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Oral contraceptives and colorectal cancer risk: a systematic review and meta-analysis

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BACKGROUND: Various studies have reported an inverse relation between oral contraceptive (OC) use and the risk of colorectal cancer, but the issue is still open.

METHODS: In order to quantify the association between OC use and colorectal cancer risk, we performed a systematic review and meta-analysis of studies on this issue. We identified all relevant studies published, in English, as original articles up to December 2008 through a search of the literature using PubMed and EMBASE, and by reviewing the references from the retrieved articles.

RESULTS: The summary relative risk of colorectal cancer for ever versus never OC use was 0.82 (95% confidence interval, CI, 0.69–0.97) from 11 case–control studies, 0.81 (95% CI, 0.75–0.89) from seven cohort studies, and 0.81 (95% CI, 0.72–0.92) from all studies combined. The results were similar for colon and rectal cancer. No difference was evident according to duration of OC use both for colon and rectal cancer, although there is an indication that the protection is stronger for more recent use (OR = 0.70, 95% CI, 0.53–0.90, on the basis of four studies).

CONCLUSION: Epidemiological data consistently indicate that OC users have a reduced risk of colorectal cancer, and that the protection is greater for recent use in the absence, however, of a duration–risk relation.

Key words: colorectal cancer / epidemiology / meta-analysis / oral contraceptives / risk

Introduction

A role of reproductive factors on colorectal carcinogenesis has long been suggested, starting from the observation of an excess colorectal cancer in nuns (Fraumeni *et al*., 1969), and of an inverse relation between parity and colorectal cancer in several studies (La Vecchia and Franceschi, 1991). Epidemiological, metabolic and animal data also indicated that endogenous and exogenous hormones could affect colorectal cancer risk (McMichael and Potter, 1980), With reference to oral contraceptives (OCs), in a meta-analysis of epidemiological studies published up to June 2000, the pooled relative risk (RR) of colorectal cancer for ever OC use was 0.81 from eight case–control studies, 0.84 from four cohort studies and 0.82 (95% confidence interval, CI, 0.74–0.92) from all studies combined (Fernandez *et al*., 2001). However, no relation with duration of use was observed. The pattern of risk was similar for colon and rectal cancer.

Among more recent investigations, a Swiss case–control study on 131 women with colorectal cancer and 373 hospital controls reported an odds ratio (OR) of 0.8 for ever OC use (Levi *et al*., 2003), in the absence of consistent relation with duration and time since first or last

OC use. In a case–control study from Wisconsin, USA, including 1122 cases of colon cancer, 366 of rectal cancer and 4297 population controls, the overall OR for ever use was 0.89, with no difference between colon (OR = 0.87) and rectal (OR = 0.87) cancer (Nichols *et al.*, 2005). No pattern in risk was seen according to duration of use, although the risk reduction was stronger for more recent use for rectal, but not colon, cancer. A case–control study from Canada on 1404 colorectal cancer cases and 1203 population controls found a significant reduced risk for ever use of OC (OR = 0.77), with no evidence, however, of a relation with duration of use (Campbell *et al.*, 2007). The Oxford Family Planning Association cohort study including 17 032 women and 46 cases of colorectal cancer reported no association with OC use (Vessey *et al.*, 2003). In a cohort study of 267 400 female textile workers in Shanghai, China, including 655 women with colon cancer, the RR was 1.09 for women who had ever used OC, in the absence of any trend in risk with duration of OC use (Rosenblatt *et al.*, 2004). In the 2003 follow-up of the Royal College of General Practitioners' OC Study (46 000 women, ~35 years follow-up) there were 323 cases of colorectal cancer, corresponding to a RR of 0.72 for ever OC users (Hannaford and Elliott, 2005). In a nested case–control study within that cohort there were 146 cases of colorectal cancer (Hannaford *et al.*, 2007). The OR was 0.84 for ever users, with greater reduction in risk for current (OR = 0.38) than for former (OR = 0.89) users. In the 11-year follow-up of the Women's Health Study, including 39 680 women and 267 cases of colorectal cancer, the RR for ever OC use was 0.67, with little evidence, however, of a duration–risk relation (Lin *et al.*, 2007). In a cohort study of Canadian women within a breast cancer screening program, including 89 835 women followed for an average of 16.4 years, there were 1142 incident colorectal cancers (Kabat *et al.*, 2008). The overall RR for ever OC use was 0.83, with no difference across colorectal subsites. There was no relation with duration of OC use.

The issue, however, is still open, and the IARC Monograph on combined estrogen–progestogen contraceptives concluded that there was evidence for a lack of carcinogenicity of OC on colorectal cancer (IARC, 2007).

In order to provide a quantification of the association between OC use and colorectal cancer risk, we performed a comprehensive review and meta-analysis including all data published up to December 2008.

Methods

Search strategy and selection criteria

In the present meta-analysis, we included all case–control and cohort studies published as original articles in English up to December 2008. They were identified through a search of the literature using PubMed and EMBASE with the keywords: ['oral contraceptives' OR 'exogenous hormones'] AND ['colorectal' OR 'colon' OR 'rectal' OR 'rectum'] AND ['cancer' OR 'neoplasm'] AND ['case–control study' OR 'cohort study']. We retrieved and assessed potentially relevant articles, and checked the reference lists of all papers of interest to identify additional relevant publications. Studies were considered only if they provided information on OC separately from hormone replacement therapy or other hormonal therapies. We did not assign quality scores to studies, and no study was excluded *a priori* for weakness of design or data quality. However, we performed sensitivity analyses, excluding studies which provided crude estimates or estimates adjusted for age and a few selected covariates only. Articles were reviewed and data were extracted and cross-checked independently by 2 investigators, and any disagreement was resolved by consensus among the 2. When multiple reports were published on the same population or subpopulation, we included in the meta-analysis only the most recent or informative one.

For each study, we abstracted information on study design, country, number of subjects (cases, controls or cohort size), length of follow-up (for cohort studies), prevalence of OC use, confounders allowed for in the analysis, RR estimates for ever OC use, and (when available) for duration and recency of use, and corresponding 95% CIs. The primary analysis concerned the risk for ever versus never OC users; whenever possible, we also abstracted information on duration and recency of OC use. In most studies, the primary outcome was colorectal cancer, but some included colon cancer only, and others provided colon and rectal cancer separately. These were also considered, whenever possible.

Statistical methods

The measure of interest was the RR (or the OR in case–control studies), giving preference to RR estimates adjusted for multiple confounding factors. When RRs were not available in published papers, we computed unadjusted RRs from the exposure distributions as given in the papers. We derived summary estimates of the RR using fixed effect models (i.e. as weighed averages using the inverse of the variance of the log (RR) as weight), and we assessed the heterogeneity between studies using the χ^2 test (Greenland, 1987). When significant heterogeneity (defined as a *P*-value for heterogeneity <0.10) was found, we used a random effect model (i.e. as weighed averages using the sum of the inverse of the variance of the log (RR) and the moment estimator of the variance between studies as weight) (DerSimonian and Laird, 1986). We also calculated summary estimates for case–control and cohort studies separately. Since duration and recency of use were not uniformly reported, we first defined for each study two categories of duration (short-term, approximately <5 years; long-term use, approximately ≥ 5 years) and of recency (shorter time since last use, approximately <10 years; longer time since last use, approximately ≥ 10 years); then we pooled the risk estimates for these categories. We also computed pooled RR estimates for <5 and ≥ 5 years of duration of OC use of use, and for <10 and ≥ 10 years since last OC use. Inadequate information was available on the type of OC used.

We provided forest plots, in which a square was plotted for each study, whose center projection on the underlying scale corresponds to the study-specific RR. The area of the square is proportional to the inverse of the variance of the natural logarithm of the RR, and gives thus a measure of the amount of statistical information available from that particular estimate. A diamond was used to plot the summary RRs, whose center represents the RR and its extremes show the 95% CIs.

Publication bias was evaluated using funnel plots and quantified by the Egger's test (Egger *et al.*, 1997; Thornton and Lee, 2000).

Results

From the initial literature search we identified and checked 57 abstracts; 18 articles were considered of interest and full-text were retrieved for detailed evaluation; references of these articles were reviewed and 11 additional relevant studies were identified; six of these articles were subsequently excluded from the meta-analysis (since they were based on the same study population), thus leaving

Table I Case–control on OCs and colorectal cancer

Reference	Country, study acronym	No. of cases			No. of controls	Source of information	Confounders
		Colorectum	Colon	Rectum			
Weiss *et al.* (1981)	Washington State, USA	143	—	—	707	Interview	Age
Potter and McMichael (1983)	Adelaide, Australia	155	99	56	311	Interview	Age[b]
Furner *et al.* (1989)	Chicago, USA	90	—	—	208	Medical records + interview + self-reported	—
Kune *et al.* (1990)	Melbourne, Australia	190	108	82	200	Interview	Age, parity, age at first birth
Peters *et al.* (1990)	Los Angeles, USA	—	327	—	327	Interview	Age[b], physical exercise, alcohol, fat, calcium, family history of cancer, parity
Wu-Williams *et al.* (1991)	North America and China	395	192	203	1112	Interview	—
Jacobs *et al.* (1994)	Seattle, USA	—	193	—	194	Interview	Age, vitamin intake
Kampman *et al.* (1994)	The Netherlands	—	102	—	123	Interview	Age[b], region[b], socioeconomic level, urbanization[b], energy intake, selected dietary habits, cholecistectomy, family history of cancer
Kampman *et al.* (1997)	USA, KPMC	—	894	—	1120	Interview	Age[b], physical exercise, body mass index, energy intake, aspirin, family history of cancer, hormone replacement therapy
Fernandez *et al.* (1996)	Italy	709	—	—	992	Interview	Age, residence, social class, family history of cancer, age at menarche, parity
Talamini *et al.* (1998)	Italy	507	—	—	2081	Interview	Age, centre, education, physical activity, energy intake
Fernandez *et al.* (1998)[a]	Italy	—	803	429	2793	Interview	Age, education, centre, body mass index, energy intake, family history of cancer, parity, age at menopause, hormone replacement therapy
Levi *et al.* (2003)	Switzerland	131	—	—	373	Interview	Age, education, physical activity, fiber, family history of cancer, parity
Nichols *et al.* (2005)	Wisconsin, USA	1488	1112	366	4297	Interview	Age, study, education, body mass index, smoking, alcohol, screening, family history of cancer, hormone replacement therapy, age at first birth
Campbell *et al.* (2007)	Canada	1404	—	—	1203	Self-reported	Age, residence, education, physical activity, body mass index, colorectal screening, post-menopausal hormones, menopausal status

KPMC: Kaiser Permanente Medical Care.
[a]Pooled data from Fernandez *et al.* (1996) and Talamini *et al.* (1998).
[b]Matching variables.

Table II Cohort studies on OCs and colorectal cancer

Reference	Country, study acronym	No. of cancers/deaths			Cohort size	Follow-up	Source of information	Confounders
		Colorectum	Colon	Rectum				
Martinez *et al.* (1997)	USA, NHS	501	396	105	89 448	12 years	Self-reported	Age, body mass index, physical exercise, smoking, alcohol, meat, aspirin, family history of cancer, menstrual factors
Bostick *et al.* (1994)	Iowa, USA, WHS	—	212	—	35 215	4 years	Self-reported	Age, height, energy intake, vitamin, parity
Troisi *et al.* (1997)	USA, BCDDP	330			57 529	10 years	Interview	Age
Van Wayenburg *et al.* (2000)	Netherlands	95[a]	—	—	10 671	18 years	Self-reported	Age, socioeconomic status, body mass index, smoking, age at first birth, type of menopause
Vessey *et al.* (2003)	UK, OPFA	46[a]	—	—	17 032	30 years	Interview	Age, social class, smoking, parity
Rosenblatt *et al.* (2004)	China	—	655	—	267 400	10 years	Interview	Age, parity
Hannaford and Elliot (2005)[b]	UK, RCGP OC	146	—	—	46 000	35 years	Medical records	Age, social class, smoking, parity, hormone replacement therapy
Hannaford *et al.* (2007)	UK, RCGP OC	323	—	—	46 000	35 years	Medical records	Age, social class, smoking, parity, hormone replacement therapy
Lin *et al.* (2007)	USA, WHI	267	205	55	39 680	11 years	Self-reported	Age, body mass index, physical activity, smoking, alcohol, meat, vitamin supplementation, family history of cancer, history of benign colorectal polyps, aspirin, treatment assignment, hormone replacement therapy
Kabat *et al.* (2008)	Canada, CNBSS	1142	790	366	89 835	16 years	Self-reported	Age, education, body mass index, smoking, menopausal status, hormone replacement therapy

BCDDP: Breast Cancer Detection Demostration Project; CNBSS: Canadian National Breast Screening Study; NHS: Nurses' Health Study; OPFA: Oxford Family Planning Association; OC: Oral contraceptives; RCGP: Royal College of General Practitioners; WHI: Women's Health Initiative; WHS: Women Health Study.

[a]Deaths.

[b]Nested case–control study within the RCGP OC cohort.

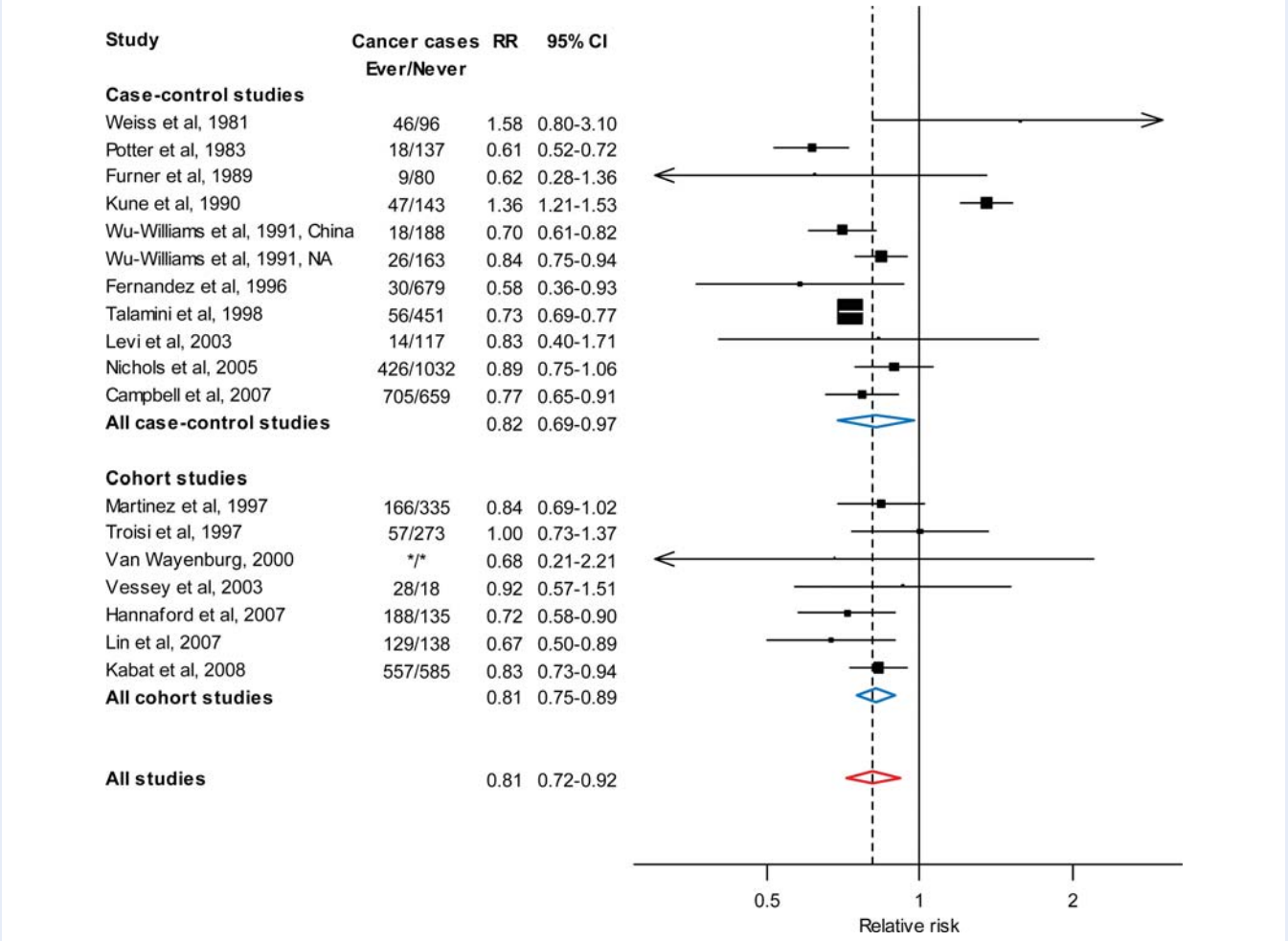

Figure 1 Summary RRs of colorectal cancer for ever versus never use of OCs from case–control and cohort studies.*Data not given. CI: confidence interval. NA: North America.

23 independent studies, 14 case–control and nine cohort studies (Appendix 1).

The main characteristic of the 14 case–control studies (Weiss *et al.*, 1981; Furner *et al.*, 1989; Kune *et al.*, 1990; Peters *et al.*, 1990; Franceschi *et al.*, 1991; Wu-Williams *et al.*, 1991; Jacobs *et al.*, 1994; Kampman *et al.*, 1994; Fernandez *et al.*, 1996, 1998; Kampman *et al.*, 1997; Talamini *et al.*, 1998; Levi *et al.*, 2003; Nichols *et al.*, 2005; Campbell *et al.*, 2007) included in the meta-analysis are given in Table I. Corresponding information for the nine cohort investigations (Bostick *et al.*, 1994; Martinez *et al.*, 1997; Troisi *et al.*, 1997; van Wayenburg *et al.*, 2000; Vessey *et al.*, 2003; Rosenblatt *et al.*, 2004; Hannaford and Elliott, 2005; Hannaford *et al.*, 2007; Lin *et al.*, 2007; Kabat *et al.*, 2008) are given in Table II. The Tables include the study reference, country and acronym; the number of cases/deaths by colorectal subsites; the number of controls (or cohort size and years of follow-up for cohort studies); the source of information (interview-administered questionnaire; self-reported; medical records); and the variables allowed for in the analyses information.

Figure 1 shows the RRs of colorectal cancer for ever OC users as compared with never users in case–control and cohort studies, and overall. The summary RR from 11 case–control studies was 0.82 (95% CI, 0.69–0.97), with significant heterogeneity across studies ($\chi^2 = 111.6$, 10 df; $P < 0.001$). This heterogeneity was largely explained by two earlier studies (Weiss *et al.*, 1981; Kune *et al.*, 1990), one of which included in the reference category OC users for <1 year (Weiss *et al.*, 1981). The summary RR from seven cohort studies was 0.81 (95% CI, 0.75–0.89), in the absence again of significant heterogeneity. Overall, the RR from all studies combined was 0.81 (95% CI, 0.72–0.92), with significant heterogeneity between studies ($\chi^2 = 116.9$, 17 df; $P < 0.001$).

Considering colon cancer, the summary RR was 0.85 (95% CI, 0.75–0.96) from 10 case–control studies, 0.86 (95% CI, 0.77–0.95) from five cohort studies, and 0.85 (95% CI, 0.79–0.93) from all studies (Fig. 2). No significant heterogeneity across studies was observed.

For rectal cancer, the summary RR was 0.80 (95% CI, 0.57–1.13) from six case–control studies, 0.80 (95% CI, 0.66–0.96) from three cohort studies and 0.80 (95% CI, 0.70–0.92) from all studies, again in the absence of significant heterogeneity (Fig. 3).

The RR for colorectal cancer was 0.82 (95% CI 0.70–0.96) after excluding studies which provided only crude estimates (Furner *et al.*,

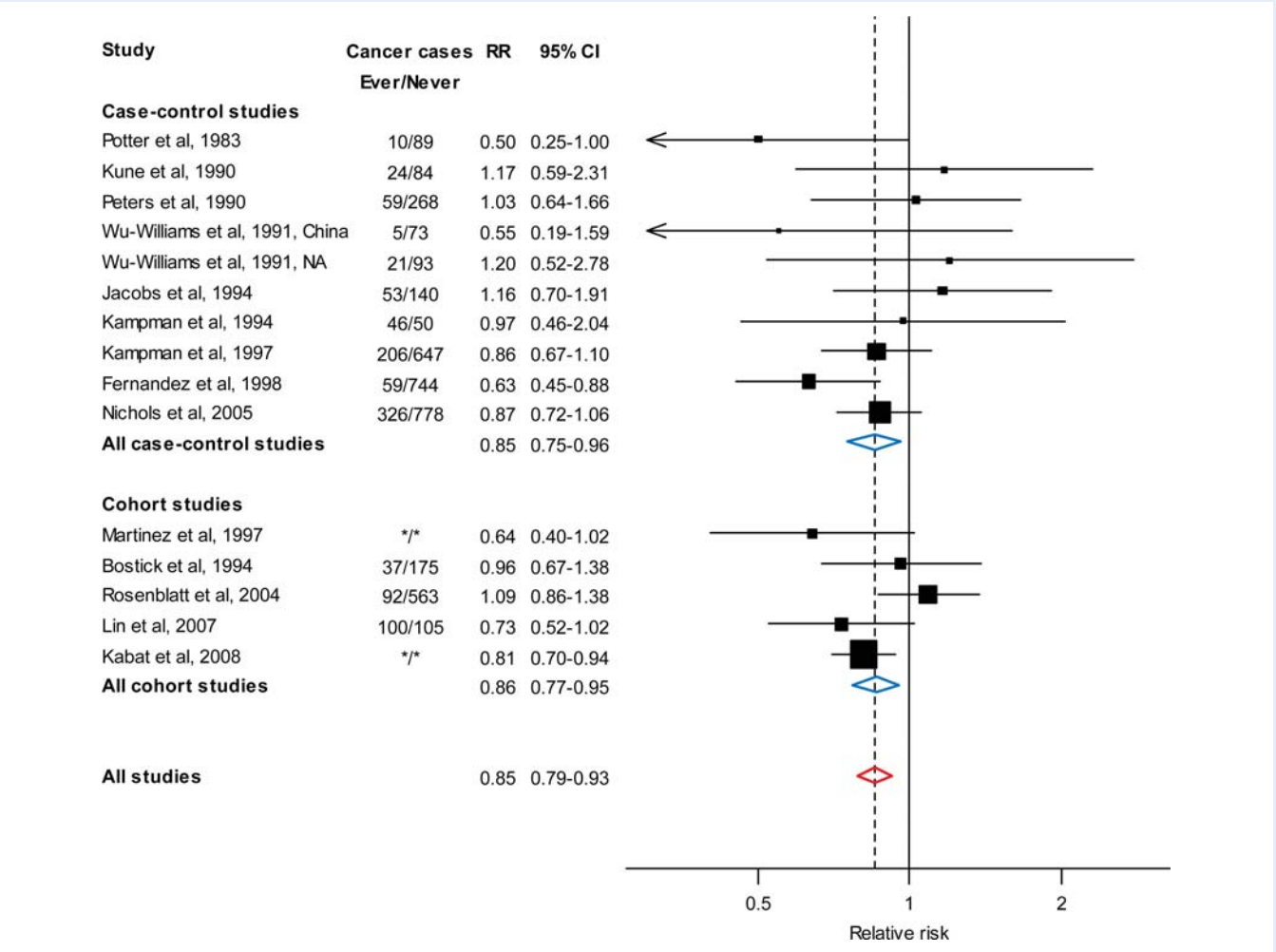

Figure 2 Summary RRs of colon cancer for ever versus never use of OCs from case–control and cohort studies. *Data not given. CI: confidence interval. NA: North America.

1989; Wu-Williams *et al*., 1991) or which adjusted for age and a few selected covariates only (Weiss *et al*., 1981; Potter and McMichael, 1983; Jacobs *et al*., 1994; Troisi *et al*., 1997). Corresponding figures, were 0.82 (95% CI, 0.75–0.89) for colon and 0.82 (95% CI, 0.66–1.03) for rectal cancer (data not shown).

Table III shows the summary RR according to duration and recency of OC use. Twelve studies provided information on duration of use and colorectal cancer; their pooled RR was 0.88 (95% CI, 0.77–1.01) for short-term use, and 0.86 (95% CI, 0.74–1.00) for long-term use. No difference was evident according to duration of OC use for cancer of the colon (RR = 0.90 for short-term and 0.87 for long-term use, based on 10 studies) and of the rectum (RR = 0.94 for short-term and 0.99 for long-term use, based on six studies) (Table III). Corresponding RRs for duration of use <5 years or ≥ 5 years were 0.84 (95% CI, 0.75–0.94) and 0.83 (95% CI, 0.74–0.94) for colorectal cancer (based on seven studies) (data not shown). Only four studies provided information on recency of OC use and colorectal cancer risk, and the overall RR was 0.70 (95% CI, 0.53–0.90) for short time since last use and 0.87 (95% CI, 0.77–0.99) for long time since last use (Table III). The RRs were 0.51 (95% CI, 0.35–0.74) for <10 years since last use and 0.77 (95% CI, 0.60–0.99) for ≥ 10 years since last use (based on three studies) (data not shown).

Discussion

The present meta-analysis confirms that ever OC users have an approximate 20% reduction in colorectal cancer risk as compared with never OC users (Fernandez *et al*., 2001; IARC, 2007). The risk reduction is similar for colon and rectal cancer, and is consistently reported in case–control and cohort studies. However, longer duration of OC use is not associated with a greater reduction in risk, but there is a suggestion that the protection is stronger for more recent use.

Observational studies considered in this meta-analysis are prone to various sources of bias. However, differential underreporting of OC use by cases is unlikely in case–control studies, since the potential association between OC and colorectal cancer risk was unknown in most study populations and the results were similar in case–control and cohort studies. With reference to confounding, apart from a few earlier studies, most investigations provided multivariate

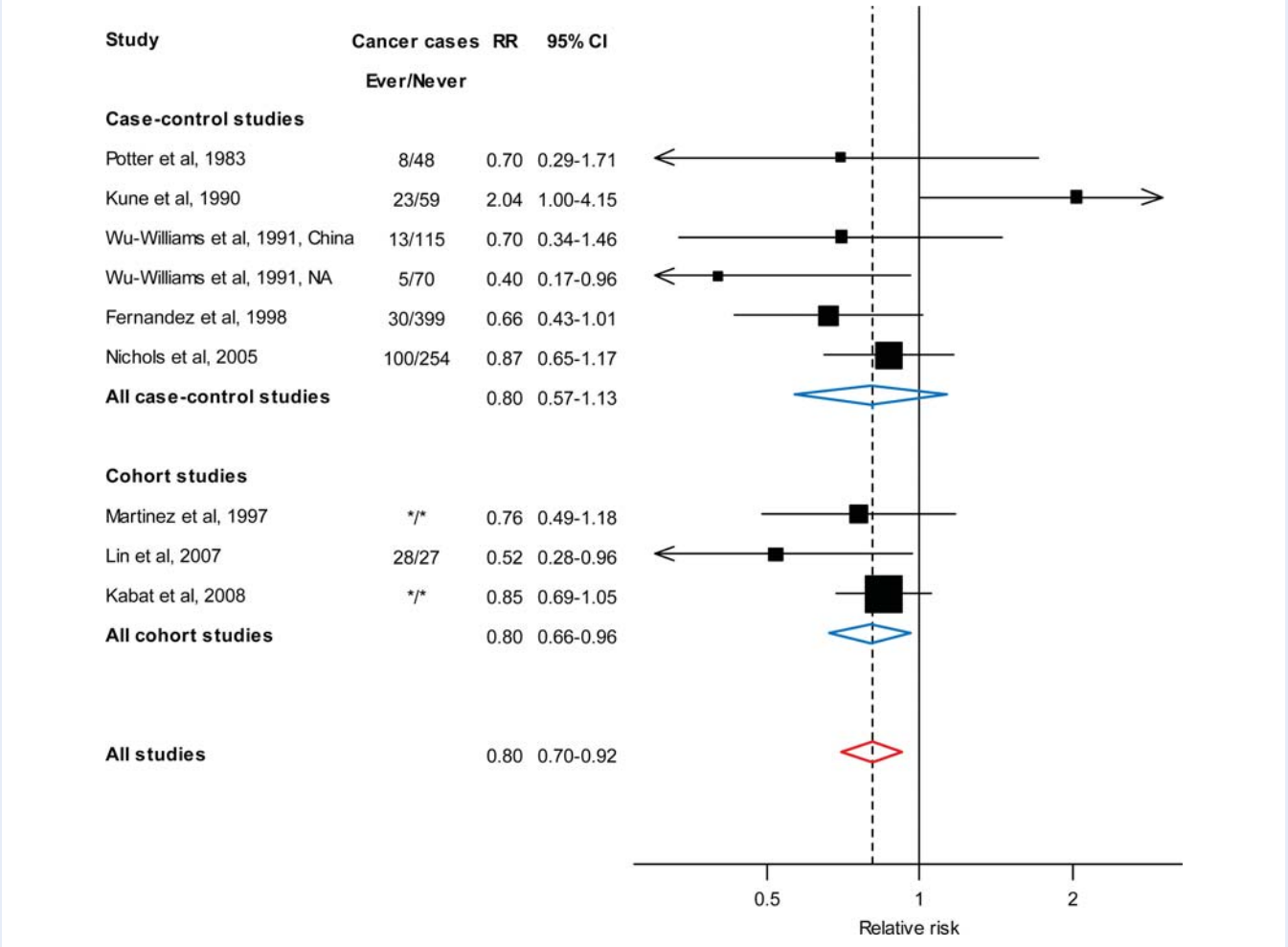

Figure 3 Summary RRs of rectal cancer for ever versus never use of OCs from case–control and cohort studies. *Data not given. CI: confidence interval. NA: north America.

estimates, including allowance for socioeconomic factors, reproductive variables as well as other potential confounding factors for colorectal cancer. Exclusion from the analyses of a few studies which provided only crude estimates or estimates adjusted for a few covariates did not meaningfully modify the pooled estimates, thus ruling out a major effect of confounding factors. Scanty information was available on type of OC. No consistent pattern of trends was, however, observed across calendar year of use, which in most countries is a valid proxy of type of preparation, since first-generation OCs (used in the 1960s) were characterized by high estrogen levels, and subsequent generation OC (used since the early 1970s) had decreased levels of estrogens and progestins (IARC, 2007).

Publication bias is also possible, with selective reporting of favorable findings. Although we did not search for unpublished data, there was no evidence of significant asymmetry in the funnel plots, thus supporting the validity of our results (Egger *et al*., 1997; Thornton and Lee, 2000).

Various biological mechanisms for the protective effect of OCs on colorectal cancer have been suggested (Newcomb *et al*., 2008). Female hormones may reduce the synthesis and secretion of bile acids, which are considered carcinogenic on the colonic epithelium (McMichael and Potter, 1980, 1985). Estrogens inhibit colon carcinogenesis in animal models, and estrogen receptors α and β have been identified in normal and neoplastic colon epithelial cells (Campbell-Thompson *et al*., 2001; Di Leo *et al*., 2001). Estrogens may also reduce circulating levels of insulin-like growth factor-I (IGF-I) and IGF binding protein-3, in turn linked to an increased risk of colorectal cancer (Giovannucci, 2001). Moreover, estrogen-plus-progestin use has been related to a decrease in microsatellite instability (Newcomb *et al*., 2007). A regression of colorectal adenoma has also been shown in a case of familial adenomatosis polyposis after the administration of OCs (Giardiello *et al*., 2005). The protective role of OC on colorectal cancer is also consistent with the evidence of a protective role of hormonal replacement therapy (Chlebowski *et al*., 2004; La Vecchia *et al*., 2005; IARC, 2007). Moreover, the data from this meta-analysis are consistent with recent trends in colorectal cancer mortality in Europe (Bosetti *et al*., 2008), North America (Jemal *et al*., 2008) and Japan (Qiu *et al*., 2009) showing larger decreases in rates in women than in men (particularly in middle-age), and within Europe more favorable patterns in countries

Table III Summary RRs and corresponding 95% CIs for colorectal cancer according to duration of use and time since last use

	RR	95% CI	No. of studies included	Studies included
Duration of use				
Colorectal cancer				
Short-term use	0.88[a]	0.77–1.01	12	Campbell *et al.* (2007); Fernandez *et al.* (1998); Hannaford *et al.* (2007); Kabat *et al.* (2008); Kune *et al.* (1990); Levi *et al.* (2003); Lin *et al.* (2007); Martinez *et al.* (1997); Nichols *et al.* (2005); Troisi *et al.* (1997); Vessey *et al.* (2003); Weiss *et al.* (1981)
Long-term use	0.86[a]	0.74–1.00		
Colon cancer				
Short-term use	0.90	0.81–1.00	10	Chute *et al.* (1991); Fernandez *et al.* (1998); Jacobs *et al.* (1994); Kabat *et al.* (2008); Kune *et al.* (1990); Lin *et al.* (2007); Nichols *et al.* (2005); Peters *et al.* (1990); Potter and McMichael (1983); Rosenblatt *et al.* (2004)
Long-term use	0.87[a]	0.72–1.06		
Rectal cancer				
Short-term use	0.94[a]	0.63–1.41	6	Chute *et al.* (1991); Fernandez *et al.* (1998); Kabat *et al.* (2008); Kune *et al.* (1990); Lin *et al.* (2007); Nichols *et al.* (2005)
Long-term use	0.99[a]	0.69–1.41		
Time since last use				
Colorectal cancer				
Shorter time	0.70	0.53–0.90	4	Fernandez *et al.* (1998); Hannaford *et al.* (2007); Levi *et al.* (2003); Nichols *et al.* (2005)
Longer time	0.87	0.77–0.99		

[a]*P*-value for heterogeneity <0.05.

(such as the UK and other northern European countries) where OC had been used earlier and most widely (Levi *et al.*, 2004).

The available epidemiological data thus consistently indicate that OC users have a reduced risk of colorectal cancer, and that the protection is greater for recent use in the absence, however, of a duration–risk relation. A better understanding of any potential relation between OC use and colorectal cancer may therefore help informed choice of contraception (IARC, 2007).

Authors' Role

C.B. supervised the work and wrote the manuscript; F.B. performed the analysis; E.N. revised the draft manuscript; C.L.V. had the original idea of the study and revised the draft manuscript.

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Appendix 1

Flowchart of selection of studies for the meta-analysis.