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Reproductive and menstrual factors and colorectal cancer incidence in the Women's Health Initiative Observational Study

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Background: Reproductive and menstrual factors have been evaluated as surrogates for long-term hormonal exposures in several prospective studies of colorectal cancer, yet findings have been conflicting.

Methods: The relation of reproductive and menstrual factors (self-reported via a reproductive history questionnaire) with incident colorectal cancer was investigated among women enrolled in the Women's Health Initiative Observational Study (WHI-OS), a longitudinal cohort of 93 676 postmenopausal women (aged 50–79 years at enrolment) in which 1149 incident cases of colorectal cancer occurred over a median follow-up of 11.9 years. Multivariable Cox proportional hazards models that included established colorectal cancer risk factors were constructed to examine the association of colorectal cancer incidence with reproductive and menstrual factors.

Results: Having had two children (*vs* nulliparous: hazard ratio (HR) = 0.80, 95% confidence interval (CI): 0.64–0.99) was inversely associated with colorectal cancer risk. Compared with never users, ever use of oral contraceptives was associated with lower colorectal cancer risk (HR = 0.74, 95% CI: 0.63–0.86); however, no relationship was observed for duration of oral contraceptives use (4 years *vs* 1 year: HR = 0.94, 95% CI: 0.67–1.32). None of the remaining reproductive and menstrual factors was associated with colorectal cancer incidence.

Conclusions: Parity and prior use of oral contraceptives were associated with lower colorectal cancer risk in this cohort of postmenopausal women.

Colorectal cancer is the third most common cancer worldwide with more than one million new cases diagnosed each year (Ferlay *et al*, 2010). Incidence rates for colorectal cancer are lower among women compared with men across all age categories and it has been proposed that this is a consequence of higher oestrogen levels in women conferring protection (McMichael and Potter, 1980). Consistent with this hypothesis are findings from a substantial body of epidemiologic literature that report a 20–40% lower incidence of colorectal cancer among users, than non-users, of postmenopausal hormone therapy (Hebert-Croteau, 1998; Grodstein *et al*, 1999; Nanda *et al*, 1999; Johnson *et al*, 2009; Green *et al*, 2012; Simon *et al*, 2012a). However, in contrast to

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these observational results, the Women's Health Initiative Clinical Trial (WHI-CT) reported no effect of oestrogen-alone therapy on colorectal cancer risk (Chlebowski *et al*, 2004). In addition, administration of oestrogen plus progestin was initially found to yield a 44% reduction in risk of developing colorectal cancer compared with the placebo group (Chlebowski *et al*, 2004), but longer follow-up revealed this finding was a probable consequence of diagnostic delay (Simon *et al*, 2012b).

To date, five prospective studies have investigated the relationships between endogenous circulating oestrogens and colorectal cancer. The first of these studies was a case-cohort analysis in the WHI Observational Study, which reported a borderline statistically significant positive association between endogenous oestradiol levels and colorectal cancer incidence (Gunter *et al*, 2008). Three subsequent follow-up studies conducted in the New York University Women's Health Study (Clendenen *et al*, 2009), a joint Nurses' Health Study and Women's Health Study analysis (Lin *et al*, 2013), and an analysis in the Breast and Bone Follow-up to the Fracture Intervention Trial (B∼FIT; Falk *et al*, 2015) reported no association between oestradiol levels and colorectal cancer risk. Most recently, a nested case–control study in the WHI clinical trial non-intervention arms reported statistically significant inverse associations between colorectal cancer risk and total oestradiol, free oestradiol, and oestrone levels (Murphy *et al*, 2015).

Another approach to investigating the potential role of oestrogen in colorectal cancer development is to use reproductive history and menstrual factors as surrogates for long-term endogenous oestrogen exposure. Recently, two large prospective investigations have reported findings on the association of reproductive history and colorectal cancer risk. The European Prospective Investigation into Cancer and Nutrition study (EPIC), which analysed data from 337 802 women and 1878 incident colorectal cancer cases, observed an inverse relation between oral contraceptive use and colorectal cancer but no statistically significant relationships for other reproductive factors (Tsilidis *et al*, 2010). In contrast, in the NIH-AARP Diet and Health Study, which evaluated 214 162 postmenopausal women and more than 2000 colorectal cancer cases, age at menopause and age at birth of first child were positively associated with colorectal cancer incidence, while age at menarche and parity were inversely related to colorectal cancer (Zervoudakis *et al*, 2011). Other smaller prospective studies that investigated the relationships between reproductive factors and colorectal cancer risk have generally reported inconsistent results (Lin *et al*, 2007; Akhter *et al*, 2008; Kabat *et al*, 2008).

To further investigate the relation between reproductive history and colorectal cancer development and, by extension, the role of lifetime oestrogen exposure in relation to colorectal cancer, we evaluated data from the WHI Observational Study (WHI-OS) – a large prospective cohort of postmenopausal women with more than 15 years of follow-up and detailed information on reproductive and menstrual parameters, and other colorectal cancer risk factors.

MATERIALS AND METHODS

Study population

Women's Health Initiative Observational Study (WHI-OS). The WHI-OS is a longitudinal cohort of 93 676 postmenopausal women aged 50–79 years who were recruited at 40 different clinical centres across the United States between 1 October 1993 and 31 December 1998 (The Women's Health Initiative Study Group, 1998). The study was approved by human subject's review committees at each of the participating institutions, and written informed consent was obtained from each study participant. Women were excluded from the current analysis if they reported a history of any cancer (except non-melanoma skin cancer) at enrolment ($n = 1764$). After these exclusions, 91 912 women were included in the analysis.

Data collection and case identification. At baseline, women completed detailed questionnaires regarding medical and behavioural history, hormone and medication use, lifestyle and demographic factors. In the reproductive history questionnaire, women were asked about age at first menstrual period, age at last regular menstrual period, were they ever pregnant, number of pregnancies, number of pregnancies lasting at least 6 months, and number of live births and induced abortions. Participants were also asked whether they had ever taken oral contraceptives and, if so, the age at which they started and age of stopping use, how many years and months they used oral contraceptives, whether they had used oral contraceptives before a first full-term pregnancy and, if so, for how many years and months. Age at menopause was defined as the youngest age at which the participant experienced any of the following: last menstrual bleeding (all participants were at least 12 months post last menstrual period at baseline), removal of both ovaries, or initiation of menopausal hormone therapy. Age at first live birth was defined as the age at first pregnancy lasting 6 months or longer. A physical examination was conducted that included measurement of waist and hip circumference, and of height and weight. Incident cancer was ascertained through annual self-administered questionnaires or by self-reports between the annual questionnaires. Case status and detailed diagnosis were confirmed through centralised review of all pathology reports, discharge and trained adjudicator reports, operative and radiology reports, and tumour registry abstracts. Cases were coded according to National Cancer Institute Surveillance, Epidemiology and End-Results guidelines (Cancer Statistics Branch, 1992; US Dept of Health and Human Services, 1993). Participants with a history of colorectal cancer were excluded from the analysis.

Statistical analysis. The distributions of baseline characteristics between case participants and non-case participants were compared using the Wilcoxon rank sum test for continuous data and the Pearson χ^2 test for categorical data. To examine the associations between reproductive and menstrual factors and risk of colorectal cancer, we estimated hazard ratios (HRs) using Cox proportional hazards regression modelling, with time from study enrolment, in days, as the underlying time metric. Individuals were censored at diagnosis of colorectal cancer, death or at the end of the current follow-up period, whichever occurred first. All multivariable models were adjusted for the following *a priori*-determined established colorectal cancer risk factors: age (categorised into 5-year age groups; <55 (referent), 55–59, 60–64, 65–69 or $\geqslant 70$ years); family history of colorectal cancer (defined as having a first-degree relative with colorectal cancer); race/ethnicity (white (referent), black, Hispanic or other); education level (less than college (referent), college or associate degree, higher than an associate degree); hormone therapy status (never (referent), former or current); a history of diabetes (no or yes); smoking status (never (referent), former or current) and body mass index (quartiles). Additional variables, including a history of colorectal polyps, use of nonsteroidal anti-inflammatory drugs, physical activity, dietary calcium, fibre, folate, red meat intake and alcohol consumption were evaluated as potential covariates, but their inclusion in our *a priori*-determined multivariable model outlined above did not alter the risk estimates and, therefore, they were not considered in subsequent models (data not shown). Statistical tests for

Table 1. Selected baseline characteristics of the study population

Variable	Case participants ($N=1149$)	Non-case participants ($N=90\,763$)	P
Mean age, years (s.d.)	66.6 (6.9)	63.5 (7.4)	<0.0001
Ethnicity, no. (%)			0.003
White	975 (84.9)	75 636 (83.3)	
Black	108 (9.4)	7336 (8.1)	
Hispanic/Latino	25 (2.2)	3488 (3.8)	
Other	39 (3.4)	4049 (4.5)	
Missing	2 (0.1)	254 (0.3)	
Mean body mass index (kg m^{-2}; s.d.)	28.1 (5.9)	27.3 (5.9)	<0.0001
Mean dietary fibre intake (s.d.)	15.8 (7.4)	16.3 (7.4)	0.02
Mean dietary folate intake (s.d.)	466.8 (218.1)	483.8 (223.9)	0.01
Mean dietary calcium intake, mg day^{-1} (s.d.)	788.2 (462.4)	819.4 (223.9)	0.03
Family history of colorectal cancer, no. (%)			<0.0001
No	834 (72.6)	69 220 (76.3)	
Yes	227 (19.8)	13 750 (15.1)	
Missing	88 (7.6)	7793 (8.6)	
Alcohol drinking, no. (%)			0.09
Non-drinker	126 (11.0)	10 133 (11.2)	
Past drinker	220 (19.1)	16 983 (18.7)	
<1 drink per week	397 (34.6)	28 563 (31.5)	
⩾1 drink per week	401 (34.9)	34 523 (38.0)	
Missing	5 (0.4)	561 (0.6)	
Smoking history, no. (%)			0.03
Never smoked	542 (47.2)	45 730 (50.4)	
Former smoker	504 (43.9)	38 261 (42.2)	
Current smoker	88 (7.7)	5600 (6.2)	
Missing	15 (1.2)	1172 (1.2)	
Education level, no. (%)			0.004
<College	356 (31.0)	28 105 (31.0)	
Some college	350 (30.5)	23 981 (26.4)	
>College	435 (37.9)	37 944 (41.8)	
Missing	8 (0.6)	733 (0.8)	
Diabetes, no. (%)			0.001
No	1056 (91.9)	85 576 (94.3)	
Yes	91 (7.9)	5097 (5.6)	
Missing	2 (0.2)	90 (0.1)	
Hormone therapy			<0.0001
Never used	577 (50.2)	36 633 (40.4)	
Current user	196 (17.1)	13 442 (14.8)	
Former user	374 (32.6)	40 613 (44.7)	
Missing	2 (0.1)	75 (0.1)	
Oral contraceptive use, no. (%)			<0.0001
Never	839 (73.0)	54 158 (59.7)	
Ever	310 (27.0)	36 605 (40.3)	
Missing	0 (0)	0 (0)	
Age at menarche (years)			0.31
⩽10	40 (3.5)	2897 (3.2)	
11–12	315 (27.4)	23 375 (25.8)	
13–14	420 (36.6)	32 814 (36.2)	
⩾15	192 (16.7)	16 845 (18.6)	
Missing	182 (15.8)	14 382 (16.2)	
Age at first child's birth (years)			0.81
<20	123 (10.7)	10 208 (11.2)	
20–29	664 (57.8)	52 991 (58.4)	
⩾30	92 (8.0)	6981 (7.7)	
No children/missing	270 (23.5)	20 583 (22.7)	
Age at last child's birth (years)			0.02
<25	112 (9.7)	9030 (9.9)	
25–29	258 (22.5)	23 032 (25.3)	
30–34	275 (23.9)	23 064 (25.4)	
35–39	178 (15.5)	11 855 (13.1)	
⩾40	49 (4.3)	3189 (3.5)	
No children/missing	277 (24.1)	20 593 (22.8)	
Parity			0.07
Nulliparous	158 (13.8)	11 513 (12.7)	
1 child only	100 (8.7)	8236 (9.1)	
2 children	269 (23.4)	23 774 (26.2)	
3 children	265 (23.1)	21 782 (24.0)	
⩾4 children	351 (30.5)	24 958 (27.5)	
Missing	6 (0.5)	500 (0.5)	
Induced abortion			0.8
Never	864 (75.2)	69 404 (76.5)	
Ever	82 (7.1)	6782 (7.5)	
Missing	203 (17.7)	14 577 (16.0)	
Breastfed for ⩾1 month			0.63
No	567 (49.3)	45 705 (50.4)	
Yes	563 (50.0)	44 110 (48.6)	
Missing	19 (1.7)	948 (1.0)	

Table 1. (Continued)

Variable	Case participants ($N=1149$)	Non-case participants ($N=90\,763$)	P
Age at menopause (years)			0.55
<40	132 (11.5)	10 707 (11.8)	
40–44	152 (13.2)	12 163 (13.4)	
45–49	269 (23.4)	20 685 (22.8)	
50–54	364 (31.7)	29 069 (32.0)	
⩾55	135 (11.7)	9180 (10.1)	
Missing	97 (8.5)	8959 (9.9)	
Hysterectomy			0.84
No	673 (58.6)	52 850 (58.2)	
Yes	476 (41.4)	37 828 (41.7)	
Missing	0 (0)	85 (0.1)	
Bilateral oophorectomy			0.8
No	886 (77.1)	70 702 (77.9)	
Yes	233 (20.3)	18 243 (20.1)	
Missing	30 (2.6)	1818 (2.0)	

trend were calculated by entering the ordinal reproductive and menstrual facts variable into the models as a continuous variable.

We also performed analyses stratified by waist circumference (<82.5 (median) *vs* ⩾82.5 cm) and ever use of hormone therapy (never use *vs* ever use). To test for statistically significant differences in the association between the reproductive factors and risk of colorectal cancer between strata of waist circumference and ever use of hormone therapy, we compared the multivariable model for the association of the reproductive factor of interest with colorectal cancer risk with a subsequent model that included the reproductive factor and an interaction term for that variable and the stratified factor. The difference between the two models was evaluated using the likelihood ratio test. All tests of statistical significance were two sided, and *P*-values less than 0.05 were considered statistically significant. The proportionality of the Cox model was verified by examination of the residual plots. All analyses were performed using SAS 9.3 (SAS Institute, Cary, NC, USA).

RESULTS

Participant characteristics. During a median follow-up period of 11.9 years, 1149 postmenopausal women were diagnosed with colorectal cancer, of which 959 were colon cancers and 147 were rectal cancers (43 cases did not have information on subsite location). The baseline characteristics of the colorectal cancer cases and non-cases are shown in Table 1. In brief, compared with non-case participants, colorectal cancer case participants were older, had a higher BMI, were less likely to be educated above college level, and more likely to have a positive family history of colorectal cancer, to be current or former smokers, and to be diabetic. Colorectal cancer case participants also reported consuming less dietary fibre, folate and calcium, and were less likely to have used oral hormone therapy, and more likely to have used oral contraceptives compared with non-case participants.

Associations with colorectal cancer. Table 2 presents age-adjusted and multivariable-adjusted HRs and 95% confidence intervals (CIs) for associations between reproductive factors and the risk of colorectal cancer. Parity was inversely associated with incident colorectal cancer in the multivariable models. For example, women who reported giving birth to two children had a 20% reduction in colorectal cancer incidence compared with nulliparous women (HR = 0.80, 95% CI:0.64–0.99). The HRs for colorectal cancer when comparing nulliparous women with those who reported giving birth to three children and four or more children were very similar and of borderline statistical significance, suggesting a possible threshold effect. When all three categories were collapsed to form a single joint parameter of ⩾2 children, the HR for comparing ⩾2 children with nulliparous women was statistically significant (HR = 0.82, 95% CI: 0.68–0.98; data not tabulated). Older age at menarche was inversely associated with colorectal cancer risk in univariate models (HR for ⩾15 *vs* 11–12 years = 0.81; 95% CI: 0.67–0.98) but was no longer significant in the multivariable model (HR for ⩾15 *vs* 11–12 years = 0.82; 95% CI: 0.67–1.00). Prior oral contraceptive use, but not duration of use, was inversely associated with colorectal cancer risk (HR = 0.74, 95% CI: 0.63–0.86). We did not observe statistically significant associations between age at menopause, age at birth of first or last child, breastfeeding, abortion, hysterectomy or oophorectomy status and risk of colorectal cancer. Simultaneous inclusion of each of the reproductive factors in the multivariable model did not meaningfully alter the associations of these parameters with colorectal cancer risk, and neither did restricting analyses to either colon or rectal cancer, and proximal colon or distal colon cancer (data not shown).

None of the associations between the reproductive factors and risk of colorectal cancer differed according to waist circumference (data not shown) strata and ever use of hormone therapy (Table 3; all $P_{\text{interaction}} > 0.05$). For age at menarche, a statistically significant lower colorectal cancer risk was observed for never users of hormone therapy (HR for ⩾15 *vs* 11–12 years = 0.72; 95% CI: 0.54–0.96; $P_{\text{trend}} = 0.10$), but not for ever users (HR for ⩾15 *vs* 11–12 years = 0.92; 95% CI: 0.69–1.22; $P_{\text{trend}} = 0.90$), although this heterogeneity was not statistically different ($P_{\text{interaction}} = 0.30$).

DISCUSSION

In this prospective study of postmenopausal women, we observed statistically significant inverse associations for parity and use of oral contraceptives with colorectal cancer development. The remaining reproductive and menstrual factors considered were not associated with colorectal cancer risk. These findings are partly consistent with prior prospective investigations of reproductive patterns and colorectal cancer incidence and suggest that the hormonal changes associated with pregnancy and use of oral contraceptives may be relevant for colorectal tumorigenesis.

In the current analysis, having given birth to at least two children was associated with a near 20% reduction in colorectal cancer risk compared with that for women who remained nulliparous. These data are consistent with findings from a previous analysis in the NIH-AARP study which reported a similar inverse association, albeit restricted to women who had not used hormone therapy (Zervoudakis *et al*, 2011). Pregnancy is associated with significant endocrinologic and metabolic changes

Table 2. Hazard ratios and 95% confidence intervals for the association of reproductive and menstrual factors with colorectal cancer incidence among women enrolled in the WHI-OS

Factor	*N* cases	Age-adjusted HR (95% CI)	Multivariable HR[a] (95% CI)
Age at menarche (years)			
⩽10	40	1.16 (0.82–1.63)	1.09 (0.76–1.56)
11–12	315	1.00 (referent)	1.00 (referent)
13–14	420	0.91 (0.78–1.06)	0.95 (0.81–1.11)
⩾15	192	0.81 (0.67–0.98)	0.82 (0.67–1.00)
P-trend		0.08	0.2
Age at first child's birth (years)			
<20	123	1.00 (referent)	1.00 (referent)
20–29	664	0.88 (0.72–1.08)	0.98 (0.78–1.23)
⩾30	92	0.85 (0.64–1.14)	0.96 (0.70–1.31)
P-trend		0.45	0.96
Age at last child's birth (years)			
<25	112	1.00 (referent)	1.00 (referent)
25–29	258	0.83 (0.66–1.05)	0.95 (0.74–1.22)
30–34	275	0.77 (0.61–0.97)	0.88 (0.68–1.13)
35–39	178	0.87 (0.67–1.11)	0.94 (0.71–1.24)
⩾40	49	0.89 (0.62–1.26)	0.91 (0.62–1.34)
P-trend		0.25	0.86
Pregnancy			
Never	123	1.00 (referent)	1.00 (referent)
Ever	1025	0.88 (0.73–1.07)	0.82 (0.67–1.00)
Parity			
Nulliparous	158	1.00 (referent)	1.00 (referent)
1 child only	100	0.89 (0.69–1.15)	0.86 (0.65–1.13)
2 children	269	0.80 (0.65–0.98)	0.80 (0.64–0.99)
3 children	265	0.81 (0.66–1.00)	0.80 (0.65–1.00)
⩾4 children	351	0.90 (0.74–1.09)	0.85 (0.69–1.04)
P-trend		0.2	0.28
Induced abortion			
Never	864	1.00 (referent)	1.00 (referent)
Ever	82	1.13 (0.89–1.44)	1.12 (0.87–1.45)
Breastfed for ⩾1 month			
No	567	1.00 (referent)	1.00 (referent)
Yes	563	0.90 (0.79–1.01)	0.95 (0.83–1.08)
Age at menopause (years)			
<40	132	1.00 (referent)	1.00 (referent)
40–44	152	0.90 (0.71–1.15)	0.88 (0.68–1.14)
45–49	269	0.96 (0.77–1.19)	0.98 (0.78–1.24)
50–54	364	0.91 (0.74–1.12)	0.90 (0.72–1.12)
⩾55	135	0.94 (0.73–1.21)	0.98 (0.75–1.28)
P-trend		0.88	0.67
Hysterectomy			
No	673	1.00 (referent)	1.00 (referent)
Yes	476	0.97 (0.86–1.10)	1.06 (0.93–1.22)
Bilateral oophorectomy			
No	886	1.00 (referent)	1.00 (referent)
Yes	233	0.97 (0.84–1.13)	1.09 (0.93–1.28)
Age at oophorectomy (years)			
⩽34	46	1.00 (referent)	1.00 (referent)
35–39	57	1.48 (1.00–2.20)	1.51 (0.99–2.31)
40–44	67	1.20 (0.82–1.77)	1.28 (0.84–1.94)
45–49	65	0.93 (0.63–1.38)	1.07 (0.70–1.63)
⩾50	111	1.13 (0.80–1.61)	1.37 (0.94–2.00)
P-trend		0.12	0.22
Oral contraceptive use			
Never	839	1.00 (referent)	1.00 (referent)
Ever	310	0.72 (0.62–0.83)	0.74 (0.63–0.86)
Duration of OC use (years)			
1	96	1.00 (referent)	1.00 (referent)
2	58	1.08 (0.77–1.52)	1.14 (0.80–1.62)
3	83	1.19 (0.87–1.61)	1.18 (0.85–1.63)
4	73	0.94 (0.68–1.29)	0.94 (0.67–1.32)
P-trend		0.52	0.55

[a]Multivariable model adjusted for age, family history of colorectal cancer, race/ethnicity, education level, hormone therapy status, a history of diabetes, smoking status and body mass index.

Table 3. Hazard ratios and 95% confidence intervals for the association of reproductive and menstrual factors with colorectal cancer incidence stratified by hormone therapy use among women enrolled in the WHI-OS

	Hormone therapy use	
	Never use	Ever use
Factor	Multivariable HR[a] (95% CI)	Multivariable HR[a] (95% CI)
Age at menarche (years)		
⩽10	1.15 (0.71–1.85)	1.00 (0.58–1.74)
11–12	1.00 (referent)	1.00 (referent)
13–14	0.89 (0.71–1.11)	1.02 (0.81–1.28)
⩾15	0.72 (0.54–0.96)	0.92 (0.69–1.22)
P-trend	0.1	0.9
P-interaction	0.3	
Age at first child's birth (years)		
<20	1.00 (referent)	1.00 (referent)
20–29	0.99 (0.71–1.38)	0.97 (0.71–1.33)
⩾30	0.88 (0.56–1.38)	1.08 (0.69–1.67)
P-trend	0.79	0.84
P-interaction	0.56	
Age at last child's birth (years)		
<25	1.00 (referent)	1.00 (referent)
25–29	0.96 (0.65–1.42)	0.94 (0.67–1.30)
30–34	0.91 (0.62–1.35)	0.84 (0.60–1.18)
35–39	1.02 (0.68–1.53)	0.85 (0.57–1.25)
⩾40	0.81 (0.47–1.41)	1.08 (0.63–1.85)
P-trend	0.88	0.74
P-interaction	0.76	
Pregnancy		
Never	1.00 (referent)	1.00 (referent)
Ever	0.84 (0.63–1.11)	0.80 (0.59–1.07)
P-interaction	0.77	
Parity		
Nulliparous	1.00 (referent)	1.00 (referent)
1 child only	0.96 (0.66–1.39)	0.77 (0.51–1.16)
2 children	0.76 (0.56–1.03)	0.83 (0.61–1.13)
3 children	0.82 (0.61–1.11)	0.79 (0.58–1.08)
⩾4 children	0.76 (0.57–1.01)	0.94 (0.70–1.28)
P-trend	0.27	0.41
P-interaction	0.49	
Induced abortion		
Never	1.00 (referent)	1.00 (referent)
Ever	1.22 (0.85–1.75)	1.03 (0.71–1.49)
P-interaction	0.57	
Breast fed for ⩾1 month		
No	1.00 (referent)	1.00 (referent)
Yes	0.92 (0.76–1.10)	0.97 (0.81–1.17)
P-interaction	0.58	
Age at menopause (years)		
<40	1.00 (referent)	1.00 (referent)
40–44	0.93 (0.63–1.37)	0.81 (0.57–1.16)
45–49	0.89 (0.63–1.27)	1.06 (0.78–1.43)
50–54	0.80 (0.57–1.13)	0.99 (0.74–1.34)
⩾55	0.95 (0.64–1.42)	0.98 (0.67–1.41)
P-trend	0.64	0.6
P-interaction	0.48	
Hysterectomy		
No	1.00 (referent)	1.00 (referent)
Yes	1.23 (1.01–1.50)	0.90 (0.75–1.08)
P-interaction	0.02	
Age at oophorectomy (years)		
⩽34	1.00 (referent)	1.00 (referent)
35–39	1.99 (1.07–3.69)	1.23 (0.69–2.20)
40–44	1.54 (0.81–2.92)	1.13 (0.66–1.96)
45–49	1.38 (0.72–2.66)	0.90 (0.52–1.56)
⩾50	1.13 (0.62–2.07)	1.40 (0.86–2.30)
P-trend	0.19	0.27
P-interaction	0.33	
Oral contraceptive use		
Never	1.00 (referent)	1.00 (referent)
Ever	0.64 (0.51–0.81)	0.82 (0.67–1.01)
P-interaction	0.22	

Table 3. (Continued)

	Hormone therapy use	
	Never use	Ever use
Factor	**Multivariable HR[a] (95% CI)**	**Multivariable HR[a] (95% CI)**
Duration of OC use (years)		
1	1.00 (referent)	1.00 (referent)
2	0.79 (0.42–1.47)	1.38 (0.89–2.13)
3	1.58 (0.98–2.54)	0.94 (0.61–1.47)
4	0.71 (0.39–1.31)	1.03 (0.68–1.57)
P-trend	0.03	0.37
P-interaction	0.03	

[a]Multivariable model adjusted for age, family history of colorectal cancer, race/ethnicity, education level, a history of diabetes, smoking status and body mass index.

that may be relevant for colorectal cancer risk. For example, during gestation, ovarian production of oestradiol ceases and oestrone becomes the predominant circulating oestrogen (Kronenberg and Williams, 2010). In experimental models, oestrone has been shown to exert antiproliferative effects in colorectal cancer cell lines (English *et al*, 1999), while oestradiol has been demonstrated to have proliferative properties in same tissues (Di Domenico *et al*, 1996). Consistent with these findings, in a recent nested case–control study conducted in the Women's Health Initiative Clinical Trial non-intervention arms, we reported a significant inverse association between circulating oestrone levels (odds ratio $(OR)_{\text{quartile 4–quartile 1}} = 0.44$, 95% CI: 0.28–0.68; $P_{\text{trend}} = 0.001$), while total oestradiol levels were more weakly related to colorectal cancer development and without a statistically significant trend between quartiles (Murphy *et al*, 2015). It is therefore possible that the inverse relationship between parity and colorectal cancer observed in the current study may be a consequence of elevated oestrone exposure during pregnancy. Other changes to the hormonal milieu during pregnancy may also be relevant to our findings, such as a continuous production of progesterone, which has been shown to oppose the mitogenic effects of oestrogen in the reproductive tract (Kronenberg and Williams, 2010). Whether a similar effect would occur in the colonic tissue, in which progesterone receptors are expressed (Oshima *et al*, 1999), is unknown. Overall, additional studies measuring circulating endogenous sex hormones are warranted to investigate whether the oestrogenic and progestogenic environment caused by pregnancy influences colorectal cancer risk after menopause. Such analyses may inform on whether the inverse relationship observed between parity and colorectal cancer in the current study as well as in the NIH-AARP analysis has a biological basis.

Similar to the results of the NIH-AARP analysis, we observed a lower risk of colorectal cancer among women who underwent menarche at a later age but only among never users of hormone therapy (Zervoudakis *et al*, 2011). Although the linear trend across menarche age groups was not statistically significant, this may have been a consequence of a lack of power for this subgroup analysis. Age at menarche may be an indicator of the duration of exposure to cyclic ovarian function and lifetime oestrogenic exposure. However, cross-sectional analyses of premenopausal and post-menopausal women have found no relationships between age at menarche and circulating oestrogen (Bernstein *et al*, 1991; Hankinson *et al*, 1995), which suggests that other non-oestrogenic pathways may explain the inverse association between age at menarche and colorectal cancer. Early pubertal development has been related to higher early life and adult adiposity (Chen *et al*, 2011; Baek *et al*, 2015; Dreyfus *et al*, 2015), insulin resistance (Chen *et al*, 2011; Baek *et al*, 2015; Dreyfus *et al*, 2015), and pre-diabetes and diabetes (Elks *et al*, 2013; Baek *et al*, 2015; Dreyfus *et al*, 2015), all of which are established positive risk factors for colorectal cancer (Pischon *et al*, 2006; Gunter *et al*, 2008; Thrift *et al*, 2015; Tsilidis *et al*, 2015; Zhang *et al*, 2015). A recent analysis in the Nurses' Health Study reported positive relationships between estimated body fatness in childhood and adolescence and colorectal cancer risk, independent of adult BMI (Zhang *et al*, 2015). Our observed inverse relationship between age at menarche and colorectal cancer risk may, therefore, be a consequence of residual confounding, or could be mediated by early life adiposity and associated metabolic abnormalities, such as hyperinsulinaemia and insulin resistance. Future analyses with larger numbers of cases may be able to investigate the interrelationships between menarcheal age, lifecourse adiposity and colorectal cancer development.

The observation of a statistically significant inverse relationship between age at menarche and colorectal cancer only among never users of hormone therapy is also notable. Hormone therapy use has been consistently linked with lower colorectal cancer risk (Hebert-Croteau, 1998; Grodstein *et al*, 1999; Nanda *et al*, 1999; Johnson *et al*, 2009; Green *et al*, 2012; Simon *et al*, 2012a), and may counter the adverse metabolic effects of early menarche, explaining why we did not observe an association with colorectal cancer in this subgroup.

The lower colorectal cancer risk observed among users of oral contraceptives in the current analysis is consistent with a recent meta-analysis of eight cohort studies, which reported a pooled 14% lower colorectal cancer risk (relative risk (RR) = 0.86, 95% CI: 0.80–0.91) for ever users when compared with never users (Luan *et al*, 2015). However, we did not observe any relationship for shorter-term duration of oral contraceptive use (4+ years). Similarly, in the EPIC study, in which lower colorectal cancer risk was found for oral contraceptive users when compared with never users (Tsilidis *et al*, 2010), no relationship was observed for longer-term duration of oral contraceptive use (10+ years). The absence of a relationship by duration of use may be a consequence of the variable formulations of oral contraceptives used among women within and between studies. In the current study, we did not have information on the formulations of oral contraceptives that had been taken throughout participants' reproductive life. More detailed information on formulation may also inform on potential alteration in folate status as early oral contraceptives have been associated with folate inadequacy (Shojania, 1982) and efforts to correct this with folic acid supplementation were with oral contraceptive 'pill pack' use, an approach that while primarily designed to reduce folate insufficiency related to oral contraceptives, may have exerted an antitumorigenic effect.

Unlike the NIH-AARP study (Zervoudakis *et al*, 2011), but similar to the EPIC and Nurses' Health Study analyses (Martinez *et al*, 1997; Tsilidis *et al*, 2010), we did not observe a positive relationship for later age at menopause and colorectal cancer risk. We also observed null associations for colorectal cancer risk and age at birth of first and last child, pregnancy, induced abortion, breastfeeding, hysterectomy and bilateral oophorectomy, consistent with most prior prospective studies (Lin *et al*, 2007; Sakauchi

and Japan Collaborative Cohort Study for Evaluation of Cancer, 2007; Kabat *et al*, 2008; Tsilidis *et al*, 2010).

The strengths of this study include the comprehensive analysis of reproductive and menstrual patterns in a large well-characterised prospective cohort of more than 90 000 postmenopausal women and with more than 1000 colorectal cancer cases verified by tumour registry data and the relatively long follow-up of the study participants. The large sample size enabled us to perform stratified analyses with adequate statistical power, which allowed the assessment of women according to waist circumference strata or hormone therapy use, two factors that could have a confounding and effect modifying influence on the association between reproductive history and colorectal cancer. A possible limitation of this analysis is that all of the primary variables of interest were based on self-reported reproductive history and thus we cannot exclude the possibility of bias related to inaccurate recall; however, self-reported reproductive history has shown good agreement with medical records in validation studies (Hankinson *et al*, 1995; Chubak *et al*, 2004). Additionally, we lacked information on oral contraceptive formulations which would have been informative for understanding potential mechanisms. Finally, we cannot rule out the possibility that survivor bias influenced the observed results, in particular for early life exposures such as age at menarche, though we did not detect any effect modification by age suggesting that the findings were not different in younger or older women

In conclusion, having given birth to at least two children and ever use of oral contraceptives were associated with lower colorectal cancer risk. Further research into the biological mechanisms underlying these relationships is warranted and may provide insight into potential preventive measures for colorectal cancer in postmenopausal women.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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