The relationship between gravidity and parity to colorectal cancer risk

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ABSTRACT

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

Methods: The study population included incident colorectal cancer cases (n=1,014), aged 50-74 years, diagnosed from 1998-2002 in Washington state and controls (n=1,064) randomly selected from population lists. All study subjects completed telephone interviews to ascertain prior pregnancies and 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, 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-trend=0.07). Compared to women who had equal numbers of pregnancies to livebirths, women who were nulligravid and nulliparous had 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.

List of abbreviations: microsatellite instability MSI

INTRODUCTION

It has been hypothesized that reproductive factors, including increasing numbers of live births, reduce the risk of colorectal cancer due to the hormonal changes of pregnancy.[1] However, from observational studies, 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 to nulliparous women,[2,4,6,10] whereas most epidemiologic 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 less than 6 months might also influence colorectal cancer risk through hormonal changes but would not contribute to the assessment of total parity. Thus, gravidity might 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 on colorectal cancer risk. We specifically addressed whether there were any 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 1998-2002 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 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 65 years and older.

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 6 months or more; 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 and/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 (QIAGEN, Inc, 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 National Cancer Institute 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 was highly reproducible.[19]

Definitions and Statistical Analysis

Gravidity was defined as the sum of all pregnancies, including all live births and pregnancies which terminated at less than 6 months or did not result in a live birth. Parity was defined as pregnancies that resulted in the delivery at 6 month or more gestation, either resulting in 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 and/or sigmoidoscopy which occurred at least two 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 to <30 % of loci unstable), or MSI-high (≥ 30 percent of loci unstable); unequivocal results for at least 5 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 do not equal the total colorectal cancer, due to cases missing site information (n=2) and cases with diagnostic code C19.9 (large bowel) which 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 degree or less, a first-degree family history of colorectal cancer, a higher BMI, to be current smokers, and to not use hormone therapy (Table 1).

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 demonstrating a reduced risk across the categories of live birth (Table 2). There were suggestions of statistically 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 increase 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 to 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 2 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 statistical difference between the pattern of associations with colon cancer compared to rectal cancer (Wald p-value=0.7)

There was a non-significant increased risk of MSI-high colorectal cancer among women who were nulligravid or nulliparous, although the estimates were imprecise due to 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 this relationship was not statistically significant. Compared to 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 colon and rectal cancer associated with one more pregnancy than live birth.

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. While the p-trend reported was statistically significant, 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 associated with increasing pregnancies, though 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 etiologic changes which 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 enhancing 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]

Further, hormonal changes in prolactin levels are different between nulliparous and nulligravid women from 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 to 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 pregnancy is likely to alter the risk of colorectal cancer.

In addition to hormonal changes due to pregnancy, there are physical changes which also occur. Any pregnancy results in pelvic crowding due to 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 than the colon. Increased pressure on the rectum could lead to increased bowel movements, which might reduce rectal cancer risk. Frequent pelvic crowding due to pregnancy might explain the reduction in risk with rectal cancer.

There is emerging evidence that there are etiologic differences between proximal and distal colon cancer and rectal cancer. Colon and rectal tumors differ by their embryologic source and function, sex differences, and risk factors (e.g., alcohol consumption and physical activity).[28] In regards to sex differences, women have a larger proportion of proximal tumors

compared to men. Further, proximal tumors are more likely to have epigenetic changes compared to 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] and hence increasing parity and gravidity would result in lower lifetime estradiol exposure. Slattery et al. demonstrated that colorectal cancer cases who were MSI-high were more likely to be nulligravid (16.4%) compared to controls (8.3%) or MSI-stable or –low (7.6%).[30] In our study, we were not able to fully confirm these results; we detected that 6.5% of MSI-high cases were nulligravid compared to 8.4% of MSI-stable/low cases and 7% of controls. We were able to 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 as 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 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 long-term impact on colorectal cancer rates. The prevalence of nulligravid and nulliparous women is changing within the US as more women choose to not to have children. In a recent US 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 gravidity and parity are consistent across other populations, in particular with respect to MSI status.

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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)[b]
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)[b]	85 (11.0)[b]	13 (7.7)
High school diploma	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)[b]	617 (82.1)[b]	156 (81.6)[b]
Yes	115 (10.8)	174 (17.3)	134 (17.9)	32 (18.4)
BMI (kg/m^2)				
<25	482 (45.5)	386 (38)[b]	281 (37.1)[b]	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[c]				
Never	551 (53.0)	700 (71.8)[b]	493 (68.9)[b]	150 (81.4)[b]
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 users	414 (39.0)	454 (44.8) [b]	338 (44.7) [b]	78 (42.1)
Former users	134 (12.6)	147 (14.7)	106 (14.6)	34 (18.3)
Current users	514 (48.4)	403 (40.4)	298 (40.8)	75 (39.6)
Smoking status				
Never	500 (52.2)	460 (45.8) [b]	341 (45.9) [b]	79 (41.9) [b]
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) [b]	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.
[b]p-value<0.05.
[c]Endoscopy screening includes a colonoscopy or sigmoidoscopy at least two years prior to diagnosis date for cases and interview date for controls.

TABLE 2. Odds ratios and 95% confidence intervals for colorectal cancer in relation to reproductive risk factors.

		Colorectal cancer[a]					
	Controls	All		Colon cancer		Rectal cancer	
Characteristic	N (%)	N (%)	OR (95% CI)[b]	N (%)	OR (95% CI)[b]	N (%)	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.

TABLE 3. Associations between differences in gravidity and parity and risk of colorectal cancer.

		Colorectal Cancer					
	Controls	All		Colon cancer		Rectal cancer	
Gravidity:Parity	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 (0.63-2.3)	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*		*.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.

TABLE 4. Association between colorectal cancer and selected reproductive characteristics by microsatellite instability.

	MSI-H		MSI-L/MSS	
	Cases N (%)	OR (95% CI)[a]	Cases N (%)	OR (95% CI)[a]
Gravidity:Parity				
Nulligravid	9 (6.6)	1.36 (0.62-2.99)	37(8.4)	1.19 (0.75-1.9)
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.