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Reproductive History and Risk of Colorectal Adenocarcinoma

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Background: Sex hormones may be associated with colorectal adenocarcinoma, although the association of pregnancy history and risk of colorectal cancer is not consistent.

Methods: We conducted a population-based nested case-control study of persons born between 1932 and 2008 who are in the Swedish Multi-Generation Register. In total, 12,915 women and 15,519 men with colorectal adenocarcinoma were identified during follow-up in the Swedish Cancer Register; 10 age- and sex-matched controls were selected for each case. Number of children and age at first and last birth were analyzed in relation to the risk of colorectal adenocarcinoma, using conditional logistic regression, to estimate odds ratios (ORs) and 95% confidence intervals (CIs).

Results: Compared with women without children, women with 1 or 2 children had an OR of 1.02 (95% CI = 0.93–1.13) of developing adenocarcinoma in the proximal colon; those with 3 or 4 children, 1.18 (1.06–1.32); and those with ≥5 children, 1.30 (1.05–1.61) (test for trend $P < 0.01$). The corresponding associations in men were 0.92 (0.84–1.00), 1.02 (0.92–1.13), and 0.97 (0.78–1.20), respectively (test for trend $P = 0.13$).

Conclusions: Higher parity in women was associated with the risk of adenocarcinoma of the proximal colon, although not the distal colon or rectum. A similar risk with family size was not seen for fathers. Still, the influence of lifestyle factors cannot be ruled out.

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Studies have suggested that sex hormones might be relevant to the development of colorectal cancer. Women exposed to exogenous estrogen, including HRT or oral contraceptives, seem to be at a decreased risk of colorectal cancer in observational studies.[1–6] An association between HRT and colorectal cancer has also been found in clinical trials, and this association may be influenced by type, duration, and timing of the hormonal therapy.[7,8]

However, studies regarding the role of endogenous hormone exposure in the etiology of colorectal cancer are few, partly because of the difficulty in measuring the exposure. Reproductive history, including parity (number of children), and age at first and last birth, is a commonly used surrogate measurement of lifetime exposure to endogenous estrogen.[9,10] The association between reproductive history and risk of colorectal cancer, however, is not consistent.[11–13] High parity and an early age at first birth have been found to be related to a reduced risk of colorectal cancer in many case-control studies,[9,10,14,15] while most cohort studies have not detected associations or have found opposite results.[1,16–20]

The available studies regarding reproductive factors and colorectal cancer have limitations. Most used a retrospective case-control design with a small sample size. In addition, although prospective cohort studies have increasingly been reported, most data collection have been based on questionnaires that could be vulnerable to biases. For example, the definition of parity is easily misunderstood. Moreover, because the proximal and distal colon originate from different embryological sources, tumors arising in these anatomical locations might have different etiologies, yet only a few studies have analyzed these tumors separately.[14,21] Similarly, different histological types of colorectal malignancies might not have a shared etiology, and the main histological type, adenocarcinoma, has not yet been specifically studied. Finally, reproductive factors have usually been studied only in women. The inclusion of men provides the possibility of evaluating the influence of confounding by shared lifestyle factors in both sexes.

Conflicting results and methodological concerns in the existing literature indicate a need for well-designed studies with large sample sizes to address the association between reproductive factors and the risk of developing colorectal cancer. We conducted a large cohort study with a long follow-up to examine associations between reproductive factors (parity, age at first and last birth) and the risk of developing colorectal adenocarcinoma by anatomical location in women and men.

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METHODS

Data Sources

This study was based on data collected from 5 nationwide Swedish population-based registers: the Multi-Generation Register, the Cancer Register, the Patient Register, the Register of the Total Population, and the Education Register. The personal identity number (a unique 10-digit identification number assigned to each resident of Sweden) was used to link each participant among the registers.

The Multi-Generation Register is based on indexed persons born in 1932 and later who were alive and residing in Sweden from 1961 onward, including the whole Swedish population since 1961. Parents, siblings, and children are identified, thus enabling data retrieval on number of children and age at childbirth. Reproductive factors such as parity, age at first birth, and age at last birth were collected from this register.

The Swedish Cancer Register was initiated in 1958. All newly diagnosed tumors in Sweden must be reported to this Register, by both the clinician and the pathologist or cytologist. The Cancer Register is approximately 98% complete.[22] We used the Cancer Register mainly to retrieve the diagnosis of colorectal cancer and other cancers.

The Swedish Patient Register was established in 1964 and has covered the entire nation since 1987. The main information collected includes discharge diagnoses, surgical procedures, hospitalization dates, and names of the hospitals and departments. The *International Classification of Diseases* (*ICD*) versions 8, 9, and 10 were used to identify patients with diagnosis codes. Comorbidities and oophorectomy were recorded using data from the Patient Register.

The Register of the Total Population provides 100% complete and continuously updated information on dates of emigration, immigration, births, and deaths. We obtained data on death and migration from this register.

The Education Register provides information on the highest attained educational level for Swedish residents. The education data for all residents are collected yearly from schools and universities.

Study Design

A nested case-control study was conducted based on a cohort from the Multi-Generation Register between 1 January 1932 and 31 December 2008. The reason for a nested case-control design rather than a cohort study is that Statistics Sweden and the Swedish National Board of Health and Welfare do not permit access to data on the entire population. Because a nested case-control study has statistical power similar to that of a cohort study, we chose a nested case-control design. The minimum age at entry into the study was 15 years.

Case Patients

The cases comprised all cohort members who were diagnosed with adenocarcinoma of the colon or rectum during 1960 and 2008. The diagnosis codes were classified using the *International Classification of Diseases*, version 7 (*ICD-7*). We considered 3 parts of the colon and rectum: (1) the proximal colon (*ICD-7* codes 1530, 1531, and 1534, including the cecum, ascending colon, transverse colon, hepatic flexure, the splenic flexure, and appendix); (2) the distal colon (*ICD-7* codes 1532 and 1533, including the descending colon and the sigmoid colon); and (3) the rectum (*ICD-7* code 1540, including the rectum and rectosigmoid junction). Colorectal adenocarcinoma cases included all adenocarcinomas in the colon or rectum (parts 1–3) and in sites within the colon or rectum that were not further specified. The histological code 096 in the WHO/HS/CANC/24.1 classification was used as the definition of adenocarcinoma.

Control Participants

For each case, 10 control subjects were randomly sampled from the study cohort based on incidence density sampling and matched for the sex and year. To be eligible, a control had to be alive, have no previous diagnosis of any gastrointestinal cancer, and have no history of emigration before the date of the diagnosis of the case. The number of births among control participants was assessed only up to the date of the diagnosis of the corresponding case.

Statistical Analyses

Multivariable conditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) as measures of association between parity and age at first birth in relation to the risk of colorectal adenocarcinoma. Parity, age at first birth, age at last birth, and time since most recent birth were included in the same model to separate the effects of each variable after mutual adjustment. We excluded time since most recent birth from the final model in order to facilitate the interpretation of the model and to evaluate the association of the other 3 reproductive variables with the risk of colorectal adenocarcinoma in the parous women (or men with children). Parity was defined as the number of live births before the study endpoints and was categorized into 4 groups: 0, 1–2, 3–4, or 5 or more. Any births occurring after the endpoint (diagnosis of the case or the corresponding endpoint of the control) were excluded from the calculation of parity. Similarly, definition of the last birth in this study might not be the last child for that woman or man but the last child before the corresponding endpoint.

Age at first birth was categorized into 4 groups: <18, 18–24, 25–34, and 35+ years. The 18 to 24 age group was set as the reference because there were few cases of men aged younger than 18 years. Age at last birth was categorized into 3 groups: <25, 25–34 (reference), and 35+ years. Comparison between nonparous and parous participants was performed when age at first birth was not included in the model, using 0 births as the reference. When parity and age at first birth or age at last birth were included in the same statistical model, the results were presented only for parous

participants, using 1 or 2 births as the reference group. To identify potential differences in effects in premenopausal and postmenopausal women, analyses were also stratified into women and men, aged younger than 50 years versus 50 years and older at diagnosis, a cutpoint consistent with that reported by previous research. An analysis of women older than 55 years was also included, assumed to represent women after menopause. To clarify whether the association of parity, age at first birth, and age at last birth with risk of colorectal adenocarcinoma varied between women and men, we report *P* values for interaction. We also compared the risk estimates in the proximal colon with the distal colon using a multinominal logit model.

The following potential confounding factors were considered in the analyses: educational level (categorized into ≤9, 10–12, or ≥13 years), diabetes (yes or no), obesity diagnosis (yes or no), diagnosis associated with tobacco smoking (yes or no), diagnosis associated with overconsumption of alcohol (yes or no), and bilateral oophorectomy (representing HRT in women; yes or no). The diagnosis codes were retrieved from the Patient Register. The final model included only education and reproductive history, because the inclusion of other evaluated variables did not materially alter the results. The *P* values for trends for parity and age at first birth were estimated based on the median value of the specific categories using conditional logistic regression.

All analyses were performed using the SAS Statistical Package (version 9.0, SAS Institute Inc., Cary, NC). The study was approved by the Regional Ethical Review Board in Stockholm.

RESULTS

Study Participants

Among 16,076 women and 18,284 men initially identified with a diagnosis of colorectal adenocarcinoma, 3161 women and 2765 men were excluded because the tumor was not the first diagnosed cancer, was found only at autopsy, or was benign.

Some basic characteristics of the case and control participants are presented in Table 1. Among the 12,915 women with colorectal adenocarcinoma, the tumor was in the proximal colon for 4,013 (31%), in the distal colon for 3,404 (26%), in the rectum for 4,452 (34%), and an unspecified location for 1,046 (8%) (Table 1). Among the 15,519 male cases, the tumor was in the proximal colon for 4,081 (26%), in the distal colon for 3,669 (24%), in the rectum for 6,646 (43%), and in an unspecified location for 1,123 (7%) (Table 1). Among the controls, 129,150 were women and 155,190 were men, respectively (Table 1).

Number of Children and Risk of Colorectal Adenocarcinoma

Compared with nonparous women, women with 3 or 4 children and ≥5 children had ORs of colorectal adenocarcinoma of 1.10 (95% CI = 1.03–1.16) and 1.13 (1.01–1.28), respectively (Table 2). The results were similar for adenocarcinoma in the proximal colon (1.18 [1.06–1.32] and 1.30 [1.05–1.61]). There was less evidence for an association for adenocarcinoma in the distal colon (1.08 [0.96–1.22] and 1.14 [0.90–1.44]) and none in the rectum (1.00 [0.90–1.11] and 0.98 [0.80–1.21]). When analyses were restricted to parous women, higher parity (3-4 children or ≥5 children) compared with 1 or 2 children showed increased risk estimates in all case groups (Table 2). An association between parity and proximal colon adenocarcinoma remained in the group for which the adenocarcinoma was diagnosed after 50 years of age (Table 3). We also compared risk estimates for cancer in the proximal colon with estimates for the distal colon using a multinominal logit model (data not shown). The trend of increased risk with higher parity suggests that parity may be associated with higher risk of adenocarcinoma in the proximal colon, but the association was modest.

In men, those with 3 or 4 children and those with ≥5 children had ORs of colorectal adenocarcinoma of 1.07 (1.02–1.13) and 1.08 (0.97–1.21), respectively, compared with men without children. The corresponding risk of adenocarcinoma in the rectum was 1.11 (1.02–1.20) and 1.18 (1.00–1.39), respectively. There was no increased risk of adenocarcinoma in the proximal or distal colon in men (Table 2). In analyses restricted to age over 50 years, higher parity compared with no children or low parity was associated with increased risk of adenocarcinoma overall and specifically in the rectum (Table 3).

The *P* values for interaction of sex and parity (1–2 children, 3–4 children, and ≥5 children) were 0.07, 0.04, and 0.05, respectively, for proximal colon adenocarcinoma, and all *P* values were <0.05 when the cancer was diagnosed older than 50 years (Table 4). There was less evidence of interaction of sex and parity in other colorectal locations.

Age at First Child and Risk of Colorectal Adenocarcinoma

Women aged 35 years or older at first child had lower risk of overall colorectal adenocarcinoma than women aged 18 to 24 years (OR = 0.90 [95% CI = 0.80–1.01]; *P* value for trend <0.01). This inverse association was similar for adenocarcinoma in the proximal colon but not for the distal colon or rectum (Table 2). Analogous results were found for women aged 50 years and older but not younger (Table 3).

An inverse association of age at first birth was found among men for overall colorectal adenocarcinoma and adenocarcinoma of the proximal colon but not for adenocarcinoma of the distal colon. Furthermore, a potentially decreased risk of rectal adenocarcinoma was observed among men of older age at first birth. Men aged 50 years and older showed a similar association as the overall group (Table 3).

For total colorectal adenocarcinoma, the *P* values for interaction of sex and age at first birth were 0.02, 0.41, and

TABLE 1. Characteristics of Cases of Colorectal Adenocarcinoma and Controls in Women and Men in Sweden, 1932–2008

Variables	Colorectal Adenocarcinoma Cases				Controls
	All Cases No. (%)	Proximal Colon No. (%)	Distal Colon No. (%)	Rectum No. (%)	No. (%)
		Women			
All women	12,915	4,013 (31)	3,404 (26)	4,452 (34)	129,150
Age at diagnosis (years); mean (SD)	57 (10)	58 (11)	56 (10)	57 (10)	57 (10)
Age (years)					
<50	2,840 (22)	805 (20)	799 (23)	971 (22)	28,404 (22)
≥50	10,075 (78)	3,208 (80)	2,605 (77)	3,481 (78)	100,746 (78)
Education (years)					
<9	3,910 (30)	1,249 (31)	975 (29)	1,333 (30	39,809 (31)
9–12	4,417 (34)	1,393 (34)	1,132 (33)	1,565 (35)	45,214 (35)
>12	2,479 (19)	781 (19)	719 (21)	814 (18)	26,835 (21)
Missing	2,109 (16)	590 (15)	578 (17)	740 (17)	17,292 (13)
Number of children					
0	1,831 (14)	564 (14)	478 (14)	649 (15)	17,735 (14)
1–2	7,364 (57)	2,271 (57)	1,974 (58)	2,545 (57)	77,094 (60)
3–4	3,359 (26)	1,059 (26)	858 (25)	1,139 (27)	31,161 (24)
≥5	361 (3)	119 (3)	94 (3)	119 (3)	3,160 (2)
Age at first birth (years)					
<18	502 (6)	158 (5)	136 (5)	163 (4)	4,516 (4)
18–24	6,155 (54)	1,944 (56)	1,613 (55)	2,083 (55)	60,361 (54)
25–34	4,105 (37)	1,262 (36)	1,079 (37)	1,439 (38)	42,909 (39)
≥35	322 (3)	85 (3)	98 (3)	118 (3)	3,629 (3)
Age at last birth (years)					
<25	2,135 (19)	701 (20)	577 (20)	697 (18)	23,398 (21)
25–34	7,272 (66)	2,235 (65)	1,894 (65)	2,529 (67)	71,343 (64)
≥ 35	1,677 (15)	513 (15)	455 (16)	577 (15)	16,674 (15)
		Men			
All men	15,519	4,081 (26.3)	3,669 (23.6)	6,646 (42.8)	155,190
Age at diagnosis (years); mean (SD)	58 (10)	57 (11)	58 (10)	58 (9)	58 (10)
Age (years)					
<50	2,994 (19)	967 (24)	665 (18)	1,106 (17)	29,944 (19)
≥50	12,525 (81)	3,114 (76)	3,004 (82)	5,540 (83)	125,246 (81)
Education (years)					
<9	5,198 (34)	1,289 (32)	1,237 (34)	2,287 (34)	53,432 (34)
9–12	5,313 (34)	1,369 (33)	1,250 (34)	2,307 (35)	54,466 (35)
>12	2,833 (18)	764 (19)	683 (19)	1,216 (18)	30,376 (20)
Missing	2,175 (14)	659 (16)	499 (13)	836 (13)	16,916 (11)
Number of children					
0	3,053 (20)	856 (21)	729 (20)	1,247 (19)	29,504 (19)
1–2	8,394 (54)	2,187 (54)	1,989 (54)	3,613 (54)	87,844 (57)
3–4	3,658 (23)	936 (23)	851 (23)	1,596 (24)	34,086 (22)
≥5	414 (3)	102 (2)	100 (3)	190 (3)	3,756 (2)
Age at first birth (years)					
<18	69 (1)	14 (0)	15 (1)	30 (1)	432 (0)
18–24	4,525 (36)	1,118 (35)	1,065 (36)	1,984 (37)	43,106 (34)
25–34	6,904 (55)	1,864 (58)	1,623 (55)	2,957 (55)	71,655 (57)
≥35	968 (8)	229 (7)	237 (8)	428 (8)	10,493 (8)
Age at last birth (years)					
<25	1,051 (8)	257 (8)	247 (8)	454 (8)	12,210 (10)
25–34	7,674 (62)	2,024 (63)	1,832 (62)	3,254 (60)	76,690 (61)
≥35	3,741 (30)	944 (29)	861 (29)	1,691 (31)	36,786 (29)

SD indicates standard deviation.

TABLE 2. Association of Parity, Age at First Birth and Age at Last Birth with Risk of Colorectal Adenocarcinoma in Sweden, 1932–2008

	All Cases OR (95% CI)	Proximal Colon OR (95% CI)	Distal Colon OR (95% CI)	Rectum OR (95% CI)
		Women		
All women				
Number of children[a]				
0[b]	1.00	1.00	1.00	1.00
1–2	0.98 (0.93–1.04)	1.02 (0.93–1.13)	1.02 (0.92–1.14)	0.91 (0.83–1.00)
3–4	1.10 (1.03–1.16)	1.18 (1.06–1.32)	1.08 (0.96–1.22)	1.00 (0.90–1.11)
≥5	1.13 (1.01–1.28)	1.30 (1.05–1.61)	1.14 (0.90–1.44)	0.98 (0.80–1.21)
Test for trend	$P < 0.01$	$P < 0.01$	$P = 0.14$	$P = 0.90$
Women with children[c]				
Number of children[c]				
1–2 [b]	1.00	1.00	1.00	1.00
3–4	1.10 (1.05–1.15)	1.12 (1.04–1.21)	1.04 (0.95–1.13)	1.10 (1.02–1.19)
≥5	1.13 (1.01–1.27)	1.21 (0.99–1.48)	1.08 (0.87–1.35)	1.08 (0.89–1.32)
Test for trend	$P < 0.01$	$P < 0.01$	$P = 0.40$	$P = 0.13$
Age at first birth (years)[c]				
<18	1.06 (0.96–1.17)	1.08 (0.91–1.29)	1.09 (0.91–1.32)	1.01 (0.86–1.20)
18–24[b]	1.00	1.00	1.00	1.00
25–34	0.97 (0.93–1.01)	0.93 (0.86–1.00)	0.94 (0.86–1.02)	1.03 (0.95–1.10)
≥35	0.90 (0.80–1.01)	0.78 (0.62–0.98)	1.00 (0.81–1.25)	0.96 (0.79–1.17)
Test for trend	$P < 0.01$	$P < 0.01$	$P = 0.22$	$P = 0.96$
Age at last birth (years)[c]				
<25	0.87 (0.82–0.93)	0.96 (0.86–1.07)	0.89 (0.79–1.00)	0.81 (0.73–0.90)
25–34[b]	1.00	1.00	1.00	1.00
≥35	1.00 (0.94–1.07)	1.05 (0.93–1.18)	0.98 (0.86–1.11)	0.97 (0.87–1.08)
Test for trend	$P = 0.29$	$P = 0.23$	$P = 0.37$	$P = 0.02$
		Men		
All men				
Number of children[a]				
0[b]	1.00	1.00	1.00	1.00
1–2	0.96 (0.92–1.01)	0.92 (0.84–1.00)	0.95 (0.87–1.04)	0.98 (0.92–1.05)
3–4	1.07 (1.02–1.13)	1.02 (0.92–1.13)	1.02 (0.91–1.13)	1.11 (1.02–1.20)
≥5	1.08 (0.97–1.21)	0.97 (0.78–1.20)	1.11 (0.89–1.38)	1.18 (1.00–1.39)
Test for trend	$P = 0.02$	$P = 0.13$	$P = 0.60$	$P < 0.01$
Men with children[c]				
Number of children[c]				
1–2[b]	1.00	1.00	1.00	1.00
3–4	1.09 (1.05–1.14)	1.09 (1.01–1.19)	1.05 (0.97–1.15)	1.10 (1.04–1.18)
≥5	1.08 (0.97–1.21)	1.03 (0.83–1.27)	1.13 (0.91–1.40)	1.16 (0.99–1.35)
Test for trend	$P < 0.01$	$P = 0.29$	$P = 0.14$	$P < 0.01$
Age at first birth (years)[c]				
<18	1.50 (1.16–1.93)	1.28 (0.73–2.24)	1.30 (0.75–2.24)	1.45 (0.98–2.13)
18–24[b]	1.00	1.00	1.00	1.00
25–34	0.94 (0.90–0.98)	1.00 (0.92–1.09)	0.94 (0.87–1.02)	0.93 (0.88–0.99)
≥35	0.90 (0.84–0.97)	0.83 (0.71–0.96)	0.97 (0.83–1.12)	0.92 (0.82–1.03)
Test for trend	$P < 0.01$	$P = 0.03$	$P = 0.36$	$P = 0.02$
Age at last birth (years)[c]				
<25	0.79 (0.73–0.85)	0.79 (0.68–0.92)	0.77 (0.66–0.90)	0.79 (0.70–0.89)
25–34[b]	1.00	1.00	1.00	1.00
≥35	1.04 (0.99–1.10)	1.05 (0.95–1.16)	0.97 (0.87–1.08)	1.10 (1.02–1.19)
Test for trend	$P < 0.0001$	$P = 0.01$	$P = 0.31$	$P < 0.0001$

[a]ORs were estimated from conditional logistic regression models, conditioned on age and sex, and adjusted for education.
[b]Reference category.
[c]ORs were estimated within parous women or men have children, using logistic regression conditioned on age and sex, adjusted for education, and when appropriate for parity and age at first birth or age at last birth.

TABLE 3. Association of Parity, Age at First Birth, and Age at Last Birth with Risk of Colorectal Adenocarcinoma, Stratified by Age and Sex, Sweden, 1932–2008

	All Cases Age (years)		Proximal Colon Age (years)		Distal Colon Age (years)		Rectum Age (years)	
	<50 OR (95% CI)	≥50 OR (95% CI)	<50 OR (95% CI)	≥50 OR (95% CI)	<50 OR (95% CI)	OR (95% CI)	<50 OR (95% CI)	≥50 OR (95% CI)
Women								
All women								
Number of children[a]								
0[b]	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
1–2	0.99 (0.88–1.10)	0.96 (0.90–1.02)	0.89 (0.72–1.08)	1.04 (0.93–1.17)	1.12 (0.90–1.39)	0.97 (0.86–1.10)	0.94 (0.77–1.14)	0.88 (0.80–0.99)
3–4	0.96 (0.85–1.10)	1.11 (1.03–1.19)	0.78 (0.62–1.00)	1.27 (1.12–1.44)	1.05 (0.82–1.35)	1.06 (0.92–1.22)	1.08 (0.87–1.34)	0.96 (0.85–1.08)
≥5	0.89 (0.66–1.20)	1.16 (1.02–1.33)	1.18 (0.70–1.97)	1.30 (1.03–1.65)	0.66 (0.36–1.21)	1.24 (0.96–1.60)	0.98 (0.61–1.59)	0.96 (0.76–1.21)
Test for trend	$P = 0.43$	$P < 0.01$	$P = 0.20$	$P < 0.01$	$P = 0.73$	$P = 0.11$	$P = 0.24$	$P = 0.66$
Women with children								
Number of children[c]								
1–2[b]	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
3–4	0.97 (0.88–1.07)	1.14 (1.08–1.20)	0.87 (0.72–1.06)	1.18 (1.08–1.29)	0.95 (0.79–1.14)	1.07 (0.97–1.18)	1.13 (0.96–1.33)	1.09 (1.00–1.19)
≥5	0.88 (0.66–1.17)	1.18 (1.05–1.34)	1.26 (0.76–2.09)	1.19 (0.96–1.48)	0.58 (0.32–1.05)	1.23 (0.96–1.56)	1.02 (0.65–1.62)	1.10 (0.88–1.37)
Test for trend	$P = 0.64$	$P < 0.01$	$P = 0.99$	$P < 0.01$	$P = 0.09$	$P = 0.07$	$P = 0.46$	$P = 0.18$
Age at first birth years[c]								
<18	1.09 (0.89–1.36)	1.05 (0.94–1.07)	1.19 (0.79–1.77)	1.05 (0.87–1.28)	1.16 (0.79–1.72)	1.08 (0.87–1.33)	1.02 (0.71–1.48)	1.01 (0.84–1.22)
18–24[b]	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
25–34	0.97 (0.88–1.06)	0.97 (0.92–1.02)	0.91 (0.76–1.09)	0.93 (0.86–1.02)	1.01 (0.85–1.21)	0.92 (0.83–1.01)	0.98 (0.83–1.15)	1.04 (0.96–1.13)
≥35	1.03 (0.81–1.31)	0.87 (0.76–0.99)	1.35 (0.87–2.09)	0.66 (0.50–0.87)	1.20 (0.79–1.82)	0.95 (0.74–1.23)	0.75 (0.48–1.17)	1.03 (0.83–1.29)
Test for trend	$P = 0.64$	$P < 0.01$	$P = 0.89$	$P < 0.01$	$P = 0.70$	$P = 0.10$	$P = 0.27$	$P = 0.56$
Age at last birth years[c]								
<25	0.94 (0.82–1.07)	0.85 (0.80–0.91)	1.10 (0.88–1.44)	0.94 (0.83–1.05)	0.91 (0.71–1.18)	0.88 (0.77–1.00)	0.92 (0.74–1.16)	0.78 (0.70–0.88)
25–34[b]	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
≥35	1.01 (0.87–1.16)	1.00 (0.92–1.07)	1.09 (0.82–1.44)	1.04 (0.91–1.18)	0.94 (0.72–1.24)	0.98 (0.85–1.14)	0.98 (0.78–1.24)	0.96 (0.85–1.09)
Test for trend	$P = 0.63$	$P = 0.002$	$P = 0.98$	$P = 0.26$	$P = 0.82$	$P = 0.22$	$P = 0.67$	$P = 0.01$
Men								
All men								
Number of children[a]								
0[b]	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
1–2	0.97 (0.88–1.07)	0.95 (0.90–1.00)	0.97 (0.82–1.14)	0.89 (0.81–0.98)	0.94 (0.77–1.14)	0.95 (0.85–1.05)	0.96 (0.82–1.12)	0.98 (0.91–1.06)
3–4	0.99 (0.88–1.11)	1.07 (1.01–1.14)	1.04 (0.84–1.28)	0.99 (0.89–1.12)	0.87 (0.67–1.11)	1.03 (0.92–1.16)	1.01 (0.84–1.23)	1.12 (1.02–1.22)
≥5	1.19 (0.90–1.57)	1.06 (0.94–1.19)	1.13 (0.67–1.91)	0.93 (0.73–1.18)	1.11 (0.62–1.97)	1.09 (0.86–1.39)	1.31 (0.85–2.02)	1.16 (0.97–1.38)
Test for trend	$P = 0.87$	$P = 0.04$	$P = 0.77$	$P = 0.63$	$P = 0.46$	$P = 0.49$	$P = 0.65$	$P = 0.01$

(*Continued*)

TABLE 3. (*Continued*)

	All Cases Age (years)		Proximal Colon Age (years)		Distal Colon Age (years)		Rectum Age (years)	
	<50 OR (95% CI)	≥50 OR (95% CI)	<50 OR (95% CI)	≥50 OR (95% CI)	<50 OR (95% CI)	OR (95% CI)	<50 OR (95% CI)	≥50 OR (95% CI)
Men with children								
Number of children[c]								
1–2[b]	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
3–4	1.01 (0.91–1.12)	1.11 (1.06–1.16)	1.06 (0.88–1.27)	1.10 (1.00–1.21)	0.92 (0.73–1.15)	1.08 (0.98–1.18)	1.05 (0.89–1.24)	1.11 (1.04–1.19)
≥5	1.21 (0.92–1.60)	1.07 (0.95–1.20)	1.21 (0.72–2.03)	1.02 (0.81–1.28)	1.20 (0.68–2.14)	1.12 (0.88–1.41)	1.35 (0.88–2.08)	1.13 (0.96–1.34)
Test for trend	$P = 0.37$	$P < 0.01$	$P = 0.46$	$P = 0.35$	$P = 0.81$	$P = 0.21$	$P = 0.33$	$P < 0.01$
Age at first birth (years)[c]								
<18	0.89 (0.46–1.73)	1.69 (1.27–2.23)	0.31 (0.04–2.27)	1.64 (0.91–2.97)	0.36 (0.05–2.72)	1.59 (0.90–2.81)	1.13 (0.44–2.90)	1.54 (1.00–2.36)
18–24[b]	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
25–34	0.98 (0.89–1.09)	0.93 (0.88–0.98)	1.06 (0.89–1.26)	0.99 (0.90–1.08)	0.90 (0.73–1.11)	0.95 (0.87–1.04)	0.99 (0.84–1.17)	0.92 (0.86–0.99)
≥35	0.92 (0.76–1.11)	0.90 (0.83–0.98)	0.67 (0.46–0.98)	0.87 (0.73–1.02)	1.06 (0.73–1.55)	0.95 (0.81–1.13)	0.99 (0.75–1.33)	0.90 (0.80–1.02)
Test for trend	$P = 0.33$	$P < 0.01$	$P = 0.23$	$P = 0.07$	$P = 0.84$	$P = 0.33$	$P = 0.59$	$P = 0.02$
Age at last birth (years)[c]								
<25	0.95 (0.79–1.14)	0.77 (0.70–0.83)	0.94 (0.68–1.31)	0.76 (0.64–0.90)	0.76 (0.51–1.12)	0.77 (0.65–0.92)	1.06 (0.79–1.43)	0.75 (0.66–0.85)
25–34[b]	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
≥35	1.00 (0.88–1.14)	1.05 (0.99–1.12)	0.96 (0.76–1.21)	1.07 (0.96–1.20)	0.92 (0.69–1.22)	0.97 (0.87–1.09)	1.12 (0.92–1.37)	1.10 (1.01–1.20)
Test for trend	$P = 0.75$	$P < 0.0001$	$P = 0.92$	$P = 0.0063$	$P = 0.81$	$P = 0.34$	$P = 0.65$	$P < 0.0001$

[a]ORs were estimated from conditional logistic regression models, conditioned on age and sex, and adjusted for education.
[b]Reference category.
[c]ORs were estimated within parous women or men have children, using logistic regression conditioned on age and sex, adjusted for education, and when appropriate for parity and age at first birth or age at last birth.

TABLE 4. *P* Values for Interaction Between Sex and Reproductive Factors Associated with Risk of Colorectal Adenocarcinoma

Variables	All Cases Age (years)			Proximal Colon Age (years)			Distal Colon Age (years)			Rectum Age (years)		
	Total	<50	≥50	Total	<50	≥50	Total	<50	≥50	Total	<50	≥50
All men and women												
Sex × parity												
Sex × parity (1–2 children, dummy)	0.53	0.89	0.74	0.07	0.49	0.03	0.35	0.27	0.73	0.20	0.89	0.13
Sex × parity (3–4 children, dummy)	0.50	0.77	0.47	0.04	0.08	0.00	0.47	0.34	0.76	0.13	0.64	0.04
Sex × parity (≥5 children, dummy)	0.53	0.16	0.27	0.05	0.87	0.04	0.88	0.19	0.47	0.18	0.39	0.20
Men and women with children												
Sex × parity												
Sex × parity (3–4 children, dummy)	0.93	0.55	0.60	0.34	0.20	0.11	0.73	0.93	0.85	0.51	0.49	0.29
Sex × parity (≥5 children, dummy)	0.89	0.09	0.41	0.23	0.62	0.29	0.84	0.03	0.41	0.28	0.43	0.35
Sex × age at first birth												
Sex × age at first birth (<18 years, dummy)	0.02	0.74	0.01	0.84	0.19	0.30	0.43	0.46	0.22	0.11	0.90	0.08
Sex × age at first birth (25–34 years, dummy)	0.41	0.61	0.53	0.11	0.49	0.18	0.78	0.12	0.58	0.07	0.98	0.04
Sex × age at first birth (≥35 years, dummy)	0.69	0.36	0.37	0.36	0.01	0.03	0.81	0.67	0.93	0.67	0.26	0.25
Sex × age at last birth												
Sex × age at last birth (<25 years, dummy)	0.28	0.99	0.30	0.03	0.26	0.05	0.24	0.65	0.27	0.56	0.38	0.63
Sex × age at last birth (≥35 years, dummy)	0.38	0.91	0.32	0.59	0.11	0.89	0.87	0.93	0.87	0.07	0.25	0.13

0.69 when dummy variables of age at first birth were defined at <18 years, 25–35 years, and ≥35 years, respectively (Table 4). *P* values were 0.08, 0.04, and 0.25, respectively, for interaction using the aforementioned 3 dummy variables when rectal adenocarcinoma was diagnosed at age 50 years and older (Table 4).

Age at Last Child and Risk of Colorectal Adenocarcinoma

Compared with women aged 25 to 34 years, for women aged <25 years, the OR of colorectal adenocarcinoma overall was 0.87 (95% CI = 0.82–0.93), and for women aged 35 and older, the OR was 1.00 (0.94–1.07). The *P* value for trend was 0.29. Results were similar for the 3 specific sites (Table 2).

In men, age at last child was associated with overall colorectal adenocarcinoma and with adenocarcinoma in the proximal colon and rectum. In age-stratified analysis, men older than 50 years showed similar results (Table 3).

The *P* values for interaction of sex and age at last birth are 0.05 and 0.89, respectively, for the 2 dummy variables (<25, ≥35 years) of age at last birth when proximal colon adenocarcinoma was diagnosed after age 50.

DISCUSSION

Parity was associated with an increased risk of adenocarcinoma of the proximal colon among women but not men. This population-based design reduces chance errors and selection bias. The complete and long-term follow-up and the high quality of the data available in the registers are also advantages. The inclusion of men made it possible to consider confounding by lifestyle factors. By testing for interaction between sex and specific reproductive factors, we further formally evaluated whether there were differences in results by sex.

A limitation was the inability to control for some potential confounders (eg, age at menarche and menopause, HRT, use of oral contraceptives, anthropometric factors, dietary factors, tobacco or alcohol use, and physical activities). Data on diabetes, obesity, tobacco use, and alcohol drinking, retrieved from the Patient Register, were considered for further adjustment. Although there may be missing, or misclassified, diagnoses, such missing data are presumably random, and misclassification would most likely be nondifferential. Educational level could be a determinant of fertility, but confounding by education was taken into consideration. Furthermore, bilateral oophorectomy was a proxy for HRT, and the results were not materially changed with adjustment for oophorectomy.

Selection and information biases were not an issue, because the case-control sampling was nested within a well-defined cohort, and the exposure information was recorded independent of the outcome. The Multi-Generation Register lacks information on stillbirths, but these constitute only a small proportion of all births in Sweden (1.7% in 1955 and 0.4% in 1985).

Several previous studies, particularly case-control studies, have found an inverse association between increasing number of children and colorectal cancer,[9,23,24] while others have not.[1,2,17,18,25,26] Our study found a positive association of parity with proximal colon adenocarcinoma in women but not in men; we did not find an association with adenocarcinoma in other locations of colorectum. Few population-based studies have examined the association of parity with colorectal cancer in both men and women. A study from Australia reported that

the relation of both parity and age at birth of the first child with colorectal cancer risk was different for men and women.[10] A study from Norway found a weak association between family size and risk of colorectal cancer in men but a lower risk of high parity in women.[21] A Japanese study suggested that having children may reduce the risk of colon cancer among women but not in men, but the associations were modest.[27] The above studies and the present study taken together suggest that confounding by lifestyle factors cannot be ruled out as the explanation for the reported associations between parity and risk of colorectal cancer.

The results from studies addressing age at first birth and risk of colorectal cancer are inconsistent. Some have found an inverse association of old age at first birth,[28] while others have observed a decreased risk of colorectal cancer with earlier age at first birth.[29] Older age at first birth might be generally related with lower parity and vice versa, which was verified in the present study (data not shown). The dissimilar reproductive patterns of adenocarcinoma in the proximal colon and rectum in the present study indicate that the association of sex hormones with colorectal adenocarcinoma might be confounded by lifestyle factors differently for colorectal cancer in different anatomical locations. The incidence of adenocarcinoma of the proximal colon was higher in women, which might be affected by the increased risk of the endogenous sex hormone estrogen. The negative association of age at first birth with rectal adenocarcinoma in men indicates that sex hormones might have less influence on the rectum compared with the proximal colon, but lifestyle factors (eg, smoking, alcohol drinking, dietary patterns, and physical activity) may contribute more to the development of rectal adenocarcinoma.

Reproductive factors such as parity, age at first, and at last birth have been investigated as indicators of ovarian hormone exposure in epidemiologic studies. However, the correlation between reproductive factors and ovarian hormone levels (eg, estrogen, androgen, and testosterone) are inconsistent. Parity seems to have a weak correlation with estrogen in many studies[30,31]) but has been found to be inversely correlated with free estradiol[32] or estrone sulfate.[33] Inconsistent results have also been found for age at first birth and hormone levels. Some studies found older age at first birth was associated with lower estrogen,[30,33] which would help support our results, but others have not found this association.[31] Whether reproductive factors such as parity and age at first birth can be a valid proxy for ovarian hormones remains unresolved.

Although many previous case-control[9,10,14,15,23,24,34–43] or cohort studies[1,2,11–13,16,17,20,23,25,44,45] examined the relation of reproductive factors and risk of colorectal cancer, most did not find associations. To the extent that pregnancy might have long-lasting effects on the hormonal milieu, it is possible that resulting changes in appetite, taste, or physical activities could contribute to the development of colorectal cancer. As McMichael and Potter[46] hypothesized in the 1980s, sex hormones may alter bile acid synthesis, which possibly acts in a more concentrated manner on the proximal colon where fecal bile acids are reabsorbed. However, it is also known that reproductive patterns are highly influenced by economic status and life style. For instance, highly educated women and men tend to have fewer children or have them at an older age.

In this large population-based study with a long and complete follow-up, women's reproductive history (number of children and age at birth of children) was associated with the incidence of colorectal adenocarcinoma. Sex hormones might increase the risk of adenocarcinoma of the proximal colon in women, but the influence of lifestyle factors cannot be ruled out.

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