REVIEW ARTICLE

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Oral Contraceptives and Cancer
An Update

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Abstract

Most up-to-date information on oral contraceptives (OCs) and breast cancer risk comes from a collaborative re-analysis of individual data on 53 297 cases and 100 239 controls. It is now established that there is a moderately increased breast cancer risk among current OC users, which tends to level off in the few years after stopping use. With regard to cervical cancer, OC use has been found to be associated with increased risk in human papilloma virus–positive women. With reference to the well known protective effects of OCs against endometrial carcinogenesis, additional information has suggested a consistent protection across types of OCs used. Further data on ovarian cancer confirm that the protection of OCs is long lasting, and may well be observed 15 to 20 years after stopping use. Several studies have suggested an inverse relationship between use of OCs and risk of colorectal cancer, and in a meta-analysis of published data the pooled relative risk of colorectal cancer for OC ever-use was 0.82 (95% confidence interval 0.74 to 0.97). There was no association with duration of use. The increased risk for hepatocellular carcinoma in the absence of hepatitis B viruses is the only established evidence of a direct association between OC use and cancer risk, which led an International Agency for Research on Cancer Working Group to classify OCs as carcinogenic to humans in 1998.

Between 1995 and 2000, several epidemiological studies were published on oral contraceptives (OCs) and cancer, which have led to a better understanding and quantification of the relationship between OC use and cancer risk at various sites. Published data include a collaborative re-analysis of epidemiological studies on OCs and breast cancer based on more than 53 000 women,[1] and a number of studies which have clarified the possible interaction between OCs and human papilloma virus (HPV) on cervical carcinogenesis.[2-6]

A new and open issue concerns the potential protective effect of combined OCs on colorectal cancer.[7,8] A few studies have confirmed the inverse relationship between OC use and ovarian[9-13] and endometrial cancer,[1,14,15] and a number of studies on other sites have been published, such as the liver[16] and thyroid,[17] showing no consistent excess risk.

Published data on OCs and cancer were reviewed in June 1998 by an International Agency for Research on Cancer (IARC) Working Group, as summarised in the IARC Monograph 72.[18] The group concluded that 'there is significant evidence for the carcinogenicity of combined oral contraceptives', based on an increased risk for hepatocellular carcinoma in the absence of hepatitis B viruses.

This paper reviews data published between 1995 and 2000 on OC use and cancer risk, thus updating our review paper published in 1996.[19]

1. Breast Cancer

Most information on the relationship between breast cancer and OC use derives from the collaborative re-analysis of individual data on 53 297 women with breast cancer and 100 239 controls from 54 epidemiological studies.[20] This re-analysis provides strong evidence that current users of combined OCs and women having stopped use no more than 10 years previously have a small increase in the relative risk (RR) of breast cancer, the estimate being 1.24 [95% confidence interval (CI) 1.15 to 1.33]. However, 10 or more years after stopping use the risk levels off to approach that of OC never-users. The results were similar in women with different background risks of breast cancer, including those with different reproductive histories and those with or without a family history of the disease. Only women who had begun use before the of age 20 years had a persistent, moderately higher risk (RR = 1.22, 95% CI 1.13 to 1.32) of breast cancer, based on 2719 cases. Other features of OC use, such as duration of use, and dose and type of hormone formulation, had little effect on breast cancer risk. The lack of a duration-of-use effect among recent users may suggest some influence of surveillance bias on the risk estimate. Up to 20 years after cessation of use, breast cancer diagnosed in OC ever-users was clinically less advanced. It is not possible to infer from these data, however, whether this could be attributable to an earlier diagnosis, to the biological effect of OCs, or to a combination of reasons.

A few additional cohort[1,21] and several case-control studies of OCs and breast cancer[22-29] have been published after 1995. A summary of their main results is shown in table I.

In the Royal College of General Practitioners oral contraception study cohort of 46 000 women, no relevant association was found between breast cancer mortality and several measures of OC use.[1] Another cohort study of 426 families of breast cancer probands in Minnesota, USA,[21] suggested that ever-users of earlier formulations of OCs with a first degree relative with breast cancer were at high risk for the disease (RR = 3.3, 95% CI 1.6 to 6.7). However, the risk was not elevated among granddaughters and nieces of the probands using OCs (RR = 1.2, 95% CI 0.8 to 1.9). This study[21] was based on 38 case users only, and contrasted with findings of the collaborative re-analysis,[20] which showed no excess risk in users with a family history of breast cancer, based on 2044 cases with a family history of breast cancer.

In general, the results of case-control studies confirmed the conclusion that breast cancer risk is not increased substantially among women who have ever used OCs; however, a moderately increased risk is observed among subgroups of recent users. Of particular relevance on a public health level is the absence of a persistent risk in the medium or

Table I. Selected cohort and case-control studies on oral contraceptives (OCs) and breast cancer, 1996-2000

Reference (country of study)	Type of study	No. of cases/controls	Relative risk (95% CI) in everusers	Comments and observations
Collaborative Group[20]	Re-analysis	53 297/100 239	1.24 (1.15 to 1.33) for current use 1.01 (0.96 to 1.05) for >10 years since use	Re-analysis from 54 epidemiological studies. Similar results in women with different background risks. Moderately increased risk in current users who were aged ≤20 years at first use
Lipworth et al.[22] (Greece)	Case-control, hospital-based	820/795 orthopaedic patients, 753 healthy visitors	1.1 (0.6 to 2.0) for women aged ≤45 years 1.6 (0.8 to 3.3) for women aged ≤45 years	No association with duration or timing of use in relation to first full-term pregnancy
Newcomb et al.[24] (USA)	Case-control, population-based	6751/9311 (aged <75 years)	1.1 (1.0 to 1.2)	No association with duration of use, age at first use or time since last use. Use prior to first pregnancy or among nulliparous women was not related to risk. The RR was 2.0 (95% CI 1.1 to 3.9) among recent users aged 35 to 45 years at diagnosis
Levi et al.[23] (Switzerland)	Case-control, population-based	230/507 (aged <70 years)	1.5 (1.0 to 2.3)	Vaud Cancer Registry. No association with age at first use, time since first and last use, or use in relation to first birth. Increased risk for ≥10-years' use (RR 2.4, 95% CI 1.4 to 4.2) in current users. Risk was related to duration of use for up to 14 years after stopping use
Tryggvadóttir et al.[25] (Iceland)	Case-control, nested in a cohort	123/711 (birthdate 1945 to 1950) 81/472 (birthdate 1951 to 1967)	1.1 (0.8 to 1.6)	The duration-risk association was present only in the group born after 1950 with RRs of 0.9, 1.7 and 3.0 for ≤4 years, >4 to 8 years, and >8 years of use, respectively
Ursin et al.[27] (USA)	Case-control, population-based	597/966 (aged 20 to 55 years)	0.9 (0.7 to 1.2)	No association with duration of use, age at first use, use before first full-term birth and time since last use. Similar results in women aged ≤45 years
Magnusson et al.[26] (Sweden)	Case-control, population based	3016/3263 (aged 50 to 74 years)	1.0 (0.9 to 1.1)	No association with duration of use or time since last use
Beral et al.[1] (UK)	Cohort	259	1.1 (0.8 to 1.4)	23 000 OC users and 23 000 non-users, Royal College of General Practitioners oral contraception study, 25-year follow-up. No association for ever-users with risk of death, time since first or last use, or duration of use
Grabrick et al.[21] (USA)	Cohort	38 sisters and daughters of the probands	3.3 (1.6 to 6.7)	6150 women from the Tumor Clinic of the University of Minnesota Hospital
		115 grand-daughters and nieces	1.2 (0.8 to 2.0)	
		86 marry-ins	1.2 (0.8 to 1.9)	
Shapiro et al.[29] (South Africa)	Case-control, hospital-based	484/1625 (aged 20 to 54 years)	1.2 (1.0 to 1.5)	No consistent association across strata of age, recency of use or duration of use
Van Hoften et al.[28] (The Netherlands)	Case-control, population-based, nested in a cohort	309/610 (aged 42 to 63 years)	1.3 (1.0 to 1.8)	DOM3 cohort of 12 184 women. No difference between women aged ≤55 years and >55 years, except the RR was 2.1 in women >55 years using OCs for >10 years. No association with duration of use, time since last use, or age at first and last use

CI = confidence interval; **DOM3** = Doorlopend Onderzoek Morbiditeit/Mortaliteit 3; **OR** = odds ratio; **RR** = relative risk.

long term after cessation of OC use, independent of duration of use. In terms of risk assessment for OC use and indications for prescription, these data indicate that the increase in risk during and in the short term after OC use is not relevant for younger women whose baseline incidence of the disease is extremely low.[20]

2. Cervical Cancer

HPV is the recognised main cause of cervical neoplasia.[30,31] Polymerase chain reaction–based tests were able to detect HPV DNA in 99.7% of cervical cancer specimens from 22 countries worldwide.[31] Such strong evidence that HPV is the main cause of cervical cancer influences the study of potential co-factors. Analysis of the OC–cervical cancer relationship was therefore restricted to carriers of HPV DNA.[32]

Five studies and a pooled analysis based on this approach have been published since 1996 (table II). The RR of cervical cancer (mostly squamous-cell carcinoma) was significantly elevated among long term OC users in a study from Morocco[2] and in a pooled analysis of 8 studies,[3] which included case-control studies previously reviewed[19] and 3 studies reported in table II.[2,33,34] In the pooled analysis,[3] an elevated risk for long term users of OCs was observed (pooled RR = 4.5, 95% CI 2.2 to 9.4).

Lacey et al.[4] found no significant associations between OC use and invasive or *in situ* squamous-cell cervical carcinomas. In their study, however, an association emerged between long term use and *in situ* adenocarcinoma of the cervix (RR = 6.2, 95% CI 0.7 to 52.7). A significant duration-risk relationship between OC use and adenocarcinoma was also found in a case-control study coordinated by the WHO in 10 participating hospitals from 8 countries. Among 377 cases of adeno- or adenosquamous carcinomas and 2887 controls, the RR for 8 or more years' use of OCs was 2.2 (95% CI 1.4 to 3.5).[5]

An Italian case-control study based on 592 cases and 616 hospital-based controls provided data on recency of use and invasive cervical cancer. The multivariate RR for ever- versus never-use was 1.21 (95% CI 0.82 to 1.74). The risk of invasive cervical cancer was above unity in current users (RR = 1.23) and in women who had stopped use less than 10 years before diagnosis, but not in those who had stopped their OC use 10 or more years before (RR = 0.85).[6] Most risk estimates were adjusted for available indicators of socioeconomic status or sexual behaviour.

Confounding by HPV status or indicators of sexual habits or hygiene remain nonetheless an open issue. However, recent data restricted to HPV-positive women indicate that long term OC use may increase the risk of invasive or *in situ* carcinoma of the cervix in women who are long term carriers of HPV.[3] Such an association may be stronger for adeno- than for squamous-cell carcinoma. Indeed, recent upward trends for adenocarcinoma of the cervix in several developed countries[36] may indirectly support this possibility. Overall, the limitations of available data and difficulties in dealing with the predominant effect of HPV leave the issue of cervical neoplasia and OC use still open.

3. Endometrial Cancer

There is substantial evidence that ever-use of OCs reduces the risk of endometrial cancer by approximately 50%,[18,19,37] but the limited number of elderly women who have used OCs does not allow a definite estimate of the protection afforded after long periods after stopping use and/or according to duration of exposure. The reduction in risk is generally directly related to duration of use, and persists for at least 15 to 20 years after cessation of use.

In the Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development (CASH),[38] the RR of endometrial cancer was 0.5 (95% CI 0.3 to 0.8) for 10 to 14 years after stopping OCs, in the WHO study[5] the RR was 0.2 (95% CI 0.0 to 0.8) for high progestogen content pills for 10 or more years after stopping, and in a multicentre US study the RR was 0.3 (95% CI 0.1 to 1.4) for 15 to 19 years and 0.8 (95% CI 0.3 to 2.0) for 20 or more years after stopping OC use.[18,38] When

Table II. Case-control studies on oral contraceptives and cervical carcinoma, in women with human papillomavirus (HPV) DNA on cervical smear

Reference (country of study)	Duration of OC use	No. of HPV-positive women		RR (95% CI)
		cases	controls	
Chaouki et al.[2]	Years of use:			
(Morocco)	≤1	20	7	1
	2 to 4	21	6	1.0 (0.2 to 6.6)
	≥5	37	3	1.6 (2.2 to 115)
Ngelangel et al.[33]	Years of use:			
(Philippines)	None	NR	NR	1
	1 to 3	NR	NR	0.3 (0.1 to 0.8)
	≥4	NR	NR	2.8 (0.2 to 3.0)
	Total	**303**	**35**	
Chichareon et al.[34]	Years of use:			
(Thailand)	None	NR	NR	1
	1 to 3	NR	NR	0.4 (0.1 to 3.2)
	≥4	NR	NR	2.2 (0.2 to 22.5)
	Total	**322**	**41**	
Lacey et al.[4]	Years of use:			
(USA)	None	21	11	1
	<2	20	9	1.1 (0.3 to 4.2)
	2 to 6	21	12	1.9 (0.4 to 8.4)
	>6	26	16	0.9 (0.2 to 3.7)
Deacon et al.[a][35]	Months of use:			
(UK)	None	32	35	1
	1 to 47	42	38	1.19 (0.58 to 2.43)
	48 to 95	43	56	0.76 (0.38 to 1.53)
	≥96	82	52	1.52 (0.80 to 2.88)
Moreno et al.[3]	Years of use:			
(8 studies)	None	NR	NR	1
	1 to 4	NR	NR	0.77 (0.46 to 1.29)
	5 to 9	NR	NR	2.72 (1.36 to 5.46)
	≥10	NR	NR	4.48 (2.24 to 9.36)
	Total	**1768**	**262**	

a High-grade intraepithelial neoplasia (CIN3).

CI = confidence intervals; **NR** = not reported; **RR** = relative risk.

the duration and recency of use were evaluated jointly in a case-control study from Washington State, USA[39] longer use (>5 years) was associated with a reduced risk, irrespective of recency. In a Swiss study,[40] the RR was 0.4 (95% CI 0.2 to 1.0) for 10 to 19 years after stopping use, and 0.8 (95% CI 0.3 to 2.2) for ≥20 years.

In the 25-year follow-up of the Royal College of General Practitioners study, uterine corpus cancer was diagnosed in 2 of the OC users and 16 of the non-users, corresponding to a RR of 0.2 (95% CI 0.0 to 0.7).[1]

A population-based case-control study from Sweden, involving 709 cases, found a multivariate RR for endometrial cancer of 0.7 (95% CI 0.5 to 0.9) for ever-use of any kind of OC preparation. The protection increased with duration of use (RR = 0.2 for 10 years or more), but was negligible 30 years after stopping use.[14] A Danish population-based case-control study indicated that use of OCs

for 1 to 5 years decreased the risk of endometrial cancer (RR = 0.2, 95% CI 0.1 to 0.3).[41] A case-control study of 232 cases among women in western New York, USA, reported a RR of 0.6 (95% CI 0.4 to 1.1) for OC ever-users.[15]

Further and more precise quantification of the possible long term impact of OCs on endometrial carcinogenesis remains a major issue for any definite risk/benefit and public health evaluation of contraceptive pills.[37]

4. Ovarian Cancer

In most developed countries, there have been substantial declines in ovarian cancer incidence and mortality in young women over the last few years, partly or largely attributable to the protection afforded by OCs.[42-45] Cohort analyses based on data from Switzerland,[46] Britain,[47] Sweden,[48] England and Wales[49] and The Netherlands,[50] as well as a systematic analysis of mortality trends in 16 major European countries[43,44,51] and in the US,[52] showed that women born from 1920 onwards, i.e. from the generations who have used OCs, have consistently reduced ovarian cancer rates. The downward trends tended to be larger in countries where OCs have been more widely utilised.[44]

Four cohort studies of OCs conducted in the US and Britain provided data on the relationship between OC use and epithelial ovarian cancer (table III). These included the US Walnut Creek Study,[53] based on a total of 16 cases of ovarian cancer, which found an age-adjusted RR for OC ever-use of 0.4.

In the Royal College of General Practitioners study of 46 000 women recruited in 1968,[1,56] 30 cases of ovarian cancer were observed up to 1987. This corresponds to a multivariate RR of 0.6 (95% CI 0.3 to 1.4) for OC ever-users, and of 0.3 for 10 or more years of use. At the 25-year follow-up for mortality,[1] 55 deaths from ovarian cancer were observed, corresponding to a RR of 0.6 for ever-use and of 0.2 for long term use. The protection persisted for 20 or more years after stopping use.

The Oxford Family Planning Association study was based on 17 032 women enrolled between 1968 and 1976 from various family planning clinics in the UK.[54] Up to October 1993, 42 cases of ovarian cancer were registered, corresponding to a RR of 0.4 (95% CI 0.2 to 0.8) for OC ever-use and of 0.3 (95% CI 0.1 to 0.7) for more than 8 years of use.

In the Nurses Health study, based on 121 700 registered nurses aged 30 to 55 years in 1976, 260 cases of ovarian cancer were prospectively observed between 1976 and 1988.[55] The multivariate RR for ever-use, which essentially reflected former use, was 1.1 (95% CI 0.83 to 1.43), but declined to 0.6 (95% CI 0.32 to 1.07) for use of 5 or more years. None of these estimates, however, was statistically significant.

Thus, the overall RR of ovarian cancer from cohort studies is around 0.6 for ever-use and 0.4 for long term use, on the basis of approximately 400 ovarian cancer cases (table III).

At least 25 out of 26 case-control studies published between 1980 and 2000 found RR below unity, the sole apparent outlier being a study conducted in China.[66] Table IV gives their main results. The studies published in or after 1995 are summarised below.

Table III. Selected cohort studies on oral contraceptives and ovarian cancer, 1980-2000

Reference (country of study)	No. of cases [age (years)]	Relative risk		Comments
		ever-use	longest duration of use	
Ramcharan et al.[53] (USA)	16 (18 to 54)	0.4		The Walnut Creek Study on Contraception
Vessey and Painter[54] (UK)	42 (all ages)	0.4	0.3	Oxford Family Planning Association cohort
Hankinson et al.[55] (USA)	260 (30 to 65)	1.1	0.6	Nurses Health Study
Beral et al.[1] (UK)	55 (25 to 55)	0.6	0.2	Royal College of General Practitioners oral contraception cohort

Table IV. Selected case-control studies on oral contraceptives and ovarian cancer, 1980-2000

References (country of study)	Type of study	No. of cases [age (years)]	Relative risk	
			ever-use	longest duration of use
Willett et al.[57] (USA)	Nested in a cohort	47 (<55)	0.8	0.8
Hildreth et al.[58] (USA)	Hospital-based	62 (65 to 74)	0.5	0.3
Weiss et al.[59] (USA)	Population-based	112 (36 to 55)	0.6	0.4
Cramer et al.[60] (USA)	Population-based	144 (<60)	0.4	0.6
Rosenberg et al.[61] (USA)	Hospital-based	136 (<60)	0.6	0.3
Risch et al.[62] (USA)	Population-based	284 (20 to 75)	0.5	NR
Tzonou et al.[63] (Greece)	Hospital-based	150 (34 to 64)	0.4	NR
CASH[38] (USA)	Population-based	492 (20 to 54)	0.6	0.2
Harlow et al.[64] (USA)	Population-based	92 (20 to 59)	0.4	0.4
Wu et al.[65] (USA)	Hospital-based	299 (18 to 85)	0.7	0.4
Shu et al.[66] (China)	Population-based	172 (18 to 79)	1.8	1.9
WHO[67] (7 countries)	Hospital-based	368 (<63)	0.8	0.5
Hartge et al[68] (USA)	Hospital-based	189 (20 to 79)	1.0	0.8
Booth et al.[69] (UK)	Hospital-based	213 (265)	0.5	0.1
Parazzini et al.[70] (Italy)	Hospital-based	505 (22 to 59)	0.7	0.5
Parazzini et al.[71] (Italy)	Hospital-based	91 (23 to 64)	0.3	0.2
Polychronopoulou et al.[72] (Greece)	Hospital-based	189 (<75)	0.8	NR
Rosenberg et al.[73] (USA)	Hospital-based	441 (<65)	0.8	0.5
Risch et al.[74,75] (Canada)	Population-based	450 (35 to 79)	0.9 for each year of use	0.3
Purdie et al.[76] (Australia)	Population-based	824 (18 to 79)	0.6	0.3
Narod et al.[12] (USA)		207 (<75)	0.4	0.3
Beard et al.[9] (USA)	Population-based	103	0.8	
Ness et al.[10] (USA)	Population-based	767 (<70)	0.6	0.3
Greggi et al.[11] (Italy)	Hospital-based	940 (≤80)	0.4	0.3
Chiaffarino et al.[13] (Italy)	Hospital-based	1031 (<80)	0.9	0.5
Overviews				
Franceschi et al.[77] (Greece, Italy, UK)	3 Hospital-based, case-control studies	971 (<65y)	0.6	0.4
Whittemore et al.[78] (USA)	12 US population- and hospital-based, case-control studies	2197 (all ages)	0.7	0.3
Harris et al.[80] (USA)	12 US population- and hospital-based, case-control studies	327	0.8	0.6
John et al.[79] (USA)	7 US population- and hospital-based, case-control studies	110	0.7	0.6

CASH = Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development.

Risch et al.[74,75] provided data on 450 cases of epithelial ovarian cancer in patients aged 35 to 79 years diagnosed between 1989 and 1992 in Ontario, Canada, and 564 controls. The overall multivariate RR per year of pill use was 0.90 (95% CI 0.86 to 0.94), and the protection was stronger for serous and endometrioid than for mucinous neoplasms.

In a population-based study conducted in 3 Australian states of 824 cases diagnosed between 1990 and 1993 and 860 controls, Purdie et al.[76] found

a RR of approximately 0.6 for ever-use, which declined to 0.26 (95% CI 0.18 to 0.38) for 10 or more years of use.

The RR for OC ever-use was 0.8 (not statistically significant) in a study of 103 cases from Olmsted County, Minnesota, USA.[9]

A study conducted in Delaware Valley, USA, between 1994 and 1998 involving 767 cases and 1367 controls below the age of 70 years, found a RR of 0.6 for ever-use and 0.3 for 10 or more years' use. The protection was similar for use of low estrogen/low progestogen pills and high estrogen/high progestogen pills.[10]

A North American and European study of 207 women with hereditary ovarian cancer (179 with BRCA1 and 28 with BRCA2 mutations) and 161 sister controls found a RR of 0.4 for OC ever-use. The risk decreased with increasing duration of use, to reach 0.3 for 6 or more years.[12]

Two hospital-based case-control studies on ovarian cancer were conducted in Italy in the 1990s. One of these[11] was conducted in the Rome area and included 440 cases and 868 controls. The multivariate RR for OC ever-use was 0.4 (95% CI 0.3 to 0.6), and for long term use was 0.3. The second study was a multicentre study, conducted in 4 areas of northern, central and southern Italy, and included 1031 cases and 2441 controls below the age of 80 years. The multivariate RR was 0.9 (95% CI 0.7 to 1.2) for ever-use and 0.5 (95% CI 0.3 to 0.9) for 5 or more years of use.[13]

The findings of 2 collaborative re-analyses of case-control studies on the issue of ovarian cancer risk and OC use are also included in table IV. The studies involved 971 cases and 2258 controls from 3 European countries,[77] and 2197 cases and 8893 controls amongst White women from 12 US studies.[78]

In the European meta-analysis[77] the multivariate RR was 0.6 (95% CI O.4 to 0.8) for ever-use, and 0.4 (95% CI 0.2 to 0.7) for longest use. In the American meta-analysis[78] the RRs were 0.7 (95% CI 0.5 to 0.6) for ever-use and 0.3 (95% CI 0.2 to 0.4) for more than 6 years' use. The results of the American meta-analysis were similar when hospital-based and population-based studies were considered separately. The RRs were 0.7 for both types of studies for OC ever-use, 0.6 for hospital-based and 0.3 for population-based for longest use (>6 years).

An inverse association was also observed in an analysis of Black women from 7 US studies involving 110 cases and 251 controls (RR = 0.7 for ever-use and 0.6 for 6 or more years' use).[79]

The 12-study US meta-analysis included data on 327 borderline malignancy epithelial ovarian neoplasms in White women. The RR of this condition was 0.8 (95% CI 0.6 to 1.1) for OC ever-use, and 0.6 (95% CI 0.4 to 0.9) for more than 5 years of use.[80]

The overall estimate of protection against ovarian cancer for OC ever-use is therefore approximately 40%, and a steady inverse relationship is observed with duration of use. The protection was over 50%, and probably around 60%, for long term use (i.e. over 5 years), and was observed for various types of combined OCs.

The inverse relationship between OCs and ovarian cancer was observed also after allowance for parity in most studies, and was consistently reproduced in several studies across separate strata of parity, as well as of age and of other potential covariates, including marital status, education, menopausal status, other types of contraceptive use, and other selected menstrual and reproductive factors. In particular, the protection was also observed in women with hereditary ovarian cancer.[12] Potential or indication biases, including selective exclusion of OC use in smokers and in women at risk of liver and thromboembolic diseases,[81] were also unlikely to materially modify the inverse association between OC use and ovarian cancer risk.

At least 2 studies,[64,71] and the meta-analysis of 12 US studies,[80] considered borderline epithelial ovarian tumours as well as confirmed ovarian cancer. An inverse relationship was also evident for these neoplasms, suggesting that OCs exert a protection on the whole spectrum of epithelial ovarian carcinogenesis. Likewise, the limited information available on different histological types of epithe-

lial invasive ovarian cancer does not indicate any histotype-specific effect.[18]

With reference to non-epithelial ovarian cancers, 38 germ cell neoplasms and 45 sex-cord-stromal neoplasms were considered from the collaborative re-analysis of 12 US case-control studies.[82] The multivariate RR among OC ever-users was 2.0 (95% CI 0.8 to 5.1) for germ cell cancers and 0.4 (95% CI 0.2 to 0.8) for sex-cord-stromal neoplasms. The few available data also indicate a consistent protection of OCs on benign epithelial tumours, i.e. ovarian cysts,[83,84] but not on benign ovarian teratomas.[85,86]

The favourable effect of OCs on epithelial ovarian cancer seems to persist for at least 15 to 20 years after OC use has ceased,[38,61,67-78] and is not confined to any particular type of OC formulation.[61,87]

From a biological viewpoint, the beneficial effect of OCs on ovarian cancer risk has been interpreted within the framework of the incessant ovulation theory, i.e. the multistage theory of ovarian carcinogenesis. Ovariostasis, induced by OCs as well as by pregnancy and menopause, avoids the exposure of ovarian epithelium to recurrent trauma and contact with follicular fluid.[37] However, OC use has a disproportionately greater protective effect than could be attributed solely to ovulation suppression.[18,37] OCs may also protect against ovarian cancer by reducing insulin-like growth factor-1 (IGF-1) levels,[88] and/or exposure to pituitary gonadotropins, which stimulate the growth of cell lines derived from human ovarian carcinoma.[89] The lack of apparent protection by hormone replacement therapy,[37,78,90] 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 of OCs corresponds to the avoidance of substantial numbers of cases and deaths, and is therefore one of the major issues in any risk/benefit and public health evaluation on the pill.[19,91]

5. Colorectal Cancer

A role of reproductive and hormonal factors on colorectal carcinogenesis has long been suggested, starting from the observation of an excess of colorectal cancer incidence in nuns.[92] A protective role for hormone replacement therapy has also been suggested.[93]

Several studies have provided information on use of combined OCs and the risk of colorectal cancer. The IARC monograph[18] reviewed 4 cohort studies, 3 of which showed RRs for OC ever-use below unity (statistically significant in 1), and 11 case-control studies, 9 of which showed RRs below unity (statistically significant in 2).

A meta-analysis considered epidemiological studies of colorectal cancer containing quantitative information on OC use, published as full papers in English up to June 2000.[94] The pooled RR of colorectal cancer for OC ever-use from the 8 case-control studies was 0.81 (95% CI 0.69 to 0.94), and the pooled estimate from the 4 cohort studies was 0.84 (95% CI 0.7 to 0.97) (tables V and VI). The pooled estimate from all studies combined was 0.82 (95% CI 0.74 to 0.92), in the absence of heterogeneity. Duration of use was not associated with a decrease in risk, since the overall RR of colorectal cancer was 0.78 for short duration and 0.85 for long duration of use. The pattern of risk was similar for colon and rectal cancer. Only 2 studies [1,7] included information on recency of use, and there was some indication that the apparent protection was stronger for women who had used OCs more recently (RR = 0.46, 95% CI 0.30 to 0.71). No information was available on type of OC, but no heterogeneity or systematic pattern of trends across calendar years was observed.

Female hormones may confer a protection against colorectal cancer as a result of changes in bile synthesis and secretion, which lead to reduced concentration of bile acids in the colon.[105] However, other biological mechanisms may be involved. Estrogens inhibit the growth of colon cancer cells *in vitro*,[106] and estrogen receptors have been identified in normal and neoplastic colon epithelial cells.[107] The estrogen receptor gene might

play a tumour suppressor role, since hypermethylation of the promoter region of the estrogen receptor gene results in reduced expression and deregulated growth in colonic mucosa.[108] Estrogens may reduce serum IGF-1,[109] a mitogen that may play an important role in the pathophysiology of colorectal cancer and has been linked to increased risk of colorectal cancer.[110,111]

Available data therefore suggest that OC use is inversely related to the risk of colorectal cancer. These results are in broad agreement with biological hypotheses of colorectal carcinogenesis,[105,112] with the epidemiological observations of an inverse relationship between hormone replacement therapy and colorectal cancer risk,[93] and with the descriptive epidemiology of colorectal cancer, which shows larger decreases in colorectal cancer mortality for females than for males[8] over the last few decades.

Given the widespread use of OCs, a better understanding of any potential relationship between OC use and colorectal cancer may help informed choice of contraception. Some aspects, however, remain undefined, including the risk profile with duration and recency of use and more adequate allowance for confounding, thus leaving the issue of causal inference for the observed association open to discussion.

6. Liver Cancer

Several epidemiological studies published up to 1996 had indicated an association between OC use and primary liver cancer, mainly for long term users of OCs in populations with low prevalences of hepatitis B and C viral infections and chronic liver disease, the major causes of liver cancer.[18,19] In the studies conducted in populations with a high prevalence of these diseases, there was little evidence of an increased risk associated with use of OCs.[18,19]

Analyses published after 1995 include the Multicentre International Liver Study,[16] based on 293 cases, 148 of whom reported OC use. The RR for OC ever-use was 0.8 (95% CI 0.5 to 1.0), and those for duration of use were 0.8 (0.5 to 1.3) for 1 to 2 years, 0.6 (0.3 to 1.1) for 3 to 5 years, and 0.8 (95% CI 0.5 to 1.1) for 6 or more years. When the analysis was restricted to the 51 cases without liver cirrhosis or evidence of infection with hepatitis viruses, however, the RR was 1.3 (95% CI 0.4 to 4.0) for use of any OC for 1 to 2 years, 1.8 (0.5 to 6.0) for 3 to 5 years, and 2.8 (1.3 to 6.3) for 6 or more years. Thus, this study[16] confirmed the positive duration-risk association only in women without liver cirrhosis or evidence of infection with hepatitis viruses.[18]

The association between OCs and risk of primary hepatocellular carcinoma has led the IARC Working Group to the overall evaluation: 'There is sufficient evidence in humans for carcinogenicity of OCs. This classification is based on an increased risk for hepatocellular liver carcinoma in the absence of hepatitis viruses observed in studies of predominantly high dose preparations'.[18]

7. Conclusions

The main established evidence on the association between OCs and cancer is as follows:

Table V. Case-control studies on oral contraceptives and colorectal cancer

References (country of study)	No. of cases/controls		Odds ratio
	ever-users	never-users	
Weiss et al.[95] (US)	47/164	96/543	1.68
Potter and McMichael[96] (Australia)	18/55	137/256	0.63
Furner et al.[97] (US)	9/32	80/175	0.64
Kune et al.[98] (Australia)	47/39	143/161	1.36
Wu-Williams et al.[99] (China)	18/74	188/544	0.72
Wu-Williams et al.[99] (North America)	26/79	163/415	0.84
Fernandez et al.[100] (Italy)	30/92	679/900	0.47
Talamini et al.[101] (Italy)	56/225	451/1323	0.74
Total	**251/760**	**1937/4317**	**0.81**

Table VI. Cohort studies on oral contraceptives and colorectal cancer

Reference	No. of cases		Odds ratio
	ever-users	never-users	
Martinez et al.[102]	156	335	0.84
Troisi et al.[103]	57	273	1.00
Beral et al.[1]	29	39	0.60
van Wayenburg et al.[104]	NR	95	0.68
Total	**252**	**742**	**0.84**

NR = not reported.

- OC use decreases the risk of ovarian cancer, the estimated protection being approximately 40% in ever-users and increasing with duration of use. The protection persists for at least 15 years after OC use has ceased.
- OCs lower the risk of endometrial cancer and the protection seems to persist in the long term, although its quantification remains open to discussion. A possible reduced risk of colorectal cancer among OC users has been suggested, but this issue is also still open to discussion.
- OC use is related to increased risk of liver and cervical cancer, but the public health importance of these associations is moderate in developed countries.
- There is a moderately increased risk among current, but not former OC users, for breast cancer.
- Several issues remain open for any quantitative risk-benefit evaluation of use of various types of OCs. OCs have been used for 40 years, and the formulations have been modified repeatedly. It is difficult to propose further modifications which may appear favourable towards the risk of selected diseases (i.e. increasing progestogen potency to reduce ovarian cancer) without increasing the risk of other adverse effects.[113]

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