Oral contraceptives, reproductive history and risk of colorectal cancer in the European Prospective Investigation into Cancer and Nutrition

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BACKGROUND: Oral contraceptive use and reproductive factors may initiate long-term changes to the hormonal milieu and thereby, possibly influence colorectal cancer risk.

METHODS: We examined the association of hormonal and reproductive factors with risk of colorectal cancer among 337 802 women in the European Prospective Investigation into Cancer and Nutrition, of whom 1878 developed colorectal cancer.

RESULTS: After stratification for center and age, and adjustment for body mass index, smoking, diabetes mellitus, physical activity and alcohol consumption, ever use of oral contraceptives was marginally inversely associated with colorectal cancer risk (hazard ratio (HR), 0.84; 95% confidence interval (CI): 0.74–0.95). Duration of oral contraceptive use and reproductive factors, including age at menarche, age at menopause, type of menopause, ever having an abortion, parity, age at first full-term pregnancy and breastfeeding, were not associated with colorectal cancer risk.

CONCLUSION: Our findings provide limited support for a potential inverse association between oral contraceptives and colorectal cancer risk.

Keywords: oral contraceptives; reproductive history; colorectal cancer; cohort study
Men tend to have a slightly higher incidence of colorectal cancer than women of similar age (American Cancer Society, 2007). Oestrogen has been implicated for this decreased risk in women through mechanisms that involve reduction of secondary bile acid production (McMichael and Potter, 1980; Bayerdorffer et al, 1995), reduction of circulating insulin-like growth factor-I (Campagnoli et al, 1993; Renahan et al, 2004), and protection of the oestrogen receptor gene from methylation (Issa et al, 1994).

The epidemiologic evidence for a causal link between oral contraceptives and colorectal cancer risk is equivocal. Some studies have suggested inverse associations (Potter and McMichael, 1983; Martinez et al, 1997; Fernandez et al, 1998; Nichols et al, 2005; Campbell et al, 2007; Hannaford et al, 2007; Lin et al, 2007; Kabat et al, 2008), whereas others have found no association (Weiss et al, 1981; Bostick et al, 1994; Jacobs et al, 1994; Platz et al, 1997; Troisi et al, 1997; Levi et al, 2003; Purdie et al, 2005; Dorjgochoo et al, 2009; Rosenblatt et al, 2009). A recent meta-analysis, summarising the results from 7 cohort and 11 case–control studies, reported a statistically significant 19% reduced risk among ever users of oral contraceptives compared with never users, although there was no clear association with increasing duration of use (Bosetti et al, 2009). No consistent association has been observed for menstrual and reproductive variables and risk of colorectal cancer (Weiss et al, 1981; Potter and McMichael, 1983; Peters et al, 1990; Wu-Williams et al, 1991; Gerhardsson de Verdier and London, 1992; Bostick et al, 1994; Jacobs et al, 1994; Kamman et al, 1997; Martinez et al, 1997; Talamini et al, 1998; Nichols et al, 2005; Purdie et al, 2005; Lin et al, 2007; Sakauchi, 2007; Akhter et al, 2008; Kabat et al, 2008; Rosenblatt et al, 2009), although the majority of the studies are case–control or small cohort studies with low power to study dose–response associations.

We examined the associations of oral contraceptive use and reproductive variables with colorectal cancer risk in the large European Prospective Investigation into Cancer and Nutrition (EPIC) cohort.

**MATERIALS AND METHODS**

Study participants included 1878 female colorectal cancer cases (1295 colon and 583 rectal cancers) and 335,924 female non-cases recruited into EPIC, a prospective cohort that was established in the 1990s in 10 European countries with more than half a million participants, mostly aged 35–70 years. Incident cancer cases were identified through linkage to population cancer registries in Denmark, Italy, The Netherlands, Norway, Spain, Sweden and the UK, or with a combination of methods including linkage to health insurance records, cancer and pathology registries, and active follow-up of study participants or their next of kin in France, Germany and Greece. The colorectal cancer diagnosis was confirmed by histology for 80.2% of the cases, by clinical examination for 11.6% and the remaining 8.2% by self-report, autopsy or death certificate. Women were excluded if they had prevalent cancer at recruitment, if they did not return the baseline lifestyle questionnaire, if they never menstruated or if they had missing information on all exposure variables. Details on the cohort population, the data collection procedures and the outcome and covariate assessment methods have been described in detail elsewhere (Riboli et al, 2002; Tsilidis et al, 2010).

Women were asked at the baseline questionnaire whether they had ever used oral contraceptives, their duration of use, and age they started use. Information on age at menarche and menopause, numbers of full-term pregnancies (live and still births) and induced or spontaneous abortions, age at the first full-term pregnancy, and the reason for menopause (natural vs surgical) was also collected. Information on breastfeeding was collected for the first three full-term pregnancies and the last one. Menopausal status was defined according to information on menstruation status and ovariectomy, details of which are provided elsewhere (Dossus et al, 2010).

**RESULTS**

The mean ages at recruitment and diagnosis for the colorectal cancer cases were 57 and 63 years, respectively, and the mean length of follow-up in the whole cohort was 9 years. Compared

**Table I** Participant characteristics at recruitment among women in the European Prospective Investigation into Cancer and Nutrition cohort

| Characteristic | Colorectal cancer cases (n = 1878) | Non-cases (n = 335,924) |
|---------------|----------------------------------|------------------------|
| Mean (s.d.) age at recruitment (years) | 57.4 (8.0) | 50.5 (9.7) |
| Mean (s.d.) body mass index (kg m⁻²) | 25.5 (4.5) | 25.0 (4.5) |
| Mean (s.d.) alcohol intake | 10 (13.7) | 9.0 (12.2) |
| (g per day)² | 31.7 | 34.2 |
| Modestly active/active (%) | 18.5 | 19.6 |
| Current smokers (%) | 3.0 | 2.3 |
| Self-reported diabetes mellitus (%) | | |
| Menopausal status (%) | | |
| Pre-menopausal | 11.2 | 34.2 |
| Peri-menopausal/unknown | 14.7 | 18.8 |
| Post-menopausal (natural/surgical) | 74.1 | 47.0 |
| Ever oral contraceptive use (%) | 43.8 | 58.4 |
| Mean (s.d.) duration of oral contraceptive use (years)³ | 9.2 (9.8) | 8.7 (9.3) |
| Mean (s.d.) age at menarche (years)³ | 13.2 (1.6) | 13.1 (1.5) |
| Mean (s.d.) age at menopause (years)³ | 49.1 (4.9) | 48.6 (5.1) |
| Ever had a full-term pregnancy (%) | 83.5 | 79.6 |
| Mean (s.d.) number of full-term pregnancies³ | 2.4 (1.1) | 2.3 (1.0) |
| Mean (s.d.) age at first full-term pregnancy, years³ | 25.0 (4.4) | 24.8 (4.4) |
| Ever breastfed (%)³ | 81.2 | 81.8 |

²Among consumers only; 8.8% of the cases and 9.2% of the non-cases were non-consumers of alcohol. ³Among ever oral contraceptive users only. ⁴Among post-menopausal women only. ⁵Among women with a full-term pregnancy only.
## Table 2

Hazard ratio (HR) and 95% confidence interval (CI) for oral contraceptive use, reproductive variables and colorectal cancer among women in the European Prospective Investigation into Cancer and Nutrition cohort.

| Variable | Number of cases/non-cases | Age and center-stratified, HR (95% CI) | Multivariable adjusted, HR (95% CI) |
|----------|---------------------------|--------------------------------------|-----------------------------------|
| Oral contraceptive use | | | |
| Never | 1040/138 359 | 1.00 (reference) | 1.00 (reference) |
| Ever | 822/196 040 | 0.93 (0.84 – 1.03) | 0.92 (0.83 – 1.02) |
| Oral contraceptive use (among post-menopausal women) | | | |
| Never | 908/89 064 | 1.00 (reference) | 1.00 (reference) |
| Ever | 469/67 757 | 0.85 (0.75 – 0.96) | 0.84 (0.74 – 0.95) |
| Oral contraceptive use (among pre-/peri-menopausal women) | | | |
| Never | 132/49 295 | 1.00 (reference) | 1.00 (reference) |
| Ever | 353/128 283 | 1.22 (0.99 – 1.51) | 1.19 (0.96 – 1.48) |
| P-interaction | | <0.01 | <0.01 |
| Duration of oral contraceptive use (years) | | | |
| ≤1 | 161/36 175 | 1.00 (reference) | 1.00 (reference) |
| 2 – 4 | 167/42 208 | 0.99 (0.80 – 1.24) | 0.99 (0.80 – 1.23) |
| 5 – 9 | 150/42 409 | 0.94 (0.75 – 1.18) | 0.93 (0.74 – 1.17) |
| ≥10 | 264/58 041 | 1.10 (0.90 – 1.36) | 1.09 (0.89 – 1.35) |
| P-trend | | 0.37 | 0.41 |
| Age at menarche | | | |
| <12 | 258/49 935 | 1.00 (reference) | 1.00 (reference) |
| 12 | 358/70 982 | 0.95 (0.81 – 1.11) | 0.95 (0.81 – 1.12) |
| 13 | 457/85 998 | 0.96 (0.83 – 1.12) | 0.97 (0.84 – 1.14) |
| 14 | 424/71 912 | 0.95 (0.82 – 1.12) | 0.97 (0.83 – 1.14) |
| ≥15 | 352/52 954 | 0.95 (0.80 – 1.12) | 0.96 (0.82 – 1.14) |
| P-trend | | 0.64 | 0.41 |
| Age at menopause | | | |
| ≤50 | 654/77 482 | 1.00 (reference) | 1.00 (reference) |
| 51 – 52 | 200/20 489 | 1.06 (0.90 – 1.25) | 1.07 (0.91 – 1.25) |
| 53 – 55 | 196/18 391 | 1.06 (0.90 – 1.25) | 1.07 (0.91 – 1.26) |
| >55 | 59/5084 | 0.99 (0.76 – 1.30) | 1.00 (0.76 – 1.31) |
| P-trend | | 0.58 | 0.54 |
| Type of menopause | | | |
| Natural | 1303/147 920 | 1.00 (reference) | 1.00 (reference) |
| Surgical | 88/9 875 | 1.14 (0.91 – 1.42) | 1.13 (0.91 – 1.41) |
| Induced or spontaneous abortion | | | |
| Never | 1129/180 995 | 1.00 (reference) | 1.00 (reference) |
| Ever | 221/45 509 | 1.01 (0.87 – 1.18) | 1.00 (0.86 – 1.17) |
| Full-term pregnancy | | | |
| Never | 231/49 342 | 1.00 (reference) | 1.00 (reference) |
| Ever | 1568/267 467 | 0.96 (0.83 – 1.10) | 0.96 (0.83 – 1.10) |
| Number of full-term pregnancies | | | |
| 1 | 250/49 177 | 1.00 (reference) | 1.00 (reference) |
| 2 | 721/129 409 | 1.16 (1.00 – 1.34)) | 1.16 (1.01 – 1.35) |
| 3 | 384/61 490 | 1.15 (0.98 – 1.36) | 1.16 (0.98 – 1.36) |
| ≥4 | 213/27 391 | 1.17 (0.97 – 1.41) | 1.17 (0.97 – 1.42) |
| P-trend | | 0.15 | 0.15 |
| Age at first full-term pregnancy | | | |
| ≤20 | 210/40 007 | 1.00 (reference) | 1.00 (reference) |
| 21 – 23 | 433/71 912 | 1.01 (0.86 – 1.19) | 1.02 (0.86 – 1.21) |
| 24 – 25 | 320/52 140 | 0.97 (0.81 – 1.16) | 0.98 (0.82 – 1.18) |
| 26 – 30 | 439/75 488 | 0.90 (0.76 – 1.07) | 0.92 (0.77 – 1.09) |
| ≥30 | 163/26 886 | 0.98 (0.79 – 1.20) | 0.99 (0.80 – 1.22) |
| P-trend | | 0.22 | 0.30 |
| Breastfeeding | | | |
| Never | 211/39 471 | 1.00 (reference) | 1.00 (reference) |
| Ever | 1273/218 695 | 1.12 (0.97 – 1.31) | 1.13 (0.97 – 1.32) |

*The number of cases and non-cases do not add up to the total number of 1878 cases and 335 924 non-cases because of missing values. From a Cox proportional hazards model stratified by the European Prospective Investigation into Cancer and Nutrition participating center and age at recruitment, and adjusted for smoking status (never, former, current), diabetes mellitus (never, ever), body mass index (<25, ≥25 – <30, ≥30 kg m⁻²), physical activity (inactive, moderately inactive, moderately active, active), and alcohol use (<0.58, ≥0.58 – <3.61, ≥3.61 – <11.08, ≥11.08 g per day). Among ever oral contraceptive users only. Among post-menopausal women only. Among women with a full-term pregnancy.
with women without colorectal cancer, cases were on average older, had slightly higher BMI, drank more alcohol, exercised less and were less likely to have ever taken oral contraceptives (Table 1).

Overall, there were no statistically significant associations between oral contraceptives, reproductive factors and colorectal cancer risk (Table 2). Ever use of oral contraceptives was marginally inversely associated with risk (HR, 0.92; 95% CI: 0.83 – 1.02), but neither duration of use (P-trend, 0.41) nor age at start of use (P-trend, 0.32) were associated with risk. However, the association of oral contraceptive use on risk varied by menopausal status (P-interaction, <0.01); ever use of oral contraceptives was associated with a significantly reduced risk in post-menopausal women (HR, 0.84; 95% CI: 0.74 – 0.95), but no significant association was observed among pre- or peri-menopausal women (HR, 1.19; 95% CI: 0.96 – 1.48). There was no evidence of an interaction for duration or age at start of oral contraceptive use by menopausal status (data not shown).

Reproductive factors, including age at menarche, age at menopause, type of menopause, ever having an abortion, parity, age at first full-term pregnancy and breastfeeding, were not associated with colorectal cancer risk (Table 2). The associations between oral contraceptive use, reproductive factors and colorectal cancer risk did not differ according to country, colorectal cancer subsite and baseline characteristics (age, BMI, menopausal hormone therapy and menopausal status).

**DISCUSSION**

In this large prospective study, ever use of oral contraceptives was associated with a small reduction in colorectal cancer risk, which was stronger among post-menopausal women compared with pre-/peri-menopausal women. Although our finding of an inverse association with use of oral contraceptives is consistent with the prior literature (Bosetti et al, 2009), most studies have not reported a reduction in colorectal cancer risk with increasing duration of oral contraceptive use (Bosetti et al, 2009). This may, in part, be because of relatively small study sizes to detect a significant association, although the present study, with over 1800 cases, also found no association with duration of oral contraceptive use. Our stronger inverse finding for oral contraceptive use and colorectal cancer risk in post-menopausal women did not change after adjustment for menopausal hormone therapy and reproductive variables, and is not explained by a longer duration of oral contraceptive use among older women as there was no association between duration of use and risk overall or in subgroups by menopausal status. In addition, post-menopausal women had only a slightly longer mean duration of oral contraceptive use compared with pre-/peri-menopausal women (9.1 vs 8.5 years), despite being older at recruitment (58 vs 44 years). However, post-menopausal women were more likely to have started using oral contraceptives during the 1960s when high-dose formulations were much more common (McMichael and Potter, 1980), which may partly explain the apparent higher risk in these women. Earlier studies have not reported significant interactions between oral contraceptive use and colorectal cancer risk by age or menopausal status (Kampman et al, 1997; Lin et al, 2007); however, one case–control study observed a non-significant reduced risk of colon cancer for ever use of oral contraceptives among women older than 62 years at recruitment, and no association among younger women (Kampman et al, 1997). Future studies with detailed information on the dose and hormonal constituent of the oral contraceptives are needed to clarify this association. No significant associations were found for reproductive factors, which is consistent with most of the literature (Gerhardsson de Verdier and London, 1992; Kampman et al, 1997; Troisi et al, 1997; Nichols et al, 2005; Lin et al, 2007; Sakauuchi, 2007; Akhter et al, 2008; Kabat et al, 2008).

The major strength of this study is its size and power to study dose-response associations, and its detailed and standardised assessment of reproductive factors across Europe. In conclusion, oral contraceptive use was associated with a reduced risk of colorectal cancer among post-menopausal women. Duration of oral contraceptive use and reproductive factors were not associated with risk. Our findings provide limited support for a potential inverse association between oral contraceptives and colorectal cancer risk.

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