DOI: 10.1093/jnci/djr101
Advance Access publication on March 29, 2011.

ARTICLE

Reproductive History and Risk of Colorectal Cancer in Postmenopausal Women

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Manuscript received September 20, 2010; revised February 23, 2011; accepted March 1, 2011.

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Background There are conflicting data regarding the role of sex hormones in colorectal cancer development. Whereas clinical trials data indicate that hormone therapy use reduces the risk of colorectal cancer, data from prospective cohort studies suggest that circulating estrogen levels are positively associated with colorectal cancer risk. A surrogate measure of lifetime estrogen exposure is reproductive history. We investigated the relationship between reproductive factors and the risk of colorectal cancer.

Methods Subjects were postmenopausal women enrolled in the National Institutes of Health–American Association of Retired Persons Diet and Health Study, a cohort of 214 162 individuals (aged 50–71 years) that included 2014 incident cases of colorectal cancer that occurred over a mean follow-up of 8.2 years. Questionnaires were used to collect data on reproductive factors, including ages at menarche, birth of first child, and menopause; parity, and use of oral contraceptives. Multivariable Cox proportional hazards models were constructed to examine associations between these reproductive factors and the risk of colorectal cancer, with adjustment for established colorectal cancer risk factors. All statistical tests were two-sided.

Results Age at menopause (≥55 vs <40 years: hazard ratio [HR] = 1.50, 95% confidence interval [CI] = 1.23 to 1.83; P_{trend} = .008) and age at birth of first child (≥30 vs ≤19 years: HR = 1.26, 95% CI = 1.01 to 1.58; P_{trend} = .05) were positively associated with the risk of colorectal cancer. Among women with no history of hormone therapy use, age at menarche (≥15 vs 11–12 years: HR = 0.73, 95% CI = 0.57 to 0.94; P_{trend} = .02) and parity (≥5 children vs no children: HR = 0.80, 95% CI = 0.63 to 1.02; P_{trend} = .10) were inversely associated with the risk of colorectal cancer.

Conclusion These data support a role for sex hormones in colorectal tumorigenesis and suggest that greater endogenous estrogen exposure may increase the risk of colorectal cancer in postmenopausal women.

J Natl Cancer Inst 2011;103:826–834

Colorectal cancer is the fourth most common cancer and the second leading cause of cancer death in the United States, with approximately 142 570 new cases and 51 370 colorectal cancer–related deaths expected in 2010 (1). Observational and experimental evidence suggest that sex hormones, particularly estrogen, play a role in colorectal cancer pathogenesis (2). Most notably, a substantial body of epidemiological data supports an inverse relationship between postmenopausal oral hormone therapy use and the risk of colorectal cancer (3), an association that was confirmed by results of the Women's Health Initiative (WHI) Clinical Trial, which reported a statistically significant decreased risk of colorectal cancer among women using estrogen plus progestin formulations (but not among women using estrogen alone) compared with women using placebo (4,5).

By contrast, two subsequent prospective studies reported a positive association between endogenous estrogen level and the risk of colorectal cancer in postmenopausal women. The first investigation, which was conducted in the WHI Observational Study, found that a high endogenous level of estrogen was associated with a 1.5-fold increased risk of developing colorectal cancer after adjustment for established colorectal cancer risk factors (6). Similarly, the New York University Women's Health Study reported a 60% increased risk of colorectal cancer for women in the highest quartile of circulating estrogen level compared with those in the lowest quartile (7). The positive associations between endogenous estrogen level and the risk of colorectal cancer reported by these investigations are consistent with laboratory data demonstrating the proliferative effects of exogenous estradiol in colorectal tissue and in colorectal cancer cell lines (8–11). The findings from these observational and experimental studies, when considered together with the data on hormone therapy use and colorectal cancer, suggest that endogenous and exogenous sex hormones may play different roles in colorectal tumorigenesis.

Reproductive factors, such as parity, age at birth of first child in parous women, age at menarche, and age at menopause, have been used as surrogate markers for lifetime exposure to endogenous estrogens (12,13), whereas serologic studies typically examine endogenous estrogen level at a specific time. These reproductive factors are associated with known sex hormone–related malignancies such as breast and endometrial cancers (14–16). Although nine prospective investigations have evaluated the associations between reproductive history and oral contraceptive use and the risk of colorectal cancer, their results were inconsistent (17–25). Possible reasons for the lack of consistent findings include the relatively small number of case subjects evaluated in the majority of these investigations [eg, only two studies (17,25) included more than 1000 colorectal cancer case subjects], and the inclusion of premenopausal women in all of the studies. The hormonal profile of premenopausal women differs markedly from that of postmenopausal women (26), and in several of the prior investigations (22,25), associations between reproductive factors and colorectal cancer risk appeared to differ according to menopausal status. In addition, the small sample size in many of the prior studies precluded stratification by hormone therapy use or body mass index (BMI), two factors that could confound the association between reproductive factors and the risk of colorectal cancer.

Therefore, to study the relationship between reproductive history and the risk of colorectal cancer and, by extension, the role of lifetime endogenous estrogen exposure in colorectal tumorigenesis, we examined associations between reproductive factors and incident colorectal cancer among postmenopausal women who were enrolled in the National Institutes of Health (NIH)–American Association of Retired Persons (AARP) Diet and Health Study, a large prospective cohort that included more than 214,000 postmenopausal women.

CONTEXT AND CAVEATS

Prior knowledge

Clinical trials and prospective studies have produced conflicting data regarding the role of sex hormones including estrogen in colorectal cancer development. Most prospective studies that have examined the association between reproductive history (a surrogate measure of lifetime estrogen exposure) and the risk of colorectal cancer have had substantial limitations.

Study design

A prospective cohort of postmenopausal women enrolled in the National Institutes of Health–American Association of Retired Persons Diet and Health Study completed questionnaires on reproductive factors, including ages at menarche, birth of first child, and menopause, parity, and use of oral contraceptives. Associations between these reproductive factors and the risk of colorectal cancer, with adjustment for established colorectal cancer risk factors, were examined.

Contribution

Older age at menopause and age at birth of first child were positively associated with the risk of colorectal cancer. Among women with no history of hormone therapy use, older age at menarche, and higher parity were inversely associated with the risk of colorectal cancer.

Implications

Greater endogenous estrogen exposure may increase the risk of colorectal cancer in postmenopausal women.

Limitations

Reproductive factors are surrogates for estrogen exposure. Reproductive history data were reported by the participants and thus the possibility of recall bias cannot be excluded. The analyses were not stratified by hormone therapy subtypes. Detailed data on other reproductive factors that have been linked with breast cancer were not available.

From the Editors

Materials and Methods

Study Population

The NIH-AARP Diet and Health Study is a large longitudinal cohort that was established in 1995–1996 to investigate the role of diet and lifestyle factors in cancer development (27). Briefly, a self-administered questionnaire was mailed to 3.5 million male and female AARP members aged 50–71 years residing in California, Florida, Pennsylvania, New Jersey, North Carolina, Louisiana, and the metropolitan areas of Atlanta, Georgia and Detroit, Michigan. A total of 567 169 questionnaires with satisfactorily completed dietary information were returned. Of the initial respondents, we excluded 179 individuals with duplicate questionnaires, 261 individuals who died before their questionnaire was processed, 321 individuals who moved out of the study area before returning their questionnaire, six individuals who withdrew from the investigation, and all men (N = 339 669), which resulted in a study sample of 226 733 women. We then excluded women who reported that they were still menstruating at baseline (ie, at questionnaire completion; n = 9684), and those who reported any prevalent cancer at baseline (n = 2887). Thus, the study population included 214 162 postmenopausal women. The Special Studies Institutional Review Board of the US National Cancer Institute approved this study and completion of the self-administered baseline questionnaire indicated informed consent.

Identification of Incident Colorectal Cancers

Incident colorectal cancers were ascertained by linkage to state cancer registries, all of which were certified by the North American Association of Central Cancer Registries as being more than 90% complete in their case ascertainment (28,29). Incident cases of colorectal cancer were defined by *International Classification of Diseases for Oncology, 3rd edition* (30) codes C180–C189, C199, or C209. Our analysis included all cases diagnosed through December 31, 2003.

Statistical Analysis

Differences in the distributions of baseline characteristics between case subjects and non-case subjects 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 factors and risk of colorectal cancer, we estimated hazard ratios (HRs) using Cox proportional hazards regression modeling, with time from study enrollment, in days, as the underlying time

metric. Individuals were censored at diagnosis of colorectal cancer, death, date of last contact for those who moved out of the study catchment area, or at the end of follow-up (December 31, 2003), whichever occurred first. Proportionality of the data was verified by graphical inspection. All multivariable models were adjusted for the following a priori–determined established colorectal cancer risk factors: age (categorized into 5-year age groups; <55 [referent], 55–59, 60–64, 65–69, or ≥70 years); BMI (classified according to the World Health Organization definition of overweight and obesity (31); <18.5, 18.5 to <25 [referent], 25 to <30, or ≥30 kg/m^2); alcohol consumption (continuous, in g/day); smoking status (never [referent], former, or current); race (white [referent], black, or other); family history of colorectal cancer (defined as having a first-degree relative with colorectal cancer); usual vigorous physical activity (at work or at home, including exercise, sport, and activities, such as carrying heavy loads, which lasted 20 minutes or more and caused either increases in breathing, heart rate, or perspiration; never or rarely [referent], 1–3 times/month, or ≥1 time/week); education level (high school diploma or less than high school diploma [referent] or more schooling); hormone therapy status (never [referent], current, or former); and a history of diabetes (yes or no). Additional variables, including a history of colorectal polyps, use of nonsteroidal anti-inflammatory drugs, red meat intake, and dietary calcium intake, 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). We also performed analyses stratified by ever use of hormone therapy (never use vs ever use) and BMI (normal body size vs overweight: <25 vs ≥25 kg/m^2). To test for statistically significant differences in the association between the reproductive factors and risk of colorectal cancer between strata of ever use of hormone therapy and BMI, 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. This study had greater than 80% statistical power to detect small-to-moderate interaction effects (defined as ratio of the HRs for the two contrasted strata [ie, never use to ever use of hormone therapy and BMI < 25 kg/m^2 to BMI ≥ 25 kg/m^2] < 1.7). All tests of statistical significance were two-sided, and P values less than .05 were considered statistically significant. All analyses were performed using Stata statistical software (version 10.1; Stata Corp, College Station, TX).

Results

Baseline Characteristics

During a mean follow-up of 8.2 years, 2014 postmenopausal women were diagnosed with colorectal cancer, of which 1483 were colon cancers and 531 were rectal cancers. Selected baseline characteristics of the study population are presented in Table 1. Compared with non-case subjects, colorectal cancer case subjects were slightly older, had a higher BMI, were more likely to have a positive family history of colorectal cancer and a personal history of polyps, were more likely to be current or former smokers, and more likely to be diabetic. In addition, colorectal cancer case subjects reported less physical activity and less education but higher consumption of saturated fat and red meat compared with non-case subjects. With respect to reproductive factors, colorectal cancer case subjects were less likely to have used oral contraceptives or hormone therapy or to have undergone oophorectomy, and, on average, underwent menopause at an older age, and gave birth to their first child at a younger age compared with non-case subjects.

Risk of Incident Colorectal Cancer

Table 2 presents age-adjusted and multivariable-adjusted hazard ratios and 95% confidence intervals (CIs) for associations between reproductive factors and the risk of colorectal cancer. Age at menopause was positively associated with incident colorectal cancer in the multivariable models (P_{trend} = .008). For example, women who were 55 years or older at menopause had an increased risk of colorectal cancer compared with women who were younger than 40 years at menopause (HR for ≥55 vs <40 years = 1.50, 95% CI = 1.23 to 1.83). This association was unaltered when the referent group was the age-at-menopause category that included the greatest number of women (HR for ≥55 vs 50–54 years = 1.33, 95% CI = 1.12 to 1.58; P_{trend} = .008). Age at birth of first child was also positively associated with risk of colorectal cancer (P_{trend} = .046). For example, compared with women who were 19 years or younger at the time of their first child's birth, those who were 30 years or older at their first child's birth had an increased risk of colorectal cancer (HR = 1.26, 95% CI = 1.01 to 1.58). We did not observe statistically significant associations between parity, age at menarche, or use of oral contraceptives and the 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 nor did restricting analyses to either colon or rectal cancer (data not shown).

In further analyses, we stratified the data by hormone therapy use (Table 3), and observed a statistically significant interaction between age at menarche, use of hormone therapy, and the risk of colorectal cancer ($P_{interaction}$ = .02). Among women with no history of hormone therapy use, having undergone menarche at age 15 years or older vs at 11–12 years of age was associated with a reduced risk of colorectal cancer (HR = 0.73, 95% CI = 0.57 to 0.94; P_{trend} = .02). However, among women who had ever used hormone therapy, there was no association between age at menarche and risk of colorectal cancer (P_{trend} = .22). We also observed a possible inverse association of parity and colorectal cancer among women who had ever used hormone therapy (P_{trend} = .10), which was not observed among women who had ever used hormone therapy (P_{trend} = .40). For example, among women who had never used hormone therapy, compared with nulliparous women, those who gave birth to five or more children were at decreased risk of colorectal cancer (HR = 0.80, 95% CI = 0.63 to 1.02). The associations between age at menopause, age at birth of first child, and use of oral contraceptives did not differ according to hormone therapy use, and none of the associations between the reproductive factors and risk of colorectal cancer differed according to BMI (data not shown).

Table 1. Selected baseline characteristics of the study population

Variable	Case subjects (N = 2014)	Non-case subjects (N = 212 148)	*P**
Mean age, y (SD)	64.1 (4.6)	62.2 (5.3)	<.001
Ethnicity, No. (%)			
White	1790 (88.9)	189 351 (89.3)	.12
Black	129 (6.4)	12 012 (5.7)	
Other	57 (2.8)	7317 (3.4)	
Missing	38 (1.9)	3468 (1.6)	
Body mass index, No. (%)			
<18.5 kg/m^2	29 (1.4)	2910 (1.4)	.001
18.5 to <25 kg/m^2	728 (36.1)	87 009 (41.0)	
25 to <30 kg/m^2	676 (33.7)	66 811 (31.5)	
≥30 kg/m^2	488 (24.2)	47 954 (22.6)	
Missing	93 (4.6)	7464 (3.5)	
Oral contraceptive use, No. (%)			
Never or <1 y	1327 (65.9)	128 874 (60.7)	<.001
≥1 y	640 (31.8)	79 892 (37.7)	
Missing	47 (2.3)	3382 (1.6)	
Family history of colorectal cancer, No. (%)			
No	1685 (83.7)	181 749 (89.9)	.007
Yes	230 (11.4)	20 482 (10.1)	
Missing	99 (4.9)	9917	
Mean alcohol intake, grams/day (SD)	6.8 (21)	6.0 (18.3)	.64
Physical activity, No. (%)			
Never or rarely	538 (26.7)	48 692 (23.0)	<.001
1–3 times/mo	249 (12.4)	29 886 (14.1)	
≥1–2 times/wk	1194 (59.3)	130 560 (61.5)	
Missing	33 (1.6)	3010 (1.4)	
Smoking history, No. (%)			
Never smoked	817 (40.6)	92 187 (43.5)	.04
Former smoker	808 (40.1)	81 752 (38.5)	
Current smoker	309 (15.3)	30 488 (14.4)	
Missing	80 (4.0)	7721 (3.6)	
Education level, No. (%)			
≤ High school	711 (35.3)	68 266 (32.2)	<.001
> High school	1221 (60.6)	136 484 (64.3)	
Missing	82 (4.1)	7398 (3.5)	
History of colorectal polyps, No. (%)			
No	1836 (91.2)	196 673 (92.7)	.008
Yes	178 (8.8)	15 475 (7.3)	
Missing	0 (0)	0 (0)	
Parity, No. (%)			
Nulliparous	295 (14.6)	31 763 (15.0)	.27
1 child	213 (10.6)	21 865 (10.3)	
2 children	478 (23.7)	54 058 (25.5)	
3–4 children	748 (37.1)	77 712 (36.6)	
≥5 children	254 (12.6)	24 260 (11.4)	
Missing	26 (1.4)	2490 (1.2)	
Age at birth of first live child, No. (%)			
Never pregnant	276 (13.7)	30 096 (14.2)	.02
≤19 y	326 (16.2)	37 701 (17.8)	
20–29 y	1229 (61.0)	128 550 (60.6)	
≥30 y	144 (7.2)	12 159 (5.7)	
Missing	39 (1.9)	3642 (1.7)	
Age at menopause, No. (%)			
<40 y	319 (15.8)	39 911 (18.8)	<.001
40–44 y	342 (17.0)	34 347 (16.2)	
45–49 y	498 (24.7)	52 636 (24.8)	
50–54 y	619 (30.7)	67 364 (31.8)	
≥55y	201 (10.0)	14 894 (7.0)	
Missing	35 (1.8)	2996 (1.4)	
Age at menarche, No. (%)			
<10 y	123 (6.1)	14 481 (6.8)	.38
11–12 y	845 (42.0)	88 333 (41.6)	
13–14 y	841 (41.8)	87 183 (41.1)	

(Table continues)

Table 1 (Continued).

Variable	Case subjects (N = 2014)	Non-case subjects (N = 212 148)	*P**
≥15 y	172 (8.5)	19 806 (9.3)	
Missing	33 (1.6)	2345 (1.2)	
Mean saturated fat intake, % total energy intake/day (SD)	17.4 (11.2)	16.9 (12.3)	.02
Mean red meat intake, g/1000 kcal/day (SD)	51.1 (47.1)	48.7 (55.3)	.003
Mean dietary calcium intake, mg/day (SD)	689.8 (438.6)	724.9 (470.2)	<.001
Hormone therapy, No. (%)			
Never used	1163 (57.7)	101 229 (47.7)	<.001
Current user	644 (32)	88 918 (41.9)	
Former user	206 (10.2)	21 422 (10.1)	
Missing	1 (0.1)	579 (0.3)	
Hysterectomy status, No. (%)			
No	1132 (56.2)	115 549 (54.5)	.05
Yes	839 (41.7)	93 578 (44.1)	
Missing	43 (2.1)	3021 (1.4)	
Status of ovaries, No. (%)			
Both removed	467 (23.2)	51 083 (24.1)	.03
Both intact	1391 (69.1)	143 106 (67.5)	
Other surgery	102 (5.0)	13 604 (6.4)	
Missing	54 (2.7)	4355 (2.0)	
Diabetes, No. (%)			
No	1805 (89.6)	195 690 (92.2)	<.001
Yes	209 (10.4)	16 458 (7.8)	
Missing	0 (0)	0 (0)	

* *P* values derived from Wilcoxon rank sum test for continuous data and the Pearson χ^2 test for categorical data. All *P* values are two-sided.

Discussion

In this large prospective investigation of postmenopausal women, we observed statistically significant positive associations between age at menopause and age at birth of first child with risk of incident colorectal cancer after controlling for multiple other colorectal cancer risk factors. In addition, among women with no history of hormone therapy use, age at menarche and parity were inversely associated with risk of colorectal cancer, although the latter association was not statistically significant. It is notable that these associations are similar to reported relationships between reproductive factors and risks of breast and endometrial cancers. For example, early age at menarche, late age at menopause, nulliparity, and later age at birth of first child are all established risk factors for breast and uterine cancers (16,32); these factors are believed to influence the risks of these malignancies by increasing lifetime exposure to endogenous sex hormones such as estrogen (14–16). Our finding that these same risk factors are also associated with the risk of colorectal cancer suggests that similar endocrinologic mechanisms may play a role in colorectal tumorigenesis.

Evidence that endogenous estrogen levels are positively associated with colorectal cancer development has recently emerged from two prospective studies conducted among postmenopausal women (6,7). Both investigations reported statistically significant positive associations between circulating estrogen levels and the risk of colorectal cancer, and one study (6) also controlled for circulating insulin and free insulin-like growth factor I (IGF-I) levels and obesity, which suggests that the relationship between estrogen and risk of colorectal cancer may be independent of obesity-related pathways. In vitro data also support a role for estrogen in colorectal tumorigenesis (8–10,33). For example, in human colorectal cancer cell lines, estradiol has been shown to activate the mitogen-activated protein kinase cascade, a pathway that plays a key role in the stimulation of DNA and protein synthesis, which induces cell growth and proliferation (10,11). In addition, colorectal cancer tissue was found to have higher levels of estradiol activity compared with nonmalignant colorectal tissue (34,35), and a cross-sectional study of colon cancer patients reported that colon carcinoma tissue had a statistically significant twofold higher level of total estrogen compared with normal colon mucosa (36). Low concentrations of intratumoral estrogen were also statistically significantly associated with better prognosis (36), and higher levels of estrogen receptor beta expression were reported in colorectal carcinomas compared with normal colonic mucosa (37).

Later age at menopause is an established risk factor for breast cancer (32); the higher number of ovulatory cycles and increased estrogen exposure associated with later menopause has been hypothesized to drive this relationship (14,15,38). Most previous studies of the association between reproductive history and the risk of colorectal cancer have generally reported a null association for age at menopause and risk of colorectal cancer. However, all of these investigations included premenopausal women and, thus, their statistical power to evaluate the association between age at menopause and risk of colorectal cancer was limited. In this study, we observed an inverse relationship between age at menarche and the risk of colorectal cancer. Like age at menopause, age at menarche is an indicator of the duration of exposure to cyclic ovarian function, and some (39,40), but not all (41), studies have demonstrated an inverse relationship between age at menarche and circulating

Table 2. Hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between reproductive factors and the risk of colorectal cancer among postmenopausal women enrolled in the National Institutes of Health–American Association of Retired Persons Diet and Health study

Variable	No. of case subjects	No. of non-case subjects	Age-adjusted HR (95% CI)	Multivariable HR* (95% CI)
Age at menopause, y				
<40	319	39911	1.00 (Referent)	1.00 (Referent)
40–44	342	34347	1.14 (0.97 to 1.32)	1.20 (1.01 to 1.42)
45–49	498	52636	1.11 (0.96 to 1.28)	1.15 (0.98 to 1.35)
50–54	619	67364	1.07 (0.93 to 1.22)	1.13 (0.97 to 1.31)
≥55	201	14894	1.44 (1.21 to 1.72)	1.50 (1.23 to 1.83)
P_{trend}†			.02	.008
Age at first live birth, y				
≤19	326	37701	1.00 (Referent)	1.00 (Referent)
20–29	1229	128550	1.01 (0.89 to 1.14)	1.08 (0.94 to 1.24)
≥30	144	12159	1.23 (1.01 to 1.50)	1.26 (1.01 to 1.58)
P_{trend}†			.13	.046
Age at menarche, y				
<10	123	14481	0.96 (0.79 to 1.16)	0.93 (0.76 to 1.14)
11–12	845	88333	1.00 (Referent)	1.00 (Referent)
13–14	841	87183	0.98 (0.89 to 1.08)	0.96 (0.86 to 1.06)
≥15	172	19806	0.87 (0.74 to 1.03)	0.88 (0.74 to 1.05)
P_{trend}†			.28	.34
Parity				
Nulliparous	295	31763	1.00 (Referent)	1.00 (Referent)
1 child	213	21865	1.05 (0.88 to 1.25)	1.05 (0.86 to 1.27)
2 children	478	54058	0.93 (0.81 to 1.08)	0.97 (0.83 to 1.14)
3–4 children	748	77712	0.95 (0.83 to 1.09)	0.98 (0.84 to 1.13)
≥5 children	254	24260	0.98 (0.82 to 1.15)	0.95 (0.79 to 1.14)
P_{trend}†			.44	.45
Oral contraceptive use				
Never or <1 y	1327	128874	1.00 (Referent)	1.00 (Referent)
≥1 y	640	79892	0.99 (0.90 to 1.09)	1.04 (0.93 to 1.16)
P_{trend}†			.82	.50

* Multivariable model adjusted for age, body mass index, education level, alcohol consumption, family history of colorectal cancer, race, smoking history, diabetes, physical activity level, and use of hormone therapy.

† Statistical significance tests for trend were calculated by entering the reproductive factor (categorical variable) into the model as a single continuous variable.

estrogen level. The Nurses' Health Study (19) and the Japan Collaborative Cohort Study (21) reported statistically significant inverse trends for the association between age at menarche and risk of colorectal cancer, which is consistent with our data. However, other investigations that evaluated the association between age at menarche and risk of colorectal cancer reported null associations (17,18,20,23,25). It is interesting that in this study, the inverse relationship between age at menarche and risk of colorectal cancer was only observed among women with no history of hormone therapy use. One potential explanation for this observation is that among women using hormone therapy, the association of earlier age at menarche and colorectal cancer incidence is masked by the strong protective effect of hormone therapy use on risk of colorectal cancer.

In this study, later age at birth of first child was positively associated with the risk of colorectal cancer. This finding is also consistent with data from the Nurses' Health Study, which reported a statistically significant positive association between age at first pregnancy and risk of colorectal cancer (relative risk for women age ≥30 years at first pregnancy vs <24 years = 1.57, 95% CI = 1.15 to 2.14) (19). Two other cohort studies also reported positive, albeit non-statistically significant associations between age at birth of first child and risk of colorectal cancer (18,21). Although later age at birth of first child has also been found to be positively associated with the risk of breast cancer (14), the mechanism underlying the positive association with colorectal cancer is less apparent than it is for breast cancer. For example, in the case of breast cancer, in the period between the onset of menarche and the first pregnancy, the breast tissue is undifferentiated and is particularly susceptible to carcinogenic insults (42,43). Therefore, the longer this period of susceptibility, the greater is the risk of breast tumorigenesis. It is unknown whether endocrinologic changes that occur during pregnancy also confer a similar type of protection against colorectal carcinogenesis or whether the colonic mucosa is particularly susceptible to mutagenic events before pregnancy. Further investigation into the mechanism underlying the association between age at birth of first child and the risk of colorectal cancer is warranted.

It is interesting that although parity was inversely associated with the risk of colorectal cancer in this study, as with the association between age at menarche and risk of colorectal cancer, this relationship was only apparent among women who had never used hormone therapy. Although most of the prior studies did not find statistically significant associations between parity and the risk of colorectal cancer, one cohort study (23) demonstrated that compared with nulliparous women, women who had given birth to two or more children had a decreased risk of malignancy in the cecum

Table 3. Hazard ratios (HRs) and 95% confidence intervals (CIs) for the association of age at menarche and parity with colorectal cancer incidence, stratified by hormone therapy use

Variable	Never used hormone therapy		Ever used hormone therapy	
	No. of case subjects/No. of non-case subjects	HR* (95% CI)	No. of case subjects/No. of non-case subjects	HR* (95% CI)
Age at menarche, y				
<10	76/7024	1.00 (0.77 to 1.30)	47/7422	0.84 (0.60 to 1.18)
11–12	486/41 236	1.00 (Referent)	359/46 920	1.00 (Referent)
13–14	478/41 158	0.92 (0.80 to 1.05)	362/45 796	1.01 (0.86 to 1.19)
≥15	93/9816	0.73 (0.57 to 0.94)	79/9926	1.13 (0.87 to 1.47)
P_{trend}†		.02		.22
$P_{interaction}$‡		.02		
Parity				
Nulliparous	185/16 062	1.00 (Referent)	110/15 635	1.00 (Referent)
1 child	122/10 185	0.96 (0.75 to 1.24)	90/11 629	1.19 (0.88 to 1.62)
2 children	264/23 584	0.94 (0.77 to 1.16)	214/30 343	1.04 (0.81 to 1.34)
3–4 children	420/36 051	0.93 (0.76 to 1.12)	328/41 457	1.07 (0.84 to 1.36)
≥5 children	152/13 295	0.80 (0.63 to 1.02)	101/10 903	1.23 (0.92 to 1.66)
P_{trend}†		.10		.40
$P_{interaction}$‡		.26		

* Multivariable model adjusted for age, body mass index, education level, alcohol consumption, family history of colorectal cancer, race, smoking history, diabetes, and physical activity level.

† Statistical significance tests for trend were calculated by entering the reproductive factor (categorical variable) into the model as a single continuous variable.

‡ Tests for statistically significant difference in the association of age at menarche or parity with colorectal cancer risk according to hormone therapy use (never vs ever used hormone therapy).

or ascending colon. Pregnancy leads to substantial changes in the hormonal milieu, which may be protective against colorectal cancer. For example, during gestation, production of ovarian estradiol ceases and the predominant estrogen in circulation is estrone (26). Whereas estradiol has been demonstrated to have proliferative properties in colorectal cancer cell lines (10), estrone has been shown to exert antiproliferative effects in these tissues (35). Therefore, it is possible that a hormonal profile in which estrone predominates confers protection against colorectal tumorigenesis. We note, however, that the New York University Women's Health Study reported a weak positive association between circulating estrone levels and the risk of colorectal cancer (7). Pregnancy is also characterized by continuous production of progesterone from the early gestation period until delivery (26). Progesterone opposes the mitogenic effects of estrogen in reproductive tract tissues (eg, the endometrium) (26), and it is conceivable that progestagens may exert similar effects on other tissues, such as the colonic epithelium. Both normal and malignant colon cells express progesterone receptors (44–46); however, the direct biological effects of progesterone on colonic tissue are not understood.

In contrast to our results, a recent study conducted in the European Prospective Investigation into Cancer (EPIC), which evaluated a similar number of colorectal cancer case subjects as in this study, found no association between reproductive history and the risk of colorectal cancer (25). We note, however, that the women enrolled in the EPIC cohort were considerably younger than the NIH-AARP participants and that 25% of the case subjects in the EPIC study were premenopausal or perimenopausal women, in whom the association between reproductive history and risk of colorectal cancer may differ from that in postmenopausal women due to substantial differences in the endocrinologic profile. In addition, a comparison of the baseline characteristics of the EPIC and NIH-AARP populations reveals some notable differences that may also influence the relationship between reproductive history and risk of colorectal cancer. For example, oral contraceptive use was much more prevalent among EPIC participants compared with NIH-AARP study subjects; the profound changes that oral contraceptive use has on the hormonal milieu (eg, reduced number of ovulation cycles and potentially lower endogenous estrogen levels) may influence the association of reproductive history with colorectal cancer risk.

The associations between reproductive history and incident colorectal cancer observed in this study suggest that increased exposure to endogenous estrogen increases risk of colorectal cancer, a finding that is consistent with the results of two prospective cohort studies of circulating estrogen levels and colorectal cancer (6,7). However, these findings stand in direct contrast to the results from the WHI Clinical Trial (4) and from a large number of observational investigations that indicate that use of hormone therapy (ie, exogenous estrogen) protects against colorectal cancer development. Several hypotheses have been advanced to explain the disparate results (6). First, oral hormone therapy may expose the liver to a large bolus of estrogen (the so-called first-pass effect), which could alter hepatic protein synthesis. It is known that oral estrogens result in decreased synthesis of insulin–IGF-I axis components (47,48), which are positively associated with the risk of colorectal cancer (6). Conversely, expression of sex hormone–binding globulin, the main estrogen-binding protein in circulation, is increased in hormone therapy users, leading to reduced levels of bioavailable estrogen (49). In addition, oral estrogens may also induce or suppress other as-yet uncharacterized pathways that play an important role in colorectal cancer pathogenesis. Second,

the protective effect of hormone therapy use against colorectal cancer may not lie in the estrogen components of oral hormone therapy. In the WHI Clinical Trial, estrogen plus progestin therapy was shown to protect against colorectal cancer, whereas estrogen alone had no effect (4,5). It is possible, therefore, that progestin is the protective component in hormone therapy and that progesterone may be etiologically relevant to colorectal cancer (5). Finally, it is also important to consider that other hormonal and physiological mechanisms related to colorectal tumorigenesis, including alterations in the insulin–IGF-I axis (6,50), may also underlie the association between reproductive history and colorectal cancer.

The strengths of this study include the large, well-characterized prospective cohort of more than 200 000 postmenopausal women with more than 2000 colorectal cancer cases verified by tumor registry data and the relatively long follow-up of the study participants. The age-specific colorectal cancer incidence rates in this study were highly consistent with those reported by the Surveillance, Epidemiology, and End Results Program (51), indicating the completeness of the colorectal cancer incidence data and suggesting that there was no substantial bias in cohort selection relating to voluntary response to the NIH-AARP dietary questionnaire. The large sample size enabled us to perform stratified analyses with adequate statistical power, which allowed the assessment of women according to BMI or hormone therapy use, two factors that could have a confounding effect on the association between reproductive history and colorectal cancer.

This study has several possible limitations. In particular, 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 (12,13). In addition, we could not further stratify the analyses by hormone therapy subtypes, and we lacked more detailed data on other reproductive factors, such as age at birth of last child, breastfeeding history, and history of induced or spontaneous abortion, which have been linked with breast cancer (52–56) and which could help further elucidate the role of sex hormones in colorectal cancer development.

In conclusion, the findings of this investigation support a role for sex hormones in colorectal tumorigenesis and suggest that greater endogenous estrogen exposure may increase the risk of colorectal cancer in postmenopausal women. Further prospective studies that directly assess levels of circulating estrogens and other sex hormones in postmenopausal women in relation to colorectal cancer risk would be highly informative.

References

1. American Cancer Society. *Cancer Facts and Figures* 2010. http://www5.cancer.org/downloads/STT/Cancer_Facts_and_Figures_2010.pdf.
2. McMichael AJ, Potter JD. Reproduction, endogenous and exogenous sex hormones, and colon cancer: a review and hypothesis. *J Natl Cancer Inst.* 1980;65(6):1201–1207.
3. Grodstein F, Newcomb PA, Stampfer MJ. Postmenopausal hormone therapy and the risk of colorectal cancer: a review and meta-analysis. *Am J Med.* 1999;106(5):574–582.
4. Chlebowski RT, Wactawski-Wende J, Ritenbaugh C, et al. Estrogen plus progestin and colorectal cancer in postmenopausal women. *N Engl J Med.* 2004;350(10):991–1004.
5. Ritenbaugh C, Stanford JL, Wu L, et al. Conjugated equine estrogens and colorectal cancer incidence and survival: the Women's Health Initiative randomized clinical trial. *Cancer Epidemiol Biomarkers Prev.* 2008;17(10):2609–2618.
6. Gunter MJ, Hoover DR, Yu H, et al. Insulin, insulin-like growth factor-I, endogenous estradiol, and risk of colorectal cancer in postmenopausal women. *Cancer Res.* 2008;68(1):329–337.
7. Clendenen TV, Koenig KL, Shore RE, et al. Postmenopausal levels of endogenous sex hormones and risk of colorectal cancer. *Cancer Epidemiol Biomarkers Prev.* 2009;18(1):275–281.
8. Narayan S, Rajakumar G, Prouix H, et al. Estradiol is trophic for colon cancer in mice: effect on ornithine decarboxylase and c-myc messenger RNA. *Gastroenterology.* 1992;103(6):1823–1832.
9. Singh S, Paraskeva C, Gallimore PH, et al. Differential growth response to oestrogen of premalignant and malignant colonic cell lines. *Anticancer Res.* 1994;14(3A):1037–1041.
10. Di Domenico M, Castoria G, Bilancio A, et al. Estradiol activation of human colon carcinoma-derived Caco-2 cell growth. *Cancer Res.* 1996;56(19):4516–4521.
11. Hennessy BA, Harvey BJ, Healy V. 17beta-Estradiol rapidly stimulates c-fos expression via the MAPK pathway in T84 cells. *Mol Cell Endocrinol.* 2005;229(1–2):39–47.
12. Hankinson SE, Colditz GA, Hunter DJ, et al. Reproductive factors and family history of breast cancer in relation to plasma estrogen and prolactin levels in postmenopausal women in the Nurses' Health Study (United States). *Cancer Causes Control.* 1995;6(3):217–224.
13. Chubak J, Tworoger SS, Yasui Y, et al. Associations between reproductive and menstrual factors and postmenopausal sex hormone concentrations. *Cancer Epidemiol Biomarkers Prev.* 2004;13(8):1296–1301.
14. Kelsey JL, Gammon MD, John EM. Reproductive factors and breast cancer. *Epidemiol Rev.* 1993;15(1):36–47.
15. Chavez-MacGregor M, Elias SG, Onland-Moret NC, et al. Postmenopausal breast cancer risk and cumulative number of menstrual cycles. *Cancer Epidemiol Biomarkers Prev.* 2005;14(4):799–804.
16. Dossus L, Allen N, Kaaks R, et al. Reproductive risk factors and endometrial cancer: the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer.* 2009;127(2):442–451.
17. Kabat GC, Miller AB, Rohan TE. Oral contraceptive use, hormone replacement therapy, reproductive history and risk of colorectal cancer in women. *Int J Cancer.* 2008;122(3):643–646.
18. Lin J, Zhang SM, Cook NR, et al. Oral contraceptives, reproductive factors, and risk of colorectal cancer among women in a prospective cohort study. *Am J Epidemiol.* 2007;165(7):794–801.
19. Martinez ME, Grodstein F, Giovannucci E, et al. A prospective study of reproductive factors, oral contraceptive use, and risk of colorectal cancer. *Cancer Epidemiol Biomarkers Prev.* 1997;6(1):1–5.
20. Akhter M, Inoue M, Kurahashi N, et al. Reproductive factors, exogenous female hormone use and colorectal cancer risk: the Japan Public Health Center-based Prospective Study. *Eur J Cancer Prev.* 2008;17(6):515–524.
21. Tamakoshi K, Wakai K, Kojima M, et al. A prospective study of reproductive and menstrual factors and colon cancer risk in Japanese women: findings from the JACC study. *Cancer Sci.* 2004;95(7):602–607.
22. Kvale G, Heuch I. Is the incidence of colorectal cancer related to reproduction? A prospective study of 63,000 women. *Int J Cancer.* 1991;47(3):390–395.
23. Kravdal O, Glattre E, Kvale G, et al. A sub-site-specific analysis of the relationship between colorectal cancer and parity in complete male and female Norwegian birth cohorts. *Int J Cancer.* 1993;53(1):56–61.
24. Fernandez E, La Vecchia C, Balducci A, et al. Oral contraceptives and colorectal cancer risk: a meta-analysis. *Br J Cancer.* 2001;84(5):722–727.
25. Tsilidis KK, Allen NE, Key TJ, et al. Oral contraceptives, reproductive history and risk of colorectal cancer in the European Prospective Investigation into Cancer and Nutrition. *Br J Cancer.* 2010;103(11):1755–1759.
26. Kronenberg HM. *Williams Textbook of Endocrinology.* 11th ed. Philadelphia, PA: Saunders; 2007.

27. Schatzkin A, Subar AF, Thompson FE, et al. Design and serendipity in establishing a large cohort with wide dietary intake distributions: the National Institutes of Health-American Association of Retired Persons Diet and Health Study. *Am J Epidemiol.* 2001;154(12):1119–1125.
28. North American Association of Central Cancer Registries (NAACCR). *Standards for Completeness, Quality, Analysis and Management of Data.* http://www.naaccr.org/StandardsandRegistryOperations/VolumeIII.aspx.
29. Michaud DS, Midthune D, Hermansen S, et al. Comparison of cancer registry case ascertainment with SEER estimates and self-reporting in a subset of the NIH-AARP Diet and Health Study. *J Reg Manag.* 2005; 32(2):70–75.
30. World Health Organization. *International Classification of Diseases for Oncology (ICD-O).* 3rd ed. Geneva, Switzerland: CAP Press and Publications; 2000.
31. World Health Organization. BMI Classification. http://apps.who.int/bmi/index.jsp?introPage=intro_3.html. Accessed September, 2010.
32. Lacey JV Jr, Kreimer AR, Buys SS, et al. Breast cancer epidemiology according to recognized breast cancer risk factors in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial Cohort. *BMC Cancer.* Mar 17;9:84.
33. Winter DC, Taylor C, CO'Sullivan G, et al. Mitogenic effects of oestrogen mediated by a non-genomic receptor in human colon. *Br J Surg.* 2000;87(12):1684–1689.
34. Oduwole OO, Isomaa VV, Nokelainen PA, et al. Downregulation of estrogen-metabolizing 17 beta-hydroxysteroid dehydrogenase type 2 expression correlates inversely with Ki67 proliferation marker in colon-cancer development. *Int J Cancer.* 2002;97(1):1–6.
35. English MA, Kane KF, Cruickshank N, et al. Loss of estrogen inactivation in colonic cancer. *J Clin Endocrinol Metab.* 1999;84(6):2080–2085.
36. Sato R, Suzuki T, Katayose Y, et al. Steroid sulfatase and estrogen sulfotransferase in colon carcinoma: regulators of intratumoral estrogen concentrations and potent prognostic factors. *Cancer Res.* 2009;69(3): 914–922.
37. Grivas PD, Tzelepi V, Sotiropoulou-Bonikou G, et al. Expression of ERalpha, ERbeta and co-regulator PELP1/MNAR in colorectal cancer: prognostic significance and clinicopathologic correlations. *Cell Oncol.* 2009;31(3):235–247.
38. Key TJ, Verkasalo PK, Banks E. Epidemiology of breast cancer. *Lancet Oncol.* 2001;2(3):133–140.
39. Apter D, Reinila M, Vihko R. Some endocrine characteristics of early menarche, a risk factor for breast cancer, are preserved into adulthood. *Int J Cancer.* 1989;44(5):783–787.
40. MacMahon B, Trichopoulos D, Brown J, et al. Age at menarche, urine estrogens and breast cancer risk. *Int J Cancer.* 1982;30(4):427–431.
41. Trichopoulos D, Brown J, MacMahon B. Urine estrogens and breast cancer risk factors among post-menopausal women. *Int J Cancer.* 1987; 40(6):721–725.
42. Russo J, Russo IH. Differentiation and breast cancer. *Medicina (B Aires).* 1997;57(suppl 2):81–91.
43. Russo J, Tay LK, Russo IH. Differentiation of the mammary gland and susceptibility to carcinogenesis. *Breast Cancer Res Treat.* 1982;2(1):5–73.
44. Oshima CT, Wonraht DR, Catarino RM, et al. Estrogen and progesterone receptors in gastric and colorectal cancer. *Hepatogastroenterology.* 1999;46(30):3155–3158.
45. Hendrickse CW, Jones CE, Donovan IA, et al. Oestrogen and progesterone receptors in colorectal cancer and human colonic cancer cell lines. *Br J Surg.* 1993;80(5):636–640.
46. Singh S, Sheppard MC, Langman MJ. Sex differences in the incidence of colorectal cancer: an exploration of oestrogen and progesterone receptors. *Gut.* 1993;34(5):611–615.
47. Weissberger AJ, Ho KK, Lazarus L. Contrasting effects of oral and transdermal routes of estrogen replacement therapy on 24-hour growth hormone (GH) secretion, insulin-like growth factor I, and GH-binding protein in postmenopausal women. *J Clin Endocrinol Metab.* 1991;72(2):374–381.
48. Campagnoli C, Abba C, Ambroggio S, et al. Differential effects of progestins on the circulating IGF-I system. *Maturitas.* 2003;46(suppl 1):S39–S44.
49. Raudaskoski T, Laatikainen T, Kauppila A. Sex-hormone binding globulin as an indicator of the hepatic impacts of continuous combined hormone replacement regimens. *Maturitas.* 1998;29(1):87–92.
50. Key TJ, Appleby PN, Reeves GK, et al. Insulin-like growth factor 1 (IGF1), IGF binding protein 3 (IGFBP3), and breast cancer risk: pooled individual data analysis of 17 prospective studies. *Lancet Oncol.* 11(6): 530–542.
51. *Surveillance, Epidemiology, and End Results (SEER) Program (*www.seer.cancer.gov*) Research Data (1973–2007).*: National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch; 2010.
52. Kvale G, Heuch I. A prospective study of reproductive factors and breast cancer. II. Age at first and last birth. *Am J Epidemiol.* 1987;126(5):842–850.
53. Trichopoulos D, Hsieh CC, MacMahon B, et al. Age at any birth and breast cancer risk. *Int J Cancer.* 1983;31(6):701–704.
54. Stuebe AM, Willett WC, Xue F, et al. Lactation and incidence of premenopausal breast cancer: a longitudinal study. *Arch Intern Med.* 2009;169(15): 1364–1371.
55. Howe HL, Senie RT, Bzduch H, et al. Early abortion and breast cancer risk among women under age 40. *Int J Epidemiol.* 1989;18(2):300–304.
56. Ewertz M, Duffy SW. Risk of breast cancer in relation to reproductive factors in Denmark. *Br J Cancer.* 1988;58(1):99–104.

Funding

This publication was made possible by the CTSA Grant UL1 RR025750 and KL2 RR025749 and TL1 RR025748 from the National Center for Research Resources, a component of the National Institutes of Health (NIH), and NIH roadmap for Medical Research.

Notes

The contents of this publication are solely the responsibility of the authors and do not necessary represent the official view of the National Center for Research Resources or NIH. The study sponsor had no role in the design of the study, data collection, the analysis or interpretation of the data, the writing of the article, or the decision to submit for publication.

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