ 60	597	665	1.0	0.5–2.2
UK National Case–Control Study (1989)	1982–85	> 8 years versus never	< 35	198	143	1.74	$p_{trend} < 0.001$
Bernstein *et al.* (1990)	1972–83	Ever versus never	< 37			RR, 1.0 per year of use	
Paul *et al.* (1990)	1983–87	Ever versus never	25–34	59	370	1.2	0.44–3.4
			35–44	286	711	1.2	0.78–1.8
			45–54	340	455	1.0	0.77–1.3
WHO Collaborative Study (1990)	1979–86	Ever versus never	< 35	160	1 613	1.3	0.95–1.7
			≥ 35	560	2 814	1.1	0.98–1.3
Weinstein *et al.* (1991)	1984–86	Ever versus never	20–49	175	145	1.4	1.0–2.0
			50–70	101	95	1.1	0.79–1.5
Wingo *et al.* (1991)	1980–82	Ever versus never	20–34	425	547	1.4	1.0–2.1
			35–44	1 190	1 031	1.1	0.9–1.3
			45–54	888	991	0.9	0.8–1.0

Table 7 (contd)

Reference	Years of diagnosis	Comparison	Age at diagnosis (years)	Users		RR	95% CI
				No. of cases	No. of controls or person–years		
Ewertz (1992)	1983–84	≥ 12 years versus never	< 40	20	22	1.1	0.5–2.2
			40–59	83	67	1.3	0.82–2.0
Rosenberg *et al*. (1992)	1982–86	≥ 10 years versus never	< 40	13	27	0.8	0.3–2.5
			40–69	46	95	0.9	0.6–1.3
Tavani *et al*. (1993a)	1983–91	Ever versus never	< 60	371	265	1.2	1.0–1.4
			< 40	130	151	0.9	0.6–1.2
Rookus *et al*. (1994)	1986–89	≥ 12 years versus never	< 35	20	8	2.9	
			36–45	75	79	1.1	
			46–54	41	21	2.3	
White *et al*. (1994)	1983–90	≥ 1 year versus < 1 year	< 46	583	733	1.0	0.81–1.3
Brinton *et al*. (1995)	1990–92	≥ 6 months versus < 6 months or never	< 35	206	193	1.7	1.2–2.6
			35–39	379	336	1.4	1.0–1.8
			40–44	674	545	1.1	0.9–1.4
			45–49	203	184	1.2	0.8–1.8
			50–54	138	142	0.94	0.6–1.4
Palmer *et al*. (1995)	1977–92	≥ 3 years versus < 1 year	< 45	87	142	2.2	1.5–3.2
			45–59	27	31	1.3	0.7–2.4
Primic- akelj *et al*. (1995)	1988–90	Ever versus never	Pre-menopausal	250	249	1.0	0.80–1.4
			Post-menopausal	48	50	1.4	0.82–2.4

Table 7 (contd)

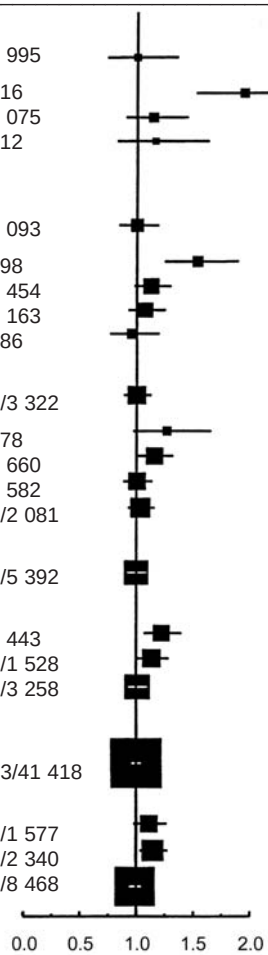
Reference	Years of diagnosis	Comparison	Age at diagnosis (years)	Users		RR	95% CI
				No. of cases	No. of controls or person–years		
Newcomb *et al.* (1996)	1988–91	Ever versus never	< 35	139	400	1.4	0.8–2.3
			35–44	723	1 155	1.0	0.8–1.3
			45–54	809	1 112	1.1	0.9–1.3
			≥ 55	591	780	1.0	0.9–1.2
Rosenberg *et al.* (1996)	1977–92	≥ 1 year versus < 1 year	25–34	184	422	1.7	1.3–2.3
			35–44	455	606	0.9	0.7–1.0
			45–59	389	333	1.2	1.0–1.4
Rossing *et al.* (1996)	1988–90	Ever versus never	50–64	253	226	1.1	0.8–1.4

RR, relative risk; CI, confidence interval

[a] Person-years

Figure 4. Age-specific relative risk for breast cancer by time since last use of combined oral contraceptives

Age at diagnosis of breast cancer and duration of use of combined oral contraceptives	RR[a] ± SD	Cases/ controls
Age < 30 at diagnosis		
never user	1.00 ± 0.118	290/2 995
< 5 years since last use; < 20 at first use	1.95 ± 0.134	348/916
< 5 years since last use; ≥ 20 at first use	1.14 ± 0.098	254/1 075
5–9 years since last use	1.16 ± 0.143	134/412
≥ 10 years since last use	insufficient data	18/48
Age 30–34 at diagnosis		
never user	1.00 ± 0.067	690/2 093
< 5 years since last use; < 20 at first use	1.54 ± 0.101	437/498
< 5 years since last use; ≥ 20 at first use	1.13 ± 0.058	745/1 454
5–9 years since last use	1.08 ± 0.060	629/1 163
≥ 10 years since last use	0.96 ± 0.085	293/586
Age 35–39 at diagnosis		
never user	1.00 ± 0.047	1 459/3 322
< 5 years since last use; < 20 at first use	1.27 ± 0.116	237/278
< 5 years since last use; ≥ 20 at first use	1.16 ± 0.055	965/1 660
5–9 years since last use	1.00 ± 0.049	899/1 582
≥ 10 years since last use	1.03 ± 0.044	1 286/2 081
Age 40–44 at diagnosis		
never user	1.00 ± 0.035	2 958/5 392
< 5 years since last use; < 20 at first use	insufficient data	45/43
< 5 years since last use; ≥ 20 at first use	1.22 ± 0.057	942/1 443
5–9 years since last use	1.13 ± 0.051	1 024/1 528
≥ 10 years since last use	1.01 ± 0.034	2 222/3 258
Age > 45 at diagnosis		
never user	1.00 ± 0.017	22 803/41 418
< 5 years since last use; < 20 at first use	insufficient data	1/4
< 5 years since last use; ≥ 20 at first use	1.11 ± 0.053	1 029/1 577
5–9 years since last use	1.15 ± 0.043	1 405/2 340
≥ 10 years since last use	0.99 ± 0.021	4 427/8 468



Test for trend with age at diagnosis in women with:
last use < 5 years ago, age at first use < 20: χ^2 (1 d.f.) = 5.2; p = 0.02
last use < 5 years ago, age at first use ≥ 20: χ^2 (1 d.f.) = 0.0; NS
last use 5–9 years ago: χ^2 (1 d.f.) = 1.2; NS
last use ≥ 10 years ago: χ^2 (1 d.f.) = 0.1; NS

Adapted from Collaborative Group on Hormonal Factors in Breast Cancer (1996a,b)
d.f., degree of freedom
[a] Relative risk (given with 99% confidence interval) relative to no use, stratified by study, age at diagnosis, parity and, where appropriate, the age when her first child was born and the age when her risk for conceiving ceased.

Table 8. Risk for breast cancer in relation to time since last use (recency of use) of combined oral contraceptives

Reference	Years of case diagnosis	Time since last use (years)	Age (years)	Users (cases/ controls)	RR (95% CI)
Vessey *et al*. (1983)	1968–80	≤ 1	16–50	58/69	0.99 (0.76–1.3)
		> 1–≤ 4		122/119	0.95 (0.7–1.3)
		> 4–≤ 8		125/101	1.3 (0.98–1.8)
		> 8		90/136	0.67 (0.48–0.94)
Meirik *et al*. (1986)	1984–85	Current use	< 45	80/80	1.5 (0.8–2.8)
		1–2		30/25	1.8 (0.9–3.7)
		3–5		45/35	1.9 (1.0–3.3)
		6–8		45/49	1.4 (0.8–2.4)
		9–11		36/55	1.0 (0.6–1.7)
		≥ 12		90/127	0.9 (0.6–1.4)
Rohan & McMichael (1988)	1982–84	≤ 8	20–69	81/71	1.2 (0.7–2.2)
		9–14		51/62	0.87 (0.50–1.5)
		≥ 15		55/52	1.1 (0.62–1.9)
Stanford *et al*. (1989)	1973–80	Current use	All	47/57	0.81 (0.5–1.2)
		1–3		93/96	1.0 (0.7–1.4)
		4–6		102/109	1.0 (0.8–1.4)
		≥ 7		221/251	0.96 (0.8–1.2)
Romieu *et al*. (1989)	1976–86	Current use	30–64	32/22 622[a]	1.6 (1.1–2.2)
		< 1		205/129 638[a]	1.1 (0.97–1.3)
		1–2		156/123 636[a]	1.1 (0.89–1.3)
		3–4		86/72 837[a]	0.97 (0.78–1.2)
		5–9		159/104 277[a]	1.1 (0.96–1.4)
		10–14		57/33 206[a]	1.1 (0.83–1.4)
		≥ 15		6/3 195[a]	1.1 (0.47–2.4)
WHO Collaborative Study (1990)	1979–86	Current use	< 62	127/747	1.7 (1.3–2.1)
		4–35 months		120/751	1.4 (1.1–1.8)
		3–9		234/1 374	1.2 (0.98–1.4)
		> 9		213/1 388	0.91 (0.77–1.1)
Clavel *et al*. (1991)	1983–87	Current use	20–55	41/45	1.4 (0.9–2.4)
		< 5		75/80	1.6 (1.0–2.5)
		5–9		66/56	1.6 (1.0–2.4)
		≥ 10		55/55	1.5 (0.9–2.3)

Table 8 (contd)

Reference	Years of case diagnosis	Time since last use (years)	Age (years)	Users (cases/ controls)	RR (95% CI)
Wingo *et al*. (1991)	1980–82	< 1 1–< 2 2–3 4–5 6–7 8–9 10–11 12–13 14–15 16–17 18–19 ≥ 20	20–34	Not given	1.7 (1.1–2.6) 1.1 (0.6–2.1) 1.2 (0.7–1.9) 1.8 (1.1–3.0) 1.5 (0.9–2.5) 1.5 (0.9–2.6) 1.3 (0.7–2.4) 1.0 (0.5–1.8) p_{trend} = 0.5
			35–44	Not given	1.2 (0.8–1.8) 1.2 (0.7–2.3) 1.5 (1.0–2.2) 1.2 (0.9–1.6) 1.1 (0.8–1.5) 1.0 (0.7–1.3) 1.0 (0.7–1.3) 0.9 (0.7–1.2) 1.0 (0.7–1.3) 1.2 (0.8–1.7) 0.9 (0.5–1.5) 0.6 (0.3–1.5) p_{trend} < 0.01
			45–54	Not given	0.8 (0.4–1.5) 0.8 (0.3–2.2) 1.0 (0.7–1.5) 1.1 (0.8–1.4) 1.0 (0.8–1.3) 1.3 (0.9–1.7) 0.9 (0.7–1.2) 0.8 (0.6–1.1) 0.8 (0.6–1.1) 0.6 (0.5–0.8) 1.0 (0.7–1.5) 0.6 (0.4–0.8) p_{trend} < 0.01

Table 8 (contd)

Reference	Years of case diagnosis	Time since last use (years)	Age (years)	Users (cases/ controls)	RR (95% CI)
Ewertz (1992)	1983–84	< 5	< 40	56/65	1.0 (0.59–1.8)
		5–9		46/37	1.5 (0.81–2.8)
		≥ 10		59/58	1.2 (0.68–2.1)
			40–59	118/92	Reference
				87/70	0.97 (0.64–1.5)
				90/121	0.58 (0.39–0.85)
Tavani *et al*. (1993a)	1983–91	<5	< 60	97/82	1.3 (1.0–1.9)
		5–9		105/75	1.1 (0.8–1.6)
		≥ 10		166/103	1.2 (0.9–1.5)
Rookus *et al*. (1994)	1986–89	< 3	46–54	Not given	1.9 (0.9–4.1)
White *et al*. (1994)	1983–90	Current use	21–45	59/88	1.3 (0.83–1.9)
		< 5		102/131	1.3 (0.91–1.8)
		5–9		135/171	1.0 (0.75–1.4)
		10–14		171/226	0.88 (0.65–1.2)
		≥ 15		116/111	0.96 (0.67–1.4)
Brinton *et al*. (1995)	1990–92	< 5	20–34	135/Not given	2.0 (1.3–3.1)
		5–9		40/Not given	1.5 (0.8–2.6)
		≥ 10		31/Not given	1.2 (0.6–2.2)
			35–39	106/Not given	1.5 (0.9–2.2)
				72/Not given	1.3 (0.9–2.0)
				201/Not given	1.3 (0.9–1.9)
			40–44	57/Not given	1.2 (0.8–2.0)
				91/Not given	1.2 (0.8–1.7)
				526/Not given	1.1 (0.9–1.4)
La Vecchia *et al.* (1995)	1991–94	< 10	< 35	Not given	1.4 (0.7–2.7)
		≥ 10		Not given	1.6 (0.4–6.0)
			35–44	Not given	1.9 (1.2–2.9)
				Not given	1.3 (0.9–2.0)
			45–64	Not given	1.3 (0.8–2.3)
				Not given	1.1 (0.8–1.4)

Table 8 (contd)

Reference	Years of case diagnosis	Time since last use (years)	Age (years)	Users (cases/ controls)	RR (95% CI)
Palmer *et al*. (1995)	1977–92	< 2	25–59 (women with ≥ 3 years of use)	19/29	3.1 (1.5–6.3)
		2–4		6/28	0.9 (0.3–2.4)
		5–9		26/37	2.5 (1.4–4.5)
		10–14		14/35	1.0 (0.5–2.1)
		≥ 15		14/7	4.7 (1.7–13)
Paul *et al*. (1995)	1983–87	< 1	25–34	18/147	1.3 (0.42–4.1)
		1–4		17/85	1.9 (0.61–6.1)
		5–9		20/96	1.4 (0.46–4.3)
		≥ 10		4/42	0.36 (0.08–1.6)
			35–44	31/76	1.2 (0.65–2.1)
				40/93	1.4 (0.82–2.5)
				65/188	1.1 (0.65–1.7)
				150/354	1.2 (0.78–1.9)
			45–54	21/20	1.5 (0.78–2.9)
				30/43	0.90 (0.53–1.5)
				63/78	1.0 (0.69–1.6)
				226/314	0.99 (0.74–1.3)
Primic- akelj *et al*. (1995)	1988–90	< 6 months	25–54	32/16	2.3 (1.2–4.5)
		7 months–5 years		43/38	1.3 (0.78–2.1)
		6–10		54/68	0.89 (0.57–1.4)
		11–15		94/102	1.0 (0.71–1.4)
		> 15		75/75	1.1 (0.76–1.7)
Levi *et al*. (1996)	1990–95	< 5	< 70	22/40	1.9 (0.9–3.6)
		5–14		33/40	2.4 (1.4–4.4)
		≥ 15		22/54	1.0 (0.6–1.8)
Newcomb *et al.* (1996)	1988–91	< 2	< 35	30/109	1.3 (0.6–2.6)
		2–4		25/64	1.9 (0.9–3.8)
		5–9		47/127	1.5 (0.8–2.7)
		≥ 10		37/100	1.1 (0.6–2.2)
			35–44	26/21	2.0 (1.1–3.9)
				19/40	0.7 (0.4–1.3)
				108/164	1.1 (0.8–1.5)
				570/930	1.0 (0.8–2.1)

Table 8 (contd)

Reference	Years of case diagnosis	Time since last use (years)	Age (years)	Users (cases/ controls)	RR (95% CI)
Newcomb *et al.* (1996) (contd)			45–54	8/8	1.4 (0.5–4.0)
				10/12	1.3 (0.5–3.1)
				45/66	0.9 (0.6–1.4)
				746/1 026	1.1 (0.9–1.3)
		< 5	55–74	11/7	2.2 (0.8–5.7)
		5–9		24/41	0.8 (0.5–1.4)
		≥ 10		556/732	1.0 (0.9–1.2)
Rosenberg *et al.* (1996)	1977–92	< 3	25–34	80/184	1.9 (1.3–2.8)
		3–4		18/57	1.8 (0.9–3.3)
		5–9		53/112	1.6 (1.0–2.4)
		10–14		22/48	1.3 (0.7–2.3)
		≥ 15		0/3	–
			35–44	36/94	0.7 (0.5–1.2)
				25/50	0.8 (0.4–1.4)
				92/176	0.8 (0.5–1.0)
				157/159	1.1 (0.8–1.5)
				124/99	0.8 (0.6–1.2)
			45–54	16/29	0.9 (0.5–1.9)
				15/17	1.7 (0.8–3.8)
				70/80	1.0 (0.7–1.5)
				110/79	1.4 (1.0–1.9)
				159/106	1.2 (0.9–1.6)
Rossing *et al.* (1996)	1988–90	≤ 10	50–64	29/24	1.1 (0.6–2.0)
		11–15		57/43	1.4 (0.9–2.1)
		16–20		65/57	1.1 (0.7–1.7)
		21–25		57/59	0.9 (0.6–1.4)
		≥ 26		43/42	0.9 (0.6–1.5)

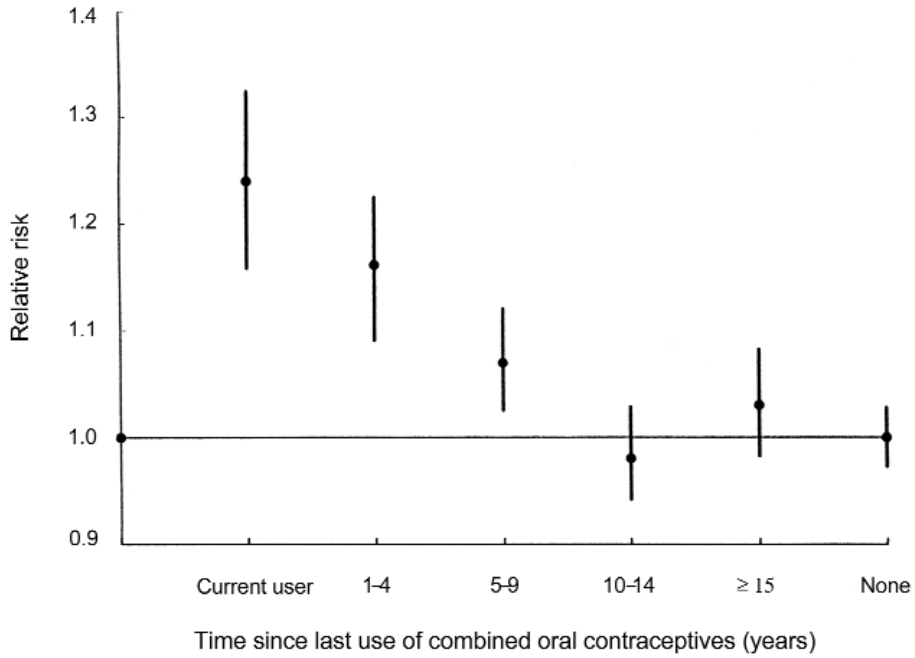
RR, relative risk; CI, confidence interval
[a] Person–years

(Meirik *et al*., 1986; Rohan & McMichael, 1988; Romieu *et al*., 1990; WHO Collaborative Study of Neoplasia and Steroid Contraceptives, 1990; Wingo *et al*., 1991; White *et al*., 1994; Brinton *et al*., 1995; Paul *et al*., 1995; Primic- akelj *et al*., 1995; La Vecchia *et al*., 1995; Levi *et al*., 1996; Newcomb *et al*., 1996; Rosenberg *et al*., 1996). In the study of La Vecchia *et al.* (1995), the increase was greater for women with longer use. Another consistent finding is that there is little or no increase in risk, or possibly even a decrease, among women who last used combined oral contraceptives at least 10 years previously (Meirik *et al*., 1986; Rohan & McMichael, 1988; Romieu *et al*., 1989; Stanford *et al*., 1989; WHO Collaborative Study of Neoplasia and Steroid Contraceptives, 1990; Wingo *et al*., 1991; White *et al*., 1994; Brinton *et al*., 1995; Paul *et al*., 1995; Primic- akelj *et al*., 1995; Levi *et al*., 1996; Newcomb *et al*., 1996; Rosenberg *et al*., 1996; Rossing *et al*., 1996); however, there was little or no variation in risk with recency of use in the studies of Vessey *et al*. (1983), Stanford *et al*. (1989), Ewertz (1992), Tavani *et al*. (1993a) or Rossing *et al*. (1996). The studies of Clavel *et al*. (1991) and Palmer *et al*. (1995) showed increased risks for users of these oral contraceptives that appeared to be unrelated to the recency of use. The estimated relative risk for breast cancer overall in the collaborative reanalysis was 1.24 (95% CI, 1.17–1.3) for current users, 1.16 (95% CI, 1.1–1.22) for users 1–4 years after stopping, 1.07 (95% CI, 1.0–1.12) for users 5–9 years after stopping and 1.0 (95% CI, 0.96–1.1) for users 10 or more years after stopping (Collaborative Group on Hormonal Factors in Breast Cancer, 1996b; Figure 5).

The relationship between recency of use and the risk for breast cancer at different ages was not assessed in many studies. Among those in which it was, that of Rookus *et al*. (1994) showed an increased risk associated with recent use for older but not younger women. In the studies of Wingo *et al*. (1991), Brinton *et al*. (1995), Paul *et al*. (1995) and Rosenberg *et al*. (1996), the increase in risk for recent users was most apparent in women under 35 years of age; in the study of La Vecchia *et al.* (1995), the increase for recent users was greatest among women aged 35–44; in the Nurses' Health Study (Romieu *et al*., 1989), the point estimates of relative risk were increased for current users aged 40–45 and 45–49 and not younger users, but there were very few current users in any age group. In the study of Newcomb *et al*. (1996), the point estimates of relative risk were elevated for recent users in every age group, from < 35 through 55 and older (see Figure 4).

Data on the duration of use have been inconsistent, some studies suggesting increasing risk with increasing duration of use overall, before a first pregnancy or after starting at a young age. Long use is highly correlated with recent use, and it has been difficult to disentangle their effects. In studies in which recency of use was taken into account, there has been no clear trend for an increased risk with increasing duration (Romieu *et al*., 1989; Paul *et al*., 1990; WHO Collaborative Study of Neoplasia and Steroid Contraceptives, 1990; Wingo *et al*., 1991; Palmer *et al*., 1995; Primic- akelj *et al*., 1995; Newcomb *et al*., 1996; Rosenberg *et al*., 1996). It is too early, however, to rule out a greater increase in risk for recent users who have used combined oral contraceptives for a very long time beginning at young ages, because the data on this issue are sparse (Collaborative Group on Hormonal Factors in Breast Cancer, 1996a,b; Figure 3).

Figure 5. Relative risk for breast cancer by time since last use of combined oral contraceptives



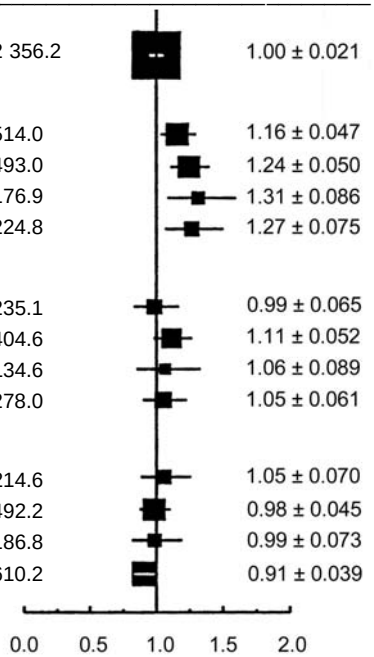
From Collaborative Group on Hormonal Factors in Breast Cancer (1996b)
Relative risk (given with 95% confidence interval (CI)) relative to no use, stratified by study, age at diagnosis, parity, age at first birth and age at which risk for conceiving ceased

It has also been suggested that the risk for breast cancer associated with use of combined oral contraceptives varies according to the constituents of the formulation, e.g. that preparations with 'high potency' progestogens (as defined by their effect on the uterus) are the most harmful (Pike *et al*., 1983). It has been difficult to study individual formulations because there are many of them, there are relatively few users of any particular one, and women tend to use several over the course of their reproductive lives. Little support for a differential effect according to the type of oestrogen or progestogen or the dose is provided in most studies (Vessey *et al*., 1983; Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development, 1986; Ravnihar *et al*., 1988; UK National Case–Control Study Group, 1989; Clavel *et al*., 1991; Ebeling *et al*., 1991; Thomas *et al*., 1992; Rookus *et al*., 1994; Collaborative Group on Hormonal Factors in Breast Cancer, 1996a; Rosenberg *et al*., 1996), although others indicate an effect (McPherson *et al*., 1987; Ewertz, 1992; White *et al*., 1994). Data from the Collaborative Group on Hormonal Factors in Breast Cancer (1996a,b) (Figures 6–10) show that there is little variation according to type or dose of oral contraceptive.

Figure 6. Relative risk (RR) for breast cancer by time since last use and oestrogen and progestogen type and dose of combined oral contraceptives last used

(a) Oestrogen type and dose

Time since last use	Cases/controls	InRR	1	Relative risk[a]	
		var(InRR)	var(InRR)	RR (99% CI)	RR ± SD
Never	15 715/29 503	0.0	2 356.2		1.00 ± 0.021
Last use < 5 years previously					
ethinyloestradiol < 50 μg	1 494/2 217	74.7	514.0		1.16 ± 0.047
ethinyloestradiol = 50 μg	1 203/2 543	107.4	493.0		1.24 ± 0.050
mestranol = 50 μg	427/1 152	48.4	176.9		1.31 ± 0.086
mestranol > 50 μg	568/780	52.9	224.8		1.27 ± 0.075
Last use 5–9 years previously					
ethinyloestradiol < 50 μg	554/796	–3.5	235.1		0.99 ± 0.065
ethinyloestradiol = 50 μg	954/1 699	43.5	404.6		1.11 ± 0.052
mestranol = 50 μg	302/673	8.4	134.6		1.06 ± 0.089
mestranol > 50 μg	676/893	13.7	278.0		1.05 ± 0.061
Last use ≥ 10 years previously					
ethinyloestradiol < 50 μg	555/637	11.4	214.6		1.05 ± 0.070
ethinyloestradiol = 50 μg	1 247/2 124	–8.1	492.2		0.98 ± 0.045
mestranol = 50 μg	423/822	–2.4	186.8		0.99 ± 0.073
mestranol > 50 μg	1 548/2 073	–56.8	610.2		0.91 ± 0.039

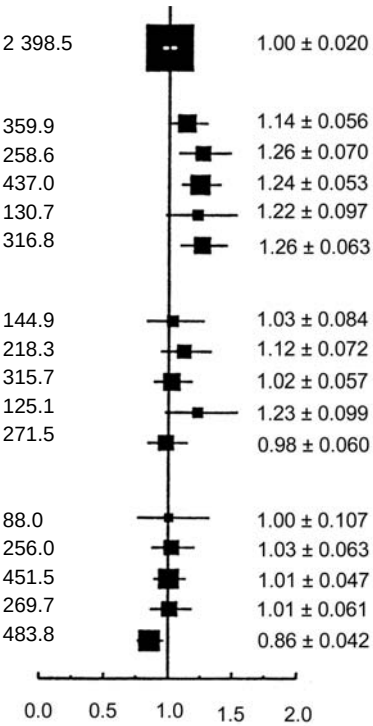


Trend for heterogeneity by type and dose of oestrogen in women with:
Last use < 5 years previously: χ^2 (3 d.f.) = 2.9; NS
Last use 5–9 years previously: χ^2 (3 d.f.) = 2.3; NS
Last use ≥ 10 years previously: χ^2 (3 d.f.) = 4.0; NS

Figure 6 (contd)

(b) Progestogen type and dose

Time since last use	Cases/controls	InRR	1	Relative risk[a]	
		var(InRR)	var(InRR)	RR (99% CI)	RR ± SD
Never	15 715/29 503	0.0	2 398.5		1.00 ± 0.020
Last use < 5 years previously					
levonorgestrel < 250 mg	931/1 613	45.6	359.9		1.14 ± 0.056
levonorgestrel > 250 mg	622/1 358	60.2	258.6		1.26 ± 0.070
norethisterone < 1000 mg	1 070/2 075	94.5	437.0		1.24 ± 0.053
norethisterone > 1000 mg	310/457	26.3	130.7		1.22 ± 0.097
other	775/1 213	73.1	316.8		1.26 ± 0.063
Last use 5–9 years previously					
levonorgestrel < 250 mg	331/527	4.3	144.9		1.03 ± 0.084
levonorgestrel > 250 mg	509/956	24.4	218.3		1.12 ± 0.072
norethisterone < 1000 mg	726/1 242	7.6	315.7		1.02 ± 0.057
norethisterone > 1000 mg	324/401	25.4	125.1		1.23 ± 0.099
other	611/975	–5.4	271.5		0.98 ± 0.060
Last use ≥ 10 years previously					
levonorgestrel < 250 mg	212/274	0.4	88.0		1.00 ± 0.107
levonorgestrel > 250 mg	633/1 095	6.6	256.0		1.03 ± 0.063
norethisterone < 1000 mg	1 157/1 683	2.3	451.5		1.01 ± 0.047
norethisterone > 1000 mg	716/960	3.0	269.7		1.01 ± 0.061
other	1 080/1 692	–74.0	483.8		0.86 ± 0.042



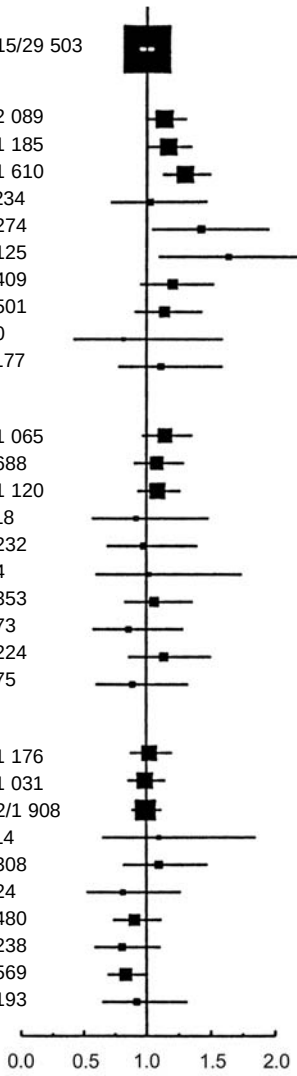
Trend for heterogeneity by type and dose of progestogen in women with:
Last use < 5 years previously: χ^2 (4 d.f.) = 2.6; NS
Last use 5–9 years previously: χ^2 (4 d.f.) = 5.4; NS
Last use ≥ 10 years previously: χ^2 (4 d.f.) = 9.1; p = 0.003

Adapted from Collaborative Group on Hormonal Factors in Breast Cancer (1996a,b)
d.f., degrees of freedom; NS, not significant; CI, confidence interval; SD, standard deviation
[a] Relative to no use, stratified by study, age at diagnosis, parity, age at first birth and age at which risk for conceiving ceased

Figure 7. Relative risk (RR) for breast cancer by time since last use and type of oestrogen and progestogen in the oral contraceptive

(a) First used

Oestrogen and progestogen	Cases/controls	Relative risk[a] RR & 99% CI	RR ± SD
Never	15 715/29 503		1.00 ± 0.020
Last use < 5 years previously			
ethinyloestradiol and norgestrel	882/2 089		1.14 ± 0.058
ethinyloestradiol and norethisterone	782/1 185		1.17 ± 0.061
mestranol and norethisterone	839/1 610		1.30 ± 0.064
ethinyloestradiol and lynoestrenol	112/234		1.03 ± 0.141
mestranol and lynoestrenol	171/274		1.42 ± 0.146
ethinyloestradiol and ethynodiol	109/125		1.64 ± 0.202
mestranol and ethynodiol	280/409		1.20 ± 0.101
mestranol and chlormadinone or norethynodrel	308/501		1.14 ± 0.095
ethinyloestradiol and desogestrel or gestodene	32/50		0.82 ± 0.234
other	117/177		1.11 ± 0.147
Last use 5–9 years previously			
ethinyloestradiol and norgestrel	540/1 065		1.14 ± 0.070
ethinyloestradiol and norethisterone	499/688		1.08 ± 0.072
mestranol and norethisterone	697/1 120		1.08 ± 0.062
ethinyloestradiol and lynoestrenol	64/118		0.92 ± 0.178
mestranol and lynoestrenol	125/232		0.98 ± 0.136
ethinyloestradiol and ethynodiol	49/84		1.02 ± 0.209
mestranol and ethynodiol	245/353		1.06 ± 0.099
mestranol and chlormadinone acetate	76/173		0.86 ± 0.145
mestranol and norethynodrel	212/224		1.14 ± 0.116
other	90/175		0.89 ± 0.145
Last use ≥ 10 years previously			
ethinyloestradiol and norgestrel	658/1 176		1.02 ± 0.062
ethinyloestradiol and norethisterone	745/1 031		0.99 ± 0.057
mestranol and norethisterone	1 372/1 908		0.99 ± 0.045
ethinyloestradiol and lynoestrenol	55/114		1.10 ± 0.213
mestranol and lynoestrenol	210/308		1.10 ± 0.121
ethinyloestradiol and ethynodiol	69/124		0.81 ± 0.154
mestranol and ethynodiol	338/480		0.91 ± 0.077
mestranol and chlormadinone acetate	128/238		0.81 ± 0.111
mestranol and norethynodrel	430/569		0.84 ± 0.067
other	123/193		0.92 ± 0.132

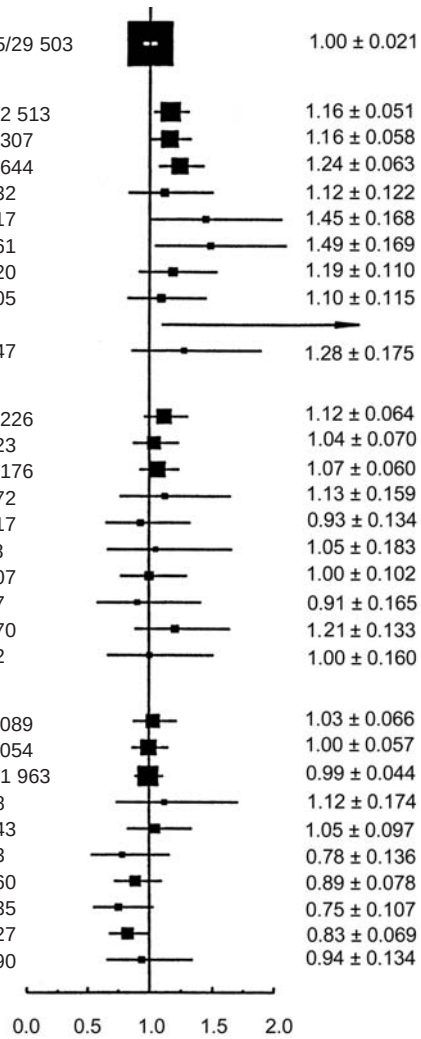


Test for heterogeneity by type of oral contraceptive in women with:
Last use < 5 years previously: χ^2 (9 d.f.) = 13.3; NS
Last use 5–9 years previously: χ^2 (9 d.f.) = 6.0; NS
Last use ≥ 10 years previously: χ^2 (9 d.f.) = 10.8; NS

Figure 7 (contd)

(b) Most used

Oestrogen and progestogen	Cases/controls	Relative risk[a] RR & 99% CI	RR ± SD
Never	15 715/29 503		1.00 ± 0.021
Last use < 5 years previously			
ethinyloestradiol and norgestrel	1 168/2 513		1.16 ± 0.051
ethinyloestradiol and norethisterone	835/1 307		1.16 ± 0.058
mestranol and norethisterone	807/1 644		1.24 ± 0.063
ethinyloestradiol and lynoestrenol	163/332		1.12 ± 0.122
mestranol and lynoestrenol	149/217		1.45 ± 0.168
ethinyloestradiol and ethynodiol	137/161		1.49 ± 0.169
mestranol and ethynodiol	241/320		1.19 ± 0.110
mestranol and chlormadinone or norethynodrel	181/305		1.10 ± 0.115
ethinyloestradiol and desogestrel or gestodene	30/22		
other	101/147		1.28 ± 0.175
Last use 5–9 years previously			
ethinyloestradiol and norgestrel	631/1 226		1.12 ± 0.064
ethinyloestradiol and norethisterone	506/723		1.04 ± 0.070
mestranol and norethisterone	729/1 176		1.07 ± 0.060
ethinyloestradiol and lynoestrenol	108/172		1.13 ± 0.159
mestranol and lynoestrenol	123/217		0.93 ± 0.134
ethinyloestradiol and ethynodiol	67/118		1.05 ± 0.183
mestranol and ethynodiol	224/307		1.00 ± 0.102
mestranol and chlormadinone acetate	66/137		0.91 ± 0.165
mestranol and norethynodrel	168/170		1.21 ± 0.133
other	85/162		1.00 ± 0.160
Last use ≥ 10 years previously			
ethinyloestradiol and norgestrel	553/1 089		1.03 ± 0.066
ethinyloestradiol and norethisterone	764/1 054		1.00 ± 0.057
mestranol and norethisterone	1 425/1 963		0.99 ± 0.044
ethinyloestradiol and lynoestrenol	83/148		1.12 ± 0.174
mestranol and lynoestrenol	335/443		1.05 ± 0.097
ethinyloestradiol and ethynodiol	82/153		0.78 ± 0.136
mestranol and ethynodiol	316/460		0.89 ± 0.078
mestranol and chlormadinone acetate	126/235		0.75 ± 0.107
mestranol and norethynodrel	398/527		0.83 ± 0.069
other	120/190		0.94 ± 0.134

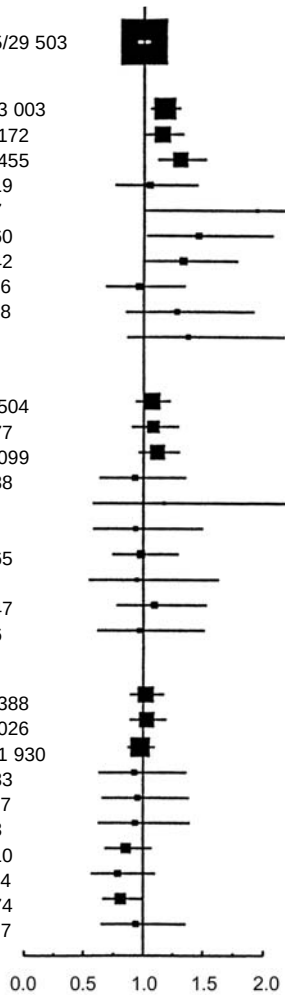


Test for heterogeneity by type of oral contraceptive in women with:
Last use < 5 years previously: χ^2 (9 d.f.) = 12.0; NS
Last use 5–9 years previously: χ^2 (9 d.f.) = 4.4; NS
Last use ≥ 10 years previously: χ^2 (9 d.f.) = 14.4; NS

Figure 7 (contd)

(c) Last used

Oestrogen and progestogen	Cases/controls	Relative risk[a] RR & 99% CI	RR ± SD
Never	15 715/29 503		1.00 ± 0.019
Last use < 5 years previously			
ethinyloestradiol and norgestrel	1 564/3 003		1.17 ± 0.045
ethinyloestradiol and norethisterone	744/1 172		1.15 ± 0.060
mestranol and norethisterone	705/1 455		1.30 ± 0.069
ethinyloestradiol and lynoestrenol	129/319		1.05 ± 0.129
mestranol and lynoestrenol	40/107		
ethinyloestradiol and ethynodiol	132/160		1.46 ± 0.168
mestranol and ethynodiol	196/242		1.33 ± 0.133
mestranol and chlormadinone or norethynodrel	117/216		0.96 ± 0.129
ethinyloestradiol and desogestrel or gestodene	109/118		1.26 ± 0.180
other	75/98		1.37 ± 0.212
Last use 5–9 years previously			
ethinyloestradiol and norgestrel	848/1 504		1.07 ± 0.055
ethinyloestradiol and norethisterone	481/677		1.08 ± 0.073
mestranol and norethisterone	685/1 099		1.12 ± 0.063
ethinyloestradiol and lynoestrenol	104/188		0.93 ± 0.142
mestranol and lynoestrenol	31/99		
ethinyloestradiol and ethynodiol	61/116		0.94 ± 0.178
mestranol and ethynodiol	199/265		0.98 ± 0.107
mestranol and chlormadinone acetate	44/82		0.95 ± 0.207
mestranol and norethynodrel	134/147		1.09 ± 0.137
other	74/126		0.97 ± 0.172
Last use ≥ 10 years previously			
ethinyloestradiol and norgestrel	856/1 388		1.02 ± 0.055
ethinyloestradiol and norethisterone	749/1 026		1.03 ± 0.059
mestranol and norethisterone	1 360/1 930		0.98 ± 0.044
ethinyloestradiol and lynoestrenol	101/183		0.93 ± 0.145
mestranol and lynoestrenol	113/217		0.95 ± 0.142
ethinyloestradiol and ethynodiol	90/143		0.93 ± 0.150
mestranol and ethynodiol	275/410		0.86 ± 0.081
mestranol and chlormadinone acetate	117/204		0.79 ± 0.115
mestranol and norethynodrel	358/474		0.81 ± 0.072
other	113/177		0.94 ± 0.139

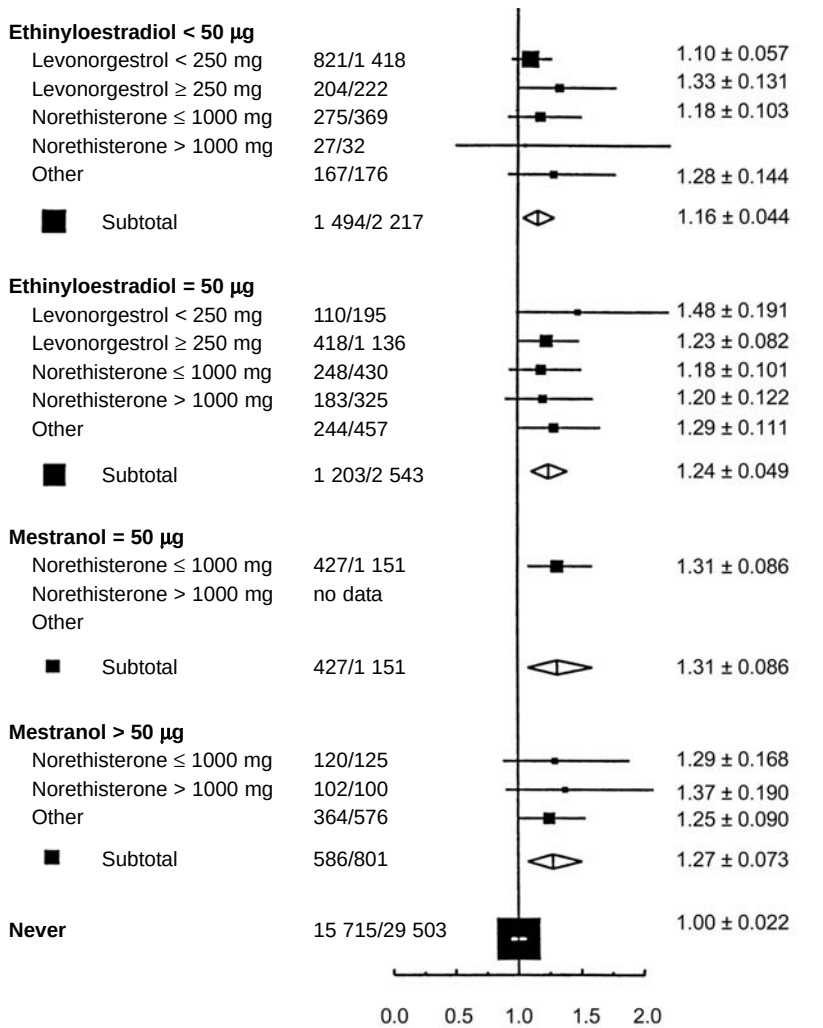


Test for heterogeneity by type of oral contraceptive in women with:
Last use < 5 years previously: χ^2 (9 d.f.) = 13.6; NS
Last use 5–9 years previously: χ^2 (9 d.f.) = 3.4; NS
Last use ≥ 10 years previously: χ^2 (9 d.f.) = 11.5; NS

Adapted from Collaborative Group on Hormonal Factors in Breast Cancer (1996a,b)
CI, confidence interval; SD, standard deviation; d.f., degrees of freedom; NS, not significant
[a] Relative to no use, stratified by study, age at diagnosis, parity, age at first birth and age at which risk for conceiving ceased

Figure 8. Relative risk (RR) for breast cancer by type and dose of progestogen in the oral contraceptive last used, grouped according to type and dose of oestrogen

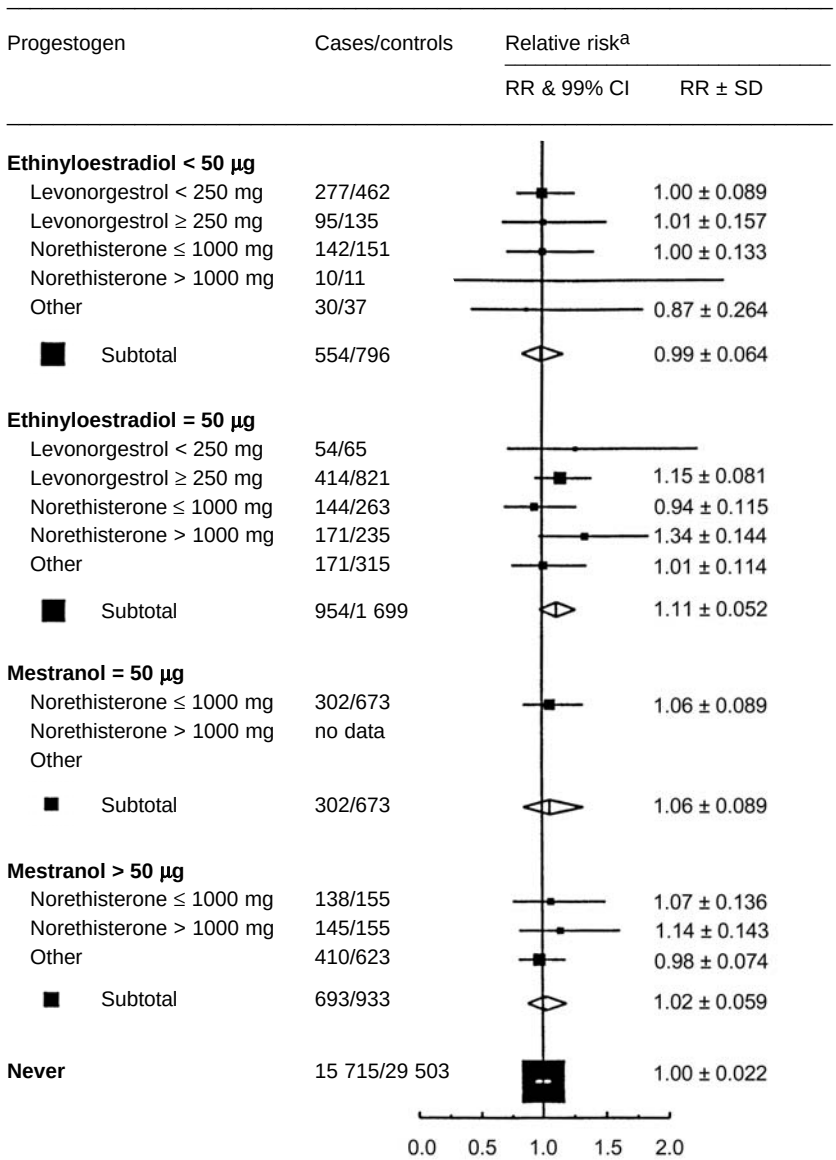
(a) Last use < 5 years previously



Test for heterogeneity by type and dose of progestogen within oral contraceptives containing:
Ethinyloestradiol < 50 µg : χ^2 (4 d.f.) = 3.2; NS
Ethinyloestradiol = 50 µg : χ^2 (4 d.f.) = 1.7; NS
Mestranol > 50 µg : χ^2 (2 d.f.) = 0.3; NS

Figure 8 (contd)

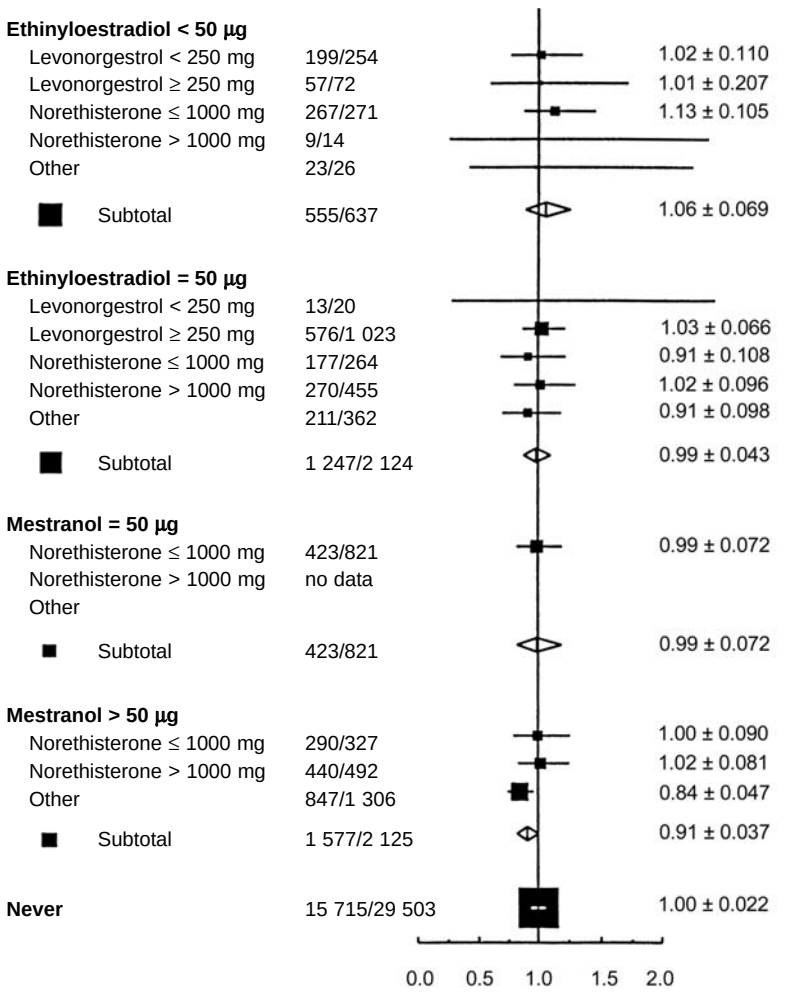
(b) Last use 5–9 years previously



Test for heterogeneity by type and dose of progestogen within oral contraceptives containing:
Ethinyloestradiol < 50 µg : χ^2 (4 d.f.) = 0.9; NS
Ethinyloestradiol = 50 µg : χ^2 (4 d.f.) = 5.6; NS
Mestranol > 50 µg : χ^2 (2 d.f.) = 1.2; NS

Figure 8 (contd)

(c) Last use ≥ 10 years previously

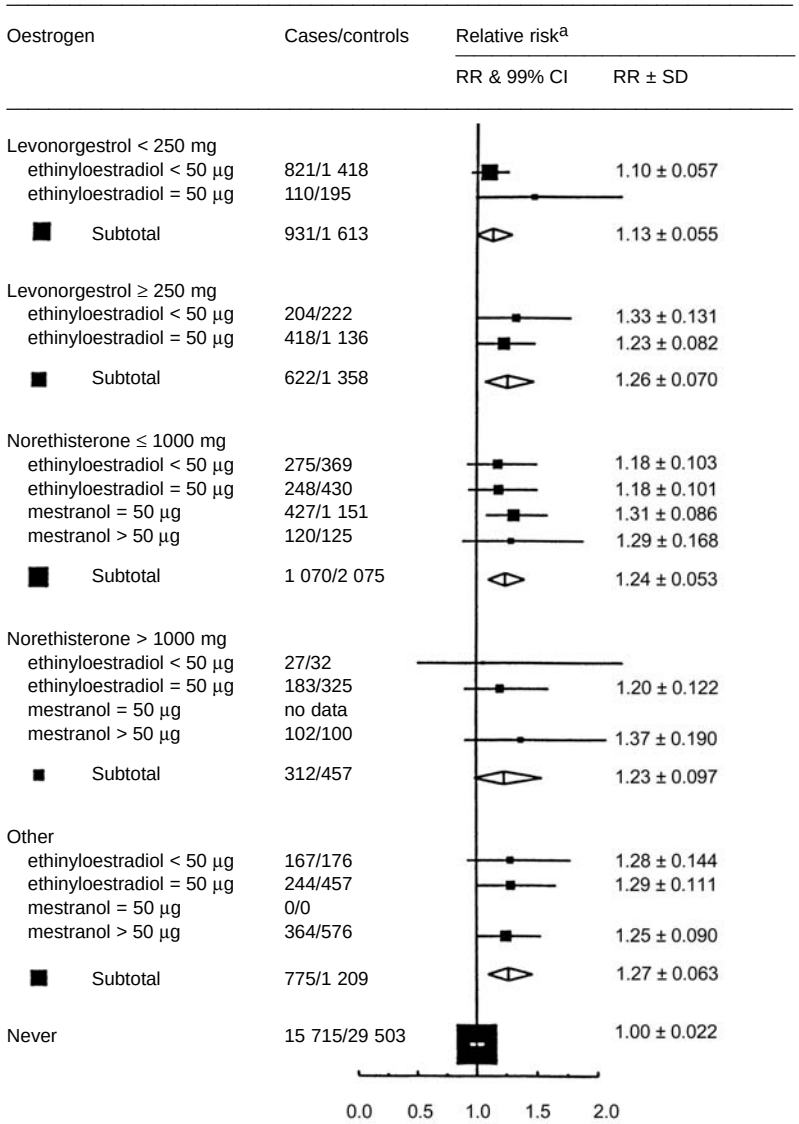


Test for heterogeneity by type and dose of progestogen within oral contraceptives containing:	
Ethinyloestradiol < 50 µg	: χ^2 (4 d.f.) = 1.2; NS
Ethinyloestradiol = 50 µg	: χ^2 (4 d.f.) = 1.8; NS
Mestranol > 50 µg	: χ^2 (2 d.f.) = 5.2; NS

Adapted from Collaborative Group on Hormonal Factors in Breast Cancer (1996a,b)
CI, confidence interval; SD, standard deviation; d.f., degrees of freedom; NS, not significant
[a] Relative to no use, stratified by study, age at diagnosis, parity, age at first birth and age at which risk for conceiving ceased

Figure 9. Relative risk (RR) for breast cancer by type and dose of oestrogen in the oral contraceptive last used, grouped according to type and dose of progestogen

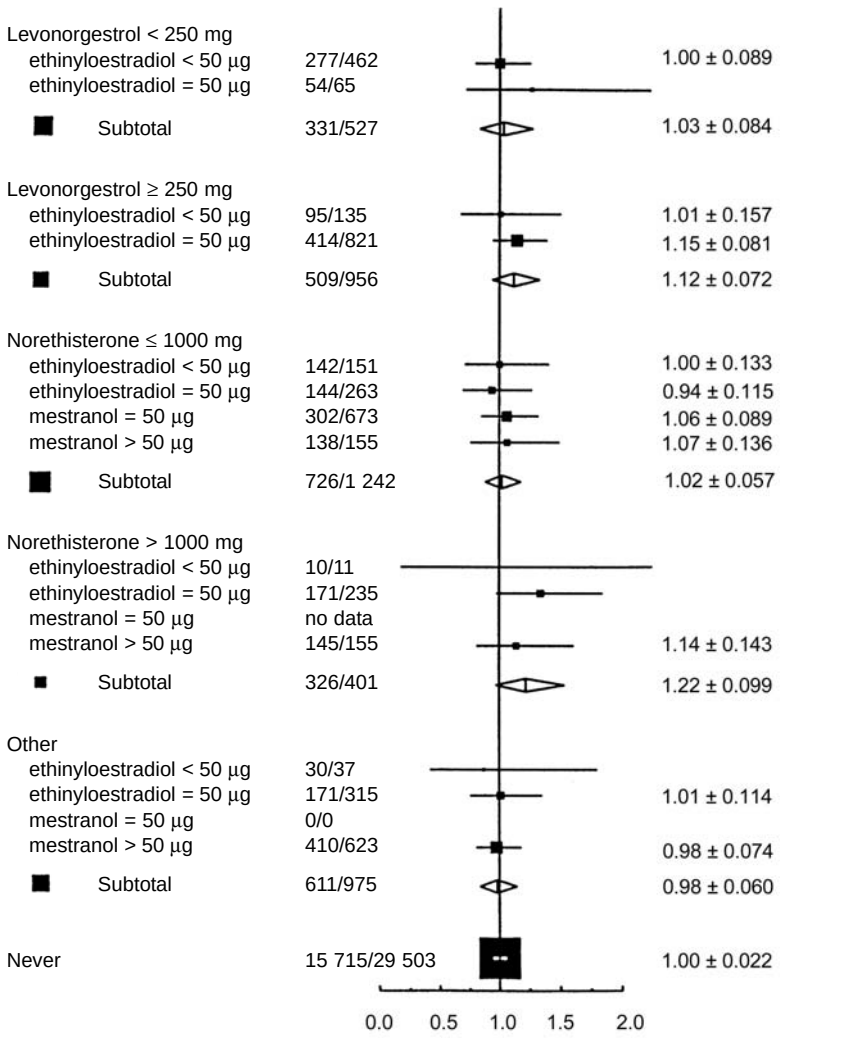
(a) Last use < 5 years previously



Test for heterogeneity by type and dose of oestrogen within oral contraceptives containing:	
Levonorgestrol < 250 mg	: χ^2 (1 d.f.) = 3.2; NS
Levonorgestrol > 250 mg	: χ^2 (1 d.f.) = 0.3; NS
Norethisterone < 1000 mg	: χ^2 (3 d.f.) = 1.2; NS
Norethisterone > 1000 mg	: χ^2 (2 d.f.) = 0.8; NS
Other	: χ^2 (2 d.f.) = 0.1; NS

Figure 9 (contd)

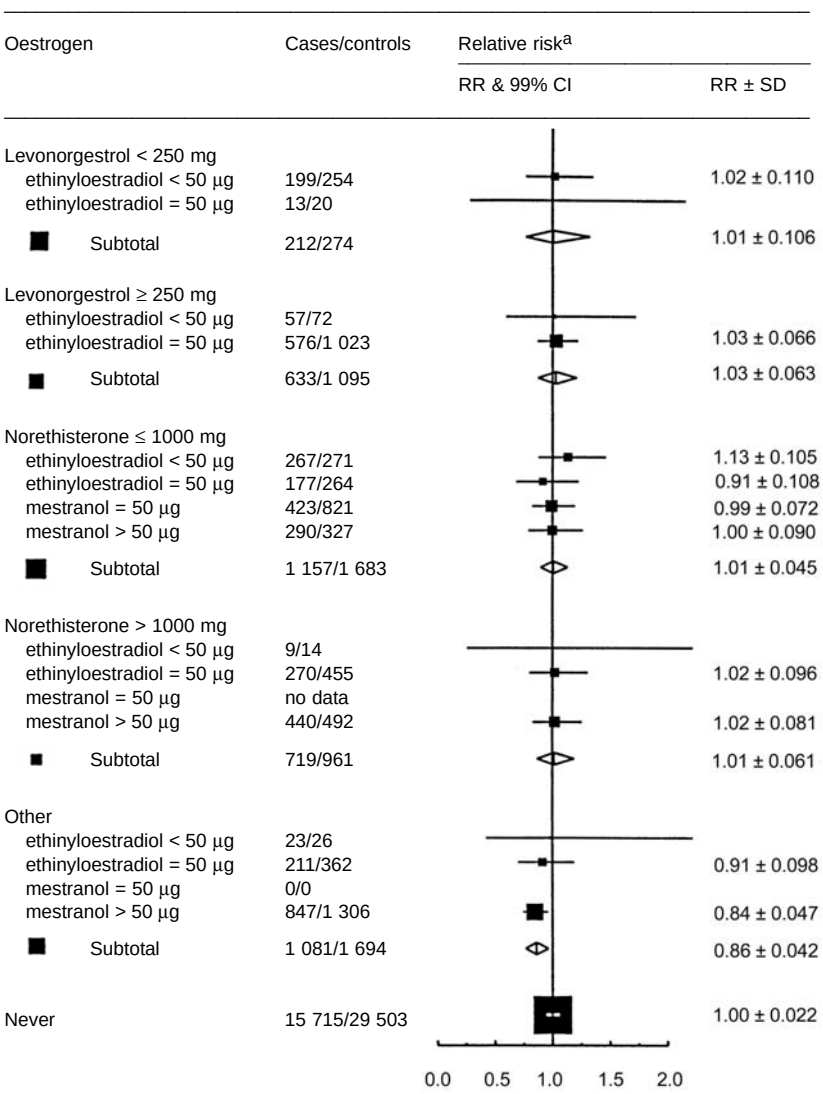
(b) Last use 5–9 years previously



Test for heterogeneity by type and dose of oestrogen within oral contraceptives containing:	
Levonorgestrol < 250 mg	: χ^2 (1 d.f.) = 1.0; NS
Levonorgestrol > 250 mg	: χ^2 (1 d.f.) = 0.5; NS
Norethisterone < 1000 mg	: χ^2 (3 d.f.) = 0.8; NS
Norethisterone > 1000 mg	: χ^2 (2 d.f.) = 2.3; NS
Other	: χ^2 (2 d.f.) = 0.2; NS

Figure 9 (contd)

(c) Last use ≥ 10 years previously

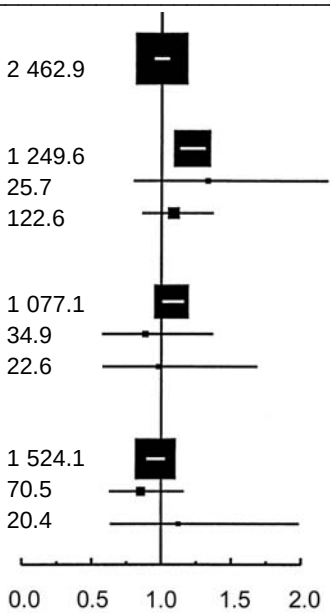


Test for heterogeneity by type and dose of oestrogen within oral contraceptives containing:	
Levonorgestrol < 250 mg	: χ^2 (1 d.f.) = 0.2; NS
Levonorgestrol > 250 mg	: χ^2 (1 d.f.) = 0.0; NS
Norethisterone < 1000 mg	: χ^2 (3 d.f.) = 2.2; NS
Norethisterone > 1000 mg	: χ^2 (2 d.f.) = 0.4; NS
Other	: χ^2 (2 d.f.) = 0.6; NS

Adapted from Collaborative Group on Hormonal Factors in Breast Cancer (1996a,b)
CI, confidence interval; SD, standard deviation; d.f., degrees of freedom; NS, not significant
[a] Relative to no use, stratifed by study, age at diagnosis, parity, age at first birth and age at which risk for conceiving ceased

Figure 10. Relative risk (RR) for breast cancer by time since last use and type of combined oral contraceptive last used

Type of oral contraceptive	Cases/controls	InRR var(InRR)	1 var(InRR)	Relative risk[a] RR & 99% CI	RR ± SD
Never	15 715/29 503	0.0	2 462.9		1.00 ± 0.020
Last use < 5 years previously					
Standard	3 467/6 423	247.7	1 249.6		1.22 ± 0.030
Sequential	56/97	7.4	25.7		1.33 ± 0.229
Phasic	303/392	10.3	122.6		1.09 ± 0.094
Last use 5–9 years previously					
Standard	2 564/4 169	75.9	1 077.1		1.07 ± 0.032
Sequential	71/112	–4.2	34.9		0.89 ± 0.159
Phasic	56/64	–0.5	22.6		0.98 ± 0.208
Last use ≥ 10 years previously					
Standard	4 018/6 048	–62.9	1 524.1		0.96 ± 0.025
Sequential	152/201	–11.1	70.5		0.85 ± 0.110
Phasic	51/50	2.4	20.4		1.12 ± 0.235



Test for heterogeneity by type of oral contraceptives in women with:
Last use < 5 years previously : χ^2 (2 d.f.) = 1.7; NS
Last use 5–9 years previously: χ^2 (2 d.f.) = 1.4; NS
Last use ≥ 10 years previously: χ^2 (3 d.f.) = 1.5; NS

Adapted from Collaborative Group on Hormonal Factors in Breast Cancer (1996a,b)
CI, confidence interval; SD, standard deviation; d.f., degrees of freedom; NS, not significant
[a] Relative to no use, stratified by study, age at diagnosis, parity, age at first birth and age at which risk for conceiving ceased

A few studies indicate that the effect of use of combined oral contraceptives on the risk for breast cancer might be greater among women who have another risk factor than among those without the factor; however, there is no consistent evidence to suggest that the effect of combined oral contraceptives is modified by important risk factors such as benign breast disease, parity and menopausal status. There has been particular concern that a family history of breast cancer might modify an effect of the use of these contraceptives on the risk for breast cancer, but the results to date suggest that the risk is similar among users of these contraceptives with and without a family history of breast cancer (see Figure 11).

Information on the relation of use of oral contraceptives to breast cancer risk among women with mutations in the *BrCA1* or *BrCA2* gene is available from one small study in which 14 such women were compared with 36 women with breast cancer who did not have the mutations (Ursin *et al.*, 1997). A statistically significantly increased relative risk was observed among women who had used oral contraceptives for more than two years before their first full-term pregnancy.

Information on the relationship between use of combined oral contraceptives and the spread of the breast cancer at the time of diagnosis is much sparser than information on overall incidence. The collaborative reanalysis found that the relative risk was greater for localized tumours than for those that had spread beyond the breast (Collaborative Group on Hormonal Factors in Breast Cancer, 1996b). The estimated relative risk for disease localized to the breast was significantly increased for women who had used combined oral contraceptives in the previous five years (1.2), but declined to 1.1 five to nine years after they had stopped use and to 1.0, 10 or more years after stopping. For cancer that had spread beyond the breast, the relative risks were 1.1 for women who had used combined oral contraceptives in the previous five years, 0.96 five to nine years after stopping and 0.93 (significant) 10 or more years after stopping; all of these estimates were compatible with 1.0.

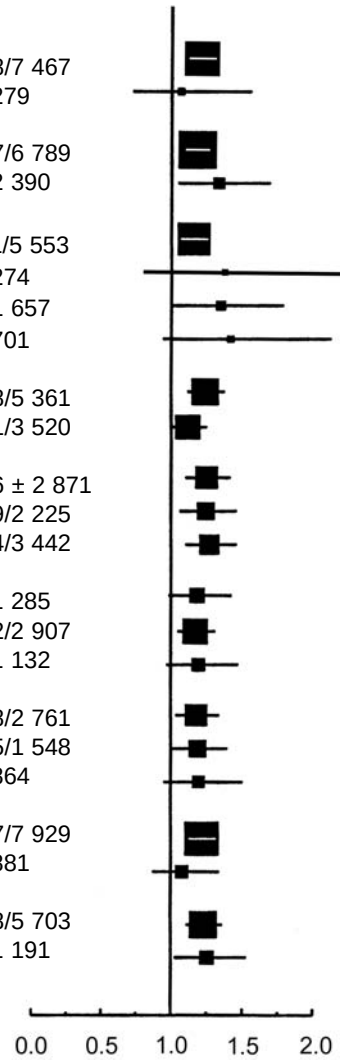
The most consistent findings to date are: a small increase in the risk for breast cancer among current and recent users of combined oral contraceptives; a decline in the risk relative to that of women who have never used them some 10 years after stopping; and little or no increase in risk with increasing duration of use after recency has been taken into account.

The possibility that biased recall might explain the observed increases was assessed in detail by the UK National Case–Control Study Group (1989) and Rookus *et al*. (1994). On the basis of reported use and records of use of combined oral contraceptives, they concluded that only a small part of the observed increase in risk could be explained by reporting bias. Data from follow-up studies are sparser than those from case–control studies. Greater assurance that reporting bias can be ruled out entirely, or that it plays only a small role, will be supplied if positive associations based on larger numbers are produced by the studies now in progress. The important known risk factors for breast cancer, such as age at first birth, parity and age at menopause, were controlled for and they seem unlikely to account for the observed increases. The increases have been observed across

Figure 11. Relative risk (RR) for breast cancer by time since last use of combined oral contraceptives and various characteristics of women

(a) Last use < 5 years previously

Characteristic	RR[a] ± SD	Cases/controls
Mother and/or sister with history of breast cancer		
No	1.21 ± 0.035	3 858/7 467
Yes	1.06 ± 0.153	454/279
Country of residence		
Developed	1.18 ± 0.031	4 777/6 789
Developing	1.33 ± 0.108	296/2 390
Ethnic origin		
White	1.16 ± 0.036	3 511/5 553
Black	1.37 ± 0.244	162/274
Asian	1.35 ± 0.128	241/1 657
Other	1.42 ± 0.188	155/701
Years of education		
< 13 years	1.24 ± 0.045	2 638/5 361
≥ 13 years	1.12 ± 0.046	2 201/3 520
Age at menarche		
≤ 12 years	1.25 ± 0.054	2 076 ± 2 871
13 years	1.24 ± 0.069	1 329/2 225
≥ 14 years	1.27 ± 0.062	1 484/3 442
Height		
< 160 cm	1.18 ± 0.079	975/1 285
160–169 cm	1.17 ± 0.047	2 392/2 907
≥ 170 cm	1.19 ± 0.089	932/1 132
Weight		
< 60 kg	1.18 ± 0.054	2 098/2 761
60–69 kg	1.19 ± 0.069	1 305/1 548
≥ 70 kg	1.20 ± 0.098	642/864
Menopausal status		
Pre-menopausal	1.22 ± 0.035	4 417/7 929
Post-menopausal	1.08 ± 0.087	433/881
Alcohol consumption		
< 50 g per week	1.23 ± 0.044	2 588/5 703
≥ 50 g per week	1.25 ± 0.087	938/1 191

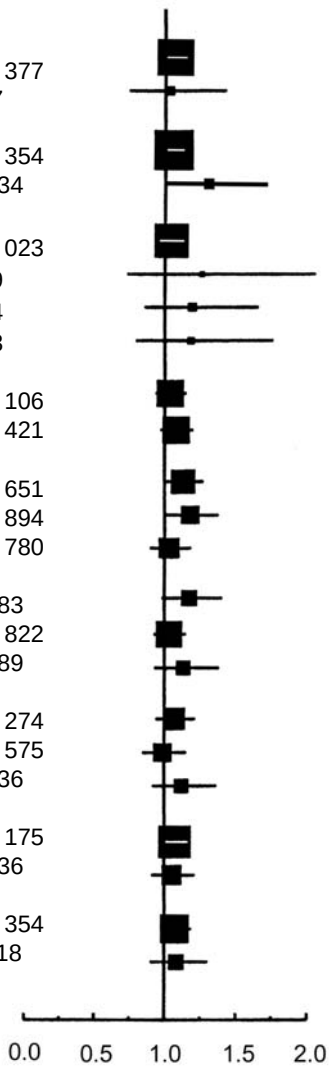


Global test for heterogeneity: χ^2 (14 d.f.) = 11.0; NS

Figure 11 (contd)

(b) Last use 5–9 years previously

Characteristic	RR[a] ± SD	Cases/controls	RR[a] & 99% CI
Mother and/or sister with history of breast cancer			
No	1.07 ± 0.031	3 270/6 377	
Yes	1.03 ± 0.128	468/367	
Country of residence			
Developed	1.06 ± 0.028	4 036/6 354	
Developing	1.31 ± 0.121	203/1 334	
Ethnic origin			
White	1.04 ± 0.033	2 974/5 023	
Black	1.26 ± 0.237	159/229	
Asian	1.19 ± 0.140	165/954	
Other	1.18 ± 0.168	135/503	
Years of education			
< 13 years	1.04 ± 0.041	2 014/4 106	
≥ 13 years	1.08 ± 0.042	2 090/3 421	
Age at menarche			
≤ 12 years	1.13 ± 0.048	1 825/2 651	
13 years	1.18 ± 0.065	1 136/1 894	
≥ 14 years	1.03 ± 0.054	1 179/2 780	
Height			
< 160 cm	1.17 ± 0.076	862/1 183	
160–169 cm	1.03 ± 0.042	1 991/2 822	
≥ 170 cm	1.13 ± 0.082	845/1 089	
Weight			
< 60 kg	1.07 ± 0.051	1 643/2 274	
60–69 kg	0.99 ± 0.059	1 088/1 575	
≥ 70 kg	1.12 ± 0.081	713/1 036	
Menopausal status			
Pre-menopausal	1.07 ± 0.035	2 987/5 175	
Post-menopausal	1.05 ± 0.057	903/1 836	
Alcohol consumption			
< 50 g per week	1.07 ± 0.039	2 121/4 354	
≥ 50 g per week	1.08 ± 0.074	870/1 118	

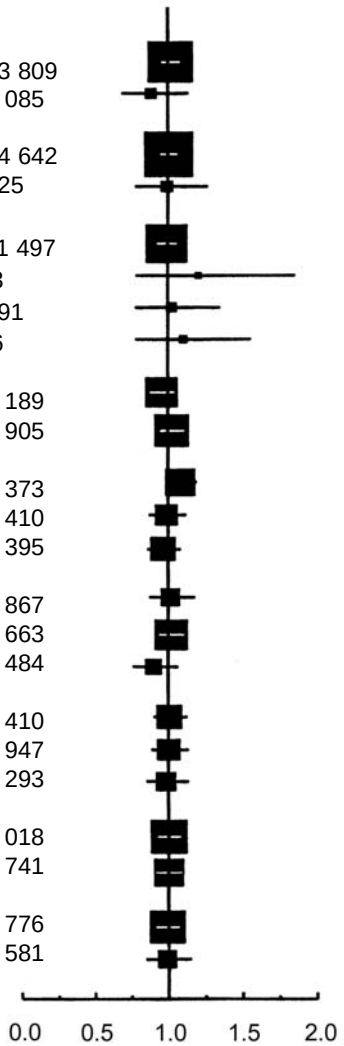


Global test for heterogeneity: χ^2 (14 d.f.) = 14.5; NS

Figure 11 (contd)

(c) Last use ≥ 10 years previously

Characteristic	RR[a] ± SD	Cases/controls
Mother and/or sister with history of breast cancer		
No	1.02 ± 0.025	6 988/13 809
Yes	0.88 ± 0.092	1 122/1 085
Country of residence		
Developed	1.01 ± 0.023	8 554/14 642
Developing	0.99 ± 0.094	264/1 825
Ethnic origin		
White	0.99 ± 0.027	6 578/11 497
Black	1.21 ± 0.185	339/463
Asian	1.02 ± 0.109	255/1 491
Other	1.10 ± 0.142	225/786
Years of education		
< 13 years	0.96 ± 0.034	3 613/7 189
≥ 13 years	1.03 ± 0.033	5 030/8 905
Age at menarche		
≤ 12 years	1.08 ± 0.039	3 963/6 373
13 years	0.99 ± 0.049	2 344/4 410
≥ 14 years	0.96 ± 0.044	2 427/5 395
Height		
< 160 cm	1.02 ± 0.059	1 724/2 867
160–169 cm	1.02 ± 0.034	4 494/6 663
≥ 170 cm	0.90 ± 0.063	1 641/2 484
Weight		
< 60 kg	1.01 ± 0.044	2 958/4 410
60–69 kg	1.00 ± 0.048	2 553/3 947
≥ 70 kg	0.98 ± 0.055	1 986/3 293
Menopausal status		
Pre-menopausal	1.00 ± 0.031	4 967/8 018
Post-menopausal	1.00 ± 0.038	2 814/5 741
Alcohol consumption		
< 50 g per week	0.99 ± 0.031	4 449/8 776
≥ 50 g per week	0.99 ± 0.059	1 746/2 581



Global test for heterogeneity: χ^2 (14 d.f.) = 13.5; NS

Adapted from Collaborative Group on Hormonal Factors in Breast Cancer (1996a,b)
SD, standard deviation; CI, confidence interval; d.f., degrees of freedom; NS, not significant
[a] Relative risk relative to no use, stratified by study, age at diagnosis, parity and, where appropriate, age when first child was born and age when risk for conceiving ceased

case–control studies of various designs, both population- and hospital-based, suggesting that selection bias in the enrolment of cases or controls is not the explanation for the observed increases. The associations have also been observed across different populations. If biased recall, selection bias and confounding are unlikely explanations of the findings, the remaining explanations are that the associations are real (i.e. combined oral contraceptives act as a tumour promoter), that they are due to detection bias (i.e. breast cancer is diagnosed earlier in women who have used combined oral contraceptives) or both. There are few data on the mortality rates of users of these contraceptives, although two studies reported estimates close to 1.0 (Colditz *et al.*, 1994; Beral *et al.*, 1999).

2.2 Endometrial cancer

Combined and sequential oral contraceptives are discussed separately in relation to the risk for endometrial cancer, as use of these two preparations may have different impacts. Most of the information on the risk for endometrial cancer in relation to use of combined oral contraceptives concerns monophasic pills, i.e. with fixed doses of an oestrogen and a progestogen during a cycle. There is no information about the specific, long-term risk for endometrial cancer associated with use of the multiphasic oral contraceptives available since the early 1980s, in which varying doses of oestrogen and progestogen are given concurrently over one cycle.

2.2.1 *Combined oral contraceptives*

The cohort studies in which use of combined oral contraceptives and the risk for endometrial cancer have been investigated are summarized in Table 9 and the case–control studies in Table 10, with the risk associated with the duration and recency of use when available. Risk estimates by weight, parity (or gravidity) or use of post-menopausal oestrogen therapy are given in the text.

(*a*) *Descriptive studies*

Several analyses have suggested that increased use of combined oral contraceptives can partially explain the decreasing rates of mortality from uterine corpus cancer (i.e. excluding those from cervical cancer) seen between 1960 and the 1980s (Beral *et al.*, 1988; Persson *et al.*, 1990; dos Santos Silva & Swerdlow, 1995). The decrease is particularly notable among women aged 55 or younger, who are most likely to have used combination oral contraceptives. Interpretation of these trends is complicated by improvements in cancer treatment over time and by lack of correction for the proportion of women who have had their uterus removed and are no longer at risk for developing (or dying from) endometrial cancer. Furthermore, the rate of death from uterine corpus cancer has generally been decreasing since the early 1950s, a decade before oral contraceptives were available. Thus, while it is plausible that increased use of combined oral contraceptives could have preceded and then paralleled the decrease in mortality from endometrial cancer, the magnitude of any decrease in the rate of death from uterine corpus cancer related to increased use of oral contraceptives remains unclear.

Table 9. Cohort studies of use of oral contraceptive pills[a] (not otherwise specified) and risk for endometrial cancer (by duration and recency of use when available)

Reference	Cohort enrolment		End of follow-up	Type/measure of therapy	No. of cases	No. of person–years	RR (95% CI)
	Year/age	Source population/ response/follow-up					
Trapido (1983)	1970/25–57 years	97 300 residents of Boston, USA, and 14 contiguous towns/70%	Dec. 1976	No use	75	296 501	Referent
				Any use	18	124 851	1.4 (NR)
				Duration (months)			
				1–11	6	33 997	1.7 (NR)
				12–23	4	21 978	1.9 (NR)
				24–35	3	21 437	1.6 (NR)
				36–59	2	28 705	0.6 (NR)
				≥ 60	3	18 734	1.5 (NR)
Beral *et al*. (1988, 1999)	May 1968–June 1969	46 000 British women identified by general practitioners/NA	April 1987 (incidence)	No use	16	182 866	Referent
				Any use	2	257 028	0.2 (0.0–0.7)
			Dec. 1993 (mortality)	No use	6	335 998	Referent
				Any use	2	517 519	0.3 (0.1–1.4)
Vessey & Painter (1995)	1968–74/ 25–39 years	17 032 patients at 17 family planning clinics, UK/NA	Oct. 1993	No use	14	NR	Referent
				Any use	1	NR	0.1 (0.0–0.7)

RR, relative risk; CI, confidence interval; NR, not reported; NA, not applicable

[a] May be use of either combined or sequential oral contraceptive pills, but the majority of women used combined

Table 10. Case–control studies of use of oral contraceptive pills and risk for endometrial cancer (by duration and recency of use when available)

Reference	Location/period/age	Source of controls	Ascertainment of use	Participation (%)		Type/measure of therapy	No. of subjects		OR (95% CI)
				Cases	Controls		Cases	Controls	
Weiss & Sayvetz (1980)	Washington State, USA/ Jan. 1975–Dec. 1977/36–55 years	General population	Personal interviews	83	96	*Combined*			
						No use, < 1 year's use	93	173	Referent
						≥ 1 year's use	17	76	0.5 (0.1–1.0)
Kaufman *et al.* (1980)	USA and Canada/ July 1976–Dec. 1979/ < 60 years	Hospital patients	Personal interviews	96[a]	96[a]	*Combined*			
						No use	136	411	Referent
						Any use	16	99	[0.4 (0.2–0.8)[b]]
						Duration (years)			
						< 1	5	14	0.8 (NR)
						1–2	6	32	0.5 (NR)
						≥ 3	5	53	0.3 (NR)
						Unknown	0	6	
						Recency (years)			
						≥ 5	12	60	0.6 (0.3–1.2)
						With duration ≥ 1 year	8	52	0.5 (0.2–1.0)
Kelsey *et al.* (1982)	Connecticut, USA/ July 1977–Mar. 1979/ 45–74 years	Hospital patients	Personal interviews	67	72	*Sequential/combined*			
						No use	NR	NR	Referent
						For each + 5 years of use	NA	NA	0.6 (0.3–1.5)
						Age 45–55 years			
						No use	31	256	Referent
						Duration (years)			
						≤ 2.5	4	42	0.9 (NR)
						> 2.5	2	44	0.5 (NR)
Hulka *et al.* (1982)	North Carolina, USA/ Jan. 1970–Dec. 1976/ < 60 years	General population	Personal interviews and medical record reviews	90[a]	90[a]	*Combined*			
						No use, < 6 months' use	74	172	Referent
						≥ 6 months' use	5	31	0.4 (NR)
						Recency (years)			
						< 1	0	13	0
						≥ 1	5	14	0.9 (NR)
						Duration (years)			
						< 5	3	14	0.6 (NR)
						≥ 5	2	17	0.3 (NR)

Table 10 (contd)

Reference	Location/period/age	Source of controls	Ascertainment of use	Participation (%)		Type/measure of therapy	No. of subjects		OR (95% CI)
				Cases	Controls		Cases	Controls	
Henderson *et al.* (1983a)	Los Angeles county, USA/Jan. 1972–Dec. 1979/≤ 45 years	Residents in neighbourhood of cases	Telephone interviews	81	NR	*Combined*			
						No use	67	50	Referent
						Duration (years)			
						< 2	23	22	0.8 (NR)
						2–3	12	11	0.8 (NR)
						4–5	4	9	0.3 (NR)
						≥ 6	4	18	0.1 (NR)
Cancer and Steroid Hormone Study (1987)	Eight US areas/Dec 1980–Dec 1982/ 20–54 years	General population	Personal interviews	73	84	*Combined*			
						No use	250	1 147	Referent
						Combined only	NR	NR	0.5 (0.4–0.6)
						Duration (months)			
						3–6	24	186	0.9 (0.5–1.5)
						–11	13	80	1.3 (0.6–2.6)
						12–23	20	266	0.7 (0.4–1.2)
						24–71	26	576	0.4 (0.3–0.7)
						72–119	12	317	0.4 (0.2–0.8)
						≥ 120	15	241	0.4 (0.2–0.8)
						Recency (years)			
						< 5	12	471	0.3 (0.1–0.5)
						5–9	22	417	0.4 (0.2–0.6)
						10–14	30	368	0.5 (0.3–0.8)
						≥ 15	9	144	0.3 (0.2–0.6)
La Vecchia *et al.* (1986)	Greater Milan, Italy/ Jan. 1979–Nov. 1985/ < 60 years	Hospital patients	Personal interviews	98[c]	98[c]	*Combined*			
						Non-user	163	1 104	Referent
						Any use	7	178	0.5 (0.2–1.1)
Pettersson *et al.* (1986)	Uppsala, Sweden/Jan. 1980–Dec. 1981/ < 60 years	General population	Personal interviews	93	80	*Not specified*			
						No use	96	91	Referent
						Any use	12	22	0.5 (0.2–1.1)
						Duration (years)			
						< 1	5	6	0.8 (0.2–2.7)
						≥ 1	7	16	0.4 (0.2–1.0)
						Any contraceptive			
						Any use	9	22	0.4 (0.2–0.9)
						Duration (years)			
						< 1	5	6	0.8 (0.2–2.7)
						≥ 1	4	16	0.2 (0.1–0.7)

Table 10 (contd)

Reference	Location/period/age	Source of controls	Ascertainment of use	Participation (%)		Type/measure of therapy	No. of subjects		OR (95% CI)
				Cases	Controls		Cases	Controls	
WHO Collaborative Study (1988); Rosenblatt *et al.* (1991)	Seven countries/Jan. 1979–Feb. 1988/ < 60 years	Hospital patients	Personal interviews	87	93	*Combined*			
						No use	118	687	Referent
						Combined only	14	149	0.5 (0.3–1.0)
						Any contraceptive			
						No use	118	655	Referent
						Any use	12	180	0.5 (0.2–1.1)
						Combined			
						Any contraceptive			
						No use	182	1 072	Referent
						Progestogen content			
						High			
						Duration (months)			
						1–24	1	85	0.1 (0.0–0.7)
						≥ 25	2	69	0.2 (0.0–0.8)
						Recency (months)			
						1–120	1	61	0.1 (0.0–0.8)
						≥ 121	2	93	0.2 (0.0–0.7)
						Low			
						Duration (months)			
						1–24	8	69	1.0 (0.5–2.4)
						≥ 25	1	56	0.1 (0.0–1.1)
						Recency (months)			
						1–120	2	72	0.3 (0.0–1.1)
						≥ 121	7	54	1.1 (0.5–2.8)
Koumantaki *et al.* (1989)	Athens, Greece/1984/ 40–79 years	Hospital patients	Personal interviews	80	95	*Not specified*			
						No use, ≤ 6 months' use	80	151	Referent
						> 6 months' use	3	13	0.6 (0.2–2.0)[d]
Levi *et al.* (1991)	Canton of Vaud, Switzerland/ Jan 1988–July 1990/ 32–75 years	Hospital patients	Personal interviews	85[a]	85[a]	*Combined*			
						No use	105	227	Referent
						Any use	17	82	0.5 (0.3–0.8)
						Duration (years)			
						< 2	9	19	1.0 (0.5–2.3)
						2–5	3	18	0.5 (0.1–1.2)
						5	5	45	0.3 (0.1–0.7)
						Recency (years)			
						< 10	4	30	0.3 (0.1–0.9)
						10–19	7	37	0.4 (0.2–1.0)
						> 19	5	15	0.8 (0.3–2.2)

Table 10 (contd)

Reference	Location/period/age	Source of controls	Ascertainment of use	Participation (%)		Type/measure of therapy	No. of subjects		OR (95% CI)
				Cases	Controls		Cases	Controls	
Shu *et al.* (1991)	Shanghai, China/April 1988–Jan. 1990/ 18–74 years	General population	Personal interviews	91	96	*Not specified*			
						No use (any birth control)	84	72	Referent
						Any use	32	46	0.8 (0.4–1.8)
						Duration (years)			
						≤ 2	NR	NR	1.4 (0.6–3.0)
						> 2	NR	NR	0.4 (0.1–1.2)
Stanford *et al.* (1993)	Five US areas/June 1987–May 1990/ 20–74 years	General population	Personal interviews	87	66	*Combined*			
						No use	321	187	Referent
						Any use	81	107	0.4 (0.3–0.7)
						Duration (years)			
						< 1	27	21	0.7 (0.3–1.4)
						1–2	16	33	0.3 (0.1–0.6)
						3–4	12	16	0.3 (0.1–0.8)
						5–9	14	15	0.7 (0.3–1.6)
						≥ 10	7	19	0.2 (0.1–0.5)
						Recency (years)			
						< 10	6	18	0.1 (0.0–0.3)
						10–14	15	27	0.3 (0.1–0.7)
						15–19	24	32	0.4 (0.2–0.8)
						≥ 20	33	27	0.7 (0.4–1.3)
						By duration (years)			
						< 3			
						Recency (years)			
						< 15	7	15	0.2 (0.1–0.6)
						15–19	10	16	0.3 (0.1–0.8)
						≥ 20	26	23	0.6 (0.3–1.3)
						≥ 3			
						Recency (years)			
						< 15	14	30	0.2 (0.1–0.5)
						15–19	12	16	0.4 (0.2–1.0)
						≥ 20	7	4	0.8 (0.2–3.3)
Jick *et al.* (1993)	Washington State, USA, Group Health Cooperative/1979–1989/50–64 years	Members of health maintenance organization	Mailed form and pharmacy database	83	79	*Not specified*			
						No use	110	737	Referent
						Any use	26	270	0.5 (0.3–0.9)
						Duration (years)			
						1	7	65	0.4 (0.1–1.4)
						2–5	11	90	0.8 (0.3–1.7)
						≥ 6	8	115	0.3 (0.1–0.9)

Table 10 (contd)

Reference	Location/period/age	Source of controls	Ascertainment of use	Participation (%)		Type/measure of therapy	No. of subjects		OR (95% CI)
				Cases	Controls		Cases	Controls	
Jick *et al.* (1993) (contd)						*Recency (years)*			
						1–10	5	67	0.4 (0.1–1.1)
						11–15	6	82	0.4 (0.1–1.2)
						16–20	4	57	0.5 (0.1–1.8)
						≥ 21	9	54	0.6 (0.2–2.1)
Voigt *et al.* (1994)[e]	Washington State, USA/1975–77 and 1985–87/40–59 years	General population	Personal interviews	83	95 and 73[f]	*Combined*			
						No use, < 1 year's use	117	284	Referent
						Recency (years)			
						> 10			
						Duration (years)			
						1–5	14	30	0.9 (0.4–1.9)
						> 5	4	16	0.4 (0.1–1.2)
						≤ 10			
						Duration (years)			
						1–5	7	28	1.0 (0.4–2.4)
						> 5	7	74	0.3 (0.1–0.6)
						Progestogen content[g]			
						Low			
						Duration (years)			
						1–5	10	22	1.1 (0.5–2.6)
						> 5	3	32	0.2 (0.1–0.8)
						High			
						Duration (years)			
						1–5	3	14	0.8 (0.2–3.1)
						> 5	3	28	0.3 (0.1–0.9)
Kalandidi *et al.* (1996)	Athens, Greece/1992–94/< 59–≥ 70 years	Hospital patients	Personal interviews	83	88	*Not specified*			
						No use	143	293	Referent
						Any use	2	5	1.3 (0.2–7.7)

OR, odds ratio; CI, confidence interval; NR, not reported; NA, not applicable
[a] Responses reported for case and control women combined
[b] Crude odds ratio and 95% confidence interval calculated from data provided in the published paper by exact methods
[c] Methods state that less than 2% of eligible case and control women refused an interview.
[d] 90% confidence interval
[e] Includes women from the study of Weiss & Sayvetz (1980)
[f] Response for controls identified 1985–1987
[g] Classified according to subnuclear endometrial vacuolization

(*b*) *Cohort studies*

A questionnaire to derive information on oral contraceptive use was sent to approximately 97 300 married women aged 25–57 in eastern Massachusetts, United States, in 1970, who were identified from the 1969 Massachusetts residence lists (Trapido, 1983). The age-adjusted rate ratio for women who had ever used oral contraceptives relative to non-users was 1.4; there was no consistent pattern of a decreasing or increasing rate ratio with longer or more recent use (Table 9). Among nulliparous women, the age-adjusted rate ratio for oral contraceptive users relative to non-users was 2.4 (95% CI, 0.6–9.2), whereas the analogous rate ratio for parous women was 1.4 (95% CI, 0.8–2.4). Among women who also reported any use of post-menopausal oestrogen therapy, the age-adjusted rate ratio for oral contraceptive users relative to non-users was 2.0 (95% CI, 0.9–4.3). No distinction was made between sequential and combined oral contraceptive use, and both preparations were available to the cohort before and during the study follow-up.

Beral *et al.* (1999) followed-up approximately 23 000 oral contraceptive users and a similar number of non-users identified in 1968 and 1969 by the Royal College of General Practitioners. Use of oral contraceptives (not otherwise specified) and the occurrence of uterine cancer were both determined from physicians' reports. Uterine corpus cancer (i.e. excluding the cervix) was diagnosed in two of the oral contraceptive users and 16 of the non-users, resulting in a rate ratio of 0.2 (95% CI, 0.0–0.7) after adjustment for age, parity, smoking, social class, number of previously normal Papanicolaou ('Pap') smears and history of sexually transmitted disease. In a 25-year follow-up of deaths in the cohort, there were eight deaths from endometrial cancer, two of women who had ever used oral contraceptives and six of women who had never used them (rate ratio, 0.3; 95% CI, 0.1–1.9).

The study of the Oxford Family Planning Association included 17 032 married white women identified at 17 family planning clinics in England and Scotland (Vessey & Painter, 1995) who had used oral contraceptives (not otherwise specified), a diaphragm or an intrauterine device for at least five months. Information on contraceptive history and any hospital referrals was obtained from physicians or from the women themselves (for those who stopped attending the clinics) during the study follow-up. A total of 15 292 women remained under observation until the age of 45; only those who had never used oral contraceptives (5881) or had used them for eight years or more (3520) were followed from then on. Endometrial cancer was diagnosed in 15 women, only one of whom had used oral contraceptives (age-adjusted rate ratio, 0.1; 95% CI, 0.0–0.7). In a previous analysis of mortality in this cohort (Vessey *et al.*, 1989b), none of the oral contraceptive users but two of those using a diaphragm or an intrauterine device (the comparison group) had died from uterine corpus cancer.

(*c*) *Case–control studies*

Weiss and Sayvetz (1980) compared 117 women identified from a population-based cancer registry with 395 control women in the general population of western Washington State, United States. Women who had used combined oral contraceptives for one year or

more had half the risk for endometrial cancer of women who were either non-users or had used oral contraceptives for less than one year, after adjustment for age and use of post-menopausal oestrogen therapy (odds ratio, 0.5; 95% CI, 0.1–1.0). No further difference in the duration of use was seen between case and control women. In stratified analyses, the reduced risk was present only for women who had never used post-menopausal oestrogen therapy (odds ratio, 0.4; 95% CI, 0.1–1.1) or who had used it for two years or less (odds ratio, 0.1; 95% CI, 0.01–1.1); no reduction was noted among women who had used it for three years or more (odds ratio, 1.3; 95% CI, 0.3–6.6).

Among 154 women with endometrial cancer and 525 control women in a hospital-based study in the United States and Canada (Kaufman *et al.*, 1980), a 60% reduction in risk was seen among women who used combined oral contraceptives relative to non-users, after adjustment for use of non-contraceptive hormones, parity, body mass, menopausal status, age at menopause, ethnic group, diabetes, education, age and area of residence. The risk for endometrial cancer declined with increasing duration of use, and a sustained reduction in risk was suggested for women who had stopped using oral contraceptives in the previous five or more years. A reduction in risk was noted for women who had used combined oral contraceptives but had never used non-contraceptive oestrogens (odds ratio, 0.4; 95% CI, 0.2–0.8), but not for the women who had ever used both oral contraceptives and non-contraceptive oestrogens (odds ratio, 0.6; 95% CI, 0.3–1.6), although the lack of information on the duration of non-contraceptive oestrogen use makes it difficult to interpret this estimate.

Kelsey *et al.* (1982) studied women admitted to seven hospitals in Connecticut, United States. The 167 newly diagnosed cases of endometrial cancer were compared with 903 control women admitted for non-gynaecological surgical services. Among the study participants aged 45–55 years—the women who had had the opportunity to use oral contraceptives—those who had used oral contraceptives for 2.5 years or more had a 50% decrease in risk.

Among 79 women treated at a hospital in North Carolina, United States, for endometrial cancer, 6.3% had used combined oral contraceptives for six months or more, whereas 15.3% of the 203 control women from 52 counties in the State (the main referral area for the hospital) had done so (Hulka *et al.*, 1982). Since only 15% of the control women reported use of combined oral contraceptives, the risk estimates for more detailed aspects of oral contraceptive use are fairly imprecise (Table 10). There is a suggestion that the risk was lower with longer use (≥ 5 years), with previous use and with use of 'progestogen-predominant' (based on the relative proportions of oestrogens and progestogens in their chemical composition) oral contraceptives. When oral contraceptive use was stratified by use of post-menopausal oestrogens, both users of at least six months' duration (0 cases, 6 controls) and non-users (odds ratio, 0.6 [95% CI not provided]) of post-menopausal oestrogens appeared to have a reduced risk associated with use of oral contraceptives.

Henderson *et al.* (1983a) identified 127 women with endometrial cancer from the population-based cancer registry for Los Angeles County and matched them to control

women of similar age who lived in the same neighbourhood as the matched case. The risk for endometrial cancer decreased with increasing duration of use of combined oral contraceptives, and this pattern remained after further adjustment for parity, current weight, infertility and amenorrhoea. Neither the recency of use of oral contraceptives nor the relative oestrogen and progestogen content of the oral contraceptives had a clear impact on the risk, beyond that explained by the duration of use (data not shown). When the analysis was stratified by body weight, a reduction in risk with longer duration of use was seen among women whose current weight was less than 170 lbs [77 kg] but not among women whose current weight was greater.

In a population-based study conducted by the Centers for Disease Control and the National Institute of Child Health and Human Development in the United States, women with newly diagnosed endometrial cancer, who were 20–54 years of age, were identified from eight cancer registries (Atlanta, Detroit, San Francisco, Seattle, Connecticut, Iowa, New Mexico, and four urban counties in Utah) in the United States Surveillance, Epidemiology and End Results (SEER) Program; 3191 controls were selected from the general population (Centers for Disease Control and the National Institute of Child Health and Human Development, Cancer and Steroid Hormone Study, 1987). Women who had used only combination oral contraceptives had half the risk for endometrial cancer of non-users (age-adjusted odds ratio, 0.5; 95% CI, 0.4–0.6). The risk generally decreased with increasing duration of oral contraceptive use, the greatest reduction in risk being seen among women who had used combined oral contraceptives for two years or more. The strength of the association was similar after adjustment for age alone and after multivariate adjustment for age, parity, education, body mass, menopausal status, geographic region, exogenous oestrogen use and infertility. The risk for endometrial cancer did not vary with recency of use of oral contraceptives or time since first use; both women who had ceased use of oral contraceptives 15 years or more before the study interview and women who had first used oral contraceptives more than 20 years before interview had a lower risk than non-users (age-adjusted odds ratios, 0.3 (95% CI, 0.2–0.6) and 0.4 (95% CI, 0.2–0.7), respectively). When the analysis was stratified by the formulation of the oral contraceptive, all formulations that had been used for at least six months or more were associated with a decreased risk for endometrial cancer. Nulliparous women who had used combined oral contraceptives for one year or more had a larger reduction in risk than non-users (age-adjusted odds ratio, 0.2; 95% CI, 0.1–0.5), but women of high parity had little difference in risk, the age-adjusted odds ratio for women who had had five or more births being 0.8 (95% CI, 0.4–1.9). No difference in risk was reported with body mass, smoking, alcohol consumption, use of exogenous oestrogens or menopausal status (data not shown) or for the different histological subtypes of endometrial cancer (adenocarcinoma, adenoacanthoma and adenosquamous carcinoma).

In a hospital-based study in the area of greater Milan, Italy, La Vecchia *et al.* (1986) compared the use of combined oral contraceptives by women admitted for endometrial cancer and women admitted for traumatic, orthopaedic, surgical and other conditions.

Seven (4%) of the 170 case women and 178 (14%) of the 1282 control women reported use of combined oral contraceptives, resulting in an odds ratio of 0.6 (95% CI, 0.2–1.3) after adjustment for age, marital status, education, parity, age at menarche, age at first birth, age at menopause, body mass index, cigarette smoking and use of non-contraceptive female hormones.

Pettersson *et al.* (1986) studied 254 women residing in the health care region of Uppsala (Sweden) who were referred to the Department of Gynaecologic Oncology with a newly diagnosed endometrial malignancy; each case was matched by age and county of residence to one control woman identified from a population registry. Use of combined oral contraceptives was analysed for women aged 60 or less, resulting in 108 cases and 113 controls. Women who had ever used these contraceptives for one year or more had a lower risk than non-users (odds ratios, 0.5 (95% CI, 0.2–1.1) and 0.4 (95% CI, 0.2–1.0), respectively). Among the women who had used combined oral contraceptives only for contraception, the reductions were slightly greater: odds ratios for any use versus none, 0.4 (95% CI, 0.2–0.9), and for one year versus none, 0.2 (95% CI, 0.1–0.7). It is unclear from the published paper if the estimates were adjusted for potentially confounding factors.

A hospital-based study was conducted in Australia, Chile, China, Colombia, Israel, Kenya, Mexico, the Philippines and Thailand to compare the use of combined oral contraceptives by 140 women with endometrial cancer and 910 women admitted to units other than obstetrics and gynaecology in each centre between 1979 and 1986 (WHO Collaborative Study of Neoplasia and Steroid Contraceptives, 1988). Women who had used only combined oral contraceptives had a lower risk for endometrial cancer than non-users (odds ratio, 0.5; 95% CI, 0.3–1.0), after adjustment for hospital, age, calendar year of interview and race. A reduction in risk was suggested at each level of the factors examined, including gravidity (odds ratios, 0.7 (95% CI, 0.3–1.5) for < 5 pregnancies and 0.3 (95% CI, 0.1–1.5) for ≥ 5 pregnancies), history of infertility (odds ratios, 0.6 (95% CI, 0.3–1.2) for none and 0.4 (95% CI, 0.0–7.3) for a positive history) and use of oestrogens for any other reason except menopausal symptoms (data not shown). The numbers of cases (total, 220) and control women (total, 1537) in this study continued to accrue through 1988 and were then further evaluated by Rosenblatt *et al.* (1991). Among the women who used combined oral contraceptives for contraception only, those who used formulations with a relatively 'high' dose of progestogen (on the basis of the ability of the preparation to induce subnuclear vacuolization in human endometrium) had a lower risk than non-users, regardless of the relative oestrogen dose (odds ratios, 0.2 (95% CI, 0.0–0.5) for high dose and 0 (95% CI, 0.0–1.1) for low dose). In contrast, women who used formulations with a relatively low dose of progestogen had little, if any, reduction in risk, regardless of the relative oestrogen dose (odds ratios, 1.1 (95% CI, 0.1–9.1) for high dose and 0.6 (95% CI, 0.3–1.3) for low dose). Additionally, the reduction in risk did not vary appreciably by the duration or recency of use for the women who used formulations with a relatively high dose of progestogen, whereas the women who used formulations with a relatively low dose of progestogen had a reduction in risk with longer duration of use (odds ratio, 0.1 (95% CI, 0.0–1.1) for ≥ 2 years' use

versus none) or with more recent use (odds ratio, 0.3 (95% CI, 0.1–1.1) for use within the last 10 years versus none). Similar results were seen for first use of oral contraceptives within the previous 14 years. All of these estimates were adjusted for age, gravidity, age at menarche, centre and year of diagnosis.

Koumantaki *et al.* (1989) studied women with endometrial cancer admitted to two hospitals in Athens, Greece, and control women admitted to the Athens Hospital for Orthopaedic Disorders. Only three (4%) of the 83 case women and 13 (8%) of the 164 controls had used oral contraceptives for six or more months (odds ratio, 0.6; 90% CI, 0.2–2.0, adjusted for age, parity, age at menarche, age at menopause, menopausal oestrogen use, years of smoking, height and weight).

Among 122 women treated at a major referral hospital in the Canton of Vaud (Switzerland) for endometrial cancer, 14% had used combined oral contraceptives, as had 27% of the 309 control women admitted to the same hospital for non-neoplastic, non-gynaecological conditions (Levi *et al.*, 1991). The risk decreased from 1.0 (95% CI, 0.5–2.3) for use for less than two years to 0.5 (95% CI, 0.1–1.2) for use for two to five years to 0.3 (95% CI, 0.1–0.7) for use for more than five years. Oral contraceptive use within the previous 10 years (odds ratio, 0.3; 95% CI, 0.1–0.9) or within the previous 10–20 years (odds ratio, 0.4; 95% CI, 0.2–1.0) and first use before the age of 30 (odds ratio, 0.3; 95% CI, 0.1–0.7) were all associated with a reduction in the risk for endometrial cancer. Women who had used oral contraceptives for five years or more had a reduction in risk even if use had occurred 20 or more years previously. The risk estimates were adjusted for age, area of residence, marital status, education, parity, body mass, cigarette smoking and use of post-menopausal oestrogen therapy. Little variation in risk was seen by categories of body mass (odds ratios, 0.6 (95% CI, 0.3–1.0) for < 25 kg/m^2 and 0.2 [95% CI not provided] for ≥ 25 kg/m^2) or cigarette smoking (odds ratios, 0.5 (95% CI, 0.2–1.2) for ever smoked and 0.6 (95% CI, 0.3–1.3) for never smoked). Stratification by use of post-menopausal oestrogen therapy was also presented (odds ratios, 0.4 (95% CI, 0.1–1.2) for ever use and 0.5 (95% CI, 0.3–1.0) for never use), but duration of post-menopausal oestrogen therapy was not analysed. While no reduction in risk was noted for nulliparous women (6 cases and 14 controls) who used oral contraceptives (age-adjusted odds ratio, 0.8; 95% CI, 0.2–2.9), the parous oral contraceptive users (11 cases and 68 controls) did have a reduced cancer risk (age-adjusted odds ratio, 0.3; 95% CI, 0.1–0.7).

Shu *et al.* (1991) studied 268 women with endometrial cancer identified from the population-based Shanghai (China) Cancer Registry and 268 age-matched control women identified from the Shanghai Residents Registry. The risk for endometrial cancer varied little between users of oral contraceptives (not otherwise specified) and women who had never used any type of contraception, after adjustment for age, gravidity and weight (odds ratio, 0.8; 95% CI, 0.4–1.8). When the duration of use was evaluated, there was a suggestion that oral contraceptive use for more than two years was associated with a reduction in risk (odds ratio, 0.4; 95% CI, 0.1–1.2).

In the United States, 405 women with endometrial cancer diagnosed at seven hospitals (in Chicago, Illinois; Hershey, Pennsylvania; Irvine and Long Beach, California;

Minneapolis, Minnesota; and Winston-Salem, North Carolina) and 297 age-, race- and residence-matched control women from the general population agreed to be interviewed (Stanford *et al.*, 1993). Use of combined oral contraceptives was reported by 20% of the case women and 36% of the control women (odds ratio, 0.4; 95% CI, 0.3–0.7, after adjustment for age, education, parity, weight and use of post-menopausal oestrogen therapy). There was no clear pattern of a decreasing risk with increasing duration of use (Table 10). Relative to non-users, a strong reduction in risk was noted for women who had used these preparations within the last 10 years (odds ratio, 0.1; 95% CI, 0.0–0.3) and for those who had used them first less than 15 years previously (odds ratio, 0.1; 95% CI, 0.0–0.4); both of these effects waned with more distant oral contraceptive use. The risk estimates varied little by age at first use (< 25, 25–29, 30–34, ≥ 35). When duration and recency were evaluated jointly, use within the previous 20 years was more strongly predictive of a risk reduction than longer duration of use (≥ 3 years). In a joint evaluation with other possible modifying factors, three or more years of combination oral contraceptive use were associated with a reduced risk for endometrial cancer among women of high parity (odds ratio for women with five or more births, 0.2; 95% CI, 0.0–0.6), women who weighed less than 150 lbs [68 kg] (odds ratio, 0.4; 95% CI, 0.2–0.9) and women who had never (odds ratio, 0.2; 95% CI, 0.1–0.6) or briefly (< 3 years) (odds ratio, 0.8; 95% CI, 0.2–3.2) used post-menopausal oestrogen therapy. No reduction and perhaps even an increase in risk was noted for use of combined oral contraceptives of three years or more by women who were nulliparous (odds ratio, 1.9; 95% CI, 0.3–11), weighed more than 200 lbs [91 kg] (odds ratio, 2.7; 95% CI, 0.8–8.5) or had used post-menopausal oestrogen therapy for three years or more (odds ratio, 4.1; 95% CI, 0.4–38). The estimates did not vary appreciably by history of smoking, infertility or menopausal status.

Jick *et al.* (1993) studied women who were members of a large health maintenance organization in western Washington State, United States. Women in whom endometrial cancer had been diagnosed (n = 142) were identified from the organization's tumour registry; the 1042 control women were also members of the organization. Both groups included only women who used the pharmacies of the organization and who had previously completed a questionnaire sent to all female members for a mammography study. Use of oral contraceptives (not otherwise specified), determined from the questionnaire, was reported by 18% of case women and 26% of controls, for an odds ratio of 0.5 (95% CI, 0.3–0.9), adjusted for age, enrolment date in the organization, body mass, age at menopause, parity and current use of post-menopausal oestrogen therapy. In comparison with non-users, the reduced risk for endometrial cancer was most pronounced for women who had used oral contraceptives for six or more years (odds ratio, 0.3; 95% CI, 0.1–0.9) or within the last 10 years (odds ratio, 0.4; 95% CI, 0.1–1.1).

Voigt *et al.* (1994) combined the study population described in the study of Weiss and Sayvetz (1980) with a similar study population identified between 1985 and 1987 in western Washington State, United States. The study included 316 cases and 501 controls. When oral contraceptive use was stratified by use of unopposed oestrogen, women who had used combined oral contraceptives for one year or more and who had also used

unopposed oestrogens for three years or more had no reduction in risk relative to women who had not used oral contraceptives or women who had used them for less than one year (odds ratio, 1.1; 95% CI, 0.4–2.6), whereas a reduction was noted for women who had never used unopposed oestrogens or had used them for less than three years and had used combined oral contraceptives for more than one year (odds ratio, 0.5; 95% CI, 0.3–0.9). Thus, further analyses were restricted to women who had used unopposed oestrogens never or for less than three years. When duration and recency of use of combined oral contraceptives were evaluated jointly, longer use (> 5 years) was associated with a reduced risk for endometrial cancer irrespective of recency (last use, ≤ 10 years ago versus > 10 years ago). When duration and the relative potency of the progestogens in the formulation were evaluated jointly, a longer duration of use (> 5 years), and not progestogen dosage, was most predictive of a reduced risk.

Kalandidi *et al.* (1996) studied 145 women with endometrial cancer admitted to two hospitals in Athens, Greece, and 298 control women admitted to the major accident hospital in Athens with bone fractures or other orthopaedic disorders. Only two (1%) of the case women and five (1.7%) of the controls had ever used oral contraceptives (not otherwise specified). Although a multivariate-adjusted risk estimate was presented (odds ratio, 1.3; 95% CI, 0.2–7.9), no useful inferences can be drawn from this small study.

(*d*) *Summary*

In general, women who have taken combined oral contraceptives have about one-half the risk for endometrial cancer of non-users (Kaufman *et al*., 1980; Weiss & Sayvetz, 1980; Hulka *et al*., 1982; Kelsey *et al*., 1982; La Vecchia *et al.*, 1986; Pettersson *et al*., 1986; Centers for Disease Control and the National Institute of Child Health and Human Development, Cancer and Steroid Hormone Study, 1987; WHO Collaborative Study of Neoplasia and Steroid Contraceptives, 1988; Koumantaki *et al*., 1989; Levi *et al*., 1991; Jick *et al*., 1993; Stanford et al., 1993; Vessey & Painter, 1995; Beral *et al*., 1999). The reduction first appears after two to five years of use (Kaufman *et al*., 1980; Hulka *et al*., 1982; Henderson *et al*., 1983a; Pettersson *et al*., 1986; Centers for Disease Control and the National Institute of Child Health and Human Development, Cancer and Steroid Hormone Study, 1987; Levi *et al*., 1991; Shu *et al*., 1991; Jick *et al*., 1993; Stanford *et al*., 1993; Voigt *et al*., 1994) and continues to decrease as the duration of oral contraceptive use increases (Kaufman *et al*., 1980; Henderson *et al*., 1983a; Centers for Disease Control and the National Institute of Child Health and Human Development, Cancer and Steroid Hormone Study, 1987; Levi *et al*., 1991; Stanford *et al*., 1993). Some studies have shown a greater reduction in risk with more recent use (Levi *et al*., 1991; Jick *et al.*, 1993; Stanford *et al.*, 1993), but others have found no difference (Kaufman *et al*., 1980; Henderson *et al*., 1983a; Centers for Disease Control and the National Institute of Child Health and Human Development, Cancer and Steroid Hormone Study, 1987; WHO Collaborative Study of Neoplasia and Steroid Contraceptives, 1988). When duration and recency of use were evaluated jointly, longer use (≥ 5 years) was associated with a reduced risk, irrespective of recency (Voigt *et al*., 1994), whereas another study showed

that recency (use within the last 15 years) and not duration of use was most predictive of a reduced risk (Stanford *et al*., 1993). Some studies found that the reduction in risk may be greatest with use of oral contraceptives in which progestogen effects predominate (Hulka *et al*., 1982) or that contain higher doses of progestogen (Rosenblatt *et al*., 1991), but another study found that a longer duration of use (≥ 5 years), and not progestogen dose, was most predictive of a reduced risk (Voigt *et al*., 1994).

While no reduction in risk was found for women in the highest categories of body weight in two studies (Henderson *et al*., 1983a; Stanford *et al*., 1993), two others found a reduced risk regardless of weight or body mass (Centers for Disease Control and the National Institute of Child Health and Human Development, Cancer and Steroid Hormone Study, 1987; Levi *et al*., 1991). Although one study noted a reduced risk only among oral contraceptive users who were nulliparous (Centers for Disease Control and the National Institute of Child Health and Human Development, Cancer and Steroid Hormone Study, 1987), three others found that the reductions were strongest among parous women (Levi *et al*., 1991) or women of higher parity (≥ 5 births) (WHO Collaborative Study of Neoplasia and Steroid Contraceptives, 1988; Stanford *et al*., 1993). In comparison with women who did not use oral contraceptives, oral contraceptive users who had also used post-menopausal oestrogen therapy for three or more years showed no reduction in risk in two studies (Stanford *et al*., 1993; Voigt *et al*., 1994). While four other studies did find a reduced risk among oral contraceptive users who had ever used post-menopausal oestrogen therapy (Kaufman *et al*., 1980; Hulka *et al*., 1982; Centers for Disease Control and the National Institute of Child Health and Human Development, Cancer and Steroid Hormone Study, 1987; Levi *et al*., 1991), the inclusion of women who had used this therapy for fewer than two or three years could have obscured any altered relationship with longer duration of use.

2.2.2 *Sequential oral contraceptives*

(*a*) *Case reports*

In the mid-1970s, case reports appeared in the United States of endometrial abnormalities—ranging from proliferative lesions to severe atypical hyperplasia (Lyon & Frisch, 1976; Kaufman *et al*., 1976; Cohen & Deppe, 1977) to endometrial cancer (Lyon, 1975; Silverberg & Makowski, 1975; Silverberg *et al*., 1977)—among women who had used a sequential oral contraceptive preparation, Oracon®, containing 0.1 mg ethinyloestradiol and 25 mg dimethisterone (Weiss & Sayvetz, 1980). In response to these reports, sequential preparations were removed from the consumer market in the United States and Canada in 1976, but the impact of exposure to these preparations continued to be evaluated in epidemiological studies.

(*b*) *Case–control studies*

The epidemiological studies of sequential oral contraceptive use and endometrial cancer are summarized in Table 11. Weiss and Sayvetz (1980) reported a seven-fold elevation in risk with use of Oracon®, but not with other types of sequential preparations, after adjustment for age, use of combined oral contraceptives and post-menopausal

Table 11. Case–control studies of use of sequential oral contraceptive pills and risk for endometrial cancer

Reference	Location/period/ages	Source of controls	Ascertainment of use	Participation (%)		Type/measure of therapy	No. of subjects		Odds ratio (95% CI)
				Cases	Controls		Cases	Controls	
Weiss & Sayvetz (1980)	Washington State, USA/Jan. 1975–Dec. 1977/36–55 years	General population	Personal interviews	83	96	No use Oracon® Other	110 6 1	376 8 11	Referent 7.3 (1.4–39) 0.3 (0.0–2.9)
Kaufman *et al.* (1980)	USA and Canada/July 1976–Dec. 1979/ < 60 years	Hospital patients	Personal interviews	96[a]	96[a]	No use Any use Oracon®	152 2 1	516 9 3	Referent [0.8 (0.2–2.8)][b] [1.1 (0.2–6.0)][b]
Henderson *et al.* (1983a)	Los Angeles county, USA/Jan. 1972–Dec. 1979/< 45 years	General population	Telephone interviews	81	NR	No use Duration (years) < 2 ≥ 2	116 2 9	121 5 1	Referent 0.4 (NR) 4.6 (NR)
Cancer and Steroid Hormone Study (1987)	Eight US areas/ Dec. 1980–Dec. 1982/ 20–54 years	General population	Personal interviews	73	84	No use Only sequential	250 7	1 147 64	Referent 0.6 (0.3–1.3)
WHO Collaborative Study (1988)	Seven countries/Jan. 1979–Feb. 1986/ < 60 years	Hospital patients	Personal interviews	87	93	No use Only sequential	118 1	687 5	Referent 0.9 (0.1–8.3)

CI, confidence interval; NR, not reported

[a] Responses reported for case and control women combined

[b] Crude odds ratio and 95% CI calculated from data provided in published paper using exact methods

oestrogen therapy, among 117 women with endometrial cancer identified from a population-based cancer registry and 395 women from the general population in western Washington State, United States.

Henderson *et al.* (1983a) evaluated oral contraceptive use among 127 white case–control pairs matched for age (in five-year age groups) and area of residence; the case women were identified from the population-based University of Southern California Cancer Surveillance Program and controls from the case's neighbourhood of residence. An almost fivefold increase in risk was found with the use of any type of sequential oral contraceptive for two years or more on the basis of use by nine case women and one control. [The particular brand of sequential oral contraceptive, or the combination of brands, used is not clear from the published paper.]

A study in the United States (Atlanta, Georgia; Detroit, Michigan; San Francisco, California; Seattle, Washington; Connecticut, Iowa, New Mexico and four urban areas of Utah; Centers for Disease Control and the National Institute of Child Health and Human Development, Cancer and Steroid Hormone Study, 1987) found that only seven of 433 case women and 64 of 3191 controls had exclusively used sequential oral contraceptives, resulting in an age-adjusted odds ratio of 0.6 (95% CI, 0.3–1.3). Among the larger group of women with any use of sequential oral contraceptives (26 cases and 152 controls), the risk for endometrial cancer for women who had used them in the previous three to 12 years, for three years or more or who had used Oracon® was 1.5 times that of other sequential oral contraceptive users. No estimates of the risk for these women relative to that of non-users was provided in the published paper.

Two other studies found neither an excess nor a decreased risk among small numbers of women who had used sequential oral contraceptives. In a hospital-based study in several metropolitan areas in the United States and Canada, Kaufman *et al.* (1980) reported that only two (1.3%) of the 154 case women and nine (1.7%) of the 525 control women had reported use of any type of sequential oral contraceptive during personal interviews; one of the case women and three control women reported using Oracon®.

In the international hospital-based study described on p. 120, only one of the 140 case women and five of the 910 control women had exclusively used sequential oral contraceptives (crude odds ratio, 0.9; 95% CI, 0.1–8.3); the specific preparations were not reported (WHO Collaborative Study of Neoplasia and Steroid Contraceptives, 1988).

In summary, the case reports that preceded the epidemiological studies were important in indicating that the risk for endometrial cancer was potentially elevated among users of sequential oral contraceptives and specifically among users of a particular brand, which contained a relatively potent oestrogen, ethinyloestradiol, and a weak progestogen, dimethisterone. In contrast, it was not clear from the case–control studies whether the increase in risk was restricted to users of this brand or included users of other sequential preparations. This was largely due to the low prevalence of sequential oral contraceptive use in these study populations: only 6% or less of the control women in all of the studies. When the analyses were further stratified by specific preparations, the numbers of women in each category were too small for useful inferences to be drawn from most of these studies.

2.3 Cervical cancer

2.3.1 *Methodological considerations*

(*a*) *Stage of disease and classification*

Cervical cancer is a particularly difficult disease to study with respect to use of oral contraceptives. It is generally accepted that invasive cervical cancer results from a series of changes in the cervical epithelium, from normal epithelial structure to various grades of pre-invasive changes and then on to invasive cervical carcinoma. As oral contraceptives could act at any stage in this process to enhance progression to the next stage, studies should include separate assessment of the effects of steroid contraceptives on risk at different stages of the neoplastic process. Early studies of oral contraceptives and cervical neoplasia included a mixture of lesion types, and these are not considered in this review. In the studies of specific types of preneoplastic lesions, there is considerable variation in the definition of the cases included. In addition, the systems used to classify precancerous cervical lesions histologically and cytologically have changed over time. Early studies included cervical dysplasia (sometimes sub-classified into mild, moderate and severe) and carcinoma *in situ*. In more recent studies, cases have been classified as cervical intraepithelial neoplasia (CIN), with a grading system of I–III to designate the severity of the lesion. Lesions have also been referred to histologically as squamous intraepithelial neoplasia and similarly graded on a scale of I–III to indicate severity. In general, the higher grades correspond roughly to carcinoma *in situ* and severe dysplasia, and the lower grades correspond roughly to mild and moderate dysplasia. In reviewing the literature on non-invasive cervical neoplasia, the terms used by the authors have been retained.

The two generally recognized histological types of invasive cervical carcinoma are squamous-cell carcinoma and adenocarcinoma. In many studies of invasive cervical cancer, these histological types have not been distinguished. In this review, such studies are usually classified with those of squamous-cell carcinoma, because squamous-cell carcinoma was the more common type at the time and in the places where the studies that did not distinguish them were conducted.

(*b*) *Confounding and effect-modifying variables*

Another difficulty in assessing the effect of oral contraceptives on the risk for cervical cancer is that the disease is caused by several types of human papillomavirus (HPV) (IARC, 1995). These viruses are sexually transmitted, and women with cervical neoplasia tend to be those whose sexual behaviour is conducive to the acquisition of sexually transmitted diseases, or who are married to men who have engaged in extramarital sexual relationships conducive to the acquisition of sexually transmitted agents. In some cultures, women who use oral contraceptives tend also to be women whose sexual behaviour is conducive to the acquisition of sexually transmitted agents. Under such circumstances, a spurious association between use of oral contraceptives and cervical neoplasia could be observed, if sexual practices are not controlled for either in the study design or in the statistical analysis. Unless otherwise stated, studies in which the sexual

behaviour of the subjects has not been taken into consideration have been excluded from this review.

In recent studies, attempts have been made to control for HPV infection when assessing possible associations between use of oral contraceptives and cervical neoplasia. To date, however, all attempts to do so have been limited by technical deficiencies. It is generally accepted that cervical neoplasia results from persistent infection with an oncogenic type of HPV. If a woman clears her infection, then she is unlikely to develop a cervical neoplasm. If oral contraceptives were to enhance the risk for cervical cancer by increasing the likelihood that an HPV infection will become persistent, women should be classified according to whether they have persistent infection with an oncogenic HPV. In a case–control study, this would require an adequate serological test for markers of HPV persistence; to date, no such test has been developed. Another approach would be to conduct a prospective follow-up study of a large group of women who have recently acquired an oncogenic HPV type for the development of cervical neoplasia. This approach has several limitations: one is that women could be monitored only until they developed mild or moderate intraepithelial lesions, since it would be unethical not to treat such lesions and allow them to progress to more severe disease; the second problem is that such studies require large numbers of women and a long duration of follow-up. Studies of mild intraepithelial lesions are under way, but the results in relation to use of hormonal contraceptives to date are limited; furthermore, the results of studies of mild lesions may not indicate a relationship between use of oral contraceptives and more severe disease.

Another possibility is that oral contraceptives enhance the risk for cervical cancer in women with persistent HPV infection. In order to address this issue in case–control studies, analyses have been restricted to cases and controls with evidence of HPV DNA in cervical scrapings. In such studies that have been conducted to date, few controls have been found to have HPV, and the relative risk estimates are therefore imprecise.

(*c*) *Studies of oral contraceptives and human papillomavirus infection*

Because oncogenic forms of HPV are involved in the etiology of cervical carcinoma, a number of investigations have been conducted to determine whether infection with HPV is associated with the use of oral contraceptives. It has been clearly shown that the sensitivity and specificity of methods for detecting HPV differ significantly. Methods involving the polymerase chain reaction (PCR) of DNA have been found to be the most sensitive and specific when compared with other methods such as filter *in situ*, dot–blot and Southern blot hybridization (IARC, 1995); and epidemiological studies of cervical carcinoma in which methods other than PCR have been used to detect HPV should be interpreted with the understanding of potential misclassification of HPV status. Studies on younger women have given inconsistent results for an association between the prevalence of HPV infection and oral contraceptive use. The following section is limited to studies in which PCR-based techniques were used.

Hildesheim *et al.* (1993) investigated the risk factors for HPV infection in 404 cytologically normal low-income women in Washington DC, United States, of a median age

of 26 years. The prevalence of HPV infection was found to be higher among current users of oral contraceptives (42.9%) than among women who had never used them (33.3%). Former users (prevalence, 40%) were also at increased risk of having a current HPV infection (difference in prevalence, 2.6%; 95% CI, -10.2–15.5), although these findings were not significant.

Ley *et al.* (1991) found an increased risk for HPV infection with oral contraceptive use in their study of 467 university women of a mean age of 23 years. A higher prevalence of HPV infection was associated with both past (crude odds ratio, 3.0; 95% CI, 1.8–5.0) and current use (crude odds ratio, 3.3; 95% CI, 2.1–5.3).

Bauer *et al.* (1993) examined factors associated with HPV prevalence among 483 cytologically normal women of a median age of 34 years. The prevalence in non-users, former users and current users of oral contraceptives was 5.3, 12.8 and 34.0%, respectively, but this difference, after adjusting for confounding factors, could have occurred by chance.

Burk *et al.* (1996) studied 439 sexually active women in Brooklyn, New York, United States, of an average age of 31 years. Women who had ever used oral contraceptives but were not current users had a higher prevalence of HPV infection (21.9%) than those who had never used them (17.1%); current users had a 14.8% rate of HPV PCR-DNA positivity.

Wheeler *et al.* (1993) found that oral contraceptive use was not associated with HPV infection among 357 cytologically normal university women in New Mexico, United States, of a median age of 23 years. The prevalences of HPV infection in former users (43.9%) and current users (41.8%) were not significantly different from that in women who had never used them (50%) after control for other confounding factors.

Muñoz *et al.* (1996) investigated the association between HPV DNA positivity and risk factors among 810 middle-aged women who were controls in case–control studies of cervical cancer conducted in Spain, Colombia and Brazil. The mean age of these women differed by site: 41.7 years in Spain, 42.8 years in Colombia and 52.7 years in Brazil. Use of oral contraceptives was not significantly associated with HPV DNA positivity. When compared with non-users, women who had used contraceptives for three years or less (odds ratio, 0.7; 95% CI, 0.4–1.4) and more than three years (odds ratio, 0.6; 95% CI, 0.3–1.2) were not at increased risk for HPV infection.

Ho *et al.* (1998), investigating the risk factors for the acquisition of HPV infection in university women, found that oral contraceptive use was not significantly associated.

In a follow-up study of 393 women with normal cervical cytology, Hildesheim *et al.* (1994) found no evidence that persistence of HPV infection was associated with use of oral contraceptives.

The inconsistent results of these studies could be due to differences in the sexual behaviour of oral contraceptive users and non-users in the studies. In the aggregate, they do not provide direct evidence that oral contraceptives interact with HPV to cause cervical cancer. Some are, nevertheless, consistent with a role for oral contraceptives in the genesis of cervical cancer, either by enhancing the likelihood of infection or persistence of infection by oncogenic types or by some direct, synergistic mechanism of HPV and oral contraceptives.

(*d*) *Influence of screening*

A third problem in assessing the effect of hormonal contraceptives on the risk for cervical cancer is the influence of the results of Pap smears. If the cases detected at screening are those more likely to be studied, and if women are more likely to have Pap smears if they have used oral contraceptives, then the women who are studied may be more likely to have used oral contraceptives than other cases in the population. This could lead to spuriously elevated relative risks in relation to oral contraceptive use in case–control studies, particularly for studies of intraepithelial lesions, which are largely asymptomatic and frequently detected at screening. Because of this potential bias, studies of intraepithelial lesions in which both the cases and the controls came from the same screening programme (the preferred design) are distinguished in this review from those in which they were not.

Screening with Pap smears may also influence the results of studies of invasive disease. If having a Pap smear protects against invasive disease, fewer cases will have used oral contraceptives than in the general population, which could result in a spuriously low relative risk. The influence of prior Pap smears must therefore be considered in assessing the risk for both intraepithelial and invasive cervical neoplasms in relation to oral contraceptive use.

2.3.2 *Descriptive studies*

Doll (1985) noted that mortality rates from cervical cancer in Britain increased in women born after 1935, corresponding to some change that took place in about 1960. This is approximately when oral contraceptives came into use, but it is also when women began to change their sexual behaviour, so that the trend could be the result of increased rates of HPV infection.

Peters *et al*. (1986a) reported an increase in the proportion of all newly diagnosed cervical adenocarcinomas in non-Hispanic white women under the age of 35 in Los Angeles County, United States, between 1972 and 1982. There was no increase in the risk for adenocarcinoma in older women, and there was a decreased prevalence incidence ratio for invasive squamous-cell cervical carcinoma in women of all ages during the same time period. The authors hypothesized that the trends were due to the introduction of oral contraceptives, which might preferentially increase the risk for adenocarcinomas over that for squamous-cell carcinomas. Schwartz and Weiss (1986) analysed data from the United States SEER Program and also noted an increase in the risk for adenocarcinomas between 1973 and 1982 in women under the age of 35. No comparable increase in the risk for adenocarcinomas was observed in older women, and no increase in the risk for adenosquamous carcinomas or squamous-cell carcinomas was observed for the same period. In fact, the rates of squamous-cell carcinomas had decreased in all age groups during those same years. The results of this study are thus consistent with those of Peters *et al.* (1986a) and are not inconsistent with the hypothesis that use of oral contraceptives is associated with an increase in the risk for adenocarcinomas. Chilvers *et al*. (1987) reported, however, an increased risk for both adenocarcinoma and squamous-cell carcinoma in women under

the age of 35 in three regions of England between 1968 and 1982, which would argue against a particularly strong increase in risk for adenocarcinomas associated with use of oral contraceptives.

Trends in the incidence rates of adenocarcinoma and adenosquamous carcinoma during the period 1973–91 were examined by Vizcaino *et al*. (1998) in 60 population-based registries in 25 countries. Consistent with the results of Doll (1985), they found a significant increase in the incidence of this condition in many countries between 1973 and 1991. The authors suggested that the increase was due in part to increased transmission of HPV; they also suggested that it was due in part to improvements in screening. With the introduction of the cyto-brush, more cervical adenocarcinomas *in situ* are being detected in some populations, which could result in a decline in the rates of invasive cervical adenocarcinoma. The patterns of the temporal changes across countries do not appear to be explained by variations in the patterns of use of oral contraceptives among these populations; and the observation that the rates of squamous and adenocarcinoma of the cervix are highly correlated among the populations studied suggests that oral contraceptives do not preferentially enhance the risk for adeno-carcinomas over that for squamous-cell carcinomas.

2.3.3 *Cohort studies*

(*a*) *Studies of cervical dysplasia and carcinoma* in situ *in the absence of assays for human papillomavirus DNA*

Peritz *et al*. (1977) reported the results of a cohort study of 17 942 women, 18–58 years of age, who received health examinations at the Kaiser Permanente Medical Center in Walnut Creek, California, United States, between 1968 and 1972. They did not provide serial Pap smears but, between 1973 and 1975, all women in the health plan who developed dysplasia or carcinoma *in situ* of the cervix were identified from medical records. After controlling for age, education, marital status, number of Pap smears before entry into the cohort, smoking and selected infections, the relative risk for either cervical dysplasia or carcinoma *in situ* was found to increase with the duration of oral contraceptive use. Carcinoma *in situ* and cervical dysplasia were combined in the estimates of relative risk, but the inclusion of squamous dysplasia in the analyses reduced the strength of the association, suggesting that the association was stronger for carcinoma *in situ* than for dysplasia.

Between 1970 and 1972, approximately 32 000 15–39-year-old women were re-cruited for a study in Ljubljana, Yugoslavia, through family planning and gynaecological clinics (Andolsek *et al*., 1983). Attempts were made to collect Pap smears from women in the cohort annually, but large numbers of women were lost during the seven-year follow-up period. After adjustment for years of follow-up, age at first pregnancy and number of Pap smears, there was no significant increase in the risk for either carcinoma *in situ* or severe dysplasia in women who had used oral contraceptives. When the two conditions were combined, there was no trend of increase in risk with duration of use.

The results of three cohort studies that specifically assessed the risk for cervical dysplasia in relation to oral contraceptive use are summarized in Table 12. The study of

Table 12. Cohort studies of use of oral contraceptives and cervical dysplasia

Reference (date cohort started)	Comparison groups	No. of cases	Relative risk (95% CI)	Comments
Zondervan *et al*. (1996) (1968–74)	No use	35	1.0	– adjusted for social class, smoking, age at first birth, diaphragm use, condom use; – *p* value of test for trend = 0.2; – 22 years of follow-up; – no increase in risk after 12 months since last use
	Any use	124	1.1 (0.7–1.7)	
	Current use	59	1.7 (1.0–2.8)	
	Months of use			
	1–12	5	0.8 (0.3–2.1)	
	13–24	5	0.7 (0.2–1.9)	
	25–48	11	0.5 (0.3–1.1)	
	49–72	34	1.8 (1.0–3.0)	
	73–96	26	1.2 (0.7–2.2)	
	≥ 97	43	1.1 (0.6–1.8)	
New Zealand Contraception and Health Study Group (1994) (1980–86)	IUD	92	1.0	– adjusted for smoking, age at first intercourse, number of partners, use of depot medroxyprogesterone acetate; – 5.5 years of follow-up
	Use	125	1.2 (0.9–1.6)	
Gram *et al*. (1992) (1979–80)	No use	NR	1.0	– adjusted for marital status, age group, smoking, alcohol abuse, oral contraceptive use; – 7 years' mean follow-up of users; – *p* value of test for trend = 0.05 – 354 women with CIN grade I or II, 44 with CIN grade III, and 3 with carcinoma; results not altered when analysis restricted to grade I or II
	Past use	NR	1.4 (1.0–1.8)	
	Current use	NR	1.5 (1.1–2.1)	
	Age started			
	> 24		1.1 (0.7–1.8)	
	20–24		1.5 (1.1–2.0)	
	< 20		1.3 (0.9–1.9)	

IUD, intrauterine device; NR, not reported; CIN, cervical intraepithelial neoplasia

the Oxford Family Planning Association (Zondervan *et al*., 1996) covered 17 032 women who were recruited at 17 large family planning clinics in England and Scotland between 1968 and 1974. The most recent results represent 22 years of follow-up. No increase in the risk for cervical dysplasia was observed with duration of oral contraceptive use. A small increase in risk, of borderline statistical significance, was observed for current users; however, this possible increase did not persist 12 months after last use.

The New Zealand Contraception and Health Study Group (1994) followed a cohort of 7199 women who had initially had two Pap smears showing no dysplasia for an average of 5.5 years of follow-up. The women were screened annually for cervical abnormalities. When the cohort was established, 2469 women were using oral contraceptives, 2072 women were using an intrauterine device and 1721 women were using depot medroxy-

progesterone acetate. In comparison with women who had used an intrauterine device, women who had used oral contraceptives were not at increased risk for cervical dysplasia. The women in the cohort had used oral contraceptives for an average of 2.5 years.

Between 1979 and 1980, 6622 women between the ages of 20 and 49 in Tromsø, Norway, were interviewed and subsequently followed-up for 10 years (Gram *et al*., 1992) by linking the cohort to computerized information in the pathology registry at the University of Tromsø. Serial Pap smears were not taken from all women, although at least one cytological smear was recorded for 96% of the women in the registry between 1980 and 1989. As most of the cases were CIN-I or -II, this study is summarized in Table 12 with the two studies that provide information on dysplasia. The risk for disease was significantly increased among women who were using oral contraceptives when the cohort was established; it was somewhat lower and of borderline statistical significance for past users. Women who first used oral contraceptives before the age of 24 were at slightly greater risk than were women who began using them later. The difference is not, however, statistically significant and could be due to differences in duration of use among women who began using oral contraceptives at different ages. No information on duration of use was reported.

Table 13 shows the results of two cohort studies of oral contraceptives and cervical carcinoma *in situ*. In the study of the Oxford Family Planning Association (Zondervan *et al*., 1996), the risk of women who had used oral contraceptives for more than 96 months was significantly increased, but no significant trend of increasing risk with duration of use was observed. The risk was also increased in current users of oral contraceptives but not in women who had stopped use for more than one year.

The study of the Royal College of General Practitioners (Beral *et al*., 1988) was begun in 1968. Over 23 000 women who were taking oral contraceptives at the time and an approximately equal number of women who had never taken oral contraceptives were recruited by 1400 general practitioners throughout the United Kingdom, who reported details of oral contraceptive use and the health status of each woman in the study twice each year. After 17–19 years of follow-up, a significantly increased risk for cervical carcinoma *in situ* was found for women who had ever used oral contraceptives. The risk was also observed to increase with duration of use.

It should be noted that information on the number of sexual partners was collected only by the New Zealand Contraception and Health Study Group. All of the associations summarized in Tables 12 and 13 could, therefore, be due to residual confounding by sexual variables. It should also be noted that all of the risk estimates for current users were increased and that the risk decreased after cessation of use. These observations are consistent with a screening bias: women taking oral contraceptives may be more likely to have Pap smears than women who are not. On balance, the results of the cohort studies do not provide strong evidence that cervical dysplasia or carcinoma *in situ* is causally related to use of oral contraceptives.

Table 13. Cohort studies of use of oral contraceptives and cervical carcinoma *in situ*

Reference (date cohort started)	Comparison groups	No. of cases	Relative risk (95% CI)	Comments
Zondervan *et al*. (1996) (1968–74)	No use	22	1.0	– adjusted for social class, smoking, age at first birth, diaphragm use, condom use; – *p* value of test for trend = 0.2; – 22 years of follow-up; – no significant increase in risk after 12 months since last use
	Any use	99	1.7 (1.0–3.0)	
	Current use	45	2.2 (1.2–4.1)	
	Months of use			
	1–12	4	1.4 (0.5–4.4)	
	13–24	7	1.8 (0.7–4.6)	
	25–48	20	1.7 (0.8–3.5)	
	49–72	18	1.5 (0.7–3.0)	
	73–96	11	1.2 (0.5–2.6)	
	≥ 97	39	2.5 (1.3–4.7)	
Beral *et al*. (1988) (1968–70)	No use	34	1.0	– adjusted for age, parity, smoking, social class, number of prior normal Pap smears; – *p* value of test for trend, < 0.001; – follow-up through 1987 (17–19 years)
	Any use	173	2.9 (2.0–4.1)	
	Years of use			
	< 5	84	2.4	
	5–9	66	3.6	
	≥ 10	23	4.8	

CI, confidence interval

(*b*) *Studies of cervical dysplasia in which assays for human papillomavirus DNA were performed*

Three cohort studies of a different design from those summarized in Tables 12 and 13 have been conducted. Koutsky *et al.* (1992) followed-up a cohort of 241 women with normal cervical cytology by cytological and colposcopic examinations every four months for approximately two years. HPV DNA was detected by dot–filter hybridization and Southern blot hybridization for confirmation. The risk for CIN-II or -III was not associated with use of oral contraceptives.

Liu *et al*. (1995) assembled a cohort of 206 women with cervical dysplasia who had been recruited into a randomized trial of the effect of folic acid supplementation on the course of cervical dysplasia; they had provided two to four cervical smears, which were tested for HPV-16 by Southern blotting. Follow-up examinations were conducted every two months for a total of six months. The risk for progression from low- to high-grade dysplasia was not associated with past or current use of oral contraceptives: the relative risk for progression in HPV-16-negative women was 1.6 (95% CI, 0.8–3.1) for past users versus never users and 1.4 (95% CI, 0.7–2.7) for current versus never users, whereas the comparable relative risks in HPV-16-positive women were 0.8 (95% CI, 0.6–1.1) and 0.8 (95% CI, 0.6–1.0), respectively. Although the differences in relative risk estimates for HPV-16-negative and -positive women could have occurred by chance, they are consistent

with the hypothesis that oral contraceptives enhance progression of dysplasia in the absence of HPV-16.

In a study of similar design (Ho *et al*., 1995), 70 women with cervical dysplasia were followed at three-month intervals for 15 months. HPV DNA was assayed by PCR techniques. The risk for persistent dysplasia was not associated with oral contraceptive use after HPV status was taken into account; results stratified by HPV status were not presented.

(*c*) *Studies of invasive cervical carcinoma*

The results of two cohort studies of the risk for invasive cervical carcinoma in relation to oral contraceptive use are summarized in Table 14. HPV status was not considered in either study. The study of the Oxford Family Planning Association (Zondervan *et al*., 1996) found an increased risk for invasive cervical carcinoma in women who had ever used oral contraceptives that was of borderline statistical significance. The risk was particularly enhanced for women who had used oral contraceptives within the past two years. There was no trend of increase in risk with duration of use.

The study of the Royal College of General Practitioners (Beral *et al*., 1988) also showed an increase in risk for invasive cervical carcinoma of borderline statistical significance among women who had ever used oral contraceptives and an increase in risk with duration of use. Beral *et al.* (1999) also found an increase in risk for deaths due to cervical carcinoma. On the basis of 25 years of follow-up and 172 deaths, the relative risk for

Table 14. Cohort studies of use of oral contraceptives and invasive cervical carcinoma

Reference (date cohort started)	Comparison groups	No. of cases	Relative risk (95% CI)	Comments
Zondervan *et al*. (1996) (1968–74)	No use	2	1.0	– adjusted for social class, smoking, age at first birth, diaphragm use, condom use; – *p* value of test for trend, 0.8; – 22 years of follow-up; – no significant increase in risk after 24 months since last use
	Any use	31	4.4 (1.0–32)	
	Use in past 2 years	21	6.8 (1.6–49)	
	Months of use			
	1–24	4	5.5 (0.8–51)	
	25–72	6	2.8 (0.5–23)	
	≥ 73	21	4.7 (1.1–33)	
Beral *et al*. (1988) (1968–70)	No use	16	1.0	– adjusted for age, parity, smoking, social class, number of prior normal Pap smears; – *p* value of test for trend, < 0.001; – follow-up through 1987 (17–19 years)
	Any use	49	1.8 (1.0–3.3)	
	Years of use			
	< 5	21	1.3	
	5–9	17	2.0	
	≥ 10	11	4.4	

CI, confidence interval

dying from cervical cancer among women who had ever used oral contraceptives was 1.7 (95% CI, 0.9–3.2). The relative risk increased with duration of use (*p* value for trend, 0.03) and was 4.1 (95% CI, 1.6–11) for users of 10 or more years' duration. The risk decreased with time since cessation of use and was not significantly increased 10 years after exposure.

Because these results are for invasive cervical cancer, they are unlikely to be due to preferential screening of women taking oral contraceptives. They could, however, be due to incomplete control of the confounding influence of sexual behaviour, since in neither of these studies was a detailed sexual history obtained.

2.3.4 *Case–control studies*

(*a*) *Studies of cervical intraepithelial neoplasia not based on screening programmes*

Ten case–control studies of CIN in relation to use of oral contraceptives are summarized in Table 15. In all of these studies, the cases were selected from clinics, hospitals or tumour registries, and controls were selected from clinics, hospitals or the general population. HPV status was not assessed in any of these investigations. Because the cases and controls were not selected from the same screening programme, these studies are more likely than studies based on screened populations to be influenced by screening bias. Nevertheless, an attempt was made in all of the studies to control for both sexual variables and prior screening, and they therefore provide useful information on the possible association between CIN and oral contraceptive use. A study by Hellberg *et al*. (1985) is omitted from Table 15 because, the controls were pregnant women and, as such, were not representative of the population from which the cases came with respect to contraceptive factors. Furthermore, no relative risk estimates were provided in the report of that study.

The study by Harris *et al*. (1980) was conducted at two hospitals in Oxford, England, between 1974 and 1979. After adjustment for pregnancy outside marriage, cigarette smoking and numerous sexual partners, the risk for carcinoma *in situ* or dysplasia was found to increase significantly with duration of oral contraceptive use.

Clarke *et al*. (1985) studied women attending the dysplasia clinic of the Toronto General Hospital, Canada, between 1979 and 1981 who had histologically confirmed cervical dysplasia. The controls were selected from the same neighbourhood as the corresponding cases. After controlling for number of sexual partners, the relative risk for women who had ever used oral contraceptives was estimated to be 1.7 ($p = 0.14$). Age at first sexual intercourse, smoking status and years of education were also considered as potential confounders. No information was presented on risk in relation to duration of use.

Irwin *et al*. (1988) identified women with carcinoma *in situ* from the population-based cancer registry of Costa Rica between 1982 and 1984. The controls were selected from a national survey. After adjustment for age, history of sexually transmitted disease or pelvic inflammatory disease, gravidity, age at first intercourse, number of sexual partners and history of Pap smears before 1982, a significant trend of increased risk with duration of use was observed. The risk was highest for women who had used oral

Table 15. Case-control studies of use of oral contraceptives and cervical intraepithelial neoplasia (CIN) in which cases and controls were not selected from the same screening programme

Reference	Definition of cases	No. of subjects		Relative risk (95% CI)[a]		Long-term use		Comments
		Cases	Controls	Ever	Current	Duration (years)	RR (95% CI)	
Harris *et al*. (1980)	Carcinoma *in situ* or dysplasia	237	422	Not reported		≥ 10	2.1 (significant trend, $p = 0.003$)	Cases from 2 hospitals, controls largely from gynaecological clinics of the same hospitals
Clarke *et al*. (1985)	Dysplasia	250	500	1.7		Not reported		Cases from dysplasia clinics, neighbourhood controls
Irwin *et al*. (1988)	Carcinoma *in situ*	583	938	1.6 (1.2–2.2)	2.3 (1.5–3.5)	≥ 10	2.0 (1.0–3.6) (p for trend = 0.04)	Cases from tumour registry, general population controls
Brock *et al*. (1989)	Carcinoma *in situ*	117	196	1.5 (0.4–6.6)	1.8 (0.4–8.6)	≥ 6	2.3 (0.5–11) (p for trend = 0.05)	Cases from 2 hospitals, controls from case's family physician's files or files of university-affiliated general practitioners
Jones *et al*. (1990)	Carcinoma *in situ*	293	801	Not reported	1.8 (1.0–3.4)	≥ 10	1.4 (0.8–2.7) (p for trend = 0.04)	Cases from clinics, general population controls
Cuzick *et al*. (1990)	CIN-I	110	833	Not reported		> 9	1.8 (NS)	Cases from many clinics, controls from general practitioners and family planning clinics
	CIN-II	103	833			> 9	2.5 (NS)	
	CIN-III	284	833			> 9	1.3 (NS)	
Coker *et al*. (1992)	CIN-II/-III	103	258	0.7 (0.3–1.6)	1.2 (0.5–2.8)	≥ 5	0.6 (0.2–1.4)	Cases from dysplasia referral clinic, controls from single family practice centre
De Vet *et al*. (1993)	Dysplasia	257	705	Not reported		> 10	2.3 (1.2–4.6)[b]	Cases from 40 municipalities, controls from populations of 6 of these municipalities

Table 15 (contd)

Reference	Definition of cases	No. of subjects		Relative risk (95% CI)[a]		Long-term use		Comments
		Cases	Controls	Ever	Current	Duration (years)	RR (95% CI)	
Kjaer *et al*. (1993)	Carcinoma *in situ*	586	614	1.4 (0.9–2.1)	1.5 (1.0–2.4)	≥ 10	1.7 (1.0–2.7) (*p* for trend = 0.01)	Cases from tumour registry, controls from general population
Ye *et al*. (1995)	Carcinoma *in situ*	231	8 364	1.0 (0.8–1.4)	1.2 (0.8–1.9)	> 5	1.5 (1.0–2.3) (*p* for trend = 0.13)	Hospitalized cases and controls; analyses restricted to cases with vaginal bleeding to minimize screening bias

CI, confidence interval; RR, relative risk; NS, not significant

[a] Controlled for various potentially confounding variables except human papillomavirus

[b] Among current users

contraceptives within the past year (current users); the relative risk was not increased after five years since cessation of use.

Brock *et al*. (1989) recruited women with histologically confirmed carcinoma *in situ* which had been diagnosed in two hospitals in Sydney, Australia, between 1980 and 1983. The controls were selected from the same clinics from which the cases came. After adjustment for number of sexual partners, age at first sexual intercourse and smoking, the risk for carcinoma *in situ* of women who had ever used oral contraceptives was estimated to be 1.5. The risk was somewhat higher for current users, and a trend of increasing risk with duration of use was observed which was of borderline statistical significance.

Jones *et al*. (1990) recruited cases of cervical carcinoma *in situ* from 24 participating hospitals in five United States cities. Controls from the same communities were ascertained through random-digit dialling. After control for age, race, interval since last Pap smear, number of abnormal smears, number of sexual partners, history of non-specific genital infection or sores and years of cigarette smoking, the relative risk was found to increase slightly with duration of oral contraceptive use. The risk was particularly high for current users of oral contraceptives (borderline statistical significance) and was not significantly elevated in former users.

Cuzick *et al*. (1990) recruited women referred to the Royal Northern Hospital in London, England, by their local general practitioners for evaluation of an abnormal cervical smear which was histologically classified as CIN-I, -II or -III. The controls came largely from one general practice and one family planning clinic. The relative risks for CIN were not significantly increased after more than nine years of oral contraceptive use, and no significant trends of increasing risk with duration of use were observed. The relative risk estimates were adjusted for age, social class, age at first intercourse, number of partners, parity and age at first birth. No information was provided on the risk of current users or risk in relation to time since last use.

Coker *et al*. (1992) recruited cases of CIN-II or CIN-III from a dysplasia clinic; controls were selected from a family practice centre [which might have biased the results with respect to hormonal contraceptive use]. No increase in risk was observed in relation to the features of oral contraceptive use considered, although the highest relative risk was observed for current users.

De Vet *et al*. (1993) studied women with dysplasia who were referred from 40 municipalities in the Netherlands to participate in a randomized clinical trial of the effects of β-carotene on cervical dysplasia. The controls were selected from the general population of six of these municipalities. After adjustment for the number of sexual partners, number of cigarettes smoked per day, marital status, number of children, age at first intercourse, current frequency of intercourse and age, the risk for dysplasia was found to be increased in current users of oral contraceptives who had used these products for over 10 years. The risk was not increased for current users who had used them for a shorter period or for former users.

Kjaer *et al*. (1993) recruited women with cervical carcinoma *in situ* who were living in the greater Copenhagen area between 1985 and 1986 through the Danish Cancer

Registry. The controls were recruited from the general population of Copenhagen. After control for age, years of smoking, number of sexual partners, proportion of sexually active life without use of barrier contraceptives, years of use of an intrauterine device, number of births, age at first episode of genital warts and ever having a Pap smear, the relative risk for cervical carcinoma *in situ* was found to increase significantly with duration of oral contraceptive use. The risk was also increased in current users of oral contraceptives and declined with years since last use, so that the relative risk was 1.0 after nine years since last exposure.

Ye *et al*. (1995) analysed data from the WHO Collaborative Study of Neoplasia and Steroid Contraceptives. Women hospitalized for treatment of carcinoma *in situ* were recruited from one centre each in Mexico and Chile and three centres in Thailand. The controls were women from the same hospitals as the cases but with diseases not considered to be associated with hormonal contraceptive use. Overall, women who had ever used oral contraceptives had a relative risk for cervical carcinoma *in situ* of 1.3 (95% CI, 1.2–1.5) and a strong trend of increasing risk with months of use: the relative risk of women who had used oral contraceptives for more than five years was 2.0 (95% CI, 1.7–2.5; p for trend < 0.001). The risk was also increased for women who had last used oral contraceptives within the previous 12 months (relative risk, 1.7) but not for women who had used them in the more distant past (relative risk, 1.2). To minimize any potential influence of screening bias, additional analyses were restricted to cases that presented with vaginal bleeding and were presumably not diagnosed by screening. In this subset (shown in Table 15), the risk was not significantly increased for women who had ever used oral contraceptives, and no significant trend of risk with duration of use was observed; there was also no increase in the risk of current users. These relative risk estimates were adjusted for age, hospital, marital status, number of pregnancies, history of induced abortion, number of Pap smears six months before the reference date, use of injectable contraceptives and use of condoms. Other potentially confounding variables that were considered but not found to be confounders included use of an intrauterine device or diaphragm, douching after intercourse, age at first sexual relationship, age at menarche, menopausal status, number of visits to a doctor for vaginal discharge, number of sexual relationships, history of any venereal disease or of gonorrhoea or syphilis, tubal ligation, ectopic pregnancy, stillbirth, miscarriage, prior dilatation and curettage, chest X-ray and family history of cancer.

Some consistencies among the results of the studies summarized in Table 15 are generally higher relative risk estimates for current users than for ever users and a tendency for the relative risks to decline with time since use. These findings suggest a bias due to screening in many of these studies. Nonetheless, most of the studies also found that the relative risk estimates were higher among long-term than short-term users of oral contraceptives, and, in many instances, a significant trend of increasing use with duration of use was observed. This too, however, could be due to selective factors. The longer a woman uses oral contraceptives, the more likely she is to have a Pap smear and to be diagnosed with CIN. The study of Ye *et al*. (1995) provides evidence that this kind of bias can occur.

(*b*) *Studies of cervical intraepithelial neoplasia based on screening programmes*

The case–control studies of CIN summarized in Table 16 are those in which the cases and controls were selected from the same screening programme. Thomas (1972) compared women with carcinoma *in situ*, dysplasia and any abnormal Pap smear (class III, IV or V) with women whose Pap smears were normal. All of the subjects were residents of Washington County, Maryland (United States). No increase in the risk for these conditions in relation to ever having used oral contraceptives was observed. These estimates were not appreciably altered by controlling for age, circumcision status of the husband, use of barrier contraceptives, smoking status, frequency of church attendance, evidence of trichomonas on the index smear, history of vaginal discharge, education, having been divorced or separated, having a husband who had previously been married, number of live births, conception of first child before marriage and age at first pregnancy. The risk in relation to duration of use was not reported, but the cases and controls did not differ with respect to mean cumulative dose of oestrogen or of progestogen received. They also did not differ with respect to time since first use of oral contraceptives or current use of oral contraceptives. The mean duration of use of oral contraceptives was slightly, but not significantly, higher for controls (21 months) than for the cases (20 months).

Worth and Boyes (1972) selected cases of carcinoma *in situ* from the British Columbia Screening Programme in Canada. The controls were women in the same medical practices as the cases who had negative Pap smears. The proportions of cases and controls who had ever used oral contraceptives were similar [the age-adjusted relative risk was 1.1], and the mean length in months of oral contraceptive use did not differ between the two groups (25.7 and 21.5 for cases and controls aged 20–24 and 33.9 and 32.0 months for women aged 25–29, respectively). Although the relative risk estimate was not controlled for other potential confounders, it is unlikely that doing so would have increased the relative risk estimate to a significant level. The results of these two early studies, although reassuring, are limited by the short duration of use and a short duration of follow-up.

Molina *et al*. (1988) recruited women with cervical carcinoma *in situ* who were referred from a screening programme to any one of three hospitals in Santiago, Chile. The controls were women with normal Pap smears who were selected from the same screening programme. After adjustment for total number of pregnancies, history of induced abortion, pay status (an indicator of socioeconomic status), age at first intercourse, number of sexual partners, history of vaginal discharge and frequency of prior Pap smears, no increase in the risk for cervical carcinoma *in situ* was observed in women who had ever used oral contraceptives, and no trend in risk with duration of use was observed. An increase in the risk of current users was found, but no increase in risk was observed for previous users.

Parazzini *et al*. (1992) recruited women with CIN from screening clinics in Milan, Italy. The controls were women with normal cervical smears selected from the same screening clinics. No increase in the risk for either CIN-I and -II or CIN-III was observed in women who had ever used oral contraceptives. No information was presented on

Table 16. Case–control studies of use of oral contraceptives and cervical intraepithelial neoplasia (CIN) in which the cases and controls were selected from the same screening programme

Reference	Definition of cases	No. of subjects		Relative risk (95% CI)[a]		Long-term use		Comments
		Cases	Controls	Ever	Current	Duration (years)	RR (95% CI)[a]	
Thomas (1972)	Carcinoma *in situ*	104	302	0.58 (NS)		Not reported		Mean duration of use and cumulative doses of oestrogen and progestogen not higher in cases than controls
	Dysplasia	105	302	1.24 (NS)				
	Pap III, IV, V (all cases)	324	302	0.91 (NS)				
Worth & Boyes (1972)	Carcinoma *in situ*	310	682	[1.1] (NS)[b]				Low response rates; no adjustment for confounders; RR calculated for age group 25–29 years
Molina *et al.* (1988)	Carcinoma *in situ*	133	254	1.0 (0.6–1.7)	3.2 (1.1–9.8)	> 6	0.7 (0.2–2.0)	
Negrini *et al.* (1990)	Low-grade SIL	208	1 423	0.9	0.8	≥ 5	0.5	Results similar in subset tested for and adjusted for HPV infection
	High-grade SIL	19	1 423	2.7	4.7	≥ 5	4.6	
Parazzini *et al.* (1992)	CIN I and II	124	323	0.9 (0.6–1.4)[b]		Not reported		No adjustment for confounders
	CIN III	138	323	1.0 (0.7–1.4)[b]				
Schiffman *et al.* (1993)	CIN	443	439	Not reported	1.3 (0.6–2.8)	Not reported		Adjusted for HPV infection
Muñoz *et al.* (1993)	CIN III							Adjusted for HPV infection
	Spain	249	242	1.3 (0.7–2.3)		≥ 5	1.8 (0.8–3.7)	
	Colombia	276	270	1.0 (0.6–1.6)		≥ 5	0.9 (0.5–1.5)	
Becker *et al.* (1994)	High-grade dysplasia	374	651	0.4 (0.2–0.9)	0.4 (0.2–1.0)	≥ 10	0.6 (0.2–1.4)	Adjusted for HPV infection

CI, confidence interval; RR, relative risk; Pap, Papanicolaou smear; NS not significant; SIL, squamous intraepithelial neoplasia; HPV, human papillomavirus

[a] Controlled for various potentially confounding variables except HPV, unless otherwise stated

[b] Adjusted only for age

duration of use or time since last use; however, because the cases were recruited between 1981 and 1990, it can be assumed that some of the women who had used oral contraceptives had done so for a considerable time.

The remaining four studies summarized in Table 16 differ from the others and from the studies in Table 15 in that the investigators attempted to make some adjustment for HPV status. In the study of Negrini *et al*. (1990), women with cervical intraepithelial lesions were selected from among women who received their diagnosis in 13 clinics associated with three hospitals in the Washington DC area (United States). Women with normal Pap smears were selected from the same clinics to serve as controls. Cervical scrapings were assayed for specific types of HPV by Southern blot analysis. No increase in the risk for low-grade cervical intraepithelial lesions was observed with respect to any use of oral contraceptives, current use or long-term use. While the study was based on small numbers, after adjustment for age, interval since last Pap smear and lifetime number of sexual partners, the risk for high-grade squamous intraepithelial neoplasia was found to be increased for women who had ever used oral contraceptives, for long-term users and for current users. The only estimate that had a 95% CI that included unity was that for women who had used oral contraceptives for more than five years. The results for both low-grade and high-grade squamous intraepithelial neoplasia were not appreciably different from those shown in the Table after stratification on HPV status.

Schiffman *et al*. (1993) selected cases of CIN from a cytological screening programme at Kaiser Permanente in Portland, Oregon (United States). The controls were women with a normal Pap smear. Specific types of HPV DNA were assayed in cervical vaginal lavage specimens by PCR techniques. After adjustment for age and HPV infection, the risk for CIN was not significantly increased in women who had used oral contraceptives in the past or were using them currently. No information was provided on risk in relation to duration of use.

Muñoz *et al*. (1993) selected women with CIN-III from hospitals, pathology laboratories and screening clinics in Spain and Colombia and selected controls from the same place of recruitment as the corresponding case but among women who had normal cytological results on the same date as the case was detected. HPV DNA in cervical scrapings was assayed by PCR. The risk for CIN-III was not increased among women who had ever used oral contraceptives in either Spain or Colombia after adjustment for age, centre, number of sexual partners, age at first intercourse, HPV infection, *Chlamydia trachomatis* infection, husband's sexual partners (in Spain) and smoking status (in Colombia). The risk was also not significantly increased for women who had used oral contraceptives for more than five years, and in neither country was there a significant trend of increasing risk with duration of use. In Spain, however, the risk was somewhat increased in long-term users and the p of the test for trend was 0.08.

Becker *et al*. (1994) recruited women with high-grade dysplasia through the University of New Mexico Women's Health Care and Maternal and Infant Care clinics in the United States. Women who were referred to the University of New Mexico colposcopy clinic and found to have high-grade dysplasia were compared with controls with normal

Pap smears selected from the same clinics from which the cases came. In this study, the term 'high-grade dysplasia' was used to cover moderate dysplasia, severe dysplasia and carcinoma *in situ* combined. Cervical smears were assayed for specific types of HPV DNA by dot–blot hybridization and PCR techniques. The relative risk estimates were adjusted for age, age at first intercourse, lifetime number of sexual partners, ethnicity and HPV infection as identified by PCR. The relative risks for high-grade dysplasia were not increased among women who had ever used oral contraceptives, were current users or were long-term users.

In the aggregate, the results of the eight studies summarized in Table 16 do not provide convincing evidence that use of oral contraceptives enhances the risk for cervical intraepithelial lesions. The large relative risks in the study of Negrini *et al.* (1990) are based on small numbers, and the increase in the risk of current users suggests that the results were influenced by screening bias. With this exception, the results of the studies summarized in the Table are consistent with no influence of oral contraceptives on the risk for these lesions.

(*c*) *Hospital-based studies of invasive squamous-cell cervical carcinoma*

Table 17 summarizes the results of seven hospital-based case–control studies of invasive squamous-cell cervical carcinoma. The case group in the study of Ebeling *et al.* (1987) consisted of 129 women with invasive cervical carcinoma treated at a university hospital or city hospital in Leipzig, Germany. The controls were selected from among women admitted to the same hospitals for skin diseases or orthopaedic conditions. After adjustment for number of pregnancies, age at first pregnancy, number of sexual partners, age at first intercourse, history of vaginal discharge, smoking and months since last Pap smear, the relative risk for invasive squamous-cell carcinoma decreased from 2.1 to 1.5 and was no longer statistically significant. In addition, the trend in risk with duration of use was reduced after adjustment to a non-significant level. The risk was higher for current users than for previous users (1.2; 95% CI, 0.6–2.5). The risk was particularly high for women who had begun use before the age of 25, but, after additional adjustment for age at first use, the relative risk of women who had used oral contraceptives for more than seven years was further reduced to 1.3. The risk of women who had first used oral contraceptives before the age of 25 remained statistically significant at 2.6 after adjustment for duration of use.

Parazzini *et al.* (1990) recruited 367 women under the age of 60 with invasive cervical cancer (assumed to be largely squamous-cell) from among women admitted to four large teaching and general hospitals in Milan, Italy. The controls were patients admitted for acute conditions to one of the hospitals in Milan and to several specialized Milan University clinics. The relative risk of women who had ever used oral contraceptives was 1.9 (95% CI, 1.0–3.1) after control for age, marital status, education, parity, number of sexual partners, age at first intercourse, cigarette smoking, history of Pap smears and use of barrier methods of contraception. The risk was further increased for women who had used oral contraceptives for more than two years, and there was a significant trend of

Table 17. Case–control studies of use of oral contraceptives and invasive squamous-cell cervical carcinoma: hospital controls

Reference	No. of subjects		Relative risk (95% CI)[a]		Long-term use			Comments
	Cases	Controls	Ever	Current	Duration (years)	RR (95% CI)[a]	*p* for trend	
Ebeling *et al.* (1987)	129	275	1.5 (0.8–2.9)	2.0 (1.0–4.1)	≥ 7	1.8 (1.0–3.8)	≥ 0.10	– includes 4 adenocarcinomas; – conducted in eastern Germany; – RR for women who first used oral contraceptives at ≤ 24 years, 3.0 (1.1–8.1)
Parazzini *et al.* (1990)	367	323	1.9 (1.0–3.1)	Not reported	> 2	2.5 (1.2–5.1)	0.007	Histological type not reported
Brinton *et al.* (1990)	667	1 429	1.1 (0.8–1.5)	1.3 (0.9–1.9)	≥ 10	1.1 (0.6–2.0)	Not reported	– conducted in 4 Latin American countries; – hospital and population controls; – RR estimates controlled for HPV 16/18 status
WHO Collaborative Study (1993)	2 361	13 644	1.3 (1.2–1.5)	1.0 (0.8–1.3)	> 8	2.2 (1.8–2.7)	< 0.001	Conducted in 11 centres in 9 countries
Eluf-Neto *et al.* (1994)	197	218	Not reported		≥ 5	2.5 (0.9–7.3)	0.11	– 9 adenocarcinomas, 9 adeno-squamous carcinomas and 3 undifferentiated carcinomas; – conducted in Brazil; – RR estimate controlled for HPV status

Table 17 (contd)

Reference	No. of subjects		Relative risk (95% CI)[a]		Long-term use			Comments
	Cases	Controls	Ever	Current	Duration (years)	RR (95% CI)[a]	*p* for trend	
Chaouki *et al*. (1998)	107	147	1.1 (0.4–3.4)	Not reported	> 5	6.4 (1.3–31)	0.004	– 107 cases and 56 controls with unknown use of oral contraceptives not included; – includes 16 adeno- and adenosquamous carcinomas; – conducted in Morocco; – RR estimate adjusted for HPV infection
Ngelangel *et al*. (1998)	323	380	Not reported		≥ 4	2.0 (0.5–7.6)	(not significant)	– conducted in the Philippines; – RR estimate adjusted for HPV infection

CI, confidence interval; RR, relative risk; HPV, human papillomavirus

[a] Controlled for various potentially confounding variables except HPV, unless otherwise stated

increasing risk with duration of use. The risk decreased slightly with time since last use, from 1.7 (95% CI, 0.8–3.7) for women who had last used oral contraceptives within the past five years to 1.5 (95% CI, 0.9–2.7) for women who had most recently used oral contraceptives more than five years previously.

Brinton *et al*. (1990) conducted a case–control study in selected hospitals in Panama, Costa Rica, Bogota, Colombia, and Mexico City, Mexico, with two age-matched controls selected for each case. In Panama and Costa Rica, one community and one hospital control were selected for each case, while in Bogota and Mexico City, both controls were selected from the same hospital from which the case was recruited. Cervical scrapings from all study subjects were tested for HPV DNA by filter in-situ hybridization. This method is now known to be of low sensitivity and specificity, so that if HPV was found to be associated with use of combined oral contraceptives, there could be residual confounding by HPV infection. After adjustment for age, number of sexual partners, age at first intercourse, interval since last Pap smear, number of births, HPV-16/-18 infection status and education, no increase in risk was seen for women who had ever used oral contraceptives. There was also no trend of increasing risk with increasing duration of use. There was, however, an increased relative risk of 1.7 (95% CI, 1.1–2.6) for women who had used oral contraceptives for more than five years and who had used them most recently within the past three years. The risk for users of this duration who had last used these compounds more than three years previously was not increased. These results are based on 667 cases of squamous-cell carcinoma and 61 cases of adeno-carcinoma. When the analyses were restricted to women with squamous-cell carcinoma, the results were not appreciably different.

The cases in the WHO Collaborative Study of Neoplasia and Steroid Contraceptives (1993) were of invasive cervical squamous-cell carcinoma and were recruited from one or more hospitals in Australia, Chile, Colombia, Israel, Kenya, Mexico, Nigeria and the Philippines. The controls were selected from among women admitted to the same hospitals as the cases for conditions not believed to be associated with the use of hormonal contraceptives. All of the relative risk estimates were controlled for age, centre, number of pregnancies and number of prior Pap smears. Control for additional variables obtained at interview did not appreciably alter the estimated relative risks. The risk of women who had ever used oral contraceptives was estimated to be 1.3 (95% CI, 1.2–1.5). A significant trend of increasing risk with duration of use was observed. Women who had used oral contraceptives in the past year (but not current users) were at increased risk, but a trend of decreasing risk with time since last use was observed. The increase in risk with duration of use was evident four to five years after first exposure, and the risk declined to that of non-users eight years after discontinuation of use.

Eluf-Neto *et al.* (1994) recruited 199 cases of invasive cervical cancer from seven hospitals in São Paulo, Brazil, and 225 controls from the same hospitals. HPV DNA was assayed in cervical scrapings from the study participants by PCR-based methods. After control for HPV status, a nonsignificantly increased risk was observed with duration of oral contraceptive use.

In a study in Rabat, Morocco, Chaouki *et al.* (1998) recruited 214 cases of invasive cervical cancer from a single cancer hospital and 203 controls from the same hospital or a nearby general hospital. HPV DNA was assayed in cervical specimens by a PCR-based assay. On the basis of 107 cases and 147 controls with a known history of use of oral contraceptives, no increase in the risk for cervical cancer was observed among women who had ever used oral contraceptives, after control for HPV status. A significant trend of increasing risk with duration of use was observed, however.

Ngelangel *et al.* (1998) recruited cases of invasive cervical cancer and controls from a single hospital in Manila, the Philippines. PCR-based assays for HPV DNA were performed on cervical scrapings from the study subjects. After control for HPV DNA status, a significant trend of increasing risk with duration of hormonal contraceptive use was observed.

(*d*) *Population-based studies of invasive squamous-cell cervical carcinoma*

The results of seven case–control studies of invasive squamous-cell cervical carcinoma in which population controls were used are summarized in Table 18. Peters *et al.* (1986b) identified 200 cases of invasive squamous-cell cervical carcinoma from the Los Angeles Cancer Registry, United States, and compared them with 200 neighbourhood controls. No trend of increasing risk with increasing duration of oral contraceptive use was observed in univariate analyses. No information on risk in relation to features of use other than duration was reported.

Celentano *et al*. (1987) identified 153 cases of invasive squamous-cell cervical cancer in women who had been admitted to Johns Hopkins Hospital in Baltimore, Maryland (United States) between 1982 and 1984. The controls were selected from among women residing in the same neighbourhood as the cases. No increase in risk was seen for women who had ever used oral contraceptives after control for use of other methods of contraception (condom, intrauterine device, diaphragm and vaginal spermicides), age at first intercourse, years of smoking cigarettes, frequency of Pap smears, use since last Pap smear and having visited an obstetrician–gynaecologist. No additional information was provided on risk in relation to various features of oral contraceptive use.

In a case–control study in the United States (Brinton *et al*., 1986, 1987), cases were recruited from 24 participating hospitals in Birmingham, Chicago, Denver, Miami and Philadelphia between 1982 and 1984. The controls were selected by random-digit dialling from the same populations from which the cases came. After control for age, ethnic origin, number of sexual partners, age at first intercourse, education, interval since last Pap smear and history of a non-specific genital infection or sore, the relative risk for invasive squamous-cell cervical carcinoma among women who had used oral contraceptives for more than 10 years was estimated to be 1.6 (95% CI, 0.9–2.9). This result is based on 417 women with squamous-cell carcinomas; when they were combined with 62 women with adenocarcinomas or adenosquamous carcinomas, the risk increased with duration of use. Analyses of both histological types indicated a higher risk for women

Table 18. Case–control studies of use of oral contraceptives and invasive squamous-cell cervical carcinoma: population controls

Reference	No. of subjects		Relative risk (95% CI)[a]		Long-term use			Comments
	Cases	Controls	Ever	Current	Duration (years)	RR (95% CI)[a]	*p* for trend	
Peters *et al.* (1986b)	200	200	Not reported		≥ 10	1.1 (0.5–2.7)	NS	– conducted in Los Angeles, USA; – risk relative to no use and use of < 2 years – univariate analysis only
Celentano *et al.* (1987)	153	153	0.7 (0.3–1.9)		Not reported			Conducted in Maryland, USA
Brinton *et al.* (1986)	417	789			≥ 10	1.6 (0.9–2.9)		Conducted in 5 US cities
Irwin *et al.* (1988)	129	631	0.8 (0.5–1.3)	0.3 (0.1–0.8)	≥ 5	0.9 (0.5–1.6)	NS	Conducted in Costa Rica
Bosch *et al.* (1992)	432	376	1.3 (0.9–2.0)					– conducted in Colombia and Spain; – RR estimates controlled for HPV status assessed by PCR; – risk increased with duration of use in HPV DNA-positive women only; in comparison with HPV-positive controls, RR = 8.9 (1.1–72)
Kjaer *et al.* (1993)	58	607	1.3 (0.5–3.3)	1.3 (0.5–3.7)	≥ 6	1.3 (0.5–3.5)	0.38	Conducted in Copenhagen, Denmark
Daling *et al.* (1996)	221	466	1.0 (0.6–1.6)		≥ 5	1.3 (0.7–2.2)	NS	– conducted in Washington State, USA; – RR, 2.3 (95% CI, 1.4–3.9) in women who used oral contraceptives before the age of 17, controlling for HPV-16 antibody status

RR, relative risk; CI, confidence interval; NS, not significant; HPV, human papillomavirus; PCR, polymerase chain reaction

[a] Controlled for various potentially confounding variables except HPV, unless otherwise stated

who had used oral contraceptives within the past year than for those who had used them in the more distant past.

In the study conducted in Costa Rica by Irwin *et al*. (1988), described above, 129 women with invasive cervical cancer (assumed to be squamous-cell) were compared with 631 controls selected from the general population of Costa Rica. No increase in risk was seen for women who had ever used oral contraceptives, and no trend of increasing risk with duration of use was found. Women who had used oral contraceptives within the past year were actually at reduced risk for disease, the estimate being 0.3 (95% CI, 0.1–0.8), but this estimate was based on only seven cases and 102 controls. No trend in risk with time since last use was observed. All of the estimates were adjusted for age, history of sexually transmitted disease or pelvic inflammatory disease, gravidity, age at first intercourse, number of sexual partners and history of prior Pap smears.

In a study of risk factors for cervical cancer in Colombia and Spain, Bosch *et al*. (1992) identified 436 women with histologically confirmed squamous-cell carcinoma and selected 387 controls from the general population in which the cases arose. No increase in risk was observed for women who had ever used oral contraceptives. Cervical scrapings from the study subjects were assayed for type-specific HPV DNA by PCR. No trend of increasing risk with duration of use was observed for women who had no HPV DNA, but a trend was observed for women who had HPV DNA, and this observation was statistically significant (p for trend = 0.027). This observation is, however, based on very small numbers of HPV DNA-positive controls: 17 among women who had never used oral contraceptives and one woman each who had used oral contraceptives for 1–9 and 10 or more years. The numbers of cases in these three categories were 110, 12 and 35, respectively. The relative risks in relation to non-users were estimated to be 3.0 (95% CI, 0.3–28) for users of oral contraceptives for 1–9 years and 8.9 (95% CI, 1.1–72) for users of more than 10 years' duration.

Kjaer *et al*. (1993) recruited 59 women with invasive cervical cancer and living in the greater Copenhagen area from the Danish Cancer Registry; the controls were selected from the general female population of greater Copenhagen. The risk for invasive squamous-cell cervical cancer was not significantly increased among women who had ever used oral contraceptives, and no significant trend of increasing risk with duration of use was observed. The relative risk of women who had used oral contraceptives within the past two years was 1.7 (95% CI, 0.6–4.7). The risk decreased to 1.0 for women who had last used oral contraceptives more than two years previously (p for trend = 0.002). The relative risks in this study were adjusted for age, years of school attendance, number of sexual partners, proportion of sexually active life without use of barrier contraceptives, ever having had gonorrhoea and ever having had a Pap smear.

In a population-based case–control study conducted in Washington State, United States, Daling *et al*. (1996) interviewed 221 women with invasive squamous-cell cervical carcinoma and 466 control women selected by random-digit dialling. Serum from most of the study subjects was tested for HPV-16 capsid antibodies. After adjustment for age, number of Pap smears in the last decade and lifetime number of sexual partners, the risk

was not increased for women who had ever used oral contraceptives, and no trend of increasing risk with duration of use was observed. After control for HPV antibody status, the risks relative to that of women who first began using oral contraceptives after the age of 20 were 1.6 (95% CI, 1.0–2.4) for women who had first used them between the ages of 18 and 19 and 2.3 (95% CI, 1.4–3.8) for women who had first begun using them at age 17 or younger. No information was given on risk in relation to time since last use of oral contraceptives.

The results of the studies summarized in Tables 17 and 18 are not totally consistent, but some generalizations can be made cautiously. If the risk is increased in women who have ever used oral contraceptives, then the increase in risk is likely to be modest. Most of the studies do show a small increase in risk for 'ever users', but the risks are small, and the 95% CIs of the estimates in most instances include unity. The relative risk estimates for long-term users are generally higher in the hospital-based studies (Table 17) than in the population-based studies (Table 18), but the estimates are not consistently higher or lower in hospital-based studies in which HPV DNA status was considered than in such studies in which it was not. The higher relative risks in hospital-based than in population-based studies are therefore probably not due to differences in confounding.

None of the studies indicates that risk is increased long after initial exposure to oral contraceptives. The only possible exception is the study of Daling *et al*. (1996), in which it was found that the risk for women who were first exposed to oral contraceptives before the age of 17 was increased. This observation requires independent confirmation.

In the three studies in which risk was considered in relation to use of oral contraceptives among women with and without other risk factors for cervical cancer (Brinton *et al*., 1986; Parazzini *et al*., 1990; WHO Collaborative Study of Neoplasia and Steroid Contraceptives, 1993), there was some suggestion that the risk in relation to oral contraceptives might be greater in women with than without such sexual risk factors as a history of non-specific genital infection or sore (Brinton *et al*., 1986), absence of use of barrier contraceptives (Brinton *et al*., 1986; Parazzini *et al*., 1990), having had multiple sexual partners (Parazzini *et al*., 1990), a history of sexually transmitted diseases and presence of herpes simplex virus-II antibodies (WHO Collaborative Study of Neoplasia and Steroid Contraceptives, 1993). These observations are consistent with the idea that oral contraceptives enhance risk in the presence of a sexually transmitted oncogenic agent such as certain strains of HPV.

Table 19 summarizes the results of the four studies (described above) in which the risk for invasive squamous-cell cervical cancer in relation to oral contraceptive use was estimated on the basis of a comparison of cases and controls with evidence of HPV DNA in cervical cells. In each study, the relative risk estimates for women with HPV DNA were increased, and evidence for a trend of increasing risk with duration of use of combined oral contraceptives is provided from three of the studies. These results should be interpreted with caution, however, because few controls were found to be HPV-positive and all of the estimates therefore have wide confidence limits. In addition, three of the four studies shown in Table 19 are hospital-based.

Table 19. Case–control studies of use of oral contraceptives and invasive squamous-cell cervical cancer in which analyses were restricted to women with human papillomavirus (HPV) DNA in cervical scrapings

Reference	Use of oral contraceptives	All subjects			HPV-positive subjects		
		No. of subjects		RR (95% CI)[a]	No. of subjects		RR (95% CI)[a]
		Cases	Controls		Cases	Controls	
Bosch *et al*. (1992)	Never	291	270	1.0	110	17	1.0
	Ever	141	106	1.3 (0.9–2.0)	50	2	6.5 (1.3–31)
Eluf-Neto *et al*. (1994); Bosch *et al*. (1995)	Years of use						
	None	125	152	1.0	97	21	1.0
	1–4	39	44	1.3 (0.7–2.3)	30	9	1.2 (0.4–4.2)
	≥ 5	33	22	2.7 (1.4–5.2)	27	2	9.0 (1.4–57)
Chaouki *et al*. (1998)	Years of use						
	< 1	8	25	1.0	20	7	1.0
	1	14	14	1.4 (0.2–8.1)			
	2–5/2–4[b]	32	35	2.8 (0.6–13)	21	6	1.0 (0.2–6.6)
	> 5/≥ 5[b]	39	42	6.4 (1.3–31)	37	3	16 (2.2–115)
Ngelangel *et al*. (1998)	Years of use						
	None	258	277	1.0	NR	NR	1.0
	1–3	40	80	0.3 (0.1–0.7)	NR	NR	0.3 (0.1–0.8)
	≥ 4	25	23	2.0 (0.5–7.6)	NR	NR	2.8 (0.2–30)
	Total	323	380	–	303	35	–

RR, relative risk; CI, confidence interval; NR, not reported

[a] Controlled for various potentially confounding variables

[b] Years of use in HPV-positive subjects

In summary, if there is an increased risk for squamous-cell cervical carcinoma in relation to use of oral contraceptives, it is more likely to be found in relation to invasive rather than in-situ disease. The available evidence indicates that the effect of oral contraceptives on risk probably requires the presence of HPV DNA in the cervical epithelium.

(*e*) *Studies of invasive cervical adeno- and adenosquamous carcinomas*

An early case–control study in Milan, Italy (Parazzini *et al*., 1988), showed a relative risk of 0.8 (95% CI, 0.2–2.4) for cervical adenocarcinoma among women who had ever used combined oral contraceptives. Five case–control studies have been conducted to assess the risk of adenocarcinomas and adenosquamous carcinomas in relation to duration of use of oral contraceptives (Table 20). The study of Brinton *et al*. (1990), described previously, included 41 women with adenocarcinoma and 20 women with adenosquamous carcinoma. The risk for either neoplasm among women who had ever used oral contraceptives was estimated to be 2.4 (95% CI, 1.3–4.6). No trend of increasing risk with duration of use was observed. The relative risk estimates were adjusted for age, number of sexual partners, age at first sexual intercourse, interval since last Pap smear, number of births, HPV-16/-18 infection status and education.

Thomas *et al*. (1996) analysed data from the WHO Collaborative Study of Neoplasia and Steroid Contraceptives, described previously. A total of 271 women with adenocarcinoma and 106 women with adenosquamous carcinoma were included in the study. The risk of women who had ever used oral contraceptives was increased for adenocarcinoma but not for adenosquamous carcinoma. A significant trend of increasing risk for adenocarcinoma was observed with duration of oral contraceptive use; no similar trend was observed for women with adenosquamous carcinoma, but, when both histological types were combined, a significant trend of increasing risk was observed. The risk for adenocarcinoma was highest among women who had used these products within the past year and generally declined with time since last use. These trends were strongest for neoplasms that developed in women under the age of 35. The association with risk was also somewhat stronger for formulations with high-potency progestogens than for low-potency products.

Brinton *et al*. (1986, 1987) analysed data from the population-based case–control study conducted in five US cities described previously to assess the risks for adenocarcinoma, adenosquamous carcinoma and both. As in the study of Thomas *et al*. (1996), the risk of long-term users of oral contraceptives was more strongly related to adenocarcinoma than to adenosquamous carcinoma.

Between 1977 and 1991, Ursin *et al*. (1994) identified 195 cases of adenocarcinoma and adenosquamous carcinoma from the Los Angeles Cancer Registry, United States, which were compared with 386 neighbourhood controls. After adjustment for education, household income, number of sexual partners before the age of 20, number of episodes of genital warts, months of diaphragm use and weight gain between the age of 18 and the time of diagnosis, the relative risk of women who had ever used oral contraceptives was

Table 20. Case–control studies of use of oral contraceptives and cervical adeno- and adenosquamous carcinomas

Reference	Type of case	No. of subjects		Ever use	Long-term use			Comments
		Cases	Controls	RR (95% CI)[a]	Duration (years)	RR (95% CI)[a]	*p* for trend	
Brinton *et al*. (1990)	Adenocarcinoma and adenosquamous carcinoma	61	1 429	2.4 (1.3–4.6)	≥ 10	1.8 (0.5–6.5)	NS	– hospital and population controls; – conducted in 4 Latin American countries
Thomas *et al*. (1996)	Adenocarcinoma	271	2 084	1.6 (1.2–2.1)	≥ 8	2.4 (1.4–4.0)	0.003	– hospital controls; – conducted in 10 centres in 8 countries
	Adenosquamous carcinoma	106	803	1.1 (0.7–1.8)	≥ 8	1.6 (0.6–4.1)	NS	
	Both	377	2 887	1.5 (1.1–1.9)	≥ 8	2.2 (1.4–3.5)	0.003	
Brinton *et al*. (1986, 1987)	Adenocarcinoma	40	801		≥ 10	2.4[b]	0.15	– population controls; – conducted in 5 US cities; – separate analyses of adenocarcinoma and adenosquamous cancer based on very small numbers of women who used oral contraceptives for 10 years or longer (5 and 2, respectively)
	Adenosquamous carcinoma	23	801		≥ 10	1.3[b]	0.77	
	Both	62	789		≥ 10	3.0 (1.1–8.2)		
Ursin *et al*. (1994)	Adenocarcinoma and adenosquamous carcinoma	195	386	2.1 (1.1–3.8)	≥ 12	4.4 (1.8–11)	0.04	– population controls; – conducted in Los Angeles, USA – 150 cases were adenocarcinomas; 15 were adenosquamous; no pathological confirmation of the other cases
Ngelangel *et al*. (1998)	Adenocarcinoma or adenosquamous carcinoma	33	380	Not given	≥ 4	4.3 (0.3–57)	NS	– hospital controls; – conducted in the Philippines; – RR adjusted for HPV infection; – RR based on 4 exposed cases and 23 exposed controls only; – use of all hormonal contraceptives reported, but largely represents use of combined oral contraceptives

RR, relative risk; CI, confidence interval; NS, not significant; HPV, human papillomavirus

[a] Controlled for various potentially confounding variables except HPV, unless otherwise stated

[b] RR adjusted only for age and race

estimated to be 2.1 (95% CI, 1.1–3.8). The risk increased significantly with duration of use. The relative risk of current users of contraceptives was 1.8 (95% CI, 0.6–5.7) and was close to unity for women who had used oral contraceptives more than one year in the past. These results did not change when the analysis was limited to the 150 cases of adenocarcinoma.

In the study in the Philippines (Ngelangel *et al.*, 1998) summarized above, data for 33 cases of adenocarcinoma or adenosquamous carcinoma indicated an increased risk for women who had used oral contraceptives for four years or more. The estimate is based on only three exposed cases, however, and the confidence limits of the estimates are wide and include unity.

In the aggregate, the results of the five studies summarized in Table 20 suggest that long-term use of oral contraceptives increases the risk for cervical carcinomas with adenomatous elements, although confounding by HPV infection cannot be ruled out. The association with use of oral contraceptives appears to be somewhat stronger for adenocarcinoma than for adenosquamous carcinoma.

It has also been suggested that use of oral contraceptives is more strongly related to adenocarcinoma than to squamous-cell carcinoma of the cervix. The results summarized in Tables 17, 18 and 20 are inconsistent in this regard. The study conducted in four Latin American countries (Brinton *et al.*, 1990) provided estimates for users of more than 10 years of 1.1 for squamous-cell carcinoma and 1.8 for adenocarcinoma or adenosquamous carcinoma. The studies in Los Angeles provide estimates of 1.1 for squamous-cell carcinoma in users of more than 10 years' duration (Peters *et al.*, 1986b) and 4.4 for adenocarcinoma or adenosquamous carcinoma combined in users of more than 12 years' duration (Ursin *et al.*, 1994); these results, however, are based on different study populations. The study in the Philippines (Ngelangel *et al.*, 1998) found relative risks of 2.0 and 4.3 in users of four years' or more duration for squamous and adenomatous carcinomas, respectively. The WHO Collaborative Study of Neoplasia and Steroid Contraceptives (1993) provided an estimate of 2.2 for both squamous-cell carcinoma and tumours with adenomatous elements (adenocarcinoma and adenosquamous carcinoma combined; Thomas *et al.*, 1996) in women who had used oral contraceptives for more than eight years. In the study conducted in five United States cities (Brinton *et al.*, 1986, 1987), the risks for adenocarcinoma and adenosquamous carcinoma combined of users of more than 10 years' duration was estimated to be 3.0, while the estimate for squamous-cell carcinoma was 1.6. The estimate for squamous-cell carcinoma adjusted only for age and race was 1.2. For adenocarcinoma and adenosquamous carcinoma separately, the relative risks adjusted for age and race were 2.4 and 1.3, respectively. The results of these studies thus do not resolve the question of whether use of oral contraceptives is more strongly related to adenocarcinoma and adenosquamous carcinoma than to squamous-cell carcinoma.

Another method that has been used to address the issue of the relative strength of the association between oral contraceptives and various histological types of cervical carcinoma is comparison of use by women with squamous and adenomatous cervical lesions. Persson *et al.* (1987) compared the oral contraceptive use of 23 women with adeno-

carcinoma with that of 46 women with squamous-cell carcinoma. The proportions of women who had used oral contraceptives in each group were similar, and the duration of use did not differ. Jones and Silverberg (1989) similarly compared 18 cases of endocervical adenocarcinoma with an equal number of cases of squamous-cell carcinoma; both groups included both *in situ* and invasive disease. The proportions of women in the two groups who had used oral contraceptives did not differ significantly. Honoré *et al*. (1991) compared each of 99 women with cervical adenocarcinoma with three comparable women with squamous-cell carcinoma, with matching on age, year of diagnosis and clinical stage. The women in the two groups did not differ with respect to any use of oral contraceptives and, among users, the two groups did not differ with respect to age at start of use, age at discontinuation of use or months of use of oral contraceptives. Hopkins and Morley (1991) compared 61 women with adenocarcinoma and 206 women with squamous-cell carcinoma who were under the age of 40. Thirty-three per cent of the women with adenocarcinomas and 31% of those with squamous-cell carcinomas had ever used oral contraceptives. The results of these clinical studies do not support the hypothesis that use of oral contraceptives is more strongly related to the development of adenocarcinoma than squamous carcinoma of the uterine cervix.

On balance, there appears to be insufficient evidence to conclude firmly that use of oral contraceptives is related to adenocarcinoma of the uterine cervix. The associations observed could be due to residual confounding by HPV infection, and a firm conclusion about the risk for adenocarcinoma of users of oral contraceptives must await the results of investigations that adequately control for HPV infection.

2.4 Ovarian cancer

2.4.1 *Descriptive studies*

Younger women in several developed countries have experienced substantial declines in the incidence and mortality rates of ovarian cancer. Cohort analyses based on data from Switzerland (Levi *et al.*, 1987), England and Wales (Beral *et al.*, 1988; dos Santos Silva & Swerdlow, 1995), Great Britain (Villard-Mackintosh *et al.*, 1989), Sweden (Adami *et al.*, 1990) and the Netherlands (Koper *et al.*, 1996) and a systematic analysis of mortality trends in 16 European countries (La Vecchia *et al.*, 1992, 1998) showed that women born after 1920—i.e. the generations that have used combined oral contraceptives—have consistently reduced ovarian cancer rates. The downward trends were greater in countries where combined oral contraceptives have been most widely used (La Vecchia *et al.*, 1998).

Thus, descriptive data on the incidence and mortality rates of ovarian cancer are consistent with the hypothesis of a favourable effect of combined oral contraceptive use on subsequent ovarian cancer rates.

2.4.2 *Cohort studies*

The results of cohort studies on use of combined oral contraceptives and ovarian cancer are summarized in Table 21. Most of the evidence refers to epithelial neoplasms, unless otherwise specified. Three cohort studies conducted in the United States and the

Table 21. Selected cohort studies on use of combined oral contraceptives and ovarian cancer, 1980–97

Reference	No. of cases (age, years)	Relative risk (95% CI)		Comments
		Any use	Longest use	
Ramcharan *et al*. (1981a), USA	16 (18–64)	0.4 (0.1–1.0)	–	Adjusted for age only; Walnut Creek Study on Contraception
Beral *et al*. (1988), UK	30 (≥ 25)	0.6 (0.3–1.4)	≥ 10 years, 0.3	Royal College of General Practitioners' cohort
Vessey & Painter (1995), UK	42 (all)	0.4 (0.2–0.8)	> 8 years, 0.3 (0.1–0.7)	Oxford Family Planning cohort
Hankinson *et al*. (1995), USA	260 (30–65)	1.1 (0.8–1.4)	≥ 5 years, 0.7 (0.4–1.1)	Nurses' Health Study

CI, confidence interval

United Kingdom provided data on a total of about 100 cases of epithelial ovarian cancer. In the Walnut Creek Study in the United States (Ramcharan *et al.*, 1981a), 16 cases of ovarian cancer were registered between 1968 and 1977, corresponding to an age-adjusted relative risk of 0.4 for any use of combined oral contraceptives.

The Royal College of General Practitioners' study was based on 47 000 women recruited in 1968 in 1400 British general practices (Beral *et al.*, 1988): 30 cases of ovarian cancer were observed up to 1987, corresponding to multivariate relative risks of 0.6 (95% CI, 0.3–1.4) for any use of combined oral contraceptives and of 0.3 for 10 years of use or more. Allowance was made in the analysis for age, parity, smoking and social class. In a subsequent follow-up study of mortality in that cohort up to the end of 1993 (Beral *et al.*, 1999), 55 deaths from ovarian cancer were reported; there was a statistically significantly reduced mortality rate from ovarian cancer among women who had ever used oral contraceptives (relative risk, 0.6; 95% CI, 0.3–1.0).

The study of the Oxford Family Planning Association was based on 17 032 women enrolled between 1968 and 1974 from various family planning clinics in the United Kingdom (Vessey & Painter, 1995). Up to October 1993, 42 cases of ovarian cancer were registered, corresponding to relative risks of 0.4 (95% CI, 0.2–0.8) for any use of combined oral contraceptives and 0.3 (95% CI, 0.1–0.7) for more than eight years of use. Adjustment was made for age and parity.

In the Nurses' Health study, based on 121 700 registered nurses aged 30–55 in 1976, 260 cases of ovarian cancer were observed prospectively between 1976 and 1988 (Hankinson *et al.*, 1995). The multivariate relative risk for any use, which essentially reflected former use, was 1.1 (95% CI, 0.8–1.4) but declined to 0.7 (95% CI, 0.4–1.1) for use for five years or more. Adjustment was made for age, tubal ligation, age at menarche, age at menopause, smoking and body mass index.

2.4.3 *Case–control studies*

The epidemiological evidence from case–control studies on use of combined oral contraceptives and ovarian cancer is well defined and consistent: at least 20 out of 21 studies published between 1980 and 1997 found relative risks below unity, the sole apparent outlier being a study conducted in China (Shu *et al.*, 1989).

Table 22 gives the main results of case–control studies of ovarian cancer published between 1980 and 1997 which included information on use of combined oral contraceptives. Table 23 gives age-specific relative risks and 95% CIs, while Table 24 gives the relative risks related to time since last use for studies that provided the relevant information. The findings of two pooled analyses of case–control studies on the issue are also included. These were conducted on 971 cases and 2258 controls in three European countries (Franceschi *et al.*, 1991a) and on 2197 cases and 8893 controls in white women from 12 studies in the United States (Whittemore *et al.*, 1992), for a total of over 3100 cases and 11 000 controls.

In a pooled analysis of individual data from three hospital-based European studies (Franceschi *et al.*, 1991a), the multivariate relative risk was 0.6 (95% CI, 0.4–0.8) for any

Table 22. Selected case–control studies of use of oral contraceptives and ovarian cancer, 1980–97

Reference, location	Type of study	No. of cases (age, years)	Relative risk (95% CI)			Comments
			Any use	Longest use	Duration (years)	
Willett *et al.* (1981), USA	Nested in a cohort	47 (< 60)	0.8 (0.4–1.5)	0.8 (0.3–2.1)	> 3	Prevalent cases from the Nurses' Health cohort study; adjusted for age
Hildreth *et al.* (1981), USA	Hospital-based	62 (45–74)	0.5 (0.1–1.7)	Not reported		Adjusted for age and parity; odds ratio based on 3 cases with use of oral contraceptives
Weiss *et al.* (1981a), USA	Population-based	112 (36–55)	0.6 (not reported)	0.4 (0.2–1.3)	≥ 9	Adjusted for age, demographic factors and parity
Franceschi *et al.* (1982), Italy	Hospital-based	161 (19–69)	0.7 (0.4–1.1)	Not reported		Adjusted for age
Cramer *et al.* (1982), USA	Population-based	144 (< 60)	0.4 (0.2–1.0)	0.6	> 5	Adjusted for age and parity
Rosenberg *et al.* (1982), USA	Hospital-based	136 (< 60)	0.6 (0.4–0.9)	0.3 (0.1–0.8)	≥ 5	Protection by use of combined and sequential oral contraceptives; independent of parity; adjusted for several variables
Risch *et al.* (1983), USA	Population-based	284 (20–74)	[0.5] (not reported)	Not reported		Multivariate odds ratio approximately 0.9 per year of use
Tzonou *et al.* (1984), Greece	Hospital-based	150 (all ages)	0.4 (0.1–1.1)	Not reported		Adjusted for age, parity, age at menopause and use of oestrogen replacement therapy
Cancer and Steroid Hormone Study (1987), USA	Population-based	492 (20–54)	0.6 (0.5–0.7)	0.2 (0.1–0.4)	≥ 10	Consistent results by type of combined oral contraceptive
Harlow *et al.* (1988), USA	Population-based	116 (20–79)	0.4 (0.2–0.9)	0.4 (0.2–1.0)	> 4	Borderline malignancy; adjusted for age and parity

Table 22 (contd)

Reference, location	Type of study	No. of cases (age, years)	Relative risk (95% CI)			Comments
			Any use	Longest use	Duration (years)	
Wu *et al.* (1988), USA	Hospital- and population-based	299 (18–74)	0.7 (0.5–1.1)	0.4 (0.2–0.7)	> 3	Combination of two studies conducted in the 1970s and 1980s
Shu *et al.* (1989), China	Population-based	229 (18–70)	1.8 (0.8–4.1)	1.9 (0.4–9.3)	> 5	Only 23 cases and 12 controls had ever used combined oral contraceptives
WHO Collaborative Study (1989a), 7 countries	Hospital-based	368 (< 62)	0.8 (0.6–1.0)	0.5 (0.3–1.0)	> 5	Similar results in developed and developing countries
Hartge *et al.* (1989a), USA	Hospital-based	296 (20–79)	1.0 (0.7–1.7)	0.8 (0.4–1.5)	> 5	Data collected between 1978 and 1981
Booth *et al.* (1989), UK	Hospital-based	235 (< 65)	0.5 (0.3–0.9)	0.1 (0.01–1.0)	> 10	Consistent results in strata of parity
Parazzini *et al.* (1991a), Italy	Hospital-based	505 (22–59)	0.7 (0.5–1.0)	0.5 (0.3–0.9)	≥ 2	Protective effect present in strata of major risk factors for ovarian cancer
Parazzini *et al.* (1991b), Italy	Hospital-based	91 (23–64)	0.3 (0.2–0.6)	0.2 (0.1–0.6)	≥ 2	Borderline malignancy; adjusted for age, parity, education, age at menopause and oral contraceptive use
Polychronopoulos *et al.* (1993), Greece	Hospital-based	189 (< 75)	0.8 (0.2–3.7)	Not reported		Multivariate RR; only three cases and seven controls had ever used combined oral contraceptives
Rosenberg *et al.* (1994), USA	Hospital-based	441 (< 65)	0.8 (0.6–1.0)	0.5 (0.2–0.9)	≥ 10	Association persisted as long as two decades after stopping and was not confined to any type of oral contraceptive formulation

Table 22 (contd)

Reference, location	Type of study	No. of cases (age, years)	Relative risk (95% CI)			Comments
			Any use	Longest use	Duration (years)	
Risch *et al.* (1994, 1996), Canada	Population-based	450 (35–79)	0.5 (0.4–0.7)	0.3 (0.2–0.6)	≥ 10	The inverse relationship was stronger for non-mucinous (RR, 0.9) for each year of use than for mucinous tumours (RR, 1.0); trend per year of use, 0.9 among all subjects
Purdie *et al.* (1995), Australia	Population-based	824 (18–79)	0.5 (0.4–0.7)	0.3 (0.2–0.4)	≥ 1	Adjusted for parity
Pooled analyses						
Franceschi *et al.* (1991a), Greece, Italy, UK	Three hospital-based studies	971 (< 65)	0.6 (0.4–0.8)	0.4 (0.2–0.7)	≥ 5	Protection was still present ≥ 15 years after stopping use (odds ratio, 0.5).
Whittemore *et al.* (1992), USA	Pooled analysis of 12 US population- and hospital-based case–control studies	2197 (all)	0.7 (0.6–0.8)	0.3 (0.2–0.4)	≥ 6	Invasive epithelial neoplasms in white women; protection present in population- and hospital-based studies
Harris *et al.* (1992), USA	Same pooled analysis as Whittemore *et al.* (1992)	327	0.8 (0.6–1.1)	0.6 (0.4–0.9)	> 5	Epithelial tumours of low malignant potential in white women
John *et al.* (1993), USA	Pooled analysis of 7 of the 12 studies in the pooled analysis of Whittemore *et al.* (1992)	110	0.7 (0.4–1.2)	0.6 (0.2–1.6)	≥ 6	Epithelial ovarian cancers in black women

CI, confidence interval; RR, relative risk

Table 23. Selected case–control studies on use of combined oral contraceptives and ovarian cancer, 1980–97; age-specific relative risks

Reference	Age group (years)	Relative risk (95% CI)
Willett *et al.* (1981)	< 35	0.3 (0.1–1.3)
	35–44	1.1 (0.4–3.2)
	≥ 45	1.3 (0.4–3.9)
Rosenberg *et al.* (1982)	18–29	0.4
	30–39	0.6
	40–49	0.5
	50–59	0.7
Centers for Disease Control (1983b)	20–29	0.3 (0.1–1.4)
	30–39	0.8 (0.3–2.0)
	40–49	0.6 (0.4–1.1)
	50–54	0.6 (0.3–1.1)
Parazzini *et al.* (1991a)	< 35	0.4 (0.2–0.9)
	35–44	0.8 (0.4–1.4)
	45–54	0.7 (0.4–1.3)
	55–59	0.8 (0.1–7.6)
Rosenberg *et al.* (1994)	< 45	0.5 (0.3–0.8)
	45–65	0.7 (0.4–1.2)
Pooled analysis		
Franceschi *et al.* (1991a)	< 45	0.6 (0.3–1.0)
	45–54	0.5 (0.3–1.0)
	55–64	0.6 (0.4–0.9)

CI, confidence interval

use and 0.4 (95% CI, 0.2–0.7) for longest (≥ 5 years) use. Allowance was made in the analysis for age, other socio-demographic factors, menopausal status and parity. The protection persisted for at least 15 years after use had ceased.

In a pooled analysis of individual data from 12 studies in the United States (Whittemore *et al.*, 1992), the corresponding values were 0.7 (95% CI, 0.6–0.8) for any use and 0.3 (0.2–0.4) for use for more than six years in the population-based studies. Adjustment was made for age, study and parity. The results were similar when the hospital-based and population-based studies were considered separately: the relative risks were 0.7 in both types of study for any use of combined oral contraceptives, 0.6 in hospital-based studies and 0.3 in population-based studies for longest use (> 6 years) and 0.95 (not significant) and 0.90 ($p < 0.001$), respectively, per added year of use.

An inverse association was also observed in a further analysis of seven studies of 110 cases and 251 controls in black women in the United States. The relative risk was 0.7 for any use and 0.6 for use for six years or more (John *et al.*, 1993). The United States pooled

Table 24. Selected case–control studies on use of combined oral contraceptives and ovarian cancer, 1980–97; results according to time since last use

Reference	Time since last use (years)	Relative risk (95% CI)
Cramer *et al.* (1982)	< 2	2.1 (NR)
	2–< 6	0.7 (NR)
	6–< 10	0.7 (NR)
	≥ 10	0.3 (NR)
Rosenberg *et al.* (1982)	< 1	0.3 (NR)
	1–4	0.4 (NR)
	5–9	0.8 (NR)
	≥ 10	0.5 (NR)
Centers for Disease Control (1983b)	< 1	1.0 (0.4–2.2)
	1–4	0.6 (0.3–1.1)
	5–9	0.5 (0.3–0.9)
	≥ 10	0.5 (0.3–0.9)
Harlow *et al.* (1988)	≤ 5	0.3 (0.1–0.9)
	> 5	0.6 (0.3–1.4)
WHO Collaborative Study (1989a)	< 0.5	0.9 (0.5–1.8)
	0.5–< 5	0.9 (0.5–1.5)
	5–< 10	0.8 (0.5–1.4)
	≥ 10	0.5 (0.3–0.9)
Hartge *et al.* (1989a)	< 1	0.5 (0.1–1.6)
	1–9	0.9 (0.5–1.6)
	≥ 10	1.4 (0.7–2.6)
Parazzini *et al.* (1991a)	< 10	0.5 (0.3–0.8)
	≥ 10	0.9 (0.5–1.5)
Rosenberg *et al.* (1994)	< 15	0.4 (0.2–0.8)
	15–19	0.5 (0.3–1.0)
	≥ 20	0.8 (0.4–1.5)

CI, confidence interval; NR, not reported

analysis also included data on 327 cases of epithelial ovarian neoplasms of borderline malignancy in white women. The relative risks were 0.8 (95% CI, 0.6–1.1) for any use of combined oral contraceptives and 0.6 (0.4–0.9) for five years of use or more (Harris *et al.*, 1992).

The most convincing aspect of the inverse relationship between use of combined oral contraceptives and risk for ovarian cancer is the consistency of the results, independently of the type of study (hospital- or population-based), geographical area (Australia, Europe, North America and developing countries) and type of analysis, including allowance for covariates which differed from study to study, although more variables tended to be included in most recent ones. Likewise, the inverse relationship

between use of combined oral contraceptives and ovarian cancer was observed for most types of formulations considered, including those with low doses (Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development, 1987; Rosenblatt *et al.*, 1992; Rosenberg *et al.*, 1994).

The overall estimate of protection for any use is approximately 40%, and a steady inverse relationship exists with duration of use. The decrease in risk was over 50%, and probably around 60% for use for more than five years; however, in contrast to the findings of the Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development (1987), no protection was evident after very short-term use, i.e. three to six months, in an analysis of factors associated with the short-term use of oral contraceptives by Gross *et al.* (1992) on the data of the above study.

Willett *et al.* (1981) conducted a case–control study of 47 cases of ovarian cancer and 470 controls nested in the Nurses' Health Study cohort (based on 121 964 registered nurses aged 30–55 in 1986 and residing in 11 large American states). They found an age-adjusted relative risk of 0.8 (95% CI, 0.4–1.5) for any use of combined oral contraceptives and 0.2 (95% CI, 0.1–1.0) for women aged 35 or younger, who were more likely to be current users.

Hildreth *et al.* (1981) considered 62 cases of epithelial ovarian cancer and 1068 hospital controls aged 45–74 in Connecticut, United States, that had been diagnosed between 1977 and 1979. The response rate was 71% for both cases and controls. The multivariate relative risk for any use of combined oral contraceptives, after allowance for age and parity, was 0.5 (95% CI, 0.2–1.7).

Weiss *et al.* (1981a), in a population-based case–control study of 112 cases diagnosed between 1975 and 1979 in Washington and Utah, United States, found a relative risk (adjusted for age, demographic factors and parity) of 0.6 for any use and 0.4 (95% CI, 0.2–1.3) for longest use, which was of borderline statistical significance ($p = 0.04$). The response rate was 66% for cases and 92% for controls.

Franceschi *et al*. (1982) considered data on 161 cases of epithelial ovarian cancer and 561 hospital controls in women interviewed in Milan, Italy, in 1979–80. The age-adjusted relative risk for ever use was 0.7 (95% CI, 0.4–1.1).

Cramer *et al.* (1982) conducted a case–control study of 144 cases and 139 population controls in 1978–81 in the Greater Boston area (United States) and found a relative risk, adjusted for age and parity, of 0.4 (95% CI, 0.2–1.0) for any use of combined oral contraceptives, in the absence of a consistent duration–risk relationship (relative risk, 0.6 for > 5 years). The latter may be due to the small number of cases. The response rates were around 50% for both cases and controls.

Rosenberg *et al*. (1982), in a hospital-based case–control study of 136 cases and 539 controls collected between 1976 and 1980 from various areas of the United States and Canada, found an age-adjusted relative risk of 0.6 (95% CI, 0.4–0.9) for any use and 0.3 for use for five years or more. The response rates were 94% for both cases and controls, and the results were not materially modified by multivariate analysis.

Risch *et al.* (1983) provided data from a case–control study of 284 cases and 705 controls from Washington and Utah (United States) diagnosed between 1975 and 1979, giving a significant multivariate relative risk estimate of 0.9 per year for use of combined oral contraceptives. The response rates were 68% for cases and 95% for controls.

In a case–control study conducted in 1980–81 on 150 cases and 250 hospital controls in Athens, Greece, Tzonou *et al.* (1984) found a multivariate relative risk (adjusted for age, parity, age at menopause and use of post-menopausal oestrogen therapy) of 0.4 (95% CI, 0.1–1.1). The lack of significance may be due to the low frequency of use of combined oral contraceptives in this study, which was only 2.7% in cases and 7.2% in controls.

The Centers for Disease Control Cancer and Steroid Hormone Study (1983b) and the Cancer and Steroid Hormone Study of the Centers for Disease Control and National Institute of Child Health and Human Development (1987) was a population-based investigation conducted between December 1980 and December 1982 in eight areas of the United States on 546 women 20–54 years of age with ovarian cancer and 4228 controls. The response rates were 71% for cases and 83% for controls. The multivariate relative risk, adjusted for age and parity, for any use of combined oral contraceptives was 0.6 (95% CI, 0.5–0.7), which decreased to 0.2 (0.1–0.4) for use for10 years or more. The results were consistent when specific formulations of combined oral contraceptives were considered separately.

Harlow *et al.* (1988) provided information on use of combined oral contraceptives in 116 cases of epithelial ovarian cancers of borderline malignancy diagnosed between 1980 and 1985 and 158 controls. The relative risk for any use, adjusted for age and parity, was 0.4, in the absence, however, of a consistent duration–risk relationship.

Wu *et al.* (1988), in a hospital-based case–control study of 299 cases diagnosed in 1983–85 and 752 hospital controls and 259 population-based controls from the San Francisco Bay area, United States, found a relative risk, adjusted for parity, of 0.7 (95% CI, 0.5–1.1) for any use and 0.4 (95% CI, 0.2–0.7) for more than three years of use. The overall relative risk per year of use was 0.9 (95% CI, 0.8–0.9). The response rate was about 70% for both cases and controls.

Shu *et al.* (1989), in a case–control study conducted during 1984–86 in Shanghai, China, on 229 ovarian cancer cases (172 epithelial) and an equal number of controls, found a relative risk (adjusted for education, parity, ovarian cysts and age at menarche) of 1.8 (95% CI, 0.8–4.1) for any use of combined oral contraceptives. Only 23 cases and 12 controls had ever used such preparations. The response rates were 89% for cases and 100% for controls. In China, use of combined oral contraceptives might have been an indication of a westernized life style.

The WHO Collaborative Study of Neoplasia and Steroid Contraceptives (1989a) included data on 368 cases of histologically confirmed cases of epithelial ovarian cancer and 2397 hospital controls. The patients were interviewed between 1979 and 1986 in seven countries, with response rates of 73% for cases and 94% for controls. The multivariate relative risk (adjusted for age, centre, year of interview and parity) for any use of combined oral contraceptives was 0.8 (95% CI, 0.6–1.0) and decreased to 0.5 (95% CI,

0.3–1.0) for five years of use or more. The reduction in risk was of a similar magnitude in developed and developing countries (Thomas, 1991).

In a case–control study conducted in 1978–81 in the Washington DC area of the United States with 296 patients with epithelial ovarian cancer and 343 hospital controls, Hartge *et al.* (1989a) found relative risks (adjusted for age and race) of 1.0 (95% CI, 0.7–1.7) for any use of combined oral contraceptives and 0.8 (95% CI, 0.4–1.5) for use for more than five years. The response rates were 74% for cases and 78% for controls.

Booth *et al.* (1989), in a hospital-based case–control study of 235 patients and 451 controls interviewed between 1978 and 1983 in London and Oxford, England, found multivariate relative risks of approximately 0.5 (95% CI, 0.3–0.9) for any use and 0.1 (0.01–1.0) for use for more than 10 years. They reported a significant inverse trend in risk with duration of use. Allowance was made for age, social class, gravidity and duration of unprotected intercourse.

Parazzini *et al.* (1991a) provided data on 505 cases of epithelial ovarian cancer in women under 60 years of age and 1375 hospital controls interviewed between 1983 and 1989 in northern Italy. The multivariate relative risk (adjusted for age, sociodemographic factors, parity, age at menarche, lifelong menstrual pattern, menopausal status and age at menopause) for any use of combined oral contraceptives was 0.7 (95% CI, 0.5–1.0), which decreased to 0.5 (0.3–0.9) for two years of use or more, with a significant inverse trend in risk with duration. The response rate was 98% for both cases and controls.

Parazzini *et al.* (1991b) also considered 91 patients with epithelial ovarian cancer of borderline malignancy and 237 hospital controls who were interviewed between 1986 and 1990 in northern Italy. The multivariate relative risk (adjusted for age, education, parity and age at menopause) for any use of combined oral contraceptives was 0.3 (95% CI, 0.2–0.6), and that for two years of use or more was 0.2 (0.1–0.6). The response rate was 98% for both cases and controls.

In a case–control study of 189 cases and 200 controls conducted in 1989–91 in greater Athens, Greece (Polychronopoulou *et al*., 1993), only three cases and seven controls had any use of combined oral contraceptives, corresponding to a multivariate relative risk of 0.8 (95% CI, 0.1–3.7). The response rate for cases was about 90%.

Rosenberg *et al.* (1994) updated their 1982 report, providing data collected between 1977 and 1991 on 441 cases of epithelial ovarian cancer and 2065 hospital controls from various areas of the United States. The response rate was 94% for both cases and controls. The multivariate relative risk for any use (adjusted for parity, hysterectomy, monolateral oophorectomy, tubal ligation, family history of ovarian cancer and sociodemographic factors) was 0.8 (95% CI, 0.6–1.0). No significant protection was observed with up to three years of use, but the relative risk declined to 0.5 (95% CI, 0.2–0.9) for 10 years of use or more. The risk estimates were similar for various types of combined oral contraceptive formulations.

Risch *et al.* (1994, 1996) provided data on 450 cases of epithelial ovarian cancer in women aged 35–79 diagnosed between 1989 and 1992 and 564 controls in Ontario, Canada. The response rates were 71% for cases and 65% for controls. The odds ratio,

adjusted for age and parity, for any use of oral contraceptives was 0.5 (95% CI, 0.4–0.7); after 10 or more years of use, it was 0.3 (0.2–0.6). The overall multivariate odds ratio per each year of use of combined oral contraceptives, adjusted for age, parity, lactation, use of postmenopausal oestrogen therapy, tubal ligation, hysterectomy and family history of breast cancer, was 0.90 (95% CI, 0.86–1.0), and the protection was stronger for serous and endometrioid cancers than for mucinous neoplasms.

Purdie *et al.* (1995) in a population-based study of 824 cases diagnosed between 1990 and 1993 and 860 controls in three Australian states found a relative risk of 0.6 (95% CI, 0.5–0.7) for any use, which declined to 0.3 (0.2–0.4) for 10 years of use or more. The response rates were 90% for cases and 73% for controls. Allowance was made in the analysis for sociodemographic factors, family history of cancer, talc use, smoking and reproductive and hormonal factors.

Parity is a well-recognized protective factor for ovarian cancer (Parazzini *et al.*, 1991c) and is a correlate of the use of combined oral contraceptives, i.e. a potentially relevant confounder. The inverse relationship between use of combined oral contraceptives and ovarian cancer was also observed, however, after adequate allowance had been made for parity and was reproduced consistently in several studies across separate strata of parity, age and other potential covariates, including marital status, education, menopausal status, other types of contraceptive use and other selected menstrual and reproductive factors.

The association between oral contraceptive use and the risk for ovarian cancer has been assessed in women with germ-line mutations in the *BRCA-1* or *BRCA-2* gene (Narod *et al.*, 1998). Thus, 207 women with such mutations and ovarian cancer were compared with 53 of their sisters who had one of these mutations. The relative risk for ovarian cancer was estimated to be 0.4 (95% CI, 0.2–0.7) for women who had ever used oral contraceptives and 0.3 (0.1–0.7) for women who had used oral contraceptives for six or more years.

At least two studies (Harlow *et al.*, 1988; Parazzini *et al.*, 1991b) and the pooled analysis of 12 United States studies (Harris *et al.*, 1992) also considered epithelial ovarian tumours of borderline malignancy. An inverse relationship was seen for these neoplasms, suggesting that combined oral contraceptives exert protection against the whole process of epithelial ovarian carcinogenesis.

Little information is available on the different histological types of epithelial ovarian cancer. In a Canadian study (Risch *et al.*, 1996), the inverse association was apparently stronger for non-mucinous (odds ratio per year of use, 0.9; 95% CI, 0.85–0.93) than for mucinous (odds ratio per year of use, 0.97; 0.93–1.04) tumours. This observation, however, requires confirmation.

In the case of non-epithelial ovarian cancers, 38 germ-cell neoplasms and 45 sex-cord-stromal neoplasms were identified from the collaborative analysis of four United States case–control studies (Horn-Ross *et al.*, 1992). The multivariate relative risks for any use of combined oral contraceptives were 2.0 (95% CI, 0.8–5.1) for germ-cell cancers and 0.4 (0.2–0.8) for sex-cord-stromal neoplasms. The data were inadequate to evaluate

duration of use or any other time–risk relationship. Similarly, the few available data indicate a consistent inverse association between use of combined oral contraceptives and benign epithelial tumours (ovarian cysts) (Parazzini *et al.*, 1989; Booth *et al.*, 1992) but not benign ovarian teratomas (Westhoff *et al.*, 1988; Parazzini *et al.*, 1995).

The favourable effect of use of combined oral contraceptives on the risk for epithelial ovarian cancer seems to persist for at least 10–15 years after use of the contraceptives has ceased (Cancer and Steroid Hormone Study of the Centers for Disease Control and National Institute of Child Health and Human Development, 1987; Franceschi *et al.*, 1991a; Whittemore *et al.*, 1992; Rosenberg *et al.*, 1994) and is not confined to a particular formulation (Rosenblatt *et al.*, 1992; Rosenberg *et al.*, 1994). There is some suggestion that formulations with lower doses of oestrogen are slightly less protective: in the WHO Collaborative Study on Neoplasia and Steroid Contraceptives (Rosenblatt *et al.*, 1992), the relative risk for ovarian cancer associated with any use of combined oral contraceptives was 0.7 (95% CI, 0.4–1.1) for high-dose preparations and 0.8 (95% CI, 0.5–1.3) for low-dose ones. The available data do not provide definite evidence of an inverse association between use of combined oral contraceptives with low-dose oestrogen and ovarian cancer for longer periods or in relation to recency of use.

The suppression of ovulation induced by oral contraceptives has been suggested to explain the inversion association, since it protects the ovarian epithelium from recurrent trauma and contact with follicular fluid (Fathalla, 1971; Casagrande *et al*., 1979; Parazzini *et al.*, 1991c). Combined oral contraceptives may also protect against ovarian cancer by reducing exposure to pituitary gonadotropins, which stimulate the growth of cell lines derived from human ovarian carcinoma (Simon *et al.*, 1983). The lack of apparent protection by post-menopausal oestrogen therapy, however, does not support the existence of a favourable role of gonadotropin stimulation on ovarian carcinogenesis.

Since the incidence of ovarian cancer is already appreciable in middle age, and survival from the disease is unsatisfactory, the protection attributable to use of oral contraceptives is important and is therefore one of the major issues in any risk–benefit, public health evaluation of the use of combined oral contraceptives (Gross & Schlesselman,1994; La Vecchia *et al.*, 1996).

2.5 Cancers of the liver and gall-bladder

The vast majority of primary liver cancers are hepatocellular carcinomas. Chronic infection with hepatitis B (HBV) or C virus causes hepatocellular carcinoma, the relative risk exceeding 50 in many studies (IARC, 1994). Drinking of alcoholic beverages also causes liver cancer (IARC, 1988). Cholangiocarcinoma is much less common, although it is frequent in parts of South-East Asia and can be caused by infection with liver flukes (Parkin *et al.*, 1991).

2.5.1 *Descriptive studies*

Forman *et al.* (1983) analysed the rates of mortality from primary liver cancer among men and women in England and Wales between 1958 and 1981. The age-standardized

death rate in women aged 20–39 increased from 0.9 per million in 1970–75 to 1.8 per million in 1976–81 ($p < 0.005$), whereas changes in death rates between these periods among women aged 40–54 and among men were small and not statistically significant. The authors suggested that the change was consistent with the idea that oral contraceptives caused some cases of liver cancer, but noted that no such trend was apparent in Australia, western Germany, the Netherlands or the United States, other countries where oral contraceptive use had been similar to that in England and Wales. In an analysis of subsequent secular trends in mortality in England and Wales, Mant and Vessey (1995) concluded that the rate of mortality from liver cancer had remained constant in women in age groups that had had major exposure to oral contraceptives, and Waetjen and Grimes (1996) found no evidence for an effect of oral contraceptive use on secular trends in liver cancer death rates in Sweden or the United States.

2.5.2 *Cohort studies*

Colditz *et al*. (1994) studied a cohort of 121 700 female registered nurses aged 30–55 in the United States in 1976 who were followed-up for deaths until 1988. Women who reported angina, myocardial infarct, stroke and cancer (other than non-melanoma skin cancer) at baseline were excluded, leaving 116 755 women for follow-up. Of these, 55% reported having used oral contraceptives, and 5% reported current use. It was estimated that 98% of the deaths were ascertained. Incidence rates with person–months of follow-up were used as the denominator and oral contraceptive use at recruitment as the exposure. The relative risks were adjusted for age and for potential confounders including smoking but not alcohol consumption. There were 2879 deaths after 1.4 million women–years of follow-up. The risks associated with any use of oral contraceptives relative to no use, adjusted for age, smoking, body mass index and follow-up interval, were 0.93 (95% CI, 0.85–1.0) for death from any cause and 0.9 (0.8–1.0) for death from any cancer. There were 10 deaths from primary liver or biliary-tract cancer during the 12 years of follow-up, two of which were among women who had used oral contraceptives, with a relative risk of 0.4 (95% CI, 0.1–2.4). No information was provided on infection with hepatitis viruses.

Hannaford *et al.* (1997) described the relationships between use of oral contraceptives and liver disease in two British prospective studies by the Royal College of General Practitioners and the Oxford Family Planning Association. In the first study, 46 000 women, half of whom were using combined oral contraceptives, were recruited in 1968–69 and followed-up until they changed their general practitioner or until 1995. Cancer diagnoses were categorized according to the woman's contraceptive status at the time. There were five cases of liver cancer, comprising one hepatocellular carcinoma in a woman who had never used oral contraceptives, three cholangiocarcinomas in women who had formerly used oral contraceptives and one cholangiocarcinoma in a woman who had never used oral contraceptives. The risk for cholangiocarcinoma associated with former use of oral contraceptives in relation to no use was 3.2 (95% CI, 0.3–31). In a study of mortality in the same cohort after 25 years of follow-up, there were five deaths

from liver cancer among women who had used combined oral contraceptives and one in a woman who had never used them, for a relative risk of 5.0 (95% CI, 0.6–43) (Beral *et al.*, 1999). In the study of the Oxford Family Planning Associaiton, 17 032 women were recruited between 1968 and 1974, and most were followed-up until 1994. Three liver cancers were reported, comprising two hepatocellular carcinomas and one cholangiocarcinoma, all in women who had formerly used oral contraceptives. No information on infection with hepatitis viruses was provided.

2.5.3 *Case–control studies*

(*a*) *Benign neoplasms of the liver*

Edmondson *et al.* (1976) interviewed by telephone 34 of 42 eligible women who had undergone surgery for hepatocellular adenoma in Los Angeles, United States, between 1955 and 1976. One age-matched friend control was interviewed for each case. Twenty-eight of the 34 cases (82%) and 19 of 34 controls (56%) had used oral contraceptives for more than 12 months. The risks relative to use of oral contraceptives for less than 12 months were 1.3 for 13–36 months of use, 5.0 for 61–84 months, 7.5 for 85–108 months and 25 for 109 months and longer.

Rooks *et al.* (1979) interviewed 79 of 89 eligible in women aged 16–50 in whom hepatocellular adenoma had been diagnosed between 1960 and 1976 at the Armed Forces Institute of Pathology, Washington DC, United States. Three age-matched neighbourhood controls were sought for each case, and 220 were interviewed. Seventy-two of the 79 cases (91%) and 99 of 220 controls (45.0%) had used oral contraceptives for more than 12 months. The risks relative to use of oral contraceptives for less than 12 months were 9 for 13–36 months of use, 116 for 37–60 months, 129 for 61–84 months and 503 for 85 months and longer.

(*b*) *Malignant tumours of the liver*

The studies on malignant tumours of the liver described below are summarized in Table 25.

Henderson *et al.* (1983b) studied women in Los Angeles County, United States, in whom liver cancer had been diagnosed and confirmed histologically during 1975–80 when they were 18–39 years of age. Two neighbourhood controls were sought for each case and matched on age and ethnic group. Twelve cases of liver cancer were identified, and interviews were obtained with 11 of the patients: eight with hepatocellular carcinoma, one with a giant-cell carcinoma, one with a sclerosing duct-forming carcinoma and one with a papillary carcinoma. Four out of 22 identified controls refused to be interviewed and were replaced, giving a response rate among those first selected of 82%; the true response rate was probably lower because the census information used to identify controls could not be obtained for 4.3% of the houses surveyed. Three patients, two with hepatocellular carcinoma, were interviewed in person by telephone; next-of-kin respondents were used for the others. None of the patients or controls reported a prior history of hepatitis or jaundice; none of the four cases had antigens to HBV surface antigen (HBsAg);

Table 25. Case–control studies of use of combined oral contraceptives and cancers of the liver

Reference and study area (period of diagnosis)	Cancer type	Combined oral contraceptives			Relative risk (95% CI)	Comments
		Use	No. of cases	No. of controls		
Henderson *et al.* (1983b) USA (1975–80)	Hepatocellular	Never	1[a]	8	[1.0]	No association with alcohol use; none of the 4 cases tested had antibodies to HBV surface antigen
		Ever	7	8	[7.0 (0.7–71)] [unmatched analysis]	
	Other	Never	0	1		
		Ever	3	5		
Neuberger *et al.* (1986) UK (1976–85)	Hepatocellular	*Total group*		*Expected no.*		No information on alcohol use
		Never	8	7.3	1.0	
		Ever	18	18.7	1.0 (0.4–2.4)	
		< 4 years	4	11.4	0.3 (0.1–1.1)	
		4–7 years	5	5.0	0.9 (0.3–3.4)	
		≥ 8 years	9	2.3	4.4 (1.5–13)	
		Excluding HBV-positive		*Expected no.*		
		Never	5	5.9	1.0	
		Ever	17	16.1	1.5 (0.5–4.4)	
		< 4 years	4	9.8	0.5 (0.1–1.9)	
		4–7 years	5	4.5	1.5 (0.4–6.3)	
		≥ 8 years	8	1.8	7.2 (2.0–26)	
Forman *et al.* (1986) UK (1979–82)	Hepatocellular	Never	4	68	1.0	No information on alcohol use; cases with hepatitis or cirrhosis excluded; no information on HBV status
		Ever	15	79	3.8	
		< 4 years	8	56	3.0	
		4–7 years	4	19	4.0	
		≥ 8 years	3	4	20	
	Cholangio-carcinoma	Never	8	68	1.0	
		Ever	3	79	0.3	
		< 4 years	1	56	0.1	
		≥ 4 years	2	23	0.9	

Table 25 (contd)

Reference and study area (period of diagnosis)	Cancer type	Combined oral contraceptives			Relative risk (95% CI)	Comments
		Use	No. of cases	No. of controls		
Palmer *et al.* (1989) USA (1977–85)	Hepatocellular	Never	1	29	[1.0]	No information on alcohol use or HBV status; one case of hepatocellular carcinoma had cirrhosis
		Ever	8	16	[14 (1.7–126)]	
		< 2 years	1	7	–	
		2–4 years	4	4	20 (2.0–190)	
		≥ 5 years	3	5	20 (1.6–250)	
	Cholangio-carcinoma	Never	0	8		
		Ever	2	2		
WHO Collaborative Study Group (1989b) Chile, China, Colombia, Israel, Kenya, Nigeria, Philippines, Thailand (1979–86)	Hepatocellular	Never	29	197	1.0	No significant difference in alcohol drinking habits between cases and controls; no information on HBV status, but all centres except one were in endemic areas
		Ever	7	69	0.6 (0.2–1.6)	
		≤ 2 years	6	45	0.8 (0.3–2.2)	
		> 2 years	1	24	0.2 (0.0–1.9)	
	Cholangio-carcinoma	Never	19	162	1.0	
		Ever	11	72	1.2 (0.5–3.1)	
		≤ 2 years	6	41	1.2 (0.4–3.7)	
		> 2 years	5	30	1.3 (0.4–4.1)	
Kew *et al*. (1990) South Africa (< 1989)	Hepatocellular	Never	39	84	1.0	Association unaltered by adjustment for alcohol use; 19 cases had antibodies to HBV surface antigen
		Ever	7	8	1.9 (0.6–5.6)	
		< 4 years	3	3	2.1 (0.4–11)	
		4–8 years	1	1	2.0 (0.1–33)	
		> 8 years	3	4	1.5 (0.3–7.2)	
Vall Mayans *et al.* (1990) Spain (1986–88)	Hepatocellular	Never	23	54	1.0	Association unaltered by adjustment for alcohol use; none of the oral contraceptive users had antibodies to HBV surface antigen
		Ever	6	3	[4.7 (1.1–20)]	

Table 25 (contd)

Reference and study area (period of diagnosis)	Cancer type	Combined oral contraceptives			Relative risk (95% CI)	Comments
		Use	No. of cases	No. of controls		
Yu *et al.* (1991) USA (1984–90)	Hepatocellular	Never	12	40	1.0	Association unaltered by adjustment for alcohol; 7 cases had antibodies to HBV or HCV: exclusion of these increased the association with oral contraceptives
		Ever	13	18	3.0 (1.0–9.0)	
		< 1 year	4	7	2.3 (0.5–11)	
		1–5 years	3	7	1.7 (0.3–9.1)	
		> 5 years	6	4	5.5 (1.2–25)	
Hsing *et al.* (1992) USA (1985–86)	Hepatocellular	*All subjects*				Adjusted for alcohol use; subjects with cirrhosis were excluded; no information on HBV status
		Never	33	306	1.0	
		Ever	39	243	1.6 (0.9–2.6)	
		< 5 years	16	121	1.2 (0.6–2.4)	
		5–9 years	13	61	2.0 (1.0–4.4)	
		≥ 10 years	8	41	2.0 (0.8–4.8)	
		Spouse or parent respondent				
		Never	17	211	1.0	
		Ever	35	180	2.7 (1.4–5.3)	
		< 5 years	15	93	2.1 (0.9–4.6)	
		5–9 years	13	48	3.9 (1.6–9.6)	
		≥ 10 years	7	26	4.8 (1.7–14)	
	Cholangio-carcinoma	*Spouse or parent respondent*				
		Never	7	211	1.0	
		Ever	6	180	0.8 (0.3–2.7)	
		< 5 years	2	93	0.5 (0.1–2.7)	
		5–9 years	1	48	0.6 (0.1–5.4)	
		≥ 10 years	3	26	3.3 (0.7–16)	

Table 25 (contd)

Reference and study area (period of diagnosis)	Cancer type	Combined oral contraceptives			Relative risk (95% CI)	Comments
		Use	No. of cases	No. of controls		
Tavani *et al.* (1993b) Italy (1984–92)	Hepatocellular	Never	34	173	1.0	Association unaltered by adjustment for alcohol use; no information on HBV status; relative risk, 4.3 (1.0–18) > 10 years after last use
		Ever	9	21	2.6 (1.0–7.0)	
		≤ 5 years	5	17	1.5 (0.5–5.0)	
		> 5 years	2	4	3.9 (0.6–25)	
Collaborative MILTS Project Team (1997) France, Germany, Greece, Italy, Spain, UK (1990–96)	Hepatocellular	*All subjects*				Association unaltered by adjustment for alcohol
		Never	145	693	1.0	
		Ever	148	1 086	0.8 (0.5–1.0)	
		1–2 years	26	238	0.8 (0.5–1.3)	
		3–5 years	26	201	0.6 (0.3–1.1)	
		≥ 6 years	90	638	0.8 (0.5–1.1)	
		No cirrhosis or HBV or HCV				
		Never	16	250	1.0	
		Ever	35	324	[1.7 (0.9–3.1)] [unmatched analysis]	
		1–2 years	5	74	1.3 (0.4–4.0)	
		3–5 years	5	57	1.8 (0.5–6.0)	
		≥ 6 years	25	193	2.8 (1.3–6.3)	

CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus

[a] This case had received injections of hormones of undetermined type for nine months.

none of the patients reported exposure to any known hepatotoxin such as vinyl chloride, and there was no difference in the frequency of alcohol consumption between cases and controls. Smoking histories were not reported. Ten of the 11 patients (seven of the eight cases of hepatocellular carcinoma) had used oral contraceptives, and the eleventh had received hormone injections of an undetermined type; 13 of the 22 controls had used oral contraceptives. The average duration of use of oral contraceptives was 64.7 months for the patients and 27.1 months for the controls (one-sided matched $p < 0.005$). [The relative risk for any use of oral contraceptives was 7.0 (95% CI, 0.7–71) for hepatocellular carcinoma and 6.9 (0.7–64) for all liver cancers (unmatched analyses).]

Neuberger *et al.* (1986) studied 26 women in whom hepatocellular carcinoma had been diagnosed and confirmed histologically in a non-cirrhotic liver when they were under the age of 50. The cases were referred from all over Britain to the Liver Unit at King's College School of Medicine and Dentistry, London, between 1976 and 1985. The controls were 1333 women who were hospital controls in a case–control study of breast cancer and had been interviewed during 1976–80; the response rate was not given. The source of information on the exposures of the cases is not specified, but may have been interviews. The results were not adjusted for smoking or alcohol use. Eighteen of the 26 case women had taken oral contraceptives. The controls were used to calculate the expected numbers of cases for each duration of pill use, within age and calendar groups. The expected number of women who had ever used oral contraceptives was 18.7, giving a relative risk of 1.0 (95% CI, 0.4–2.4). The relative risks for durations of use were 0.3 (95% CI, 0.1–1.1) for < 4 years, 0.9 (0.3–3.4) for 4–7 years and 4.4 (1.5–13) for ≥ 8 years. None of the case women had HBsAg, but one had antisurface antibodies and three had anticore antibodies. Exclusion of these four cases changed the relative risks associated with oral contraceptive use to 1.5 (95% CI, 0.5–4.4) for any use, 0.5 (0.1–1.9) for < 4 years, 1.5 (0.4–6.3) for 4–7 years and 7.2 (95% CI, 2.0–26) for ≥ 8 years. Three cases in this study were also included in the study of Forman *et al.* (1986), described below.

Forman *et al.* (1986) identified all women certified to have died from liver cancer at the age of 20–44 in England and Wales between 1979 and 1982. Deaths from secondary liver cancer or from benign liver tumours were excluded. Two controls were selected for each case from among women who had died from cancer of the kidney, cancer of the brain or acute myeloid leukaemia, and, for 1982 only, two further controls were selected for each case from among women who had died as a result of a road traffic accident. Information on exposure was obtained from a questionnaire sent to the general practitioners of cases, and information was obtained for 46 of 85 (54.1%) potential cases and for 147 of 233 (63.1%) eligible controls. Further information, including pathological data, was sought for potential cases and resulted in 35 confirmed cases of primary liver cancer, of which 24 were hepatocellular carcinoma and 11 were cholangiocarcinoma. Five of the deaths from hepatocellular carcinoma were excluded from the analysis, two because they had had chronic active hepatitis, two because they had had severe alcoholic disease and associated liver cirrhosis and one because she had had Down's syndrome, which might have prejudiced the prescription of oral contraceptives. Eighteen of the 30 case women

(15 of the 19 with hepatocellular carcinoma) had used oral contraceptives, compared with 79 of the 147 controls. Information on smoking and alcohol habits was not available. The relative risks, adjusted for age and year of birth, were: for hepatocellular carcinoma, 3.8 for any use, 3.0 for use for < 4 years, 4.0 for 4–7 years and 20.1 for ≥ 8 years; for cholangiocarcinoma, 0.3 for any use, 0.1 for < 4 years and 0.9 for ≥ 4 years. [The published relative risks were adjusted for age and year of birth, but confidence intervals were not given. The unadjusted relative risks and 95% confidence intervals, calculated from the published data, were: hepatocellular carcinoma, any use, 3.2 (95% CI, 1.0–10); < 4 years, 2.4 (0.7–8.5); 4–7 years, 3.6 (0.8–16); and ≥ 8 years, 13 (2.1–78); cholangiocarcinoma, any use, 0.3 (95% CI, 0.1–1.3); < 4 years, 0.2 (0.0–1.3); ≥ 4 years, 0.7 (95% CI, 0.2–3.7).] There was no information on infection with hepatitis viruses. Three cases in this study were also included in the study of Neuberger *et al.* (1986), described above.

Palmer *et al.* (1989) conducted a hospital-based case–control study of women in whom liver cancer had been diagnosed when they were 19–54 years of age in five United States cities in 1977–85. They identified 12 cases of liver cancer, of which nine were hepatocellular carcinoma, two were cholangiocarcinoma and one was undetermined. None of the case women reported a history of hepatitis, nor was there mention in their hospital discharge summaries of HBV infection; liver cirrhosis was discovered at the time of surgery in one case of hepatocellular carcinoma. Five controls were selected for each case and matched on hospital, age and date of interview; the diagnoses of controls were trauma for 16, eight herniated discs, five acute respiratory infections and 31 eye, ear and gastrointestinal conditions. Information on exposure was obtained from case and control women at interview. Overall, 95% of the subjects approached were interviewed. Smoking status was not reported, but alcohol intake was similar in cases and controls. Eleven of the 12 case women (eight of the nine cases of hepatocellular carcinoma) and 20 of the 60 controls had used oral contraceptives. The risk for hepatocellular carcinoma relative to women who had used oral contraceptives for < 2 years was 20 (95% CI, 2.0–190) for 2–4 years of use and 20 (1.6–250) for ≥ 5 years of use. [The unmatched relative risk for any use was 15 (95% CI, 1.7–126).]

The WHO Collaborative Study of Neoplasia and Steroid Contraceptives (1989b) was a hospital-based case–control study conducted in eight countries. The eligible cases were those of women in whom liver cancer was diagnosed between 1979 and 1986 and who were born after 1924 or 1929. A total of 168 eligible cases were identified; 122 (72.6%) of the diagnoses were confirmed, and these women were interviewed. Histological typing was available for 69 cases: 36 were hepatocellular carcinoma, 29 were cholangiocarcinoma, one was an adenocarcinoma and three were other types. Controls were selected from among individuals admitted to the same hospitals as the cases with conditions not thought to be related to use of oral contraceptives. The aim was to select two controls for each case, but controls were not individually matched to cases; there was thus a pool of over 14 000 controls, from whom up to eight were selected for each case of liver cancer, matched on age, study centre and year of interview. The overall response rate of controls was 94.3%. All case and control women were interviewed. Information

on smoking was not collected; there was no statistically significant difference between case and control women in alcohol consumption, 17.2% of the cases and 26% of the controls having ever drunk alcohol. The finding that 25 of the 122 cases (20.5%) and 216 of the 802 controls (26.9%) had used oral contraceptives gave relative risks, adjusted for number of live births and occupation, of 0.7 (95% CI, 0.4–1.2) for any use, 0.8 (0.4–1.5) for use for 1–12 months, 0.7 (0.3–1.7) for 13–36 months and 0.7 (0.3–1.7) for ≥ 37 months. The relative risks for any use by histological subtype were 0.6 (95% CI, 0.2–1.6) for hepatocellular carcinoma, 1.2 (0.5–3.1) for cholangiocarcinoma and 0.5 (0.2–1.3) for a clinical diagnosis with no histological confirmation. Information on prior infection with hepatitis viruses was not collected, but all except one of the study centres were in countries with high rates of liver cancer and where HBV infection is endemic.

Kew *et al.* (1990) conducted a hospital-based case–control study in Johannesburg, South Africa, among patients in whom histologically confirmed hepatocellular carcinoma was diagnosed when they were aged 19–54. Two controls per case were selected and matched on age, race, tribe, rural or urban birth, hospital and ward. Patients with diseases in which contraceptive steroids might be causally implicated were not considered eligible as controls. All of the subjects were interviewed, but the response rates were not given. Smoking and alcohol intake were associated with the risk for liver cancer, but inclusion of these variables in the analysis did not alter the results. Seven of 46 cases (15.2%) and eight of 92 controls (8.7%) had used oral contraceptives, giving an overall relative risk of 1.9 (95% CI, 0.6–5.6). The relative risks were 2.1 (95% CI, 0.4–11) for use for < 4 years, 2.0 (0.1–33) for 4–8 years and 1.5 (95% CI, 0.3–7.2) for > 8 years. Nineteen of the 46 cases were HBsAg-positive, 25 had evidence of past infection with HBV, and two had never been infected. The relative risk for hepatocellular carcinoma in HBsAg-negative patients who used contraceptive steroids of any type was 0.4 (95% CI, 0.2–1.0).

Vall Mayans *et al.* (1990) conducted a hospital-based case–control study in Catalonia, north-eastern Spain, where 96 patients admitted to the Liver Unit of the University Hospital in Barcelona between 1986 and 1988 were identified, 74 of whom had histologically or cytologically confirmed hepatocellular carcinoma. Liver cirrhosis was present in 83 (86.5%) cases. For the 29 cases in women, two controls were selected per case and matched on sex, age, hospital and time of admission. Patients with diagnoses related to use of oral contraceptives were considered ineligible as controls. One control was excluded from the analysis because of later confirmation of liver cirrhosis. Serum from all patients was tested for HBsAg, antibody to hepatitis B core antigen and antibody to hepatitis surface antigen. All patients were interviewed, but the response rates were not given. Smoking was not associated with risk, and adjustment for alcohol intake did not alter the results. Six of the 29 female cases (20.7%) and three of the 57 female controls (5.3%) had used oral contraceptives [unmatched relative risk, 4.7 (95% CI, 1.1–20)]. Overall, 9.4% of cases and 2.1% of controls were HBsAg-positive, and all of the users of oral contraceptives were HBsAg-negative.

Yu *et al.* (1991) used a population-based cancer registry to identify cases of histologically confirmed hepatocellular carcinoma diagnosed in black or white non-Asian

women residents aged 18–74 in Los Angeles County, United States, between 1984 and 1990. Two neighbourhood controls were sought for each case and matched on sex, year of birth and race. Eighty-four of 412 eligible patients (20.4%) were interviewed (70.6% died before contact could be made), of which 10 were excluded from the analysis because the diagnosis of hepatocellular carcinoma was not confirmed. The response rate among the controls first selected was 71%. Adjustment for smoking and alcohol did not alter the results. Thirteen of the 25 case women (52%) and 18 of the 58 controls (31%) had used oral contraceptives. The relative risks were 3.0 (95% CI, 1.0–9.0) for any use, 2.3 (0.5–11) for use for ≤ 12 months, 1.7 (95% CI, 0.3–9.1) for 13–60 months and 5.5 (95% CI, 1.2–25) for ≥ 61 months. For the 11 case women who had formerly used oral contraceptives, the mean time since last use was 14.5 years. Seven case women had antibodies to one or more markers of hepatitis viral infection; when these cases were excluded, the association between use of oral contraceptives and the risk for hepatocellular carcinoma became stronger.

Hsing *et al.* (1992) studied deaths from primary liver cancer among women aged 25–49 in the United States (except Oregon) in 1985 and in the National Mortality Followback Survey in 1986. Of the 203 deaths from liver cancer identified, 52 cases not specified as primary, four cases of chronic liver disease and 29 cases with a history of liver cirrhosis were excluded. This left 98 cases for analysis, of which 76 were primary liver cancer and 22 were cholangiocarcinoma. Controls were selected from among women in the National Mortality Followback Study who had died in 1986 from causes other than liver cancer and whose next-of-kin returned the questionnaire. Potential controls with evidence of chronic liver disease or whose causes of death were thought to be associated with oral contraceptive use were excluded, leaving 629 controls for analysis. Information on exposure was obtained from next-of-kin by postal questionnaire. The results were presented both for all subjects and for subjects for whom the respondent was the spouse or parent (thought to be more reliable). The relative risks were adjusted for smoking and alcohol use. For all subjects with complete data, 39 of 72 cases (54.2%) and 243 of 549 controls (44.3%) had ever used oral contraceptives; the relative risks were 1.6 (95% CI, 0.9–2.6) for any use, 1.2 (0.6–2.4) for use for < 5 years, 2.0 (1.0–4.4) for 5–9 years and 2.0 (0.8–4.8) for ≥ 10 years. For subjects whose spouse or parent responded, the relative risks were 2.7 (95% CI, 1.4–5.3) for any use, 2.1 (0.9–4.6) for use for < 5 years, 3.9 (1.6–9.6) for 5–9 years and 4.8 (1.7–14) for ≥ 10 years. When the four Asian cases and 10 controls, from populations presumed to have a higher prevalence of HBV infection, were excluded from the analysis, higher risk estimates were seen for any use (2.8; 95% CI, 1.4–5.5) and for long-term (≥ 10 years) use (5.2; 1.7–15). The relative risks for the 13 cases of cholangiocarcinoma were 0.8 (95% CI, 0.3–2.7) for any use, 0.5 (0.1–2.7) for < 5 years of use, 0.6 (0.1–5.4) for 5–9 years and 3.3 (0.7–16) for ≥ 10 years.

Tavani *et al.* (1993b) conducted a hospital-based case–control study of women with histologically or serologically confirmed hepatocellular carcinoma diagnosed at the age of 28–73 in the greater Milan area, Italy, between 1984 and 1992. The controls were women admitted to hospital for acute non-neoplastic diseases (37% traumas, 13% other ortho-

paedic disorders, 40% acute surgical conditions, 10% other). Since none of the women aged 60 or over had ever used oral contraceptives, the analysis was restricted to women under that age. All of the participating subjects were interviewed; the response rates were not given but were close to 100% in other reports of this study. The results were not adjusted for smoking or alcohol use. Nine of the 43 cases (20.9%) and 21 of the 194 controls (10.8%) had ever used oral contraceptives. The relative risks, adjusted for age, education and parity, were 2.6 (95% CI, 1.0–7.0) for any use, 1.5 (0.5–5.0) for use for ≤ 5 years and 3.9 (0.6–25) for use for > 5 years. In relation to time since oral contraceptives were last used, the relative risks were 1.1 (95% CI, 0.3–4.6) for ≤ 10 years and 4.3 (1.0–18) for > 10 years. There was no information on infection with hepatitis viruses.

The Multicentre International Liver Tumour Study (Collaborative MILTS Project Team, 1997) included women with hepatocellular carcinoma diagnosed before the age of 65 between 1990 and 1996 in seven hospitals in Germany and one each in France, Greece, Italy, Spain and the United Kingdom. The diagnoses were based on histological examination or on imaging and increased α-fetoprotein concentration. An average of four controls was sought for each case: two general hospital controls without cancer, one hospital control with an eligible tumour diagnosis and one population control. The controls were frequency matched for age, and living controls were obtained for cases who had died. Of the 368 eligible cases, 317 (86.1%) were included in the study, although 24 of these were excluded from the analysis because of missing information on confounding factors. Information was obtained at interview, except for 136 case women (42.9%) who had died or who could not be interviewed for other reasons, for whom a next-of-kin was interviewed. The overall response rate for controls was not given, but that for hospitalized patients (cases and hospital controls) varied from 68 to 100% between centres, whereas the response rate for population controls varied from 60 to 80% between countries. Smoking and alcohol use were considered as confounders but were not included in the models presented. Oral contraceptive use was reported for 148 of the 293 cases (50.5%) and 1086 of the 1779 controls (61.0%). The relative risk for any use of oral contraceptives was 0.8 (95% CI, 0.5–1.0), and those for durations of use were 0.8 (0.5–1.3) for 1–2 years, 0.6 (0.3–1.1) for 3–5 years and 0.8 (95% CI, 0.5–1.1) for ≥ 6 years. For use of oral contraceptives containing cyproterone acetate, the relative risks were 0.9 (95% CI, 0.5–1.6) for any use, 0.9 (0.4–2.4) for use for 1–2 years, 0.9 (0.3–2.4) for 3–5 years and 0.9 (95% CI, 0.4–2.0) for ≥ 6 years. When the analysis was restricted to the 51 cases without liver cirrhosis or evidence of infection with hepatitis viruses, the relative risks were 1.3 (95% CI, 0.4–4.0) for use of any oral contraceptives for 1–2 years, 1.8 (0.5–6.0) for 3–5 years and 2.8 (1.3–6.3) for ≥ 6 years.

(*c*) *Gall-bladder*

Yen *et al*. (1987) studied extrahepatic bile-duct cancers in Massachusetts and Rhode Island, United States, between 1975 and 1979 in 27 women with histologically confirmed bile-duct cancer and 152 controls, who were patients with a variety of other cancers. All of the subjects were interviewed. Of the women under 60 years of age, four of 10 cases

and six of 76 controls reported use of combined oral contraceptives (age-adjusted relative risk, 7.8; 95% CI, 2.0–30).

The relationship between use of combined oral contraceptives and risk for primary gall-bladder cancer was examined in 58 case and 355 control women who were participating in an international hospital-based case–control study during 1979–86 (WHO Collaborative Study of Neoplasia and Steroid Contraceptives, 1989c). Any use of combined oral contraceptives was not associated with risk, adjusted for age and history of gall-bladder disease (relative risk, 0.6; 95% CI, 0.3–1.3), and no increase in risk was seen among women who had taken combined oral contraceptives for more than three years (0.6; 0.2–2.2) or more than 12 years before cancer diagnosis (0.6; 0.2–1.8).

2.6 Colorectal cancer

2.6.1 *Cohort studies*

The Walnut Creek Contraceptive Drug Study (1981) showed no association between use of combined oral contraceptives and all cancers of the digestive tract (age-adjusted relative risk, 0.9; 95% CI, 0.4–2.0). [The majority of these cancers were probably colorectal cancers.] The results of cohort studies that specifically addressed colorectal cancers are shown in Table 26.

Reports on the association between use of combined oral contraceptives and the risk for colorectal cancer were made from the the Nurses' Health Study (Chute *et al*., 1991; Martinez *et al.*, 1997). Follow-up until 1992 of 89 448 nurses for over 1 million person–years, with 501 incident cases of colorectal cancer, showed a relative risk adjusted for age, body mass index, exercise, family history of cancer, aspirin use, alcohol use, smoking, meat intake and reproductive factors of 0.8 (95% CI, 0.7–1.0). Women who had used combined oral contraceptives for 96 months or more were at significantly lower risk (0.6; 95% CI, 0.4–0.9). The results for colon cancer were similar to those for rectal cancer.

In the Iowa Women's Health Study cohort (Bostick *et al*., 1994), described in the monograph on 'Post-menopausal oestrogen therapy', the prevalence of any use of combined oral contraceptives was 17% among women with colon cancer and 19% among women without colon cancer. Any use was associated with a relative risk, adjusted for age, height, parity, energy intake and vitamin intake, of 1.0 (95% CI, 0.7–1.4).

Beral *et al.* (1999) reported on a 25-year follow-up of 46 000 women who were recruited in 1968-69 by general practitioners throughout Britain. At recruitment, 49% of the women were using combined oral contraceptives; by the end of the follow-up, 63% had used them at some time, the median duration of use being four years. The relative risk for death from colorectal cancer among women who had ever used combined oral contraceptives, adjusted for age, parity, social class and smoking, was 0.6 (95% CI, 0.4–0.9). The trend in risk by duration of use was not significant. The relative risk of women who had last used combined oral contraceptives 15 years or more previously was 1.0 (95% CI, 0.5–2.0) and that for death from all cancers combined for any use was 1.0 (95% CI, 0.8–1.1).

Table 26. Cohort studies of use of combined oral contraceptives and colorectal cancer

Reference	Country	Study population (follow-up) no. of cancers	RR (95% CI) (any versus no use)			Duration of use	Adjustment/comments
			Colon–rectum	Colon	Rectum		
Martinez *et al*. (1997) (Nurses Health Study)	USA	89 448 (12 years) 501	0.8 (0.7–1.0)	0.6 (0.4–1.0)	0.8 (0.5–1.2)	Significant trend (RR for ≥ 8 years' use, 0.6; 95% CI, 0.4–0.9)	Age, body mass index, exercise, family history of cancer, aspirin use, alcohol use, smoking, meat intake and reproductive factors Prevalence of combined oral contraceptive use, 32%; mostly past use
Bostick *et al*. (1994)	Iowa, USA	35 215 (4 years) 212	–	1.0 (0.7–1.4)	–	Not reported	Adjusted for age, height, parity, energy and vitamin intake Prevalence of combined oral contraceptive use, 19%
Beral *et al*. (1999)	United Kingdom	46 000 (25 years) 170 deaths	0.6 (0.4–0.9)	–	–	No trend	Mortality rates, adjusted for age, parity, social class and smoking RR for ≥ 10 years of use, 0.3 (0.1–1.2); RR for last use ≥ 15 years previously, 1.0 (0.5–2.0)

RR, relative risk; CI, confidence interval

2.6.2 *Case–control studies*

(*a*) *Colorectal polyps*

In a study by Jacobson *et al.* (1995) in New York City, United States, described in detail in the monograph on 'Post-menopausal oestrogen therapy', a lower frequency of any use of combined oral contraceptives was found among cases of colorectal polyps (72/280) than among control women (19/126) (relative risk, 0.6; 95% CI, 0.3–1.1).

Potter *et al*. (1996) in a study in Minnesota, United States, described in detail in the monograph on 'Post-menopausal oestrogen therapy', found similar proportions of women who had ever used combined oral contraceptives among women with and without polyps; the risk associated with ≥ 5 years of use relative to that of women who had not undergone colonoscopy was 0.8 (95% CI, 0.5–1.4) and that relative to community controls was 1.1 (0.6–1.8).

(*b*) *Colorectal cancer*

Several of the case–control investigations on use of combined oral contraceptives and colorectal cancer risk are also described in the monographs on 'Post-menopausal oestrogen therapy' and 'Post-menopausal oestrogen–progestogen therapy', and are summarized only briefly here. Table 27 lists the studies summarized below.

Weiss *et al*. (1981b), in a study in the United States described in detail in the monograph on 'Post-menopausal oestrogen therapy', reported that any use of combined oral contraceptives was commoner among cases (33%) than among controls (23%), but the difference was not significant. The age-adjusted relative risks were 1.3 (95% CI, 0.5–3.1) for < 5 years of use and 2.0 (0.7–5.2) for ≥ 5 years of use. The relative risks for any use were 1.0 for colon cancer and 2.6 ($p = 0.09$) for rectal cancer.

Potter and McMichael (1983), in Adelaide, Australia, found that use of combined oral contraceptives was slightly less common among cases of colon cancer than among controls, with a relative risk adjusted for reproductive variables of 0.5 (95% CI, 0.3–1.2) for any versus no use. The relative risk for rectal cancer was 0.7 (95% CI, 0.3–1.8), with a trend of decreasing risk with increasing duration of use (relative risk for ≥ 25 months of use, 0.2; 95% CI, 0.0–1.0).

In the case–control study of Furner *et al*. (1989) described in detail in the monograph on 'Post-menopausal oestrogen therapy', the crude relationship between colorectal cancer and the use of combined oral contraceptives was 0.6 (95% CI, 0.3–1.3); only nine case and 32 control women had ever used combined oral contraceptives.

A case–control study conducted by Kune *et al*. (1990) in Melbourne, Australia, between 1980 and 1981 included all local incident cases of colorectal cancer (108 colon and 82 rectum) and 200 age-matched female controls representing a random sample of local population. The relative risks, adjusted for reproductive factors, of women who had ever used combined oral contraceptives were 1.2 (95% CI, 0.6–2.3) for colon and 2.0 (95% CI, 1.0–4.1) for rectal cancer. The relative risks associated with more than nine years' duration of use, however, were 0.7 for colon and 0.9 for rectal cancer [confidence intervals not given].

Table 27. Case–control studies of use of combined oral contraceptives and colorectal cancer

Reference	Country	Cases : controls (type of controls)	RR (95% CI) (any versus no use)			Duration of use	Recency of use	Adjustments/Comments
			Colon–rectum	Colon	Rectum			
Weiss *et al.* (1981b)	Washington, USA	143 : 707 (population)	≤ 5 years, 1.3 (0.5–3.1) ≥ 5 years, 2.0 (0.7–5.2)	1.0	2.6 (p = 0.09)	No significant trend	Not reported	Age Prevalence of combined oral contraceptive use was about 30% (22% for ≥ 5 years' use)
Potter & McMichael (1983)	Adelaide, Australia	155 : 311 (population)	–	0.5 (0.3–1.2)	0.7 (0.3–1.8)	Inverse trend (RR for > 2 years' use, 0.20; 95% CI, 0.0–1.0)	Not reported	Reproductive variables (diet was influential) Prevalence of combined oral contraceptive use among controls, 18%
Furner *et al.* (1989)	Chicago, USA	90 : 208 (spouses)	0.6 (0.3–1.3)	–	–	Not reported	Not reported	Unadjusted Prevalence of combined oral contraceptive use among controls, 6%
Kune *et al.* (1990)	Melbourne, Australia	190 : 200 (population)	–	1.2 (0.6–2.3)	2.0 (1.0–4.1)	No effect (RR for > 9 years use, 0.7 for colon and 0.9 for rectum; not significant)	Not reported	Age, parity and age at birth of first child Prevalence of combined oral contraceptive use among controls, 20%
Fernandez *et al.* (1998a)	Italy	1232 : 2793 (hospital)	0.6 (0.5–0.9)	0.7 (0.5–0.9)	0.7 (0.5–1.1)	No effect	Stronger protection from recent use (RR for < 10 years, 0.4; 95% CI, 0.3–0.7)	Age, education, cancer family history, body mass index, oestrogen replacement therapy, parity, menopause and energy intake Prevalence of use of combined oral contraceptives among controls, 12%

Table 27 (contd)

Reference	Country	Cases : controls (type of controls)	RR (95% CI) (any versus no use)			Duration of use	Recency of use	Adjustments/Comments
			Colon–rectum	Colon	Rectum			
Peters *et al.* (1990)	Los Angeles, USA	327 : 327 (neighbours)	–	**< 5 years**: 1.0 (0.6–1.8); right colon, 1.4 (0.6–3.3); left colon, 0.7 (0.3–1.5) **≥ 5 years**: 1.1 (0.4–2.9); right colon, 1.3 (0.3–5.5); left colon, 1.0 (0.2–4.8)	–	No effect	Not reported	Family history of cancer, parity, exercise, fat, alcohol and calcium intake Prevalence of combined oral contraceptive use among controls, 19%
Franceschi *et al.* (1991b)	North-eastern Italy	89 : 148 (hospital)	0.2 (0.0–2.0)	–	–	Not reported	Not reported	Unadjusted Only 1 case and 9 controls had ever used combined oral contraceptives
Wu-Williams (*et al.* (1991)	North America and China	395 : 1112 (neighbours)		North America: 1.2 (p = 0.67); China: 0.6 (p = 0.27)	North America: 0.4 (p = 0.04); China: 0.7 (p = 0.34)	No trend	Not reported	Unadjusted (but unaltered by exercise, saturated fat and years in the USA) Prevalence of combined oral contraceptive use among controls, 16% in North America and 12% in China
Jacobs *et al.* (1994)	Seattle, USA	193 : 194 (population)	–	1.2 (0.7–1.9); right colon, 1.2 (0.7–2.3); left colon, 1.1 (0.6–2.1)	–	No trend	Not reported	Age, age at birth of first child and vitamin intake Prevalence of combined oral contraceptive use among controls, 27%

Table 27 (contd)

Reference	Country	Cases : controls (type of controls)	RR (95% CI) (any versus no use)			Duration of use	Recency of use	Adjustments/Comments
			Colon–rectum	Colon	Rectum			
Kampman *et al.* (1997)	USA	894 : 1120 (members of medical care programme)	–	0.9 (0.7–1.1)	–	Not reported	Not reported	Age, family history of colorectal cancer, aspirin use, energy intake, post-menopausal oestrogen therapy and exercise Prevalence of combined oral contraceptive use among controls, 25%

RR, relative risk; CI, confidence interval

Franceschi *et al*. (1991b) carried out a case–control study in north-eastern Italy which included a very few users of combined oral contraceptives (one case and nine controls). The crude relative risk was 0.2, but the 95% CI (0.0–2.0) was very broad.

A pooled analysis of a case–control study from Milan (Negri *et al.*, 1989; Fernandez *et al*., 1996) and a multicentre study from Italy (Talamini *et al*., 1998) which involved 803 cases of colon cancer, 429 of rectal cancer and 2793 hospital controls (Fernandez *et al.*, 1998) provided a relative risk estimate (adjusted for age, education, family history of cancer, body mass index, parity, menopause, use of post-menopausal oestrogen therapy and energy intake) of 0.6 (95% CI, 0.5–0.9) for colon cancer and 0.7 (0.4–1.0) for rectal cancer for women who had ever used combined oral contraceptives. Increasing duration of use was related to a decreasing risk for colon cancer. The relative risk for recent users (< 10 years since last use) was 0.4 (95% CI, 0.3–0.7). Similar patterns of risk were found for various strata of age, educational level, parity, family history of colorectal cancer and body mass index.

In the case–control study of Peters *et al*. (1990) in Los Angeles, United States, described in detail in the monograph on 'Post-menopausal oestrogen therapy', use of combined oral contraceptives was not associated with an increased risk for colon cancer. The relative risk, adjusted for family history of cancer, parity, exercise and fat, alcohol and calcium intake, was 1.1 (95% CI, 0.4–2.9) for ≥ 5 years of use. This estimate was based on very few long-term users (13 cases and 15 controls).

The study by Wu-Williams *et al*. (1991), among Chinese women in North America and China, also described in the monograph on 'Post-menopausal oestrogen therapy', included small proportions of women who had ever used combined oral contraceptives: 16% in North America and 12% in China. The crude relative risks for rectal cancer were 0.4 ($p = 0.04$) in North America and 0.7 ($p = 0.34$) in China, and those for colon cancer were 1.2 ($p = 0.67$) and 0.55 ($p = 0.27$), respectively.

In the study of Jacobs *et al*. (1994) in Seattle, United States, described in the monograph on 'Post-menopausal oestrogen therapy', any use of combined oral contraceptives was reported by about 25% of both women with colon cancer and controls. The relative risk, adjusted for age and vitamin intake was 1.2 (95% CI, 0.7–1.9).

Kampman *et al*. (1997), in a study described in the monograph on 'Post-menopausal oestrogen therapy', did not find a significant association between the risk for colon cancer and use of combined oral contraceptives, which was reported by about 25% of cases and controls. The relative risk, adjusted for age, family history of colorectal cancer, aspirin use and energy intake, was 0.9 (95% CI, 0.7–1.1).

2.7 Cutaneous malignant melanoma

2.7.1 *Cohort studies*

In the late 1960s, three large cohort studies of users of combined oral contraceptives were begun (Table 28). All three provided information on the risk for cutaneous malignant melanoma according to use of combined oral contraceptives, but were based on small numbers of observed cases. Furthermore, it was not possible in any of the studies

Table 28. Cohort studies of use of combined oral contraceptives and risk for cutaneous malignant melanoma

Reference	Country, study	Population (follow-up), no. of cancers	RR (95% CI) any versus no use	Duration of use	Recency of use	Adjustments/comments
Hannaford *et al*. (1991)	United Kingdom, Oxford Family Planning Association	17 032 (15 years) 32	0.8 (0.4–1.8)	No trend (RR for ≥ 10 years' use, 1.0; 95% CI, 0.2–1.6)	No effect	Age, parity, social class and smoking No increase in risk for any combined oral contraceptive formulation
	United Kingdom, Royal College of General Practitioners	23 000 (20 years) 58	0.9 (0.6–1.5)	No trend (RR for ≥ 10 years' use, 1.8; 95% CI, 0.8–3.9)	No effect	Age, parity, social class and smoking No risk increase for any combined oral contraceptive formulation
Ramcharan *et al*. (1981b)	California, USA, Walnut Creek Contraceptive Drug Study	17 942 (8 years) 20	3.5 (1.4–9.0)	No trend	Not reported	Age
Bain *et al*. (1982)	USA, Nurses' Health Study	121 964 (at start) 141	0.8 (0.5–1.3) women < 40 years, 1.4 (0.8–2.5)	No trend	No effect	Age, parity, height and hair dye use Nested case–control investigation (141 non-fatal cutaneous malignant melanomas and 2820 age-matched controls)

RR, relative risk; CI, confidence interval

to make allowance for major determinants of cutaneous malignant melanoma such as solar exposure and phenotypic characteristics.

Between 1968 and 1974, 17 032 white married women aged 25–39 were recruited at 17 family planning clinics in the United Kingdom, in the framework of a study by the Oxford Family Planning Association (Adam *et al*., 1981; Hannaford *et al*., 1991). On entry, 56% of women were taking oral contraceptives, 25% were using a diaphragm and 19% were using an intrauterine device. Since, during the course of the study, each woman's oral contraceptive status could change, users of these preparations might have contributed periods of observation for either current or former users. After 266 866 woman–years of follow-up, 32 new cases of cutaneous malignant melanoma were recorded, 17 of which were among women who had ever used oral contraceptives (relative risk, 0.8; 95% CI, 0.4–1.8). None of the rates observed in any category of duration of use was materially different from that seen in women who had never used these preparations. The relative risks, adjusted for age, parity, social class and smoking, were 0.6 (95% CI, 0.2–1.6) for < 5 years of use, 1.0 (0.4–2.6) for 5–9 years and 1.0 (0.2–3.1) for ≥ 10 years. There was no relationship between time since stopping use of oral contraceptives and the risk for cutaneous malignant melanoma. None of the formulations resulted in a specific risk pattern. The distribution of cutaneous malignant melanomas by site was similar in users and non-users of oral contraceptives.

Between 1968 and 1969, 1400 general practitioners throughout the United Kingdom recruited 23 000 women who were using oral contraceptives and a similar number of age-matched women who had never used them, in the framework of the study of the Royal College of General Practitioners (Kay, 1981; Hannaford *et al*., 1991). After 482 083 woman–years of follow-up, 58 new cases of cutaneous malignant melanoma had been recorded, 31 of which were among women who had ever used combined oral contraceptives; the relative risk, adjusted for age, parity, social class and smoking, was 0.9 (95% CI, 0.6–1.5). No significant trend of increasing risk with duration of use was seen, the relative risk for 10 years or more of use being 1.8 (95% CI, 0.8–3.9), and the relative risk did not vary according to recency of use, the oestrogen or progestogen content of the contraceptives or the site of cutaneous malignant melanoma.

A cohort study of 17 942 women who were members of the Kaiser-Permanente Health Plan, in California, United States, aged 18 and older, was established in 1970 within the Walnut Creek Contraceptive Drug Study. Ramcharan *et al*. (1981b) updated the preliminary findings of Beral *et al*. (1977) to approximately eight years of follow-up and observed 20 cases of cutaneous malignant melanoma (age-adjusted relative risk, 3.5; 95% CI, 1.4–9.0). All five cases in women 18–39 years of age occurred among users of combined oral contraceptives. The influence of duration and recency of use was not assessed. The percentage distribution of hours of exposure to the sun by current, past or no use of combined oral contraceptives was similar.

In a postal survey of 121 964 registered nurses in the United States in 1976 (Bain *et al*., 1982), no overall relationship was found between risk for cutaneous malignant melanoma and use of combined oral contraceptives among 141 women with non-fatal

cutaneous malignant melanoma and 2820 age-matched control women. The relative risk, adjusted for age, parity, height and hair dye use, was 0.8 (95% CI, 0.5–1.3). No significant trends emerged with duration of use or time since first use. For women who were under the age of 40 at the time cutaneous malignant melanoma was diagnosed, the relative risk was 1.4 (95% CI, 0.8–2.5). For women under 40 who had used combined oral contraceptives for more than two years at least 10 years before diagnosis of cutaneous malignant melanoma, the relative risk was 2.3 (95% CI, 0.8–6.9). An analysis restricted to the 84 histologically documented cases of cutaneous malignant melanoma showed similar results [not shown].

2.7.2 *Case-control studies*

These studies are summarized in Table 29.

Adam *et al*. (1981) investigated 169 cases of cutaneous malignant melanoma in women aged 15–49 years that had been notified to the cancer registries of south-western England during 1971–76, and 507 age-matched control women drawn from the lists of the same general practitioners as the cases. Data were obtained from the general practitioners' records and for about 70% of the study women from postal questionnaires. The risk for cutaneous malignant melanoma was not significantly increased among women who had ever used combined oral contraceptives, the unadjusted relative risk being 1.3 (95% CI, 0.9–2.0) from the practitioners' records and 1.1 (95% CI, 0.7–1.8) from the postal questionnaires.

In an Australian investigation by Green and Bain (1985), described in detail in the monograph on 'Post-menopausal oestrogen therapy', there was no increased risk for cutaneous malignant melanoma in relation to use of combined oral contraceptives, with an age-adjusted relative risk of 0.7 (95% CI, 0.4–1.5), and no trend of increasing risk with increasing duration of use, the relative risk for > 4 years' use being 0.4 (95% CI, 0.2–1.1). The risk was also not elevated among women who had first used combined oral contraceptives 10 or more years before diagnosis of cutaneous malignant melanoma, with a relative risk of 0.9 (95% CI, 0.4–2.2).

In the case–control study of Holly *et al*. (1983) in Seattle, United States, described in detail in the monograph on 'Post-menopausal oestrogen therapy', use of combined oral contraceptives for five years or more was commoner among cases than controls, with age-adjusted relative risks of 1.5 for 5–9 years of use and and 2.1 for ≥ 10 years' duration (not significant). This relationship was seen only with long-term use of combined oral contraceptives among women with superficial spreading melanoma, with relative risks of 2.4 for 5–9 years and 3.6 for ≥ 10 years of use, and a highly significant trend ($p = 0.004$) with increasing duration of use. Adjustment was not made for the pattern of exposure to the sun.

In the study of Lew *et al*. (1983), in Massachusetts, United States, described in detail in the monograph on 'Post-menopausal oestrogen therapy', no data were given on hormonal treatment, but it was reported that cases and controls did not differ with respect to use of combined oral contraceptives.

Table 29. Case–control studies of use of combined oral contraceptives and malignant melanoma

Reference	Country	Cases : controls (type of controls)	Subgroup	RR (95% CI) any versus no use	Duration of use	Recency of use	Adjustment/Comments
Adam *et al.* (1981)	England	169 : 507 (same general practitioner)	General practitioners' records, postal questionnaires	1.3 (0.9–2.0) 1.1 (0.7–1.8)	No significant trend (RR for ≥ 5 years, 1.6; 95% CI, 0.8–3.0)	No effect	Unadjusted Responses to postal questionnaire (response rate about 70%) did not show an association between use of combined oral contraceptives and exposure to the sun
Green & Bain (1985)	Queensland, Australia	91 : 91 (population)		0.7 (0.4–1.5)	No trend (RR for > 4 years' use, 0.4; 95% CI, 0.2–1.1)	No effect (RR for use ≥ 10 years before diagnosis, 0.9; 95% CI, 0.4–2.2)	Age After allowance for phenotypic characteristics and solar exposure, RR for > 4 years' use, 0.4 (95% CI, 0.1–2.0)
Holly *et al.* (1983)	Seattle, USA	87 : 863 (population)	1–4 years 5–9 years ≥ 10 years	1.0 1.5 (NS) 2.1 (NS)	Significant trend only for SSM (RR ≥ 10 years use, 3.6)	Increased risk for ≥ 12 years since first use: 4.4 (95% CI, 2.0–9.7)	Age No data on solar exposure
Lew *et al.* (1983)	Massachusetts USA	111 : 107 (friends of cases)	–	–	–	–	No difference in combined oral contraceptive use
Beral *et al.* (1984)	Sydney, Australia	287 : 574 (hospital and population)		1.0 (NS)	No significant trend	No significant effect	Unadjusted (but altered by education, phenotype, history of sunburn and solar exposure) Increased risk for women who had begun taking combined oral contraceptives at least 10 years before and with ≥ 5 years' duration of use: 1.5 (95% CI, 1.0–2.1). No difference by location, thickness or type of CMM

Table 29 (contd)

Reference	Country	Cases : controls (type of controls)	Subgroup	RR (95% CI) any versus no use	Duration of use	Recency of use	Adjustment/Comments
Helmrich *et al.* (1984)	United States and Canada	160 : 640 (hospital)		0.8 (0.5–1.3)	No trend (RR for ≥ 10 years' use, 1.0; 95% CI, 0.4–2.9 [only age-adjusted])	No effect of time since first use (RR for first use ≥ 10 years previously, 1.1; 95% CI, 0.7–1.8)	Age, area, religion, education and hormone-related variables
Holman *et al.* (1984)	Western Australia	276 : 276	CMM SSM	1.0 (0.6–1.6) 1.1 (0.6–2.2)	No significant trend (RR for ≥ 5 years use, 1.1; 95% CI, 0.6–2.0)	No effect (RR for ≥ 10 years' use before diagnosis, 1.1; 95% CI, 0.7–1.7)	Age and residence
Gallagher *et al.* (1985)	Canada	361 : 361 (members of health plans)	CMM < 1 year 1–4 years ≥ 5 years SSM < 1 year 1–4 years ≥ 5 years	 1.0 0.9 0.8 1.1 1.1 0.9	No trend	No effect (RR for use ≥ 10 years prior to diagnosis, 1.0)	Age, education, phenotype and freckling Allowance for phenotypic characteristics
Østerlind *et al.* (1988)	Denmark	280 : 536	CMM SSM	0.8 (0.5–1.2) 0.9 (0.6–1.3)	No trend (RR for ≥ 10 years' use, 1.0; 95% CI, 0.6–1.7)	No effect (RR for use ≥ 10 years before diagnosis, 1.3; 95% CI, 0.7–2.2)	Age, phenotype and sunbathing No difference according to type and potency of combined oral contraceptives
Zanetti *et al.* (1990)	Northern Italy	186 : 205 (population)	CMM SSM	1.0 (0.5–1.9) 1.3 (0.4–4.5)	No trend (RR for ≥ 3 years' use, 1.0; 95% CI, 0.5–2.7)	No effect	Age, education, phenotype and sunbathing Risk did not change according to CMM type or location, age or combined oral contraceptive potency

Table 29 (contd)

Reference	Country	Cases : controls (type of controls)	Subgroup	RR (95% CI) any versus no use	Duration of use	Recency of use	Adjustment/Comments
Augustsson *et al.* (1991)	Sweden	69 : 196 (population)			Not reported		No difference in combined oral contraceptive use
Lê *et al.* (1992)	France	91 : 149 (hospital)	< 10 years ≥ 10 years	1.1 (0.6–2.0) 2.1 (0.7–5.9)	No significant trend	No effect of use 15–20 years before diagnosis (RR, 1.9; 95% CI, 0.8–4.5)	
Palmer *et al.* (1992)	Philadelphia and New York, USA	615 : 2107	Severe Not severe	1.1 (0.8–1.5) 1.5 (1.1–2.4)	No trend (RR for not severe for ≥ 10 years' use, 2.0; 95% CI, 0.9–4.3)	No effect (RR for first use ≥ 20 years before severe CMM, 1.1; 95% CI, 0.7–1.8)	Age, education, body mass index, menopause and phenotype Elevated risk among not severe cases of CMM was attributed to surveillance bias; similar RR for different types
Zaridze *et al.* (1992)	Moscow, Russian Federation	96 : 96		0.04 (0.0–0.5)	Not reported	Not reported	Phenotype, naevi and sunbathing Only one case and seven controls
Holly *et al.* (1995)	San Francisco, USA	452 : 930 (population)	CMM SSM	0.7 (0.5–0.9) 0.7 (0.5–1.0)	No trend (RR for ≥ 10 years' use: CMM, 0.8; 95% CI, 0.5–1.3; SSM, 1.0; 95% CI, 0.6–1.6)	No effect (RR for use ≥ 17 years before diagnosis, 0.6; 95% CI, 0.4–0.7)	Age (unaltered by education, phenotype and solar exposure)

Table 29 (contd)

Reference	Country	Cases : controls (type of controls)	Subgroup	RR (95% CI) any versus no use	Duration of use	Recency of use	Adjustment/Comments
Westerdahl *et al*. (1996)	Sweden	180 : 292 (population)		1.6 (0.9–2.8)	No effect (RR for > 8 years' use, 1.0; 95% CI, 0.5–2.0)	No effect	Phenotype, naevi and sunburns Age at use and timing of use in relation to first child did not influence risk
Ocular melanoma							
Hartge *et al*. (1989b)	Wilmington and Philadelphia, USA	238 : 223 (detached retina)		0.9 (0.4–1.7)	No trend (RR for ≥ 10 years' use, 0.2; NS)	No effect	Age

RR, relative risk; CI, confidence interval; NS, not significant; CMM, cutaneous malignant melanoma; SSM, superficial spreading melanoma

In the study of Beral *et al*. (1984) in Sydney, Australia, described in detail in the monograph on 'Post-menopausal oestrogen therapy', women who had ever used combined oral contraceptives were not at increased risk for cutaneous malignant melanoma (relative risk, 1.0). There was, however, an increased risk for women who had used these formulations for five years or more and who had begun use at least 10 years before diagnosis of cutaneous malignant melanoma, with a relative risk of 1.5 (95% CI, 1.0–2.1). The increase in risk persisted after control for phenotypic characteristics, number of moles and measures of exposure to ultraviolet light. The risk did not vary according to the location, thickness or type of melanoma.

In a case–control study carried out in several parts of the United States and Canada between 1976 and 1982 (Helmrich *et al*., 1984), the case series consisted of 160 women aged 20–59 years with a recent histological diagnosis of cutaneous malignant melanoma, and the controls were 640 women aged 20–59 years admitted to hospital for trauma or orthopaedic and surgical conditions. The age-adjusted relative risk for those who had ever used combined oral contraceptives was 0.8 (95% CI, 0.5–1.3), and there was no trend in risk with increasing duration of use, the relative risk for ≥ 10 years of use being 1.0 (95% CI, 0.4–2.9). For the 40 case and 140 control women who had first used combined oral contraceptives at least 10 years previously, the relative risk was 1.1 (95% CI, 0.7–1.8) and for women with more advanced cutaneous malignant melanoma (i.e. Clark's level IV and V), the relative risk was 0.6 (95% CI, 0.2–2.3).

In the study of Gallagher *et al*. (1985), in Canada, described in detail in the monograph on 'Post-menopausal oestrogen therapy', no association was seen between the risk for cutaneous malignant melanoma and use of combined oral contraceptives in 361 cases and an equal number of controls aged 20–69. The relative risks for < 1, 1–4 and ≥ 5 years' use, adjusted for age, phenotypic characteristics and freckling, were 1.0, 0.9 and 0.8, respectively. No association was seen between type of superficial spreading melanoma and duration of use or years since last use, the relative risk for women who had used combined oral contraceptives 10 or more years before diagnosis of cutaneous malignant melanoma being 1.0.

In the Danish study of Østerlind *et al*. (1988), described in detail in the monograph on 'Post-menopausal oestrogen therapy', use of oral contraceptives was not related to the risk for cutaneous malignant melanoma (relative risk adjusted for age, phenotypic characteristics and sunbathing, 0.8; 95% CI, 0.5–1.2) or superficial spreading melanoma (relative risk, 0.9; 95% CI, 0.6–1.3), and there was no evidence of a dose–response relationship, the relative risk for ≥ 10 years' use being 1.0 (95% CI, 0.6–1.7). No specific risk pattern was seen with the type of oral contraceptive, such as sequential, progestogen only and high-potency combined oral contraceptives, assessed separately, but there were few women in each group.

Zanetti *et al*. (1990) carried out a case–control study in Turin, northern Italy, between 1984 and 1987 of 186 women aged 19–92 with histologically confirmed cutaneous malignant melanoma out of 211 identified from the Turin Cancer Registry and 205 control women aged 17–92 drawn from the National Health Service Registry (out of the 300 initially contacted). Use of combined oral contraceptives, analysed only in women

aged 60 or younger, was not associated with cutaneous malignant melanoma, the relative risk adjusted for age, education, phenotypic characteristics and sunbathing being 1.0 (95% CI, 0.5–1.9); no association was seen with superficial spreading melanoma (relative risk, 1.3; 95% CI, 0.4–4.5). Similarly, the longest duration of use (≥ 3 years: 1.0; 95% CI, 0.5–2.7) or use that had started 10 or more years before the diagnosis of cutaneous malignant melanoma was not associated with an increased risk. The relative risks were identical for use of combined oral contraceptives containing high oestrogen doses (≥ 50 μg) and low oestrogen doses.

Augustsson *et al*. (1991) studied 69 cases of cutaneous malignant melanoma in Swedish women aged 30–50 and compared them with 196 controls drawn from the same population. Skin type, phenotypic characteristics, number of naevi and dysplastic naevi were taken into account. Although the relative risk was not reported, no difference in the use of combined oral contraceptives was reported between cases and controls.

Lê *et al*. (1992) assessed the effect of use of combined oral contraceptives on the risk for cutaneous malignant melanoma risk in France between 1982 and 1987. The cases were those of 91 white women under 45 years of age who had new, histologically confirmed melanomas, and the controls were 149 women consulting for diagnosis or treatment of diseases unrelated to use of combined oral contraceptives, including skin diseases. No significant association was found between the total duration of use of combined oral contraceptives (relative risk, adjusted for age at menarche for ≥ 10 years' use, 2.1; 95% CI, 0.7–5.9) or the time since first use (relative risk 15–20 years since first use, 1.9; 95% CI, 0.8–4.5) and the risk for cutaneous malignant melanoma, and no difference was found between superficial spreading melanoma and other types of cutaneous malignant melanoma. The relative risk for 49 case women and 78 matched controls who were aged 30–40 and had used oral contraceptives for 10 or more years, however, was significantly increased: 4.4 (95% CI, 1.1–17). In a subgroup of 57 case women and 65 controls for whom allowance could be made for phenotypic characteristics and solar exposure, the relative risks were similar.

A case–control study on cutaneous malignant melanoma was carried out between 1979 and 1991 in Philadelphia and New York, United States (Palmer *et al*., 1992), in which the cases were in 615 women under the age of 70 (median age, 40) who had recently received a first diagnosis of cutaneous malignant melanoma. Patients with melanoma *in situ* were not included. Two control groups of white women with a median age of 41 years with other malignancies (610 patients) or non-malignant illnesses (1497 patients) judged to be unrelated to use of combined oral contraceptives were selected. In order to address the possibility of selection bias due to differential surveillance of combined oral contraceptive users and non-users, the cases were subdivided by severity. For severe cases (thickness ≥ 0.75 mm, or Clark's level IV or V), the relative risks adjusted for age, education, menopause and phenotypic characteristics were 1.1 (95% CI, 0.8–1.5) for any use, 1.1 (0.6–2.1) for ≥ 10 years' use and 1.1 (0.7–1.8) for ≥ 20 years' use. For non-severe cases, increased risks were found for any use (1.5; 95% CI, 1.1–2.2) and for ≥ 10 years' use (2.0; 0.9–4.3). The relative risks did not vary by type of cutaneous

malignant melanoma. According to the authors, the increased risks seen for non-severe cases of cutaneous malignant melanoma were probably due to greater surveillance of combined oral contraceptive users.

Zaridze *et al*. (1992) evaluated risk factors in 96 cases of cutaneous malignant melanoma in Moscow, Russian Federation. Controls matched by age were recruited from among persons visiting cancer patients. Use of combined oral contraceptives could be analysed for 54 women with cutaneous malignant melanoma and 54 controls and showed a strong inverse association: the relative risk, adjusted for phenotypic characteristics, naevi and sunbathing, was 0.04 (95% CI, 0.0–0.5). Only one case and seven controls, however, had ever used combined oral contraceptives.

In the study of Holly *et al*. (1995), described in detail in the monograph on 'Post-menopausal oestrogen therapy' (Holly *et al*., 1994), 72% of the cases of cutaneous malignant melanoma and 79% of the control subjects in San Francisco, United States, reported ever having used combined oral contraceptives. The age-adjusted relative risk was 0.7 (95% CI, 0.5–0.9) for all cutaneous malignant melanoma and 0.7 (95% CI, 0.5–1.0) for superficial spreading melanoma. Examination by latency and duration of use showed no significant trend. The relative risk for ≥ 10 years' use was 0.8 (95% CI, 0.5–1.3) for all cutaneous malignant melanoma and 1.0 (95% CI, 0.6–1.6) for superficial spreading melanoma. Use beginning ≥ 17 years before diagnosis was associated with relative risks of 0.6 (95% CI, 0.4–0.7) for cutaneous malignant melanoma and 0.6 (95% CI, 0.4–0.8) for superficial spreading melanoma.

In the Swedish study of Westerdahl *et al*. (1996), described in the monograph on 'Post-menopausal oestrogen therapy', any use of combined oral contraceptives (40% of cases and 37% of controls) was associated with a non-significantly elevated risk of 1.6 (95% CI, 0.9–2.8) after adjustment for phenotypic characteristics, naevi and sunburns. No trend in risk was seen with duration of use (relative risk for > 8 years' use, 1.0; 95% CI, 0.5–2.0), age at first use or age at last use.

A meta-analysis of 18 published case–control studies on cutaneous malignant melanoma and use of combined oral contraceptives, including 17 of the papers reviewed here and that of Beral *et al*. (1977), showed a pooled relative risk of 1.0 (95% CI, 0.9–1.0) (Gefeller *et al*., 1997). The data for 3796 cases and 9442 controls showed no significant heterogeneity of the effect of combined oral contraceptives in the different studies, and analysis of various subgroups, defined by the design characteristics of the studies, did not materially alter this result.

2.8 Retinal melanoma

In a case–control study of ocular melanoma in the United States (Hartge *et al*., 1989b), described in the monograph on 'Post-menopausal oestrogen therapy', use of combined oral contraceptives was reported by about 13% in both cases and controls, to give an age-adjusted relative risk of 0.9 (95% CI, 0.4–1.7). The estimated risk was not related to duration of use (relative risk for ≥ 10 years' use, 0.2; 95% CI, 0.3–1.2) or to the interval since first or last use.

2.9 Thyroid cancer

None of the cohort studies provided information on use of combined oral contraceptives and the risk for thyroid cancer. The case–control studies are summarized in Table 30.

In the case–control study of McTiernan *et al*. (1984), in Seattle, United States, described in detail in the monograph on 'Post-menopausal oestrogen therapy', the use of combined oral contraceptives (prevalence: 93/141 cases and 130/219 controls) was associated with a slightly increased risk for thyroid cancer (1.6; 95% CI, 1.0–2.5). The magnitude of the excess risk did not increase with increasing duration of use (relative risk for > 3 years' duration, 1.2). The risk was higher among women with follicular thyroid cancer (3.6; 95% CI, 1.1–12.8) and among those women who discovered their own tumours as compared with those whose tumour was found by a physician.

Preston-Martin *et al*. (1987) evaluated the risk factors for thyroid cancer in women aged 40 or less in Los Angeles, United States, between 1980 and 1981. The cases were in 108 white women with papillary, follicular or mixed thyroid cancer (out of 135 identified through Southern California Cancer Surveillance Program) and controls were 108 age-matched women who lived near the case women (neighbourhood controls). More cases (67/78) than controls (76/106) had ever used combined oral contraceptives (unadjusted relative risk, 2.4; 95% CI, 1.1–5.7). Cases and controls did not differ with respect to age at first use. There was no trend of increasing risk with increasing duration of use, the relative risk for > 5 years' duration of use being 2.4 (95% CI, 0.9–6.9).

In a study conducted in Connecticut, United States (Ron *et al*., 1987), described in the monograph on 'Post-menopausal oestrogen therapy', similar proportions of cases (55/109) and controls (110/208) had ever used combined oral contraceptives, the relative risk adjusted for age, parity, radiotherapy to the head and neck and benign thyroid disease being 0.8 (not significant). For women under the age of 35 at the time of diagnosis, the relative risk was 1.8 (not significant). Duration and latency of use were not assessed.

Franceschi *et al*. (1990) found relatively few users of combined oral contraceptives among cases of thyroid cancer in Italy (23/165 cases and 28/214 controls). The age-adjusted relative risks were 1.1 (95% CI, 0.5–2.4) for use for < 24 months and 1.1 (95% CI, 0.4–3.0) for use for ≥ 24 months.

In a case–control study in Hawaii (Kolonel *et al*., 1990), described in the monograph on 'Post-menopausal oestrogen therapy', women who had ever used combined oral contraceptives (43% among controls) showed no increased risk for thyroid cancer. The relative risk, adjusted for age and ethnic group was 0.9 (95% CI, 0.5–1.5). The effects of duration and latency of use were not reported.

Levi *et al*. (1993), in study in Switzerland, described in detail in the monograph on 'Post-menopausal oestrogen therapy', found a prevalence of any use of combined oral contraceptives of 56% among thyroid cancer cases and 44% among control women; the relative risk, adjusted for age and a history of benign thyroid disease, was 1.2 (95% CI, 0.7–2.3). There was no trend of increasing risk with increasing duration of use, the relative risk for ≥ 5 years' use being 1.4 (95% CI, 0.7–2.7). Analyses restricted to women under 45 years of age or to cases of papillary thyroid cancer yielded similar risk estimates.

Table 30. Case–control studies on use of combined oral contraceptives and thyroid cancer

Reference	Country	Cases : controls (type of controls)	RR (95% CI), any versus no use	Duration of use	Adjustment/comments
McTiernan *et al*. (1984)	Seattle, USA	141 : 319 (population)	1.6 (1.0–2.5)	No trend (RR for > 3 years' use, 1.2)	Age Greatest risk increase seen for follicular thyroid cancer (RR, 3.6; 95% CI, 1.1–13)
Preston-Martin *et al.* (1987)	Los Angeles, USA	108 : 108 (population)	2.4 (1.1–5.7)	No trend (RR for > 5 years' use, 2.4; 95% CI, 0.9–6.9)	Unadjusted. Only women aged 40 or less
Ron *et al*. (1987)	Connecticut, USA	109 : 208 (population)	0.8	Not reported	Age, parity, radiotherapy to the head and neck and benign thyroid diseases RR for women < 35 was 1.8 (not significant)
Franceschi *et al*. (1990)	Italy	165 : 214 (hospital)	< 2 years, 1.1 (0.5–2.4) ≥ 2 years, 1.1 (0.4–3.0)	No effect	Age and area of residence
Kolonel *et al*. (1990)	Hawaii, USA	140 : 328 (population)	0.9 (0.5–1.5)	Not reported	Age and ethnic group Increased risk for women with difficulty in conceiving (RR, 1.8; 95% CI, 1.0–3.1) and those who used fertility drugs (RR, 4.2; 95% CI, 1.5–11)
Levi *et al*. (1993)	Vaud, Switzerland	91 : 306 (hospital)	1.2 (0.7–2.3)	No trend (RR for ≥ 5 years' use, 1.4; 95% CI, 0.7–2.7)	Age and history of benign thyroid disease Similar risk estimates for women under 45 and for papillary thyroid cancer
Preston-Martin *et al.* (1993)	Shanghai, China	207 : 207 (population)	1.7 (1.0–3.1)	No trend (RR for > 5 years' use, 0.9; 95% CI, 0.4–2.4)	Age
Wingren *et al*. (1993)	South-eastern Sweden	93 : 187 (population)	No risk (RR not reported)	Not reported	Only papillary carcinomas

Table 30 (contd)

Reference	Country	Cases : controls (type of controls)	RR (95% CI), any versus no use	Duration of use	Adjustment/comments
Hallquist *et al*. (1994)	Northern Sweden	123 : 240 (population)	All, 0.8 (0.5–1.4) Papillary, 0.6 (0.3–1.2)	No trend	Age Risk did not vary by timing in relation to age at first pregnancy
Galanti *et al*. (1996)	Sweden and Norway	191 : 341 (population)	0.9 (0.6–1.5)	No trend (> 2 years' use RR, 0.8; 95% CI, 0.5–1.3)	Age and parity

RR, relative risk; CI, confidence interval

Preston-Martin *et al*. (1993) carried out a study in Shanghai, China, between 1981 and 1984, which included 207 women aged 18–54 listed in the Shanghai Cancer Registry as having a histologically confirmed thyroid cancer; 20% of the cases were reviewed by a pathologist. The 207 control women, matched to the cases by year of birth, were chosen randomly from the Shanghai Residents' Registry; over 90% of the eligible subjects were interviewed. Few women had used combined oral contraceptives (43/207 cases and 29/207 controls), but any use of such formulations was associated with a marginally increased risk (unadjusted relative risk, 1.7; 95% CI, 1.0–3.1). Among users, however, there was no trend in risk with the duration of use, the relative risk for > 5 years' use being 0.9 (95% CI, 0.4–2.4).

Wingren *et al*. (1993) studied 93 cases of thyroid cancer and 187 controls aged 20–60 in south-east Sweden and reported that use of combined oral contraceptives was not associated with an increased risk. No data were shown.

Hallquist *et al*. (1994), in Sweden, reported that 42/123 cases and 92/240 controls had reported any use of combined oral contraceptives, giving an age-adjusted relative risk of 0.8 (95% CI, 0.5–1.4). The corresponding relative risk for papillary thyroid cancer was 0.6 (95% CI, 0.3–1.2). The risk did not vary by duration of use, being 0.6 (95% CI, 0.2–1.5) for ≥ 7 years' use, or by timing of use in relation to age at first pregnancy.

Galanti *et al*. (1996), in a study in Sweden and Norway described in the monograph on 'Post-menopausal oestrogen therapy', reported that 98/179 cases and 180/334 controls had used combined oral contraceptives. No relation was found between use and the risk for thyroid cancer; the age- and parity-adjusted relative risk for any use was 0.9 (95% CI, 0.6–1.5). Use for > 2 years was associated with a relative risk of 0.8 (95% CI, 0.5–1.3).

2.10 Other cancers

A 25-year follow-up of 46 000 women in Great Britain in the framework of a study on oral contraceptives by the Royal College of General Practitioners did not show significant excess mortality from lung cancer (relative risk, 1.2; 95% CI, 0.8–1.8) or any other cancer (Beral *et al*., 1999).

In a study by La Vecchia *et al*. (1994), from Milan, Italy, described in detail in the monograph on 'Post-menopausal oestrogen therapy', use of combined oral contraceptives was not related to the risk for gastric cancer. Six of 229 cases and 19 of 614 controls had ever used such formulations, giving a relative risk adjusted for age, education, a family history of cancer and dietary habits of 1.3 (95% CI, 0.5–3.5).

Chow *et al*. (1995) in a study in Minnesota, United States, described in detail in the monograph on 'Post-menopausal oestrogen therapy', found no relation between use of combined oral contraceptives and the risk for renal-cell cancer; the relative risk, adjusted for age, smoking and body mass index was 0.8 (95% CI, 0.4–1.3). For use longer than 10 years, the relative risk was 0.3 (95% CI, 0.1–1.0).

The risk for renal-cell cancer and use of combined oral contraceptives was also evaluated in an international study by Lindblad *et al*. (1995), described in detail in the monograph on 'Post-menopausal oestrogen therapy'. Any use of combined oral contraceptives

was associated with a relative risk, adjusted for age, smoking and body mass index, of 0.7 (95% CI, 0.5–0.9). There was an inverse trend in risk with increasing duration of use, the relative risk for > 10 years' use being 0.5 (95% CI, 0.3–0.9).