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Original Article

The Relationship between Gravidity and Parity and Colorectal Cancer Risk

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Abstract

Objectives: The influence of hormonal changes caused by pregnancy has been well studied in relation to colorectal cancer risk, but the association remains undefined. The purpose of this investigation was to examine in a case-control study the relationship between differences in gravidity and parity and colorectal cancer risk and if the association varied by microsatellite instability (MSI), a feature more common in women.

Methods: The study population included incident colorectal cancer patients ($n = 1014$), aged 50–74 years, diagnosed in 1998–2002 in Washington state and controls ($n = 1064$) randomly selected from population lists. All study subjects completed telephone interviews to ascertain prior pregnancies, live births, and other covariates. Case tissue samples were obtained for MSI analyses. Multivariable logistic regression models estimated odds ratios (OR) and 95% confidence intervals (CI), adjusting for age, family history of colorectal cancer, body mass index (BMI), education, endoscopy screening, oral contraceptive use, hormone therapy use, smoking, and alcohol consumption.

Results: There was an approximate 30%–50% reduction in risk of colon cancer associated with gravidity, which was attenuated in the analysis with parity. Increasing gravidity and parity were associated with a suggestion of a decreasing trend in risk for rectal cancer (p for trend $= 0.07$). Compared with women who had equal numbers of pregnancies and live births, women who were nulligravid and nulliparous had a 40%–60% increased risk of colon cancer. There was a suggestion of a reduced risk of both colon and rectal cancer associated with one more pregnancy than live birth. There was a suggestion of an increased risk of MSI-high tumors with nulligravidity and nulliparity.

Conclusions: These results confirm the importance of pregnancy events in the etiology of colon and rectal cancer.

Introduction

It has been hypothesized that reproductive factors, including increasing numbers of live births, reduce the risk of colorectal cancer because of the hormonal changes of pregnancy.[1] From observational studies, however, a consistent association between parity and colorectal cancer has not been strongly evident.[2–15] Some studies have demonstrated a 20%–40% reduction in colorectal cancer risk at 4–5 live births compared with nulliparous women,[2,4,6,10] whereas most epidemiological studies have detected no association with increasing parity.[3,5,7–9,11,12,15] When results are stratified by site, there has been no clear pattern in the association between parity and either colon or rectal cancer.

Only two studies have reported on the role of any pregnancy, including those that either resulted in live birth or ended in miscarriage, tubal pregnancy, or induced abortion.[2,3] One study suggested an elevated colorectal cancer risk with increasing number of pregnancies,[3] whereas the second suggested a 16% decreased risk associated with five or more pregnancies.[2] A pregnancy lasting <6 months might also influence colorectal cancer risk through hormonal changes but would not contribute to the assessment of total parity. Thus, gravidity would be a more comprehensive evaluation of the role of both incomplete and complete pregnancies.

The purpose of this analysis was to evaluate the roles of gravidity and parity, separately and together, in colorectal cancer risk. We specifically addressed whether there were any

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differences in association between a full-term pregnancy and any pregnancy. Further, we examined the association between gravidity and parity by microsatellite instability (MSI) status, a phenotype that tends to be more common in women than in men.

Materials and Methods

Eligible case subjects included all women aged 50–74 years, residing in 13 counties in western Washington state, who were diagnosed between 1998 and 2002 with incident invasive colorectal adenocarcinoma (*International Classification of Diseases for Oncology* codes C18.0, C18.2–18.9, C19.9, C20.0–20.9).[16] Cases were reported to the Cancer Surveillance System, a population-based registry that is part of the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) program. Eligibility for this study was limited to English-speaking subjects with available telephone numbers and without a prior personal history of colorectal cancer.

After the cases were identified (usually within 4 months of diagnosis), physicians were contacted about their patients' eligibility for this study. If the physicians had no objection to participation, an introductory letter was mailed to the case subject and followed up with a telephone call. Community-based control women were randomly selected according to the age distribution (5-year age intervals) of the eligible cases using lists of licensed drivers from the Washington State Department of Licensing for women aged 50–64 years and rosters from the Health Care Financing Administration (currently the Centers for Medicare and Medicaid) for women $\geq$65 years.

A structured 60-minute telephone interview was used to obtain information from all study participants on possible reproductive risk factors for colorectal cancer. Questions included total number of pregnancies (i.e., miscarriages, stillbirths, tubal pregnancies and abortions), number of pregnancies lasting $\geq$6 months, number of pregnancies resulting in a live birth, and ages at first and last live birth. The interview also elicited use of exogenous hormones, menstrual history, smoking history, height and weight, endoscopy screening (including a colonoscopy or sigmoidoscopy), first-degree family history of cancer, and demographic factors. We interviewed 1014 cases (73% response) and 1064 control subjects (66% response).

The study was approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center in accordance with assurances filed with and approved by the U.S. Department of Health and Human Services. Informed consent was obtained from all participants.

Pathology materials

We were able to obtain the release of paraffin-embedded colorectal tumor tissue and diagnostic pathology reports for 90% of consenting cases ($n = 648$). Sections were cut from the most representative tumor and normal tissue blocks and stained with hematoxylin and eosin (H&E). Stained sections were reviewed by a pathologist, who selected for further sectioning a block of normal tissue and a block with colorectal tumor consisting of approximately 80% of the tissue. DNA was extracted from tumor and normal tissue using tissue DNA extraction kits from Qiagen (Valencia, CA).

Microsatellite instability (MSI) analysis

MSI testing was completed on 590 tumors with sufficient tissue using a standard panel: four mononucleotide markers (BAT25, BAT26, BAT40, BAT34C4), four dinucleotide repeats (ACTC, D5S346, D18S55, and D10197), and one complex marker (MYCL). This panel included the five recommended markers in the panel proposed during the NCI workshop on microsatellite instability for cancer detection.[17] PCR fragments were tagged with a fluorescent dye and analyzed on an ABI3100 generic analyzer, using a previously described protocol.[18] For all of the cases, we corroborated the MSI results with immunohistochemistry testing for hMLH1, hMSH2, and hMSH6. In a round-robin reading by pathologists of MSI status in six laboratories, this approach and interpretation were highly reproducible.[19]

Definitions and statistical analysis

Gravidity was defined as the sum of all pregnancies, including all live births and pregnancies that terminated at <6 months or did not result in a live birth. Parity was defined as pregnancies that resulted in the delivery at $\geq$6 months gestation, of either a live birth or a stillbirth.

To assess the relationship between differences in gravidity and parity, a categorical variable was created as follows: nulligravid, nulliparous, 0 (number of pregnancies equals the number of live births), 1 (woman had one more pregnancy than live birth), and 2+ (woman had two or more pregnancies than live births). Nulligravid and nulliparous were considered mutually exclusive categories.

Women who reported a colonoscopy or sigmoidoscopy or both that occurred at least 2 years prior to the diagnosis date for cases and the interview date for controls were considered to have been screened via endoscopy for colorectal cancer.

Tumors were classified as microsatellite stable-low (0–<30% of loci unstable) or MSI-high ($\geq$30% of loci unstable); unequivocal results for at least five markers were required in order to classify a tumor's MSI status.[17]

Odds ratios (OR) and 95% confidence intervals (CI) for the association between reproductive risk factors and colorectal cancer incidence were estimated using logistic regression models, adjusting for age (in 5-year intervals), first-degree family history of colorectal cancer, body mass index (BMI, kg/m^2), education, endoscopy screening, oral contraceptive use, hormone therapy, smoking status, and alcohol consumption. Results are presented for colorectal cancer cases combined and also stratified by site within the bowel. The sum of the colon and rectal cancer does not equal the total colorectal cancer because of cases missing site information ($n = 2$) and cases with diagnostic code C19.9 (large bowel) that could not be further classified ($n = 73$). Tests of trend were conducted by including the variable in the model as an ordinal variable. All statistical analyses were performed using SAS v8.2 (SAS Institute Inc, Cary, NC); all statistical significance tests were two-sided.

Results

Cases were more likely than controls to have a high school education or less, a first-degree family history of colorectal cancer, and a higher BMI, to be current smokers, and to not use hormone therapy (Table 1).

Table 1. Demographic Characteristics of Female Colorectal Cancer Cases and Controls

	Colorectal cancer[a]			
	Control (n = *1064*) n *(%)*	*All* (n = *1014*) n *(%)*	*Colon cancer* (n = *751*) n *(%)*	*Rectal cancer* (n = *188*) n *(%)*
Age, years				
50–54	145 (13.6)	145 (14.3)	92 (12.2)	41 (21.8)*
55–59	156 (14.7)	160 (15.8)	115 (15.3)	30 (16.0)
60–64	181 (17.0)	181 (17.9)	128 (17.0)	36 (19.1)
65–69	308 (28.9)	241 (23.8)	183 (24.4)	43 (22.9)
70–74	274 (25.7)	287 (28.3)	233 (31.0)	38 (20.2)
Education				
Less than high school	60 (5.6)	104 (10.2)*	85 (11.0)*	13 (7.7)
High school	346 (32.5)	371(36.8)	275 (36.6)	64 (35.3)
Some college	321 (30.2)	294 (29.2)	206 (27.8)	65 (34.6)
College degree or higher	337 (31.7)	244 (23.8)	185 (24.6)	45 (22.4)
Family history of colorectal cancer				
No	949 (89.2)	840 (82.7)*	617 (82.1)*	156 (81.6)*
Yes	115 (10.8)	174 (17.3)	134 (17.9)	32 (18.4)
BMI (kg/m^2)				
<25	482 (45.5)	386 (38)*	281 (37.1)*	76 (40.2)
25–29.9	344 (32.5)	319 (31.5)	241 (32)	56 (31.5)
≥30	233 (22.0)	307 (30.5)	227 (30.9)	56 (28.3)
Endoscopy screening[b]				
Never	551 (53.0)	700 (71.8)*	493 (68.9)*	150 (81.4)*
Ever	489 (47.0)	273 (28.2)	225 (31.1)	32 (18.6)
Oral contraceptive use				
Never	508 (53.1)	563 (56.9)	425 (56.6)	102 (59.9)
Ever	449 (46.9)	436 (43.1)	314 (43.4)	86 (40.1)
Hormone replacement therapy				
Never user	414 (39.0)	454 (44.8)*	338 (44.7)*	78 (42.1)
Former user	134 (12.6)	147 (14.7)	106 (14.6)	34 (18.3)
Current user	514 (48.4)	403 (40.4)	298 (40.8)	75 (39.6)
Smoking status				
Never	500 (52.2)	460 (45.8)*	341 (45.9)*	79 (41.9)*
Former	340 (35.5)	382 (38.2)	288 (38.9)	72 (38.7)
Current	117 (12.2)	161 (16)	113 (15.3)	37 (19.4)
Alcohol consumption (per week)				
Never	552 (58.2)	633 (63.7)	473 (64.4)*	113 (60.1)
1–6 drinks	222 (23.4)	195 (19.6)	143 (19.5)	37 (19.9)
7 drinks	47 (5.0)	37 (3.8)	22 (2.9)	11 (6.4)
>7 drinks	128 (13.5)	128 (12.9)	96 (13.1)	26 (13.7)

[a]Percentages are age-adjusted to the distribution of controls.
*$p < 0.05$.
[b]Endoscopy screening includes a colonoscopy or sigmoidoscopy at least 2 years prior to diagnosis date for cases and interview date for controls.

There were few strong associations between reproductive factors and colorectal cancer risk (Table 2). Approximately 9% of cases and 7% of controls were nulligravid. Overall, there was a decreasing risk of colorectal cancer associated with gravidity. There was a statistically significant decreasing trend in risk of colon cancer associated with increasing gravidity; however, there was an approximately 30%–50% reduction in risk across all categories of numbers of pregnancies. The results by parity were attenuated and imprecise but demonstrated a reduced risk across the categories of live birth (Table 2). There were suggestions of statistical dose-response relationships between increasing gravidity and parity and reduced risk of rectal cancer. Women who had an early first birth had a borderline statistically significant increased risk of colon cancer but not rectal cancer. There were no associations between colorectal cancer risk and ages at menarche and last birth (Table 2).

Compared with women who had an equal number of pregnancies to live births, women who were nulligravid and nulliparous had an approximately 40%–60% elevated risk of colon cancer but no increased risk of rectal cancer (Table 3). Among women with one more pregnancy than live birth, there was a statistically significant 24% reduced risk of colon cancer; there was no evidence of a reduced risk among women with two or more pregnancies than number of live births. For rectal cancer, there were no statistically significant associations with nulligravidity and nulliparity. Similar to colon cancer, there was a 25% reduction in risk associated with one more pregnancy than live birth, but this association was not statistically significant (Table 3). There was no

Table 2. Odds Ratios and 95% Confidence Intervals for Colorectal Cancer in Relation to Reproductive Risk Factors

Characteristic	Controls n (%)	Colorectal cancer[a] All n (%)	All OR (95% CI)[b]	Colon cancer n (%)	Colon cancer OR (95% CI)[b]	Rectal cancer n (%)	Rectal cancer OR (95% CI)[b]
Age at menarche, years							
<12	168 (17.8)	206 (20.9)	1.00 (reference)	151 (20.8)	1.00 (reference)	45 (24.3)	1.00 (reference)
12	239 (25.3)	241 (24.4)	0.87 (0.65–1.16)	178 (24.6)	0.89 (0.65–1.21)	50 (26.1)	0.89 (0.55–1.44)
13	282 (29.8)	261 (26.5)	0.82 (0.62–1.08)	190 (26.0)	0.82 (0.60–1.11)	51 (28.5)	0.73 (0.45–1.19)
14+	256 (27.1)	278 (28.2)	0.97 (0.73–1.28)	211 (28.6)	0.99 (0.73–1.35)	37 (21.1)	0.62 (0.37–1.04)
p_{trend}			*0.9*		*0.9*		*0.06*
Gravidity							
Nulligravid	68 (7.1)	95 (9.4)	1.00 (reference)	75 (10.1)	1.00 (reference)	17 (9.1)	1.00 (reference)
1	67 (7.0)	70 (6.9)	0.75 (0.46–1.20)	49 (6.6)	0.63 (0.38–1.06)	14 (6.2)	0.98 (0.42–2.26)
2	199 (20.8)	225 (22.3)	0.75 (0.51–1.10)	163 (22.1)	0.68 (0.45–1.02)	45 (24.8)	0.85 (0.43–1.68)
3	226 (23.6)	212 (21.1)	0.64 (0.43–0.94)	149 (20.1)	0.55 (0.37–0.84)	47 (24.2)	0.84 (0.43–1.65)
4	181 (18.9)	158 (15.8)	0.55 (0.36–0.82)	119 (15.9)	0.50 (0.33–0.77)	26 (14.5)	0.57 (0.27–1.19)
5+	216 (22.6)	243 (24.4)	0.66 (0.45–0.98)	187 (25.0)	0.62 (0.41–0.94)	39 (21.2)	0.65 (0.32–1.33)
p_{trend}			*0.02*		*0.03*		*0.08*
Parity[c]							
Nulliparous	87 (9.1)	118 (11.7)	1.00 (reference)	93 (12.5)	1.00 (reference)	21 (10.9)	1.00 (reference)
1	89 (9.3)	102 (10.1)	0.88 (0.44–1.77)	71 (9.7)	0.75 (0.35–1.58)	21 (10)	1.09 (0.31–3.86)
2	282 (29.5)	283 (28.1)	0.80 (0.41–1.53)	198 (26.8)	0.69 (0.34–1.38)	63 (33)	0.99 (0.3–3.29)
3	252 (26.3)	230 (23.0)	0.72 (0.37–1.39)	173 (23.3)	0.66 (0.32–1.34)	42 (22.6)	0.78 (0.23–2.65)
4	143 (14.9)	145 (14.5)	0.70 (0.35–1.39)	111 (14.9)	0.65 (0.31–1.35)	22 (12.5)	0.59 (0.16–2.12)
5+	104 (10.9)	125 (12.6)	0.79 (0.39–1.59)	96 (12.7)	0.74 (0.35–1.57)	19 (11)	0.71 (0.19–2.59)
p_{trend}			*0.3*		*0.7*		*0.07*
Age at first birth, years							
<20	167 (19.3)	239 (27.2)	1.25 (0.96–1.63)	185 (28.6)	1.31 (0.99–1.74)	39 (23.4)	1.09 (0.67–1.77)
20–<25	429 (49.5)	411(46.7)	1.00 (reference)	297 (45.8)	1.00 (reference)	83 (49)	1.00 (reference)
25–<30	197 (22.7)	163 (18.3)	0.95 (0.72–1.24)	114 (17.6)	0.89 (0.66–1.2)	34 (20.5)	1.03 (0.63–1.67)
30+	74 (8.5)	69 (7.8)	1.06 (0.72–1.56)	52 (8)	1.06 (0.7–1.61)	10 (7.1)	0.8 (0.37–1.72)
p_{trend}			*0.3*		*0.1*		*0.6*
Age at last birth, years							
<20	7 (0.9)	7 (0.9)	0.59 (0.19–1.85)	3 (0.5)	0.30 (0.07–1.30)	2 (1.2)	1.05 (0.16–7.09)
20–24	114 (14.6)	153 (19.6)	1.00 (reference)	113 (19.8)	1.00 (reference)	31 (20.5)	1.00 (reference)
25–29	277 (35.5)	264 (33.8)	0.75 (0.55–1.03)	194 (33.8)	0.77 (0.55–1.07)	51 (35.4)	0.69 (0.40–1.18)
30–34	247 (31.7)	235 (30.2)	0.77 (0.56–1.06)	171 (29.6)	0.74 (0.52–1.05)	42 (29.9)	0.68 (0.38–1.22)
35+	135 (17.3)	122 (15.6)	0.74 (0.51–1.07)	96 (16.3)	0.77 (0.51–1.15)	19 (13)	0.62 (0.31–1.23)
p_{trend}			*0.2*		*0.3*		*0.2*

[a]Percentages are age-adjusted to the distribution of controls.
[b]Adjusted for age, family history of colorectal cancer, BMI, education, endoscopy screening, oral contraceptive use, hormone replacement therapy, smoking, and alcohol consumption.
[c]Additional adjustment for gravidity.

statistical difference between the pattern of associations with colon cancer compared with rectal cancer (Wald $p = 0.7$).

There was a nonsignificant increased risk of MSI-high colorectal cancer among women who were nulligravid or nulliparous, although the estimates were imprecise because of small numbers (Table 4). There were no associations between MSI-stable/MSI-low tumors by gravidity/parity.

Discussion

Overall, we detected a reduction in risk of colon and rectal cancer independently associated with gravidity, which attenuated for parity. For rectal cancer, the observed decreased risk is not evident until either the second or subsequent pregnancy or live birth, although these relationship were not statistically significant. Compared with women with equivalent gravidity and parity, there was an increased risk of colon cancer but not rectal cancer associated with being nulligravid or nulliparous. There was a decreased risk of colorectal cancer associated with one more pregnancy than live births.

The majority of studies investigating increasing parity in relation to colon cancer have detected no association.[3,5,7–15] In our study, we demonstrated a step-function reduction in colon cancer risk with the first pregnancy. The p_{trend} reported was statistically significant, but when we excluded the baseline category, the p_{trend} was no longer statistically significant. These results suggest that the hallmark of a first pregnancy or live birth might be sufficient to decrease colon cancer.

Most studies have shown no association between increasing parity and rectal cancer.[6–8,10,15,20,21] To our knowledge, no studies have reported the role of gravidity alone in relation to rectal cancer. We detected a decreasing trend in risk associ-

Table 3. Associations between Differences in Gravidity and Parity and Risk of Colorectal Cancer

		Colorectal cancer					
		All		Colon cancer		Rectal cancer	
Gravidity/parity	Controls n (%)	n (%)	OR (95% CI)[a]	n (%)	OR (95% CI)[a]	n (%)	OR (95% CI)[a]
Nulligravid	68 (7.1)	95 (9.4)	1.42 (0.99–2.02)	75 (10.1)	1.59 (1.09–2.31)	17 (9.1)	1.20 (0.64–2.25)
Nulliparous	19 (2.0)	23 (2.3)	1.20 (0.63–2.30)	18 (2.4)	1.36 (0.68–2.71)	4 (1.7)	1.03 (0.31–3.38)
0	504 (52.7)	546 (54.5)	1.00 (reference)	398 (53.7)	1.00 (reference)	105 (57.5)	1.00 (reference)
1	240 (25.1)	207 (20.6)	0.77 (0.61–0.97)	148 (19.9)	0.76 (0.58–0.98)	38 (20.1)	0.75 (0.49–1.14)
2+	126 (13.2)	132 (13.2)	0.96 (0.72–1.27)	103 (13.9)	1.01 (0.74–1.37)	24 (11.5)	0.93 (0.55–1.57)
p_{trend}			*0.01*		*0.009*		*0.265*

[a]Adjusted for age, family history of colorectal cancer, BMI, education, endoscopy screening, oral contraceptive use, hormone replacement therapy, smoking, and alcohol consumption.

ated with increasing pregnancies, although not statistically significant, as well as a reduced risk of rectal cancer associated with a higher difference in gravidity to parity.

Changes in maternal hormones during pregnancy might lead to etiological changes that affect colon and rectal cancer risk. Estradiol and estriol are produced by the placenta, and maternal levels continue to increase over the course of the pregnancy.[22] It is hypothesized that the role of estrogen might influence cellular proliferation, but it has also been shown to inhibit growth of the colon. For example, estrogen has been shown to reduce bile acids, decrease the growth enhancement of insulin-like growth factors (IGFs), and maintain the transcription and expression of estrogen and progesterone receptors.[23] Exogenous hormone therapy use, specifically estrogen plus progestin, is associated with a reduction in risk of both colon and rectal cancer.[24]

Hormonal changes in prolactin levels are different among nulliparous and nulligravid women and parous women. Serum prolactin levels increase during pregnancy but then decrease after birth, even among breastfeeding mothers.[22] Parous women have been found to have low levels of prolactin following pregnancy, and the effect can last as long as 12–13 years after pregnancy. Conversely, nulliparous women have higher levels of prolactin.[25] Women with colorectal cancer tend to have higher levels of prolactin compared with similarly aged controls,[26] and the tumor is not the likely source of the increased prolactin levels.[27] Therefore, the combination of maternal hormones as a result of pregnancy may alter the risk of colorectal cancer.

In addition to hormonal changes due to pregnancy, there are physical changes that also occur. Any pregnancy results in pelvic crowding because of the increased uterine size. As a result of pregnancy, the uterus does not return to its prior size. The pressure of pelvic crowding might affect the rectum differently from the colon. Increased pressure on the rectum could lead to increased bowel movements, which might hypothetically reduce rectal cancer risk. Frequent pelvic crowding caused by pregnancy might explain the reduction in risk with rectal cancer.

There is emerging evidence that there are etiological differences between proximal and distal colon cancer and rectal cancer. Colon and rectal tumors differ by their embryological source and function, sex differences, and risk factors (e.g., alcohol consumption and physical activity).[28] In regard to sex differences, women have a larger proportion of proximal tumors than do men. Further, proximal tumors are more likely to have epigenetic changes compared with distal or rectal tumors, suggesting that a hormonal component might be etiologically relevant in these tumors.[23] Estradiol has also been associated with epigenetic changes in carcinogenesis[29]; hence, increasing parity and gravidity would result in lower lifetime estradiol exposure. Slattery et al.[30] demonstrated that colorectal cancer cases who were MSI-high were more likely to be nulligravid (16.4%) compared with controls (8.3%) or MSI-stable or MSI-low (7.6%). We were not able to fully confirm these results in our study; we detected that 6.5% of MSI-high cases were nulligravid compared with 8.4% of MSI-stable/low cases and 7% of controls. We were able to

Table 4. Association between Colorectal Cancer and Selected Reproductive Characteristics by Microsatellite Instability

	MSI-H		MSI-L/MSS	
Gravidity/parity	Cases n (%)	OR (95% CI)[a]	Cases n (%)	OR (95% CI)[a]
Nulligravid	9 (6.6)	1.36 (0.62–2.99)	37 (8.4)	1.19 (0.75–1.90)
Nulliparous	3 (1.8)	1.32 (0.35–4.96)	7 (1.6)	0.81 (0.32–2.05)
0	77 (58.3)	1.00 (reference)	239 (54.3)	1.00 (reference)
1	31 (20.4)	0.85 (0.53–1.36)	96 (22)	0.80 (0.59–1.08)
2+	18 (12.9)	0.94 (0.53–1.68)	61 (13.7)	1.04 (0.72–1.49)
p_{trend}		*0.3*		*0.2*

[a]Adjusted for age, family history of colorectal cancer, BMI, education, endoscopy screening, oral contraceptive use, hormone replacement therapy, smoking, and alcohol consumption.

demonstrate an increased risk of MSI-high tumors among nulliparous or nulligravid women, but these results were not statistically significant. Further studies should attempt to replicate these findings.

Our analysis was limited in several ways. First, there were only 188 rectal cancer detected during the study, limiting the statistical power in the study. Our sample, though, reflects the overall distribution of colorectal cancer in the US population.[31] Larger studies might be able to detect statistically significant associations between parity and gravidity and rectal cancer. There is the possibility of recall bias, but our main measures of association were reproductive events, which are highly recalled by mothers.[32] Cases and controls were asked to report on a variety of screening mechanisms. We report in this analysis the combination of either a sigmoidoscopy or colonoscopy, which are the most common and efficacious screening tests. The large size of the study, its population-based design, and standardized assessment lend confidence to our findings.

Changes in reproductive events might have a long-term impact on colorectal cancer rates. The prevalence of nulligravid and nulliparous women is changing within the United States as more women choose to not to have children. In a recent U.S. cohort study, the prevalence of nulliparity has increased from 18% to 34% from 1975 to 1995.[33] This changing demographic of childbearing has already impacted breast cancer incidence.[34] Prior investigations of reproductive factors and colorectal cancer might consider reanalyzing their data to determine if these findings with regard to gravidity and parity are consistent across other populations, in particular with respect to MSI status.

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Disclosure Statement

The authors have no conflicts of interest to report.

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