2. Studies of Cancer in Humans

2.1 Breast cancer

2.1.1 *Results of published studies*

Eight studies have been published on the relationship between the incidence of breast cancer and use of progestogen-only hormonal contraceptives, i.e. progestogen-only pills or injectable progestogen (depot medroxyprogesterone acetate). They are described in Table 4. The studies were similar in that all were case–control studies of breast cancer in relation to oral contraceptive use; information was obtained on contraceptive use and other factors through interviews, with the exception of the study of Ewertz (1992), in which self-administered questionnaires were used; they confirmed the cancer diagnosis through medical records or cancer registry data; and important risk factors for breast cancer were controlled for in the analyses.

(*a*) *Mini-pills*

A case–control study in the United Kingdom (Vessey *et al*., 1983), in which 1176 cases and 1176 controls aged 16–50 years in 1968–80 were enrolled, showed no association between the risk for breast cancer and use of progestogen-only pills. Such use was reported by 2.8% of the cases and 2.5% of the controls; the relative risk estimate was not given.

A population-based study (Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development,

Table 4. Case–control studies of use of progestogen-only contraceptives and breast cancer

Reference	Country	Years of case diagnosis	Age (years)	No. of cases	No. of controls	Participation rates (%) (cases/ controls)	Type of progestogen assessed	Any use of progestogen-only contraceptives (%) (cases/ controls)	RR (95% CI) for any versus no use
Vessey *et al*. (1983)	United Kingdom	1968–80	16–50	1 176	1 176	Not given	Pill	2.8/2.5	Not given
				Hospital-based					
Cancer and Steroid Hormone Study (1986)	United States	1980–82	20–54	4 711 Population-based	4 676 Random digit-dialling	80/83	Pill	Not given	1.3 (CI not given)
Paul *et al*. (1989) (New Zealand National Study)	New Zealand	1983–87	25–54	891 Population-based	1 864 Electoral rolls	79/82	Injectable (DMPA)	12/14	1.0 (0.8–1.3)
UK National Case–Control Study Group (1989)	United Kingdom	1982–85	< 36	775 Population-based	755 General practice	72/89	Pill	16/15	0.85 (per year of use)
Clavel *et al*. (1991)	France	1983–87	25–56	464	542	99/99	Pill	1.9/1.9	1.1 (0.4–2.7)
				Hospital-based					
WHO Collaborative Study (1991a)	Kenya, Mexico, Thailand	1979–88	< 65	869	11 890	97/98	Injectable (DMPA)	13/12	1.2 (0.96–1.5)
				Hospital-based					
Ewertz (1992)	Denmark	1983–84	< 40	203	212	90/88	Pill	Not given	0.99 (0.57–1.7)
			40–59	856	778	89/80			
				Population-based					
Skegg *et al*. (1996) (New Zealand National Study)	New Zealand	1983–87	25–54	891 Population-based	1 864 Electoral rolls	79/82	Pill	5.6/8.7	1.1 (0.73–1.5)

RR, relative risk; CI, confidence interval; DMPA, depot medroxyprogesterone acetate

1986), conducted between 1980 and 1982 in the United States, involved 4711 cases and 4676 controls 20–54 years of age. The investigators reported a relative risk estimate of 1.3 for use of progestogen-only pills; the confidence interval and numbers of case and control women who had used the formulations were not given.

In a multicentre study in the United Kingdom (UK National Case–Control Study Group, 1989), cases in women under the age of 36 years in 1982–85 were ascertained and matched to a control from the general practice in which the case was treated. Replies about contraceptive use obtained at interview were supplemented by the general practitioner for 90% of the 755 pairs. Progestogen-only pills had been used in 16% of cases and 15% of controls, but only 2.9% of the controls had used them for more than eight years. The relative risk estimate for use of progestogen-only pills was 1.35 for less than four years of use (90 cases and 67 controls), 0.73 for > 4–8 years of use (19 cases and 27 controls) and 0.59 for > 8 years of use (14 cases and 22 controls). The trend for the relative risk to decrease with increasing duration of use was of borderline statistical significance ($p = 0.05$).

Clavel *et al*. (1991) carried out a hospital-based case–control study in France between 1983 and 1987. Among 464 cases and 542 controls aged 25–56 years, nine cases (1.9%) and 10 controls (1.9%) had use of progestogen-only pills, yielding a multivariate relative risk estimate of 1.1 (95% confidence interval [CI], 0.4–2.7).

Ewertz (1992) carried out a population-based case–control study in Denmark of cases notified in 1983–84 and obtained data on contraceptive use from self-administered questionnaires. A total of 1059 cases and 990 controls were included. Among the 377 cases and 364 controls for which data on the type of preparation used were available, 28 cases and 29 controls had used a progestogen-only pill, yielding a relative risk estimate of 0.99 (95% CI, 0.57–1.71). For five or more years' use of progestogen-only pills, the estimate was 0.65 (95% CI, 0.28–1.5), based on nine case and 14 control users.

Skegg *et al*. (1996) assessed use of progestogen-only pills in data from the New Zealand National Study. On the basis of 50 cases (5.6%) and 163 controls (8.7%) with use of progestogen-only pills, the relative risk estimate for breast cancer was 1.1 (95% CI, 0.73–1.5) after adjustment for a number of factors, including age. There was a statistically significant increased risk (2.3; 95% CI, 1.2–4.3) among women aged 25–34, on the basis of 18 case and 70 control users. The corresponding estimates were 0.97 (95% CI, 0.6–1.6) for women aged 35–44, on the basis of 28 case and 80 control users, and 0.37 (95% CI, 0.12–1.2) for women aged 45–54, on the basis of four case and 13 control users; neither estimate was statistically significant. Virtually all of the women had used the preparations for fewer than six years; the estimates for fewer than two and two to five years of use were similar. In further analyses of women of all ages together, the relative risk estimate was increased for use that had begun in the previous 10 years (1.6; 95% CI, 1.0–2.4; 40 case and 111 control users) and reduced for use that had begun 10 or more years previously (0.44; 95% CI, 0.22–0.90; 10 case and 52 control users). When time since last use was assessed, the relative risk estimate was 1.4 (95% CI, 0.86–2.2) for last use fewer than five years previously (29 case and 91 control users), 1.0 (95% CI, 0.56–1.9) for use that had

ceased five to nine years previously (16 case and 48 case users) and 0.44 (95% CI, 0.16–1.2) for use that had ceased at least 10 years previously (five case and 24 control users). There was no clear evidence of an effect of the age at which use began or the timing with respect to the first pregnancy.

(*b*) *Depot medroxyprogesterone acetate*

Paul *et al*. (1989) reported on the use of the injectable progestogen, depot medroxyprogesterone acetate, in a population-based case–control study of women aged 25–54 conducted in New Zealand between 1983 and 1987. A total of 110 (12%) of 891 cases and 252 (14%) of 1864 controls had used this preparation. There was no increase in risk overall (relative risk, 1.0; 95% CI, 0.8–1.3), but the relative risk estimate was increased among women aged 25–34 (2.0; 95% CI, 1.0–3.8; 16 case and 55 control users). The estimate was not increased in women aged 35–44 (0.94; 95% CI, 0.45–3.3; 48 case and 133 control users) or 45–54 (0.95; 95% CI, 0.63–1.4; 46 case and 64 control users). There was no trend in the overall data for an increase in risk with increasing duration of use, but only 1.5% of controls had used depot medroxyprogesterone acetate for six years or more. The relative risk estimates, although based on small numbers, were higher for women with two to five years of use before the age of 25 or before the first pregnancy than among women with less than two years of use. The relative risk estimate tended to be increased for recent users: it was 1.7 (95% CI, 0.88–3.4) for women who had begun use in the previous five years (16 case and 24 control users) and declined to 1.2 (95% CI, 0.76–1.9) five to nine years after first use, 0.92 (95% CI, 0.64–1.3) 10–14 years after first use and 0.73 (95% CI, 0.39–1.4) 15 or more years after first use; none of these estimates was statistically significant. A similar trend was seen with time since last use: the relative risk was 1.6 (95% CI, 1.0–2.5) for use within the previous five years, 0.99 (95% CI, 0.65–1.5) five to nine years after last use and 0.78 (95% CI, 0.53–1.2) 10 years or more after last use.

The WHO Collaborative Study of Neoplasia and Steroid Contraceptives (1991a) assessed use of depot medroxyprogesterone acetate in centres in Kenya, Mexico and Thailand in a hospital-based study conducted between 1979 and 1988 among women under 65 years of age. Among the 869 cases of breast cancer and 11 890 controls, 109 cases (13%) and 1452 controls (12%) reported use of depot medroxyprogesterone acetate, yielding an overall multivariate relative risk estimate of 1.2 (95% CI, 0.96–1.5). The relative risk estimate was 1.4 (95% CI, 0.88–2.2) for breast cancer at age < 35, 1.1 (95% CI, 0.75–1.55) at age 35–44 and 1.0 (95% CI, 0.68–1.5) at age 45 or older; none of these estimates was statistically significant. There was no trend for the risk to increase with duration of use; indeed, the largest relative risk estimate was for the shortest duration of use; however, only 3.6% of controls had been exposed for more than three years. The relative risk estimates tended to be highest among recent users: 2.0 (95% CI, 1.4–3.0) for women whose use had begun in the previous two years (31 case and 342 control users) and 1.6 (95% CI, 1.1–2.5) for current users (27 case and 291 control users).

2.1.2 *Pooled analysis of individual data*

The Collaborative Group on Hormonal Factors in Breast Cancer (1996) carried out a combined analysis of data on use of progestrogen-only oral contraceptives from 27 studies that provided information on these preparations to the investigators in 1995. On the basis of 725 of 27 054 cases and 528 of 25 551 controls with any use of these preparations, the relative risk estimate was 1.1 (95% CI, 0.99–1.2) (Figure 1). There was no significant trend with duration of use, time since first use or time since last use (Figures 2–4), although there was some suggestion that the risk was slightly elevated in current and recent users (1.2; 95% CI, 1.0–1.3) (Figure 4).

Skegg *et al*. (1995) published the results of a pooled analysis of individual data from two studies (Paul *et al*., 1989; WHO Collaborative Study of Neoplasia and Steroid Contraceptives, 1991a) on depot medroxyprogesterone acetate. As had been observed in the separate studies, there was no association between use and overall risk, but an increased risk (not statistically significant) was found for women under 35 years of age and an increased risk (statistically significant) for women who had last used the preparation during the previous five years. The age-specific results for time since first use suggested an increased risk for use begun in the previous year in each age group: 2.0 (95% CI, 1.2–3.3) for < 35 years of age, 1.5 (95% CI, 0.9–2.4) for 35–44 years of age and 1.8 (95% CI, 0.81–4.0) for 45 years of age and older, although only the estimate for women < 35 years of age was statistically significant.

The Collaborative Group on Hormonal Factors in Breast Cancer (1996) also carried out a combined analysis of use of injectable progestogens. On the basis of any use in 339 of 17 639 cases and 1935 of 38 248 controls, the relative risk estimate was 1.0 (95% CI, 0.89–1.2) (Figure 5). There was no significant trend with duration of use (Figure 6). There was some evidence of an increased risk for users of depot progestogens (Figures 7 and 8), with a significant trend of decreasing risk with time since first use (Figure 7).

2.2 Endometrial cancer

2.2.1 *Cohort studies*

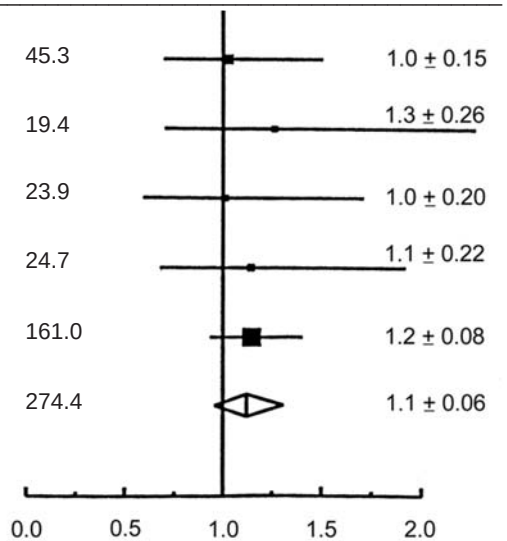
In a study at a family planning clinic in Atlanta, United States, one case of uterine cancer was found among 5000 African–American women aged 50 in 1967–76 who were receiving injections of depot medroxyprogesterone acetate, with 0.83 expected (relative risk, 1.2; 95% CI, 0.1–6.7) on the basis of the rates from the national Surveillance, Epidemiology and End Results programme (Liang *et al*., 1983).

2.2.2 *Case–control studies* (Table 5)

In a multi-centre case–control study among women under 55 years of age in the United States, only one of the 433 women with endometrial cancer and six of the 3191 control women reported use of a progestogen-only oral contraceptive (odds ratio, 0.6; 95% CI, 0.1–5.0) in personal interviews (Centers for Disease Control and the National Institute of Child Health and Human Development, Cancer and Steroid Hormone Study, 1987).

Figure 1. Relative risks for breast cancer among women with any versus no use of progestogen-only oral contraceptives

Reference, study	Any use (no. of cases/ no. of controls)	No use (no. of cases/ no. of controls)	Statistics		Relative risk[a]	
			O-E	var (O-E)	RR & 99% CI	RR ± SD
UK National case–control study group (1989)	123/116	632/639	1.1	45.3		1.0 ± 0.15
Meirik *et al.* (1986)	59/62	363/465	4.5	19.4		1.3 ± 0.26
Paul *et al.* (1989, 1990); Skegg *et al.* (1996)	50/163	841/1 701	0.2	23.9		1.0 ± 0.20
Vessey *et al.* (1983)	68/58	2 315/2 333	3.3	24.7		1.1 ± 0.22
Other	425/129	22 178/19 885	22.0	161.0		1.2 ± 0.08
All studies	725/528	26 329/25 023	31.1	274.4		1.1 ± 0.06



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

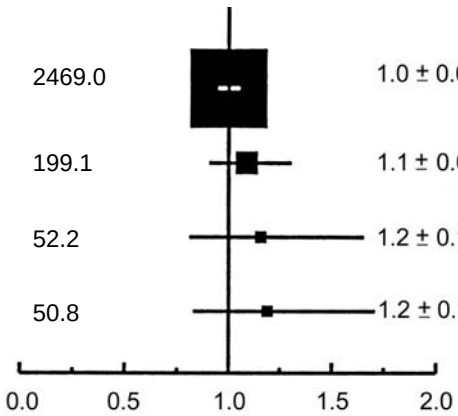
Adapted from Collaborative Group on Hormonal Factors in Breast Cancer (1996)

O, observed; E, expected; RR, relative risk; 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 of conception ceased

Figure 2. Relative risk for breast cancer by duration of use of progestogen-only oral contraceptives

Duration of use (years)	No. of cases/ no. of controls	Statistics		Relative risk[a]	
		InRR	1	RR (99% CI)	RR ± SD
		var(InRR)	var(InRR)		
Never	29 625/50 515	0.0	2469.0		1.0 ± 0.02
< 2	467/641	16.8	199.1		1.1 ± 0.07
2–3	120/150	7.6	52.2		1.2 ± 0.15
≥ 4	125/145	8.8	50.8		1.2 ± 0.15



Adapted from Collaborative Group on Hormonal Factors in Breast Cancer (1996)
Test for trend with duration of use χ^2 (1 d.f.) = 0.4; NS
RR, relative risk; CI, confidence interval; SD, standard deviation; d.f., degree 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 conception ceased

A study in Bangkok and Chiang Mai, Thailand, found that the incidence of endometrial cancer was approximately 80% lower (odds ratio, 0.2; 95% CI, 0.1–0.8) among women (three cases and 84 controls) who reported using depot medroxyprogesterone acetate than among those who reported no use (119 cases and 855 controls) in personal interviews (WHO Collaborative Study of Neoplasia and Steroid Contraceptives, 1991b). All three case women who had used this preparation had also used pre-menopausal oestrogens.

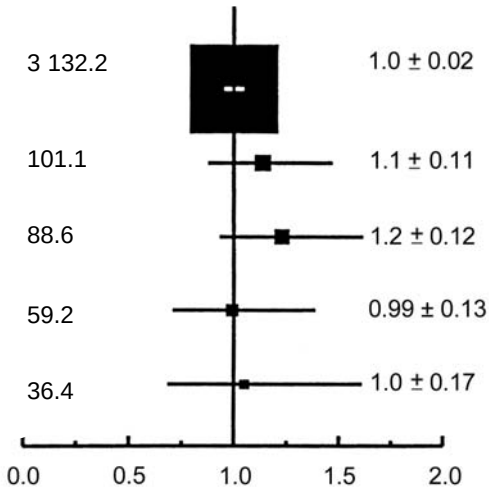
2.3 Cervical cancer

2.3.1 *Methodological considerations*

The same methodological issues as are described in section 2.3 of the monograph on 'Oral contraceptives, combined' must be considered when assessing associations between use of injectable contraceptives and cervical carcinoma.

Figure 3. Relative risk for breast cancer by time since first use of progestogen-only oral contraceptives

Time since first use (years)	No. of cases/ no. of controls	Statistics		Relative risk[a]	
		lnRR	1	RR (99% CI)	RR ± SD
		var(lnRR)	var(lnRR)		
Never	29 625/50 515	0.0	3 132.2		1.0 ± 0.02
< 5	250/335	12.9	101.1		1.1 ± 0.11
5–9	218/271	18.2	88.6		1.2 ± 0.12
10–14	129/195	–0.5	59.2		0.99 ± 0.13
≥ 15	84/103	1.8	36.4		1.0 ± 0.17



Adapted from Collaborative Group on Hormonal Factors in Breast Cancer (1996)
Test for trend with time since first use: χ^2 (1 d.f.) = 0.6; NS
RR, relative risk; CI, confidence interval; SD, standard deviation; d.f., degree 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 conception ceased

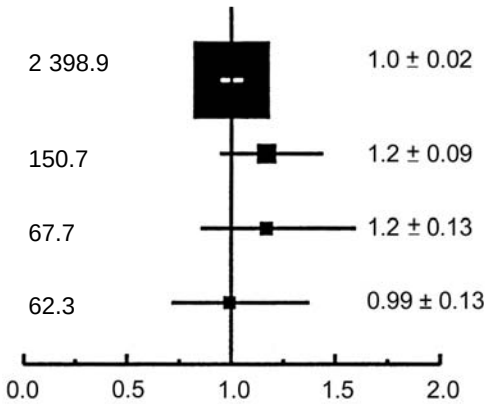
2.3.2 *Cervical dysplasia and carcinoma* in situ

The New Zealand Contraception and Health Study Group (1994) followed a cohort of 7199 women for about five years. All of the women had two normal cervical smears at entry into the cohort and were using either oral contraceptives, an intrauterine device or depot medroxyprogesterone acetate as their method of contraception. The risk for dysplasia per 1000 women was 58.7 for the users of depot medroxyprogesterone acetate and 44.4 for those with an intrauterine device. This difference was not statistically significant. The incidence rate of more severe dysplasia or carcinoma *in situ* was 0.9/1000 in both groups. After control for multiple confounding factors, including the number of sexual partners, the risk of the progestogen users relative to that of women with an intrauterine device was 1.2.

From data on women included in the WHO Collaborative Study of Neoplasia and Steroid Contraceptives in Mexico and Thailand, Thomas *et al.* (1995a) estimated that the

Figure 4. Relative risk for breast cancer by time since last use of progestogen-only oral contraceptives

Time since last use (years)	No. of cases/ no. of controls	Statistics		Relative risk[a]	
		InRR	1	RR (99% CI)	RR ± SD
		var(InRR)	var(InRR)		
Never	29 625/50 515	0.0	2 398.9		1.0 ± 0.02
< 5	375/492	23.4	150.7		1.2 ± 0.09
5–9	162/210	10.6	67.7		1.2 ± 0.13
≥ 10	134/186	–0.5	62.3		0.99 ± 0.13



Adapted from Collaborative Group on Hormonal Factors in Breast Cancer (1996)
Test for trend with time since last use: χ^2 (1 d.f.) = 1.0; NS
RR, relative risk; CI, confidence interval; SD, standard deviation; d.f., degree 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 conception ceased

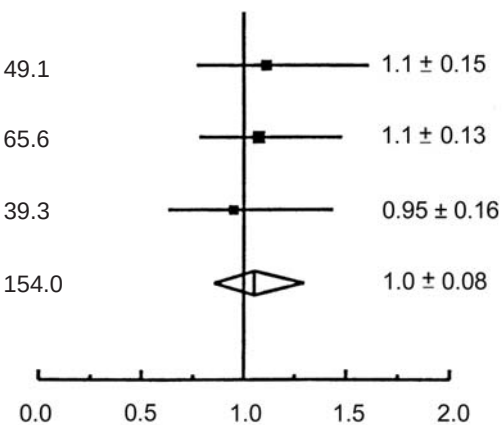
relative risk for cervical carcinoma *in situ* of women who had ever used depot medroxyprogesterone acetate was 1.4 (95% CI, 1.2–1.7); however, when the analyses were restricted to women with symptoms of vaginal bleeding or discharge, to minimize the possibility of bias due to selective screening of women on this preparation, the relative risk estimate was 1.2 (95% CI, 1.0–1.5). Nonetheless, women with symptoms had a significant trend ($p = 0.017$) in risk with duration of use: women who had used depot medroxyprogesterone acetate for more than five years had a relative risk of 1.8 (95% CI, 1.2–2.6). There was no trend in risk with time since first or last use. When considering women who had used this preparation for more than five years, the risk was increased for those who had last used it within the previous 10 years but not for those who had used it before that time.

2.3.3 *Invasive cervical carcinoma*

Two case–control studies have been conducted of the risk for invasive cervical cancer and use of injectable contraceptives. Herrero *et al*. (1990) recruited cases from six hospitals in Colombia, Costa Rica, Mexico and Panama. Controls were selected from the

Figure 5. Relative risk for breast cancer among women with any use of depot progestogens versus those who had never used them

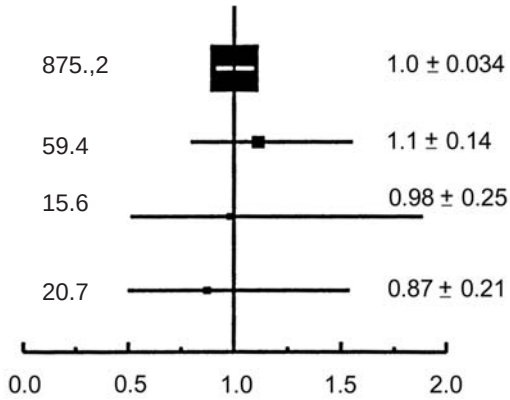
Reference, study	Any use (no. of cases/ no. of controls)	No use (no. of cases/ no. of controls)	Statistics		Relative risk[a]	
			O-E	var (O-E)	RR & 99% CI	RR ± SD
Paul *et al.* (1989, 1990); Skegg *et al.* (1996)	110/252	781/1 612	5.2	49.1		1.1 ± 0.15
WHO Collaborative Study (1991a)	138/1 525	3 156/17 577	4.7	65.6		1.1 ± 0.13
Other	91/158	13 363/17 124	–2.0	39.3		0.95 ± 0.16
All studies	339/1 935	17 300/36 313	7.9	154.0		1.0 ± 0.08



Adapted from Collaborative Group on Hormonal Factors in Breast Cancer (1996)
Test for heterogeneity between studies: χ^2 (2 d.f.) = 0.6; NS
O, observed; E, expected; RR, relative risk; CI, confidence interval; SD, standard deviation; d.f., degree 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 conception ceased

Figure 6. Relative risk for breast cancer by duration of use of depot progestogens

Duration of use (years)	No. of cases/ no. of controls	Statistics		Relative risk[a]	
		InRR	1	RR (99% CI)	RR ± SD
		var(InRR)	var(InRR)		
Never	25 612/45 437	0.0	875.,2		1.0 ± 0.034
< 2	129/257	6.3	59.4		1.1 ± 0.14
2–3	28/65	–0.3	15.6		0.98 ± 0.25
≥ 4	37/88	–2.8	20.7		0.87 ± 0.21

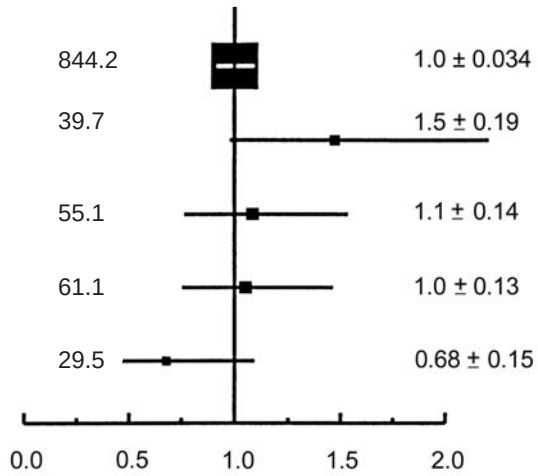


Adapted from Collaborative Group on Hormonal Factors in Breast Cancer (1996)
Test for trend with duration of use χ^2 (1 d.f.) = 0.4; NS
RR, relative risk; CI, confidence interval; SD, standard deviation; d.f., degree of freedom; NS, not significant
[a] Relative to no use, stratified by study, age at diagnosis, parity, age at first birth and age at which risk for conception ceased

same hospitals from which the cases were recruited; in Costa Rica and Panama, community controls were also selected. The results were reported for use of all injectable contraceptives combined and not separately for specific agents. Of the users, 55% reported using injectable contraceptives monthly and 45% reported using them every three months. The preparation used more frequently than every three months was probably norethisterone oenanthate and that used every three months was probably depot medroxyprogesterone acetate. Cervical swabs were taken from the study subjects and tested for type-specific human papillomavirus DNA by filter in-situ hybridization. After control for age, age at first intercourse, number of sexual partners, number of pregnancies, detected presence of human papillomavirus type-16/-18 DNA, interval since last Papanicolaou (Pap) smear and socioeconomic status, the risk of women who had ever used injectable contraceptives for six or more months, relative to non-users, was estimated to be 0.8 (95% CI, 0.5–1.2). The risk was not increased for women who had used these products for fewer than five years (0.5; 95% CI, 0.3–0.9) but was 2.4 (95% CI, 1.0–5.7) for women who had used them for five or more years. There were no significant trends in risk with time since first or last use;

Figure 7. Relative risk for breast cancer by time since first use of depot progestogens

Time since first use (years)	No. of cases/ no. of controls	Statistics		Relative risk[a]	
		InRR / var(InRR)	1 / var(InRR)	RR (99% CI)	RR ± SD
Never	25 612/45 437	0.0	844.2		1.0 ± 0.034
< 5	84/516	15.4	39.7		1.5 ± 0.19
5–9	94/592	4.4	55.1		1.1 ± 0.14
10–14	110/534	3.0	61.1		1.0 ± 0.13
≥ 15	44/281	–11.4	29.5		0.68 ± 0.15



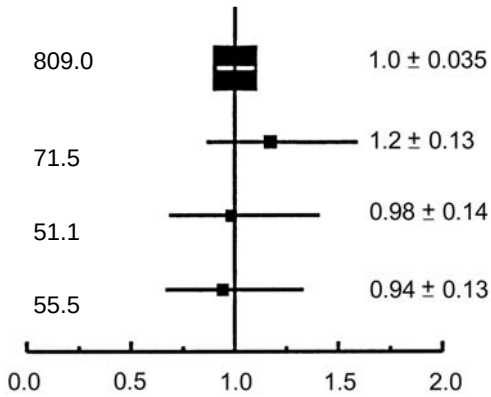
Adapted from Collaborative Group on Hormonal Factors in Breast Cancer (1996)
Test for trend with duration of use χ^2 (1 d.f.) = 8.8; p = 0.003
RR, relative risk; CI, confidence interval; SD, standard deviation; d.f., degree of freedom
[a] Relative to no use, stratified by study, age at diagnosis, parity, age at first birth and age at which risk for conception ceased

however, the highest relative risks were observed for women who had used these products for more than five years and who had first used them more than 10 years previously (relative risk, 3.4; 95% CI, 1.1–25) and for women who had used the products for more than five years and who had last used them more than five years previously (relative risk, 5.3; 95% CI, 1.1–10). These increased risks must be interpreted with caution, however, because significantly reduced risks were observed for women who had used the products for fewer than five years and had used them for the first time within the past 10 years (relative risk, 0.4; 95% CI, 0.2–0.8) or within the past five years (relative risk, 0.4; 95% CI, 0.2–0.8). The reduced risks in relatively recent users could be due to more intensive screening in women receiving depot medroxyprogesterone acetate, so that earlier stages of disease are detected before progression to invasive disease.

In the WHO Collaborative Study of Neoplasia and Steroid Contraceptives (1992), described in section 2.1.1(b), 2009 women with invasive cervical cancer were compared

Figure 8. Relative risk for breast cancer by time since last use of depot progestogens

Time since last use (years)	No. of cases/ no. of controls	Statistics		Relative risk[a]	
		InRR	1	RR (99% CI)	RR ± SD
		var(InRR)	var(InRR)		
Never	25 612/45 437	0.0	809.0		1.0 ± 0.035
< 5	137/921	11.4	71.5		1.2 ± 0.13
5–9	82/514	–0.9	51.1		0.98 ± 0.14
≥ 10	101/467	–3.3	55.5		0.94 ± 0.13



Adapted from Collaborative Group on Hormonal Factors in Breast Cancer (1996)
Test for trend with duration of use χ^2 (1 d.f.) = 1.6; NS
RR, relative risk; CI, confidence interval; SD, standard deviation; d.f., degree 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 conception ceased

with 9583 hospital controls. After taking into consideration age, total number of pregnancies, number of prior Pap smears, use of oral contraceptives and centre, the relative risk for women who had ever used depot medroxyprogesterone acetate was estimated to be 1.1 (95% CI, 1.0–1.3).

Using data from this study, Thomas *et al*. (1995b) also assessed risks for adenocarcinoma and adenosquamous carcinoma in relation to use of depot medroxyprogesterone acetate. On the basis of 239 women with adenocarcinoma and 85 with adenosquamous carcinoma, the risks of women who had ever used this preparation relative to 2534 age-matched hospital controls were estimated to be 0.8 (95% CI, 0.5–1.3) for adenocarcinomas and 0.7 (95% CI, 0.3–1.7) for adenosquamous carcinoma. All of the relative risks in this study were assessed for possible confounding by variables including numbers of pregnancies, live births and sexual partners, history of abortion and stillbirths, age at first live birth, age at first sexual intercourse, marital status, history of a variety of sexually transmitted diseases, serological evidence of herpes simplex virus infection, prior Pap smears, level of education and use of other methods of contraception. Because the relative

Table 5. Case–control studies of use of progestogen-only contraceptives and endometrial cancer

Reference	Location/period/ ages	Source of controls	Ascertain-ment	Participation (%)		Type/measure of therapy	No. of subjects		OR (95% CI)
				Cases	Controls		Cases	Controls	
Centers for Disease Control (1987)	Eight US SEER areas/Dec. 1980–Dec. 1982/ 20–54 years	General population	Personal interviews	73	84	Never used POC Any use of POC	250 1	1 147 6	Referent 0.6 (0.1–5.0)
WHO Collaborative Study (1991b)	Bangkok, Chiang Mai, Thailand/ Jan. 1979–Feb. 1986/< 60 years	Hospital patients	Personal interviews	98	96	Never used DMPA Ever used DMPA	119 3	855 85	Referent 0.2 (0.1–0.81)

OR, odds ratio; CI, confidence interval; POC, progestogen-only contraceptives; DMPA, depot medroxyprogesterone acetate

risk estimates for the two histological types were similar, the data for the two types were combined, giving a relative risk of 0.8 (95% CI, 0.5–1.1) for women who had ever used depot medroxyprogesterone acetate. No trends in relative risk with length of use or time since first or last use were observed. The relative risk of women who had used the product for more than four years was estimated to be 0.7 (95% CI, 0.4–1.4).

2.4 Ovarian cancer

2.4.1 *Cohort studies*

In the study of Liang *et al.* (1983) described in section 2.2, one case of ovarian cancer was observed with 1.2 expected, corresponding to a relative risk of 0.8 (95% CI, 0.1–4.6).

2.4.2 *Case–control studies*

Within the framework of the WHO Collaborative Study of Neoplasia and Steroid Contraceptives (1991c), hospital-based data from Mexico and Thailand were analysed with reference to use of depot medroxyprogesterone acetate and the risk for epithelial ovarian cancer. A total of 224 cases and 1781 hospital controls were collected between 1979 and 1988. The multivariate relative risk for any use was 1.1 (95% CI, 0.6–1.8) in the absence of any duration–risk relationship (relative risk, 1.1 for ≥ 5 years of use; 95% CI, 0.4–3.2).

Little information is available on progestogen-only oral contraceptives. In a hospital-based case–control study of 441 cases and 2065 controls recruited between 1977 and 1991 from various areas of the United States (Rosenberg *et al.*, 1994), 1% of cases and 3% of controls had ever used such preparations. [The unadjusted odds ratio was 0.3.]

2.5 Liver cancer

The WHO Collaborative Study of Neoplasia and Steroid Contraceptives (1991d) also addressed the association between use of depot medroxyprogesterone acetate and the risk for cancer of the liver. Cases were women diagnosed with cancer in three centres in Thailand in 1979–88 and one centre in Kenya in 1979–86. Of the 94 eligible cases, 71 (75.5%) were interviewed. About two controls were identified for each case, chosen from the same hospital but not otherwise matched; women were not eligible as potential controls if they had been admitted to the hospital for conditions that might have altered their use of steroid contraceptives. Of 10 796 eligible controls that were identified, 10 382 (96.2%) were interviewed. Eight controls per case of liver cancer were randomly selected from the pool, resulting in the inclusion of 530 controls, matched on hospital, age and date of diagnosis. Information on smoking was not collected. As alcohol intake was not associated with the risk for liver cancer in these women, the relative risks were not adjusted for alcohol intake. Subjects were not tested for evidence of infection with hepatitis B virus, but both countries are endemic for this infection. The relative risks were adjusted for age, centre, date of diagnosis and number of live births and were presented separately for Kenya and Thailand. In Kenya, four out of 22 cases (18.2%) had used

depot medroxyprogesterone acetate; the relative risks were 1.6 (95% CI, 0.4–6.6) for any use, 0.7 (95% CI, 0.1–6.8) for use for 1–26 months and 2.9 (95% CI, 0.5–15.2) for use for more than 26 months. Fifteen of the 22 cases in Kenya were diagnosed only on clinical grounds. In Thailand, four out of 49 cases (8.2%) had used depot medroxyprogesterone acetate; the relative risks were 0.3 (95% CI, 0.1–1.0) for any use, 0.2 (95% CI, 0.0–1.2) for use for 1–26 months, 0.3 (95% CI, 0.0–2.5) for 27–58 months and 0.7 (95% CI, 0.2–3.2) for more than 58 months.

Kew *et al.* (1990) conducted a hospital-based case–control study in Johannesburg, South Africa. The cases were those of patients with histologically confirmed hepatocellular carcinoma which had been diagnosed when they were aged 19–54. Two controls per case were selected, 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 eligible as controls. 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. Five of 46 cases (11%) and 21 of 92 controls (23%) had used injectable progestogens, giving an overall relative risk of 0.4 (95% CI, 0.1–1.2). Nineteen of the 46 cases had antibodies to hepatitis B surface antigen, 25 had evidence of past infection with hepatitis B virus, and two had no evidence of infection.

2.6 Malignant melanoma

One Danish case–control study of malignant melanoma (Østerlind *et al.*, 1988), described in detail in the monograph on ‘Post-menopausal oestrogen therapy’, provided data on the use of progestogens alone. These preparations were used as oral contraceptives by 14 cases and 23 controls (relative risk, 1.2; 95% CI, 0.6–2.6) and as post-menopausal therapy by three cases and four controls (crude relative risk, 1.5; 95% CI, 0.3–8.1).