Cervical cancer and use of hormonal contraceptives: a systematic review

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Summary

Background Human papillomavirus (HPV) is believed to be the most important cause of cervical cancer. Recent studies suggest that long duration use of oral contraceptives increases the risk of cervical cancer in HPV positive women.

Methods Results from published studies were combined to examine the relationship between invasive and in situ cervical cancer and duration and recency of use of hormonal contraceptives, with particular attention to HPV infection.

Findings 28 eligible studies were identified, together including 12 531 women with cervical cancer. Compared with never users of oral contraceptives, the relative risks of cervical cancer increased with increasing duration of use: for durations of approximately less than 5 years, 5–9 years, and 10 or more years, respectively, the summary relative risks were 1·1 (95% CI 1·1–1·2), 1·6 (1·4–1·7), and 2·2 (1·9–2·4) for all women; and 0·9 (0·7–1·2), 1·3 (1·0–1·9), and 2·5 (1·6–3·9) for HPV positive women. The results were broadly similar for invasive and in situ cervical cancers, for squamous cell and adenocarcinoma, and in studies that adjusted for HPV status, number of sexual partners, cervical screening, smoking, or use of barrier contraceptives. The limited available data suggest that the relative risk of cervical cancer may decrease after use of oral contraceptives ceases. However, study designs varied and there was some heterogeneity between study results.

Interpretation Although long duration use of hormonal contraceptives is associated with an increased risk of cervical cancer, the public health implications of these findings depend largely on the extent to which the observed associations remain long after use of hormonal contraceptives has ceased, and this cannot be evaluated properly from published data.

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Introduction

Cancer of the uterine cervix is the second most common cancer among women in less-developed countries.[1] Persistent infection of cervical epithelial cells with certain high-risk types of the human papillomavirus (HPV) is believed to be the most important cause of cervical cancer.[2,3] The types of HPV associated with cervical cancer are transmitted sexually and it seems that a high proportion of sexually active women are infected by one or more of these viruses at some time during their lives.[2] Whether women who have been infected by HPV develop a persistent infection or cervical cancer may be affected by other factors, including the use of hormonal contraceptives. Recent studies have suggested that there is an increased risk of cervical cancer in HPV-DNA positive women if they use oral contraceptives for longer than 5 years.[4] Due to the potential public health importance of any effects of oral contraceptives on cervical cancer WHO commissioned a systematic review of published evidence.[5] Here, we present the results of this review with particular attention to the role of HPV infection, and to the pattern of risk according to duration of use and time since last use of hormonal contraceptives.

Methods

Definitions and identification of eligible studies

Epidemiological studies were identified through a Medline search (January, 1966, to July, 2002) and from references cited in identified papers. Key search words included the terms: cervical intraepithelial neoplasia, cervix dysplasia, cervix neoplasms, risk factors, contraceptive agents, papillomavirus human, and (pre-1994) papillomavirus. The search was limited to human studies and restricted to peer-reviewed articles. No language or date limitations were imposed. Studies were potentially eligible if they reported on the duration of use of hormonal contraceptives, including oral contraceptives, depot medroxyprogesterone acetate (DMPA) injectables, progestagen-only pills, or combined monthly injectables. In most studies the term "oral contraceptive" was used irrespective of the specific dose or formulation of contraceptive pills, and thus in most studies it was impossible to distinguish between the use of combined and progestagen-only pills, or to determine the dose of hormone used. It is likely, however, that the large majority of oral contraceptive users had used preparations containing combined oestrogen and progestagen and that the majority of injectable contraceptives used were progestagen-only preparations.[6]

For this review of the association between hormonal contraceptives and cervical neoplasia, only studies with an outcome of invasive cervical cancer, carcinoma in situ, or cervical intraepithelial neoplasia grade 3 (CIN3) were included, with the exception of Hildesheim and colleagues[7] (which included women with invasive cancer, CIN3, and CIN2). Moreover, each study was required to have published information on the number of study participants

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and on age-adjusted or age-matched relative risks (RRs) (or odds ratios, subsequently referred to as RRs), and their corresponding 95% CIs according to duration of hormonal contraceptive use. Cohort studies were defined as those in which information on use of hormonal contraceptives was obtained before the diagnosis of cervical cancer. For studies that included a measurement of HPV infection, the minimum sample size for inclusion was 50 cases of invasive cervical cancer or carcinoma in situ/CIN3. For studies without a measurement of HPV infection, the minimum sample size for cohort studies was a total of at least 100 cases of invasive carcinoma, carcinoma in situ, or CIN3, and for case-control studies was 100 cases of invasive cancer or 200 cases of carcinoma in situ/CIN3.

For every eligible study, the following information was extracted: country and year of diagnosis of the cases; study design (cohort or case-control with population-based or hospital controls); type of cervical neoplasms (invasive/in situ/CIN3); histological type (squamous cell, adenocarcinoma [including adenosquamous carcinoma], or unspecified); measure of HPV infection, if any; RRs and CIs associated with use of hormonal contraceptives; and whether or not the RRs were adjusted for HPV infection, number of sexual partners, previous cervical screening, smoking or use of barrier methods of contraception. For studies of injectable contraceptives, information was also extracted on whether the RRs were adjusted for the use of oral contraceptives. The most fully adjusted RRs were entered into the database from each published article. Summary tables and the listing of the variables used in these analyses were double checked to confirm data accuracy.

Study (Country)[ref]	Study design	Type of cervical neoplasia	Measure of HPV	Cases/controls status	Year of diagnosis for cases	Use of hormonal contraceptives in controls		Relative risk estimates for oral contraceptive use adjusted for:				
						% ever use of oral contraceptives (% use for >5 years)	% ever use of injectable contraceptives (% use for >5 years)	1	2	3	4	5
Cohort studies, including case-control studies nested within a cohort (nested c/c)												
Beral, 1988 (UK)[24]	Cohort	Invasive/in situ	None	272/NA	1968–87	NA	NA	No	No	Yes	Yes	No
Zondervan, 1996 (UK)[25]	Nested c/c	Invasive/in situ	None	154/1531	1968–94	NA	NA	No	No	No	Yes	Yes
Ylitalo, 1999 (Sweden)[28]	Nested c/c	In situ	PCR	366/371	1969–95	77 (36)	NK	No	Yes	No	Yes	No
Deacon, 2000* (UK)[29]	Nested c/c	CIN3	PCR	199/181	1987–93	81 (60)	NK	NA	No	No	No	No
Case-control studies, including those with population (pop) and/or hospital controls (hosp)												
Brinton/Jones, 1986 (USA)[12,11]	Pop	Invasive/in situ	None	772/801	1982–84	51 (18)	NK	No	Yes	Yes	Yes	Yes
Peters, 1986 (USA)[12]	Pop	Invasive†	None	200/200	1980–81	26 (NK)‡	NK	No	No	No	No	No
Ebeling, 1987 (Germany)[13]	Hosp	Invasive	None	129/275	1983–85	66 (46)	NK	No	Yes	Yes	Yes	No
Irwin, 1988 (Costa Rica)[15,16]	Pop	Invasive/in situ†	None	496/631	1982–85	48 (16)	6 (NK)§	No	Yes	Yes	No	No
Brinton, 1990 (4 countries¶)[17,18]	Pop/hosp	Invasive	FISH	759/1429	1986–87	25 (11)	6 (1)	Yes	Yes	Yes	No	No
Kjaer, 1993 (Denmark)[19]	Pop	Invasive/in situ†	None	644/614	1987–88	83 (29)	NK	No	Yes	Yes	Yes	Yes
WHO, 1993 (9 countries‖)[21, 42–45]	Hosp	Invasive/in situ	None	3848/13 644	1979–88	41 (8)	15 (4)§	No	No	Yes	No	No
Ursin, 1994 (USA)[21]	Pop	Invasive**	None	195/386	1977–91	81 (36)	NK	No	Yes	No	No	Yes
Lazcano-Ponce, 1995 (Mexico)[22]	Pop	Invasive/CIN3	None	630/1005	1990–92	34 (10)	NK	No	Yes	No	No	No
Cuzick, 1996 (UK)[23]	Pop	Invasive	None	121/241	1985–91	92 (62)	NK	No	Yes	No	No	No
Daling, 1996 (USA)[24]	Pop	Invasive†	PCR/serology	221/466	1986–92	87 (35)	NK	No	Yes	Yes	No	No
Parazzini, 1998 (Italy)[26]	Hosp	Invasive	None	592/616	1981–93	19 (NK)	NK	No	Yes	Yes	Yes	No
Lacey, 1999 (USA)[27]	Pop	Invasive/in situ	PCR	263/307	1992–96	75 (25)	NK	Yes	Yes	Yes	No	No
Hildesheim, 2001* (Costa Rica)[7]	Pop	Invasive/CIN2–3	HC/PCR	146/843	1993–94	65 (20)	NK	NA	No	No	Yes	No
Madeleine, 2001 (USA)[31]	Pop	In situ**	PCR/serology	132/478	1990–96	84 (29)	NK	No	Yes	Yes	No	No
Berrington, 2002 (UK)[33]	Pop	Invasive	Serology	221/393	1984–88	88 (47)	NK	Yes	Yes	Yes	Yes	No
Moreno, 2002 (8 studies††)[4]	Pop/hosp	Invasive/in situ†	PCR	2171/2299	1985–97	36 (11)	NK	Yes	Yes	Yes	No	No

1=HPV, 2=sexual partners, 3=previous cervical screening, 4=smoking, 5=barrier methods of contraception, NA=not applicable, NK=not known, FISH=filter in situ hybridisation, HC=hybrid capture, Nested c/c=case-control studies nested within a cohort, Pop=population controls, Hosp=hospital controls. *Results presented for HPV positive women only. †Squamous cell carcinoma only. ‡Ever use=>2 years' use. §Relative risks for injectable contraceptives adjusted for oral contraceptive use. ¶Costa Rica, Colombia, Mexico, Panama. ‖Australia, Chile, Colombia, Israel, Kenya, Mexico, Nigeria, Philippines, Thailand. **Adenocarcinoma of the cervix only. ††Moreno and colleagues published results of a pooled analysis for squamous carcinoma of the cervix from eight studies done in Brazil, Colombia, Morocco, Paraguay, Peru, Philippines, Spain, and Thailand.

Studies that have published results on the relation between cervical neoplasia and duration of use of hormonal contraceptives (eligibility criteria given in Methods)

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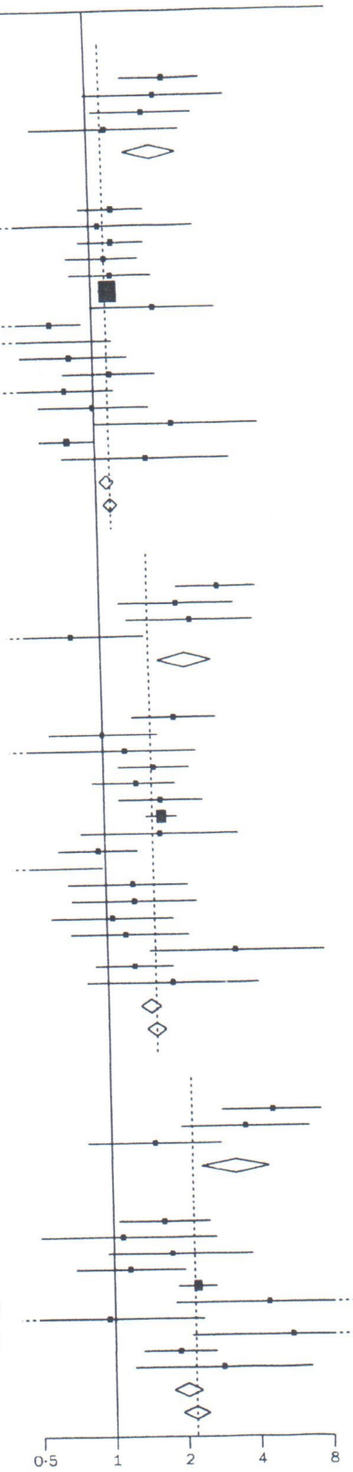
Study	Cancer type	Duration of use (years)	Cases/controls: Users	Cases/controls: Never users	RR (95% CI)
(a) Short duration users (<5 years of use)					
Cohort studies					
Beral, 1988	Invas/in-situ	<5	105/··	50/··	2·1 (1·4–3·0)
Zondervan, 1996	Invas/in-situ	<5	24/··	24/··	1·9 (1·0–3·8)
Ylitalo, 1999	In-situ	<5	145/155	48/84	1·7 (1·0–2·8)
Deacon, 2000*	CIN3	<4	42/38	32/35	1·2 (0·6–2·4)
All cohort studies					1·8 (1·4–2·4)
Case-control studies					
Brinton/Jones, 1986	Invas/in-situ	<5	221/260	356/396	1·2 (0·9–1·7)
Ebeling, 1987	Invas	<4	21/36	24/94	1·1 (0·5–2·7)
Irwin, 1988	Invas/in-situ	<5	163/192	192/331	1·2 (0·9–1·7)
Brinton, 1990	Invas	<5	101/204	568/1072	1·1 (0·8–1·6)
Kjaer, 1993	Invas/in-situ	<5	291/322	70/106	1·2 (0·8–1·8)
WHO, 1993	Invas/in-situ	<5	1217/NA	1987/8111	1·2 (1·1–1·3)
Ursin, 1994	Invas	<5	96/202	19/74	1·8 (1·0–3·3)
Lazcano-Ponce, 1995	Invas/CIN3	<4	113/236	443/666	0·7 (0·5–0·9)
Cuzick, 1996	Invas	<4	25/72	13/19	0·5 (0·2–1·2)
Daling, 1996	Invas	<5	96/242	27/62	0·8 (0·5–1·4)
Parazzini, 1998	Invas	<2	62/56	467/502	1·2 (0·8–1·8)
Lacey, 1999	Invas/in-situ	<6	121/151	57/76	0·8 (0·5–1·2)
Hildesheim, 2001*	Invas/CIN2–3	<5	55/379	53/293	1·0 (0·6–1·7)
Madeleine, 2001	In-situ	<6	64/250	8/74	2·1 (1·0–4·8)
Moreno, 2002	Invas/in-situ	<5	343/442	1321/1439	0·8 (0·6–1·0)
Berrington, 2002	Invas	<5	73/159	12/49	1·6 (0·7–3·6)
All case-control studies					1·1 (1·0–1·2)
ALL STUDIES					1·1 (1·1–1·2)
(b) Medium-duration users (=5–9 years of use)					
Cohort studies					
Beral, 1988	Invas/in-situ	5–9	83/··	50/··	3·1 (2·1–4·5)
Zondervan, 1996	Invas/in-situ	≥6	71/··	24/··	2·1 (1·2–3·6)
Ylitalo, 1999	In-situ	5–10	97/86	48/84	2·4 (1·3–4·3)
Deacon, 2000*	CIN3	4–7	43/56	32/35	0·8 (0·4–1·5)
All cohort studies					2·2 (1·7–2·9)
Case-control studies					
Brinton/Jones, 1986	Invas/in-situ	5–9	125/83	356/396	2·0 (1·3–3·0)
Peters, 1986†	Invas	2–9	42/42	147/148	1·0 (0·6–1·7)
Ebeling, 1987	Invas	4–6	14/39	24/94	1·2 (0·4–2·5)
Irwin, 1988	Invas/in-situ	≥5	129/100	192/331	1·6 (1·1–2·3)
Brinton, 1990	Invas	5–9	61/101	568/1072	1·4 (0·9–2·0)
Kjaer, 1993	Invas/in-situ	≥6	268/173	70/106	1·7 (1·1–2·6)
WHO, 1993	Invas/in-situ	5–7	329/NA	1987/8111	1·7 (1·5–2·0)
Ursin, 1994	Invas	6–8	28/57	19/74	1·7 (0·8–3·6)
Lazcano-Ponce, 1995	Invas/CIN3	≥4	74/103	443/666	0·9 (0·6–1·4)
Cuzick, 1996	Invas	4–8	25/82	13/19	0·3 (0·1–1·0)
Daling, 1996	Invas	≥5	98/162	27/62	1·3 (0·7–2·2)
Parazzini, 1998	Invas	≥2	63/56	467/502	1·3 (0·7–2·4)
Lacey, 1999	Invas/in-situ	≥6	81/77	57/76	1·1 (0·6–1·9)
Hildesheim, 2001*	Invas/CIN2–3	≥5	38/171	53/293	1·2 (0·7–2·2)
Madeleine, 2001	In-situ	6–12	40/101	8/74	3·4 (1·5–8·0)
Moreno, 2002	Invas/in-situ	5–9	227/204	1321/1439	1·3 (0·9–1·9)
Berrington, 2002	Invas	5–9	76/117	12/49	1·9 (0·8–4·3)
All case-control studies					1·5 (1·4–1·7)
ALL STUDIES					1·6 (1·4–1·7)
(c) long-duration users (=≥10 years of use)					
Cohort studies					
Beral, 1988	Invas/in-situ	≥10	34/··	50/··	4·7 (2·9–7·5)
Ylitalo, 1999	In-situ	≥10	76/46	48/84	3·6 (2·0–6·7)
Deacon, 2000*	CIN3	≥8	82/52	32/35	1·5 (0·8–2·9)
All cohort studies					3·3 (2·4–4·5)
Case-control studies					
Brinton/Jones, 1986	Invas/in-situ	≥10	69/60	356/396	1·6 (1·1–2·5)
Peters, 1986†	Invas	≥10	11/10	147/148	1·1 (0·5–2·7)
Ebeling, 1987	Invas	≥7	70/106	24/94	1·8 (0·9–3·8)
Brinton, 1990	Invas	≥10	27/51	568/1072	1·2 (0·7–2·0)
WHO, 1993	Invas/in-situ	≥8	218/NA	1987/8111	2·2 (1·9–2·7)
Ursin, 1994	Invas	≥12	25/18	19/74	4·4 (1·8–10·8)
Cuzick, 1996	Invas	≥8	58/67	13/19	0·9 (0·4–2·4)
Madeleine, 2001	In-situ	≥12	20/33	8/74	5·5 (2·1–14·6)
Moreno, 2002	Invas/in-situ	≥10	280/214	1321/1439	1·9 (1·3–2·7)
Berrington, 2002	Invas	≥10	60/68	12/49	2·8 (1·2–6·6)
All case-control studies					2·0 (1·8–2·3)
ALL STUDIES					2·2 (1·9–2·4)



Test for heterogeneity by duration between:
Cohort studies: (a) χ^2_3=2·0, p>0·1; (b) χ^2_3=12·1, p=0·007; (c) χ^2_3=7·8, p=0·02
Case-control studies: (a) χ^2_{15}=33·7, p=0·004; (b) χ^2_{16}=29·2, p=0·03; (c) χ^2_9=18·7, p=0·03
Cohort and case-control studies: (a) χ^2_1=13·5, p=0·0002; (b) χ^2_1=7·7, p=0·006; (c) χ^2_1=7·4, p=0·03
All studies: (a) χ^2_{19}=49·2, p=0·0002; (b) χ^2_{20}=49·1, p=0·0003; (c) χ^2_{12}=33·9, p=0·0007

Figure 1: **Relative risk (RR) and 95% CI of cervical cancer for short, medium, and long-duration users versus never users of oral contraceptives**
Invas=invasive. CIN=cervical intraepithelial neoplasia. NA=not available. *HPV positive women only. †Never use means <2 years use.

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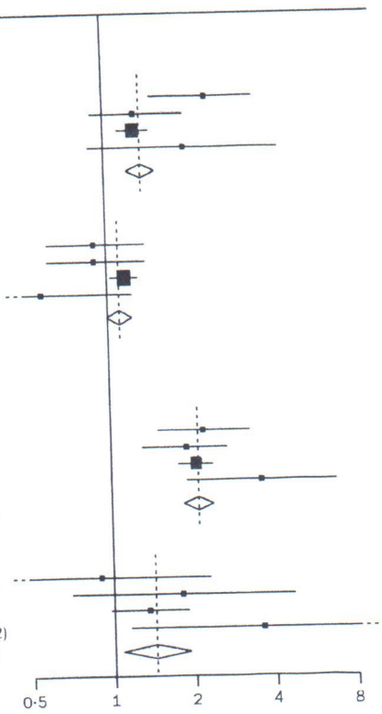
Study	Cancer type	Duration of use (years)	Cases/controls: Users	Cases/controls: Never users	RR (95% CI)
Short duration users (—<5 years of use)					
(a) Current and recent users (last use —<8 years previously)					
Irwin, 1988	Invas/in-situ	<5	NA	192/331	2·4 (1·5–3·6)
Kjaer, 1993*	In-situ	<6	177/195	70/106	1·3 (0·9–2·0)
WHO, 1993†	Invas/in-situ	<5	NA	1987/8111	1·3 (1·1–1·5)
Moreno, 2002‡	Invas/in-situ	<5	91/13	978/152	2·0 (0·9–4·4)
ALL STUDIES					1·4 (1·2–1·5)
(b) Past users (last use —≥8 years previously)					
Irwin, 1988	Invas/in-situ	<5	NA	192/331	0·9 (0·6–1·4)
Kjaer, 1993*	In-situ	<6	80/123	70/106	0·9 (0·6–1·4)
WHO, 1993†	Invas/in-situ	<5	NA	1987/8111	1·2 (1·0–1·3)
Moreno, 2002‡	Invas/in-situ	<5	175/46	978/152	0·6 (0·3–1·2)
ALL STUDIES					1·1 (1·0–1·2)
Medium and long-duration users (—≥5 years of use)					
(c) Current and recent users (last use —<8 years previously)					
Irwin, 1988	Invas/in-situ	≥5	NA	192/331	2·2 (1·5–3·3)
Kjaer, 1993*	In-situ	≥6	233/162	70/106	1·9 (1·3–2·7)
WHO, 1993†	Invas/in-situ	≥5	NA	1987/8111	2·1 (1·8–2·4)
Moreno, 2002‡	Invas/in-situ	≥5	214/19	978/152	3·6 (1·9–6·8)
ALL STUDIES					2·1 (1·8–2·4)
(d) Past users (last use —≥8 years previously)					
Irwin, 1988	Invas/in-situ	≥5	NA	192/331	0·9 (0·3–2·3)
Kjaer, 1993*	In-situ	≥6	14/11	70/106	1·8 (0·7–4·7)
WHO, 1993†	Invas/in-situ	≥5	NA	1987/8111	1·4 (1·0–1·9)
Moreno, 2002‡	Invas/in-situ	≥5	114/7	978/152	3·6 (1·1–11·2)
ALL STUDIES					1·4 (1·1–1·9)



Test for heterogeneity by duration between all studies: (a) χ^2_3=7·9, p=0·05; (b) χ^2_3=5·2, p>0·1; (c) χ^2_3=3·1, p>0·1; (d) χ^2_3=3·6, p>0·1

Figure 2: **Relative risk (RR) and 95% CI of cervical cancer by recency and duration and use of oral contraceptives (versus never users)**
Invas=invasive. NA=not available. *Past use is use of oral contraceptives that ceased >10 years previously. CIs estimated using the unadjusted SE. †Past use is use of oral contraceptives that ceased >8 years previously. ‡Past use is use of oral contraceptives that ceased >6 years previously (HPV positive women only).

Statistical analysis and presentation of results

Published results from each study were grouped, as far as was possible, into the closest of the following categories of duration of hormonal contraceptive use: never use; short-duration use (generally <5 years of use); medium-duration use (generally 5–9 years of use); and long-duration use (generally ≥10 years of use); and of time since last use: current use or use that ceased less than 8 years, and 10 or more years previously. Although this approach could be strictly applied to most studies, a few studies reported different categories of duration of use or time since last use. For studies that had multiple data points for a given category of duration or time since last use of hormonal contraceptives, data were combined into one data point per duration of use category. For example the relative risks for 1–2 and 3–4 years of use were combined to give an estimate for 1–4 years of use. This was done using the method of generalised least squares taking into account the correlations between the two relative risks.[8] Similarly, for studies that had reported results separately for invasive and in situ cancers or for squamous and adenocarcinomas, adjusted odds ratios were combined to give a result for both types of cancer combined using the same method. For studies that included information on analyses restricted to HPV positive or HPV negative participants, separate analyses were done to compare results with and without restriction based on HPV status. HPV positivity is determined by PCR unless otherwise noted.

Results are presented graphically, stratified by the duration of contraceptive use (short, medium, and long). Within each figure, data are presented first for results of cohort studies and then for case-control studies. RRs for each study are plotted as black squares whose size is inversely proportional to the variance of the logarithm of the RR. Diamonds represent summary RRs for the pooled data, calculated using the method of empirically weighted least squares.[9] This method was also used to

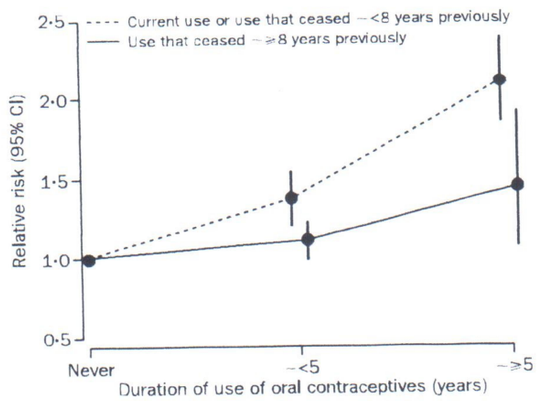


Figure 3: **Summary of results on the relative risk of cervical cancer, according to time since last use and duration of use of oral contraceptives**

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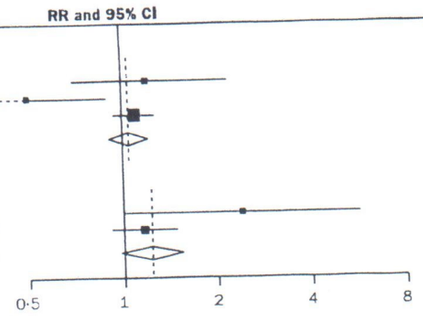
Study	Cancer type	Duration of use (years)	Cases/controls: Users	Cases/controls: Never users	RR (95% CI)
(a) Short-duration users (—<5 years of use)					
Oberle, 1988*	All	<1	23/22	464/606	1·2 (0·7–2·2)
Herrero, 1990†	Invas	<5	21/66	726/1346	0·5 (0·3–0·9)
WHO, 1992‡	Invas	<4	242/1072	1671/8168	1·1 (0·9–1·3)
ALL STUDIES					1·0 (0·9–1·2)
(b) Medium and long-duration users (—≥5 years of use)					
Herrero, 1990†	Invas	≥5	11/16	726/1346	2·4 (1·0–5·7)
WHO, 1992‡	Invas	≥4	96/338	1671/8168	1·2 (0·9–1·5)
ALL STUDIES					1·2 (1·0–1·6)



Test for heterogeneity by duration between all studies: (a) χ^2_2=7·6, p=0·02; (b) χ^2_1=2·4, p>0·1.

Figure 4: **Relative risk (RR) and 95% CI of cervical cancer for short and medium/long-duration users versus never users of injectable contraceptives**

*Described as Irwin, 1988 in table 1. †Described as Brinton, 1990 in table 1. ‡Described as WHO, 1993 in table 1.

test for heterogeneity between the RRs for each of the groups or subgroups of studies.

Role of the funding source

The sponsors of the paper had no role in study design, data collection, data analysis, data interpretation, or in the writing of the report.

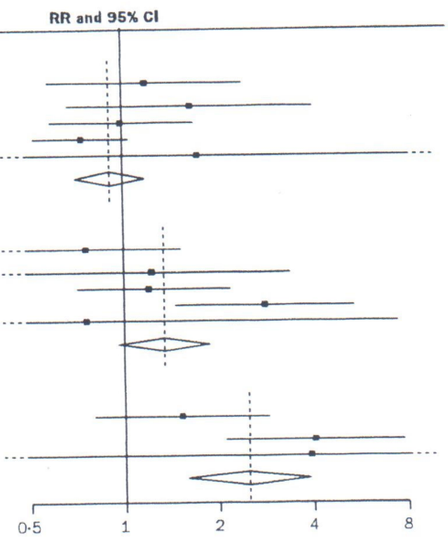
Results

Overall 28 studies were eligible for this systematic review; these studies are described in the table.[4,7,10–31] The details of the eight studies[32–41] included in the pooled analysis of squamous cell carcinoma by Moreno and colleagues are combined in the table, since not all of the eight contributing studies have published relevant data separately. Results from the WHO Collaborative Study of Neoplasia and Contraceptives have been presented in several publications[20,42–46] and these have been combined as appropriate for the analyses.

The 28 eligible studies (four cohort and 24 case-control) included a total of 12 531 women with invasive or in situ cervical cancer. Half of the studies (16 of 28) were done in developed countries, with approximately half in the USA and half in Europe. Among the controls 19–92% in developed and 25–65% in developing countries had ever used oral contraceptives, and use for longer than 5 years ranged from 18% to 62% in developed countries and from 8% to 20% in developing countries.

Figure 1 shows results on the association between cervical cancer and duration of oral contraceptive use for the 28 studies that had presented results for all women; two of these studies were restricted to HPV positive women.[7,29] Some studies were of women with both invasive and in situ cancer, and others were of women with only one of these tumour types; this is indicated in figure 1. When the results from all studies were combined, the relative risk of cervical cancer increased with increasing duration of use. The relative risks for cervical cancer associated with duration of oral contraceptive use of approximately less than 5 years, 5–9 years, and 10 years or longer, respectively, were: 1·1 (95% CI 1·1–1·2), 1·6 (1·4–1·7), and 2·2 (1·9–2·4). Within each category of duration of oral contraceptive use, the relative risks were consistently higher in the cohort studies than in case-control studies (χ^2 test for heterogeneity, p<0·01 in each category).

Study	Cancer type	Duration of use (years)	Cases/controls: Users	Cases/controls: Never users	RR (95% CI)
(a) Short-duration users (—<5 years of use)					
Deacon, 2000	CIN3	<4	42/38	32/35	1·2 (0·6–2·4)
Lacey, 1999	Invas/in-situ	<6	121/21	57/11	1·7 (0·7–4·1)
Hildesheim, 2001	Invas/CIN2–3	<5	55/379	53/293	1·0 (0·6–1·7)
Moreno, 2002	Invas/in-situ	<5	266/59	978/152	0·7 (0·5–1·0)
Berrington, 2002*	Invas	<5	16/18	4/8	1·7 (0·2–16·0)
ALL STUDIES					0·9 (0·7–1·2)
(b) Medium-duration users (—5–9 years of use)					
Deacon, 2000	CIN3	4–7	43/56	32/35	0·8 (0·4–1·5)
Lacey, 1999	Invas/in-situ	≥6	81/16	57/11	1·2 (0·4–3·4)
Hildesheim, 2001	Invas/CIN2–3	≥5	38/171	53/293	1·2 (0·7–2·2)
Moreno, 2002	Invas/in-situ	5–9	156/12	978/152	2·8 (1·5–5·4)
Berrington, 2002*	Invas	5–9	12/15	4/8	0·8 (0·1–7·5)
ALL STUDIES					1·3 (1·0–1·9)
(c) Long-duration users (—≥10 years of use)					
Deacon, 2000	CIN3	≥8	82/52	32/35	1·5 (0·8–2·9)
Moreno, 2002	Invas/in-situ	≥10	172/14	978/152	4·0 (2·1–7·8)
Berrington, 2002*	Invas	≥10	11/4	4/8	3·9 (0·3–44·0)
ALL STUDIES					2·5 (1·6–3·9)



Test for heterogeneity by duration between all studies: (a) χ^2_4=4·0, p>0·1; (b) χ^2_4=7·9, p=0·1; (c) χ^2_2=4·5, p>0·1.

Figure 5: **Relative risk (RR) and 95% CI of cervical cancer in HPV-positive women for short, medium, and long-duration users versus never users of oral contraceptives**

Invas=invasive. *Non-PCR measure of HPV infection—serology.

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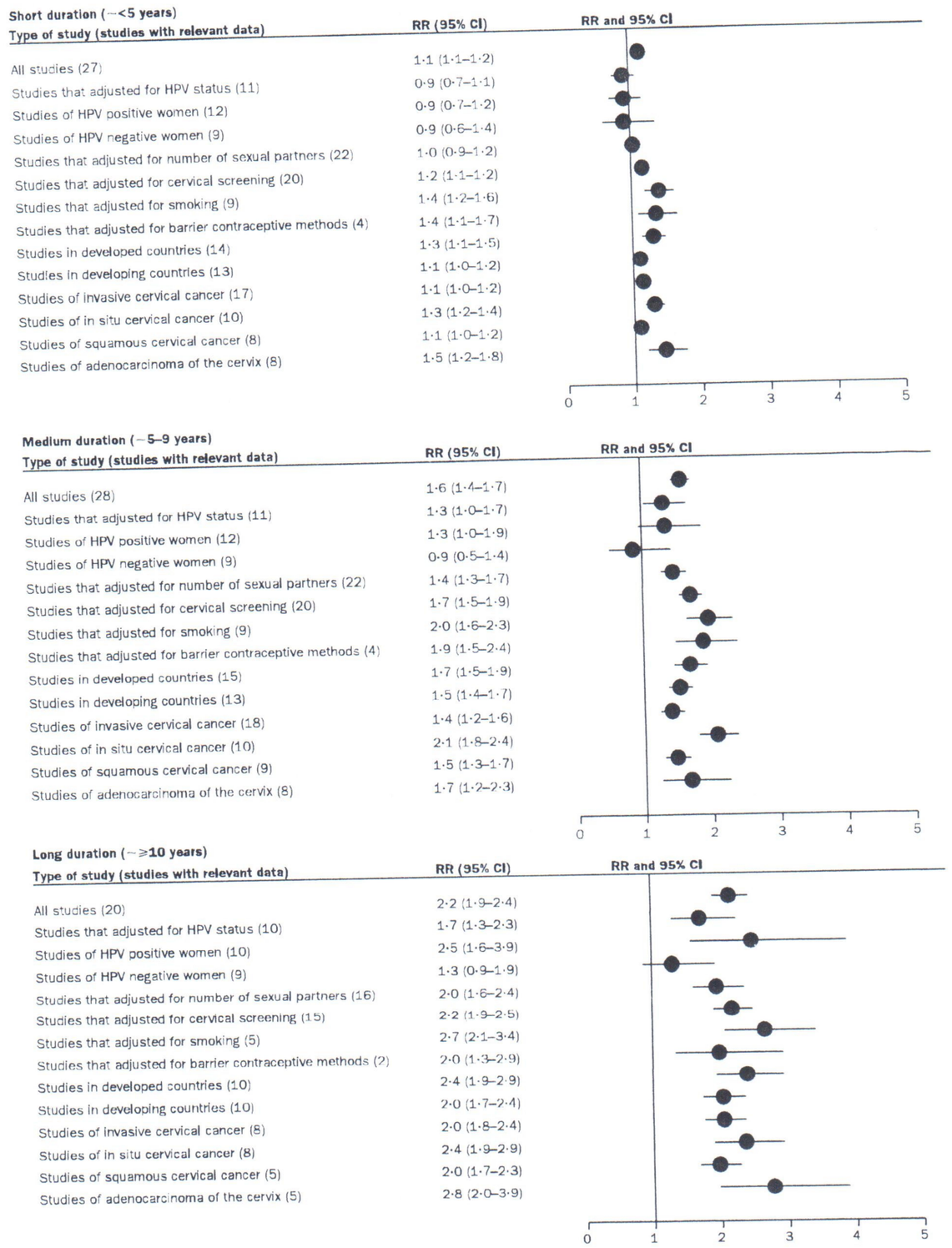

Figure 6: **Summary of results on the relative risk of cervical cancer, according to duration of oral contraceptive use, in various subgroups**

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20 of the eligible studies presented data on the risk of cervical cancer according to time since ceasing use of oral contraceptives, and **the relative risk declines with increasing time since last use** (http://image.thelancet.com/extras/02art8187webappendix1.pdf). However, women who use oral contraceptives for a long period also tend to be current or recent users.[47] 11 of these studies that include 6606 cases (53% of the total) presented data on time since last use according to duration of use. The relative risks for cervical cancer associated with use more than 8 years ago were lower than those for use that ceased less than 8 years ago (figures 2 and 3). **There are few relevant data for women who used oral contraceptives for a duration of 5 years or longer, and among these women the relative risks were 2·1 (1·8–2·4) for current use or use that ceased less than about 8 years ago, and 1·4 (1·1–1·9) for use that ceased more than about 8 years ago.**

Three case-control studies presented results for duration of use of injectable contraceptives (figure 4); but no study presented results on duration of use of progestagen-only oral contraceptives. **Use of injectable contraceptives for 5 years or longer was associated with a slight increase of borderline significance in the relative risk of cervical cancer (relative risk 1·2, 1·0–1·6).**

Taking HPV status into account

One approach to taking HPV status into account when looking at the effect of hormonal contraceptives on cervical cancer is to restrict analyses to women who tested positive for HPV. Figure 5 summarises the results from the 12 studies that included 3000 cases (24% of the total) that have done so: the relative risks for short, medium, and long duration use of oral contraceptives of approximately less than 5 years, 5–9 years, and 10 years or longer, were, respectively, 0·9 (0·7–1·2), 1·3 (1·0–1·9), and 2·5 (1·6–3·9). 11 of the studies used highly sensitive PCR-based assays to detect cervical HPV DNA. One study[31] used HPV serology, which is known to have a lower sensitivity than PCR methods with respect to current HPV infection.

Although some studies have reported results of analyses restricted to women who tested negative to HPV, these are difficult to interpret because, if HPV is the most important cause of all, or almost all the cases of cervical cancer, women with cervical cancer who tested negative for HPV may well have been false negatives. Likewise, results from studies that have been adjusted for HPV status are difficult to interpret. Nevertheless, the results from individual studies for women who tested negative for HPV and those adjusted by HPV status are shown in webappendices 2 and 3 (http://image.thelancet.com/extras/02art8187webappendix2.pdf and http://image.thelancet.com/extras/02art8187webappendix3.pdf) and the summary results are shown in figure 6. Figure 6 also shows the summary results from figure 1 (all women) and from figure 5 (women who tested positive for HPV). In each instance, the overall results show that the relative risk of cervical cancer increases with increasing duration of use of oral contraceptives. One possible exception is in HPV negative women, in whom this effect appears to be less marked.

Potential confounding by other factors and subgroup analyses

The studies listed in table 1 had adjusted their main results on the relative risk of cervical cancer in relation to use of oral contraceptives by various potential confounding factors, although the precise adjustment factors varied from study to study. To assess whether adjustment for number of sexual partners, previous cervical screening, smoking, or use of barrier methods of contraceptives might have affected the results with respect to the use of oral contraceptives, published results were combined for studies that had adjusted for each of these factors (http://image.thelancet.com/extras/02art8187webappendix4.pdf, http://image.thelancet.com/extras/02art8187webappendix5.pdf, http://image.thelancet.com/extras/02art8187webappendix6.pdf, http://image.thelancet.com/extras/02art8187webappendix7.pdf). The summary results are shown in figure 6, and it can be seen that they are broadly similar to the results obtained using different approaches. Likewise, results were combined for women with invasive cervical cancer, in-situ cervical cancer, squamous cervical carcinoma and adenocarcinoma or adenosquamous carcinoma of the cervix (http://image.thelancet.com/extras/02art8187webappendix8.pdf, http://image.thelancet.com/extras/02art8187webappendix9.pdf, http://image.thelancet.com/extras/02art8187webappendix10.pdf, http://image.thelancet.com/extras/02art8187webappendix11.pdf, respectively). Fewer than half of the eligible studies had presented results separately for each of these types of cervical cancer; however for each type the relative risks tended to increase with increasing duration of oral contraceptive use (figure 6). Results were also similar for studies conducted in developing and developed countries (http://image.thelancet.com/extras/02art8187webappendix12.pdf and http://image.thelancet.com/extras/02art 8187webappendix13.pdf).

The overall results thus show fairly consistently that the relative risk of cervical cancer increases with increasing duration of oral contraceptive use (figure 6). It should be stressed however, that each summary result shown in figure 6 includes data from a varying number of different studies, and thus relative risk estimates cannot be formally compared. A proper evaluation of whether or not the findings vary according to the factors mentioned in figure 6 would require that each study be analysed specifically in each of the ways listed.

Discussion

The results of this systematic review of published data show that the **relative risk of cervical cancer increases with increasing duration of oral contraceptive use, in virtually every way that data were examined.** When the results from all studies are combined, the findings are broadly similar for all women, for HPV positive women, for studies that adjusted for HPV status, sexual partners, previous cervical smears, smoking, and use of barrier methods of contraception, and for invasive, in-situ, squamous, and adenocarcinoma of the cervix (figure 6). The study design, methods of analysis, and methods for measuring HPV status varied from study to study and there was evidence of statistical heterogeneity between studies; the magnitude of the summary relative risks should therefore be interpreted cautiously. The main source of variation in the results at each level of duration of oral contraceptive use was between cohort and case-control studies (see figure 1) and the reason for this is unclear. Although there was only limited published data, the results for injectable contraceptives also suggest a slight increase in the risk of cervical cancer associated with use for 5 years or longer.

This systematic review included data for 12 531 women with cervical cancer from 28 studies. Webappendix 14 (http://image.thelancet.com/extras/02art8187webappendix14.pdf) lists ten studies including a total of 2728 women with cervical cancer, that were large enough to be included in this review but could not be, because results on age-adjusted RRs, CIs, or both, according to duration of use of hormonal contraceptives had not been published. For six of these studies (all case-control), information was available for ever versus never use of oral contraceptives. There was

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no difference between the results of these studies and those of the 15 case-control studies included in the review when summary relative risks for cervical cancer in ever versus never users of oral contraceptives were compared (see webappendix14 http://image.thelancet.com/extras/02art8187webappendix14.pdf; summary relative risks were 1·2 [95% CI 1·1–1·3] for included studies and 1·1 [0·9–1·4] for the studies from appendix 14; for heterogeneity between included and appendix 14 studies p>0·1). A further 13 studies, including a total of 1033 cases, were ineligible because they were too small (these studies are also listed in appendix 14, together with studies that were ineligible because the cases had cervical lesions less severe than CIN3). Thus the published data reviewed here includes at least 80% of the potentially available information worldwide on duration of hormonal contraceptive use and the risk of cervical cancer.

Since persistent cervical HPV infection is likely to be the most important cause of cervical cancer,[2,3] a central question is whether the results presented here are biased or confounded by HPV infection. Oral contraceptive use might be related to HPV status. One way of potentially eliminating confounding by HPV infection is to restrict analyses to HPV positive women, and when this is done the results are broadly similar to those obtained without such restriction. The results relating to use of oral contraceptives are also similar in studies that have adjusted for HPV status and in HPV negative women (figure 6), although it appears that in HPV negative women the increase in cervical cancer risk with increasing duration of oral contraceptive use may be less marked than in all women or in HPV positive women. As already discussed, both HPV adjusted and HPV negative results are difficult to interpret. The fact that the results are broadly similar, whichever strategy is adopted for dealing with HPV infection is, perhaps, not surprising, since the prevalence of HPV infection does not appear to increase with increasing duration of oral contraceptive use.[4,29,48] Nevertheless it is possible that all the studies of the relation between oral contraceptive use and cervical cancer suffer from the same unknown bias or biases.

In all the studies reviewed here, tests for HPV status were done at one point in time only. Since the majority of cervical HPV infections in women without cervical cancer are transient, controls who tested positive for HPV DNA are likely to have a transient infection at the time of testing, whereas most, if not all, the cases are likely to have had a persistent HPV infection. Hence, an HPV test done at one point in time could be a biased measure of HPV infection for epidemiological studies. Also, it is not known whether HPV infection may at times be present but undetectable among women with no cervical lesions, or whether hormonal contraceptive use affects HPV detection.

Cervical screening is an important potential confounding factor in studies of cervical cancer risk and hormonal contraceptives. Women using hormonal contraceptives are more likely to be screened, and in screened women cervical lesions are more likely to be detected at a pre-invasive stage. As far as can be ascertained from the published data, the results relating to duration of oral contraceptive use do not appear to be substantially confounded by cervical screening; the risks for cervical cancer for those studies which had adjusted for screening were similar to the risks for all studies, and the risks in developing countries, in which many women were not screened, did not differ from those in developed countries. Similarly there was no evidence for substantial confounding by women's previous sexual partners, smoking or the use of barrier methods of contraception (figure 6). However, none of the studies adjusted for all of these factors simultaneously and it would be necessary to analyse individual subject data from these studies, with and without adjustment for each factor in turn, to investigate fully the role of these potential confounding factors.

The question of the persistence of any effects of oral contraceptives on the risk of cervical cancer is critical when considering the absolute risk of disease among ever-users and hence the public health implications of these findings. Although the limited published data suggest that the relative risk of cervical cancer associated with oral contraceptive use might decline after cessation of use, this systematic review is severely hampered by the lack of published data cross-classifying women by duration of use and time since last use (figures 2 and 3). A collaborative re-analysis of individual data from all relevant studies, defining variables in a similar way across studies, should provide much needed reliable information on the effects of duration of use within categories of time since last use.

Contributors

S Franceschi and V Beral initiated the study, which was commissioned by WHO for a meeting on Hormonal Contraceptives, HPV, and Cervical Cancer held in Geneva on March 11, 2002. All authors contributed to data analyses and to writing of the paper.

Conflict of interest statement

None declared.

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