

# Do Factors Related to Endogenous and Exogenous Estrogens Modify the Relationship between Obesity and Risk of Colorectal Adenomas in Women?

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## Abstract

Obesity has consistently been associated with increased colorectal cancer risk in men, but not in women. In the absence of postmenopausal hormone use (PMH), adipose-derived estrogen is the primary determinant of circulating estrogen levels in postmenopausal women, perhaps ameliorating the mitogenic effects of obesity in this group. Using data from a case-control study in the United States, we examined associations among obesity, potential modifying effects of factors related to endogenous and exogenous estrogen levels, and risk of colorectal adenoma. Cases ( $n = 219$ ) were women of ages 30 to 74 years with colonoscopy proven, incident, sporadic, pathology-confirmed, adenomatous polyps of the colon and rectum. Two control groups were recruited: colonoscopy-confirmed polyp-free women ( $n = 438$ ) and age- and zip code frequency-matched women randomly selected from the

community ( $n = 247$ ). Multivariate odds ratios and 95% confidence intervals (95% CI) for obese [body mass index (BMI)  $\geq 30.0$ ; compared with nonobese, BMI  $< 25.0$ ] premenopausal women were 2.09 (95% CI, 0.81-5.41) versus colonoscopy controls, and 5.18 (95% CI, 1.40-19.32) versus population controls. For PMH users, the corresponding odds ratios were 0.29 (95% CI, 0.12-0.70) versus colonoscopy controls and 0.64 (95% CI, 0.23-1.83) versus population controls. There was no significant association of BMI with adenoma risk for PMH nonusers. Findings for waist-to-hip ratio were similar to those for BMI. These data support the hypothesis that risk for colorectal adenoma may be increased with obesity among premenopausal women but decreased among postmenopausal women, especially if they also take PMH. (Cancer Epidemiol Biomarkers Prev 2007;16(4):676-83)

## Introduction

Among women in the United States, colorectal cancer is the third most common type of cancer and the second most deadly after lung cancer (1). The results from international ecologic and migration studies clearly indicate a strong environmental component to colorectal cancer incidence (2-5). One such environmental influence has been hypothesized to be the role of a Western lifestyle, including minimal physical activity and diets high in fat and total energy intake (6). A consequence of the energy imbalance that results from high total energy intake with insufficient metabolic expenditure is the accumulation of body fat. Obesity is a known risk factor for several chronic diseases including stroke, coronary heart disease, non-insulin-dependent diabetes mellitus, gall bladder disease, dyslipidemia, respiratory difficulties, and certain forms of cancer (7).

The role of obesity, as indicated by a high body mass index [BMI; weight (kg)/height (m<sup>2</sup>)], in colorectal cancer etiology has been examined in 21<sup>4</sup> epidemiologic studies over the past two decades (6, 8-28). Strong positive associations of elevated BMI with colorectal cancer, including mortality from colon cancer, have been consistently found in men (6, 9-16, 21, 25, 27-29). However, the association among women has been weaker and less consistent. In fact, most studies have not found an association between BMI and colorectal cancer among women (6, 8, 11, 14, 15, 19, 21, 25-27). The paucity of data supporting an association in women has led some to speculate that an association between obesity and colorectal

cancer is confined primarily to men (19, 25, 30). This discrepancy in risk for colorectal cancer implies a considerable sex-based distinction in colorectal cancer etiology.

Recently, a few investigations suggest that the association between obesity and colorectal cancer risk among women is limited to certain subgroups, perhaps based on their estrogen status. Indeed, there seems to be an overall increased risk of colorectal cancer among younger women (e.g.,  $< 50$  years) but not in older women (8, 11). This shift in colorectal cancer risk among women seems to correspond with the timing of menopause, which suggests possible effect modification by factors related to estrogen status. This observation, along with studies that show the use of postmenopausal hormones (PMH) decreases the risk of colorectal cancer among postmenopausal women who have low endogenous estrogen levels (31-35), has led some investigators to consider estrogen as a potential effect modifier of the association between obesity and colorectal cancer (8, 10, 11, 26).

The apparent sex-based distinction in obesity-related colorectal cancer risk may also be related to the insulin/insulin-like growth factor (IGF) axis, coupled with alterations in levels of sex hormone-binding globulin and subsequently bioavailable sex hormones. Obesity is associated with elevated insulin and IGF levels, both of which are independent risk factors for colorectal cancer in men and women (36). Sex hormone-binding globulin, a primary determinant of bioavailable sex hormone levels in men and women (37), is inversely associated with BMI for both sexes (37) and positively associated with age for men (38). For premenopausal women, obesity-related declines in sex hormone-binding globulin do not correspond with increased bioavailable estrogen the way they do for

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<sup>4</sup> Refs. 6, 16, and 28 defined BMI as kg/m<sup>1.5</sup>.

postmenopausal women because ovarian estrogen production is tightly regulated whereas adipose tissue-derived estrogen is not. Therefore, the increase in bioavailable estrogen that occurs in women, primarily after menopause and with elevated BMI, may be beneficial and counteract the increased colorectal cancer risk from the insulin/IGF axis, whereas men do not experience a similar benefit.

Most colorectal neoplasms are believed to develop from benign adenomatous polyps (39), making understanding the etiology of adenomas and their malignant transformation important in colorectal cancer prevention. No study to date has examined the combined effect of both obesity, indicated by either BMI or waist-to-hip ratio, and factors related to endogenous estrogen levels on the incidence of colorectal adenomas. Given the known benefits of PMH in preventing colorectal cancer and the inconsistencies in obesity-related colorectal cancer risk for men and women, which could be explained by sex-based variations in bioavailable sex hormones, we hypothesize that there is no apparent association between obesity and colorectal adenoma risk among women overall. However, among postmenopausal PMH users who have elevated bioavailable estrogen plus high levels of exogenous estrogen, obesity will be protective for colorectal adenomas. In the population-based case-control study reported here, we investigated the association between various measures of obesity/overweight and colorectal adenomas in women. We further considered whether or not factors related to circulating estrogen levels modify these associations.

## Materials and Methods

**Study Subjects.** Data used in this analysis came from the Minnesota Cancer Prevention Research Unit colon polyps case-control study, and detailed study methods and subject recruitment have been described elsewhere (40). Cases and colonoscopy controls were recruited through a large multi-clinic private gastroenterology practice, Digestive Healthcare, in the metropolitan Minneapolis-St. Paul area. Patients scheduled for colonoscopy between April 1991 and April 1994 at Digestive Healthcare clinics were screened for eligibility and recruited before colonoscopy. Indications for colonoscopy for cases and Digestive Healthcare controls were collected and classified according to American Society of Gastrointestinal Endoscopists criteria in place at the time of the study. Eligibility criteria for cases and polyp-free controls included (a) residence in the Minneapolis-St. Paul metropolitan area; (b) 30 to 74 years of age; (c) able to speak English; (d) no previous colorectal adenoma; (e) no known genetic syndrome associated with predisposition to colonic dysplasia; (f) no individual history of cancer (except non-melanoma skin cancer); and (g) no history of inflammatory bowel disease.

Eligible subjects recruited from the Digestive Healthcare clinics were mailed materials describing the study, questionnaires (including a food frequency questionnaire), and a consent form before their colonoscopy visit. Two to five days after sending the study materials, a nurse from Digestive Healthcare called the study subject, confirmed the arrival of the study materials, sought verbal permission, ascertained further eligibility of the subject, and explained and answered any questions about the study. At colonoscopy, completed forms and questionnaires were collected and blood was drawn. Polyp size was measured *in vivo* using fully opened, standard-sized flexible colonoscopy forceps as a reference. All polyps were examined by the study pathologist using diagnostic criteria established for the National Polyp Study (41). For the purpose of this analysis, cases were female subjects found to have adenomatous polyps ( $n = 219$ ) and Digestive Healthcare controls were females free of all polyps

( $n = 438$ ). Hyperplastic polyp cases are not included in the Digestive Healthcare control group and are no longer considered in this article. The participation rate for eligible patients who underwent complete colonoscopy was 68%.

A second control group that was representative of the general population was recruited from the Minnesota Drivers Registry, which included all individuals with a Minnesota driver's license or identification card. Population controls were frequency matched to cases on age (using 5-year intervals), sex, and zip code ( $n = 247$ ). Eligibility criteria for population controls were identical to those for polyp-free controls. However, the presence/absence of adenomas in population controls was unknown. The participation rate for population controls was 65%. Prospective population controls were contacted via an initial phone call. Those found to be eligible and who gave consent were mailed a packet identical to that sent to clinic subjects. Subjects returned completed questionnaires by prepaid mail. No blood was collected from population controls.

**Data Collection.** Information from cases and both sets of control groups was solicited using questionnaires on physical activity, smoking habits, medical history, reproductive history and exogenous hormone use (including duration of use), demographic and anthropometric information, and family history of polyps and cancer. Dietary history, including alcoholic beverage consumption, was assessed using an expanded, 153-item, semiquantitative Willett food frequency questionnaire. Because self-reported anthropometrics have been shown to be both accurate and valid (42), measurements of subjects' height (in inches), weight (in pounds), and waist and hip circumferences were by self-report only.

**Statistical Analysis.** Subjects were excluded from analysis if they responded "don't know" to questions about PMH (2.3%) or oral contraceptive use (0.8%), hysterectomy (1.3%), or oophorectomy status (2.0%), or if the waist-to-hip ratio was considered to be implausibly high (i.e.,  $>1.2$ ; 0.3%). The final sample included 209 cases, 408 polyp-free controls, and 238 population controls.

BMI was defined as the subject's weight (converted to kilograms) divided by the subject's height (converted to meters and squared; i.e.,  $\text{kg}/\text{m}^2$ ). BMI categorization was based on the WHO criteria for obesity: "nonobese" (BMI,  $<25.0$ ), "pre-obese" (BMI,  $25.0$ - $<30.0$ ), and "obese" (BMI,  $\geq 30.0$ ; ref. 7). Menopausal status was ascertained by whether or not the subject had had a noninduced period within the year before interview (yes, premenopausal women; no, postmenopausal women). Small adenomas were considered to be  $<10$  mm in diameter; large adenomas had diameters that were  $\geq 10$  mm. Adenomas were also categorized as proximal (to the splenic flexure) or distal (to the splenic flexure).

All statistical analyses were conducted using SAS version 9.1. Unconditional logistic regression analyses were used to evaluate the association between each exposure and the incidence of adenomas, with appropriate control for confounding. Results are presented as odds ratios (OR) and 95% confidence intervals (95% CI). Separate analyses were conducted for cases versus colonoscopy controls and cases versus population controls. All statistical significance tests were two sided.

Unadjusted ORs for incident adenomas were first calculated for each exposure. Potential confounders were assessed by fitting a model with the main exposure (BMI or waist-to-hip ratio) and each potential confounder to evaluate the effect on the OR of interest. Covariates were considered to be confounders when they altered the OR by at least 10%. Covariates evaluated as potential confounders of the association between BMI and adenoma incidence included age; education; marital status; total energy intake; fat intake; dietary fiber intake; waist-to-hip ratio; smoking status (never, current,

past smokers); number of cigarettes smoked per day; pack-years of smoking; years of smoking; total MET-hours of physical activity, including occupational (e.g., scrubbing floors, mowing lawns) and recreational activity (e.g., jogging, swimming, weightlifting); alcohol (non, current, past drinkers); total alcohol consumed per week; family history of colon cancer; family history of polyps; number of live births; hysterectomy status; oophorectomy status; PMH use (never/ever); duration of PMH use; oral contraceptive pill use (never/ever); duration of oral contraceptive pill use; duration of menopause; and menopausal status. Where appropriate, covariates were modeled as continuous variables. Models using waist-to-hip ratio as the main exposure were constructed using the same method.

## Results

The demographic, reproductive, and anthropometric characteristics for cases, colonoscopy controls, and population controls are displayed in Table 1. Cases did not differ significantly from either set of controls for most characteristics, although cases were more likely to be current or former smokers. Colonoscopy controls were more likely to be younger, have a positive family history of colon cancer, use PMH and oral contraceptives, be premenopausal, and be younger when their periods stopped. Population controls were more likely to abstain from drinking or be ex-drinkers and were less likely to have positive family histories of colon cancer. Reasons for colonoscopy among cases and Digestive Healthcare controls included treatment for bleeding (1.0% versus 0.0%), planned polyp excision (62.2% versus 2.9%), abnormal barium enema (2.3% versus 3.7%), hematochezia (5.3% versus 14.2%), iron deficiency/anemia (3.3% versus 11.3%), positive fecal occult blood test (12.9% versus 24.5%),

melenia (0.5% versus 0.2%), rule out possible inflammatory bowel disease (0.0% versus 7.8%), diarrhea (1.4% versus 7.4%), strong family history of colon cancer (7.2% versus 22.1%), and reasons not otherwise specified (2.9% versus 3.4%). No information was available from 1.0% of cases and 2.5% of Digestive Healthcare controls. Comparisons by adenoma size indicated that cases with small adenomas (<10 mm) were more likely to be never smokers and current drinkers when compared with cases with large adenomas ( $\geq 10$  mm; Table 2).

Multivariable-adjusted associations of BMI and adenomas by menopausal and PMH status for cases and colonoscopy controls are presented in Table 3. Overall, BMI was not associated with adenomas after controlling for age, family history of colon cancer, family history of polyps, and pack-years of smoking. Stratification by menopausal status indicated a statistically nonsignificant increase in adenoma risk with increasing BMI for obese premenopausal women (OR, 2.09; 95% CI, 0.81-5.41) and a statistically nonsignificant inverse association for obese postmenopausal women after also controlling for PMH use (OR, 0.61; 95% CI, 0.36-1.05). Further stratification by PMH use among postmenopausal women indicated a statistically significantly lower risk for obese postmenopausal PMH users (OR, 0.29; 95% CI, 0.12-0.70) and statistically nonsignificant lower risk for pre-obese postmenopausal PMH users (OR, 0.65; 95% CI, 0.35-1.22). Obese and pre-obese postmenopausal women not taking PMH did not have statistically significantly different adenoma risk from the nonobese reference group. Obese PMH users had a statistically nonsignificantly decreased risk of small adenomas (OR, 0.53; 95% CI, 0.11-2.70) when compared with obese non-PMH users, whereas the risk of large adenomas was statistically nonsignificantly increased (OR, 1.88; 95% CI, 0.37-9.53) for obese PMH users when they were compared with obese PMH nonusers (data not shown). The

**Table 1. Characteristics of female colorectal adenoma cases, colonoscopy controls, and population controls; Minnesota Cancer Prevention Research Unit Case-Control Study, 1991-1994**

Characteristic	Cases (n = 209), mean (SE)*	Colonoscopy controls (n = 408), mean (SE)	Population controls (n = 238), mean (SE)
Age categories (y), %			
30-39	5.3	13.7	9.7
40-49	15.3	24.3	14.7
50-59	30.6	31.1	30.7
60+	48.8	30.9	45.0
Smoking status, %			
Current smoker	22.0	15.7	17.7
Ex-smoker	34.9	30.6	26.1
Never smoker	43.1	53.7	56.3
Drinking status, %			
Current drinker	70.8	71.0	71.4
Ex-drinker	22.0	18.2	14.7
Not drinker	7.2	10.8	13.9
Positive family history of colon cancer, %	18.8	30.7	6.8
Ever use PMH, %	39.1	51.0	45.4
Duration of PMH use, y	5.9 (0.9)	5.8 (0.5)	6.0 (0.7)
Ever use oral contraceptive, %	50.7	60.8	50.0
Duration of oral contraceptive use, y	4.3 (0.4)	4.7 (0.3)	4.8 (0.4)
Noninduced menstrual period in last year, %	16.8	32.3	23.5
Age when periods stopped, y	47.3 (0.5)	45.5 (0.5)	46.8 (0.5)
BMI <sup>†</sup> (kg/m <sup>2</sup> ), %			
<25.0	45.6	43.9	54.4
25.0-30.0	32.0	33.1	27.2
$\geq 30.0$	22.3	23.0	18.7
Waist-to-hip ratio, %			
$\leq 0.770$	23.4	27.8	24.4
0.771-0.820	18.1	23.3	23.1
0.821-0.880	31.7	21.6	28.6
$\geq 0.881$	26.8	27.3	23.9

NOTE: Primary indication for colonoscopy was not available for 14.4% of cases and 0.01% of Digestive Healthcare controls.

\*Mean and SE unless otherwise indicated.

<sup>†</sup>BMI categories based on WHO cutoff points.

**Table 2. Characteristics of female colorectal adenoma cases by adenoma size; Minnesota Cancer Prevention Research Unit Case-Control Study, 1991-1994**

Characteristic	Small (<10 mm; <i>n</i> = 124), mean (SE)*	Large (≥10 mm; <i>n</i> = 63), mean (SE)
Age categories (y), %		
30-39	57.0	4.8
40-49	15.3	17.5
50-59	30.7	31.8
60+	48.4	46.0
Smoking status, %		
Current smoker	16.9	31.8
Ex-smoker	34.7	31.8
Never smoker	48.4	36.5
Drinking status, %		
Current drinker	74.2	61.9
Ex-drinker	16.9	33.3
Not drinker	8.9	4.8
Positive family history of colon cancer, %	20.2	21.0
Positive family history of polyps (%)	31.5	31.8
Ever use PMH, %	42.3	30.2
Duration of PMH use, y	6.0 (1.1)	4.1 (1.1)
Ever use oral contraceptive, %	50.8	49.2
Duration of oral contraceptive use, y	4.2 (0.5)	4.7 (0.8)
Noninduced menstrual period in last year, %	15.3	19.1
BMI <sup>†</sup> (kg/m <sup>2</sup> ), %		
<25.0	45.5	44.4
25.0-30.0	32.2	30.2
≥30.0	22.3	25.4

\*Mean and SE unless otherwise indicated.

†BMI categories based on WHO cutoff points.

sample size was too small to allow a meaningful analysis of associations of adenomas by colon subsite (i.e., proximal versus distal colorectum) stratified on hormonal status. However, when all women were combined, the risk of adenomas did not differ by subsite (data not shown).

The associations of BMI with adenomas for cases and population controls are also presented in Table 3. BMI was associated with a slight, statistically nonsignificant increase in overall adenoma risk when cases were compared with population controls. Stratification by menopausal status indicated that adenoma risk was positively associated with BMI for premenopausal but not postmenopausal women. Adjustment for covariates resulted in findings of a statistically significantly elevated risk in obese premenopausal women (OR, 5.18; 95% CI, 1.40-19.32). Pre-obese premenopausal women also had a statistically nonsignificant elevated adenoma risk with increased BMI. Overall, there was no association of BMI with adenoma risk among postmenopausal women with additional control for PMH use. However, among postmenopausal PMH users, the risk for the obese was statistically nonsignificantly reduced (OR, 0.64; 95% CI, 0.23-1.83). In contrast, postmenopausal women not using PMH had risks that were not different from 1.0 and unchanged with increasing BMI.

The associations of waist-to-hip ratio for cases and colonoscopy controls and for cases and population controls are presented in Table 4. Premenopausal women with the highest waist-to-hip ratio had an increase in adenoma risk, and the increase in risk was statistically significant when cases were compared with population controls. When compared with colonoscopy controls, a statistically significant reduction in risk was observed for postmenopausal women in the highest quartile of waist-to-hip ratio (OR, 0.48; 95% CI, 0.25-0.91). A similar but statistically nonsignificant reduction in risk was observed among postmenopausal women with the largest waist-to-hip ratio when cases were compared with population controls. In addition, when cases were compared with colonoscopy controls, there was a borderline statistically significant trend ( $P = 0.06$ ) for reduction in adenoma risk with increasing waist-to-hip ratio for postmenopausal PMH nonusers. No similar reduction in adenoma risk was seen when population controls were used in the analysis.

## Discussion

Consistent with our a priori hypothesis of no apparent association between obesity and adenomas among women overall but an inverse association for postmenopausal PMH users, the results of this study suggest a decreased risk of adenomas among obese postmenopausal women regardless of the index of obesity used in the analysis. The results of our study also indicated that obese premenopausal women had an increased risk of colorectal adenomas. This finding is consistent with the results from previous studies (11, 26) that found a 2- to 3-fold increase in risk of colorectal cancer among obese premenopausal women, or those younger than 50 years of age, and adds the observation that this pattern begins at the adenoma (precancer) stage of disease. Furthermore, the finding of a generally weak or nonexistent association between obesity and adenoma risk in postmenopausal women also supports the findings of previous cancer studies (8, 10, 26). This provides an explanation for the inconsistent and generally null (or weakly positive) associations in studies of obesity and colorectal cancer risk in women, as most participants were postmenopausal at study enrollment. This further suggests that obesity prevention among young women may be particularly valuable in public health efforts at colorectal cancer prevention.

Our finding of decreased adenoma risk with increasing obesity among postmenopausal, PMH-positive women is difficult to explain. No published study to date has examined the role of estrogen in modifying the association between obesity and adenomas. Two studies reported an association between indicators of obesity (e.g., BMI and waist-to-hip ratio) and colorectal cancer risk in postmenopausal women stratified on PMH use. However, these studies presented results that conflict with the data presented here. A population-based case-control study by Slattery et al. (10) found a statistically significant positive association between high BMI and colorectal cancer risk among PMH users. The second study, by Pischon et al. (27), found no association between BMI and colorectal cancer in women. However, when stratified by postmenopausal PMH use, the authors found a statistically significantly positive association of waist-to-hip ratio among postmenopausal PMH nonusers but not PMH users. It is

unclear whether these results differ because of different study outcomes (i.e., colorectal cancer versus adenomas) or because of differences in sample size (the study by Pischon examined nearly 240,000 women, whereas our study had just more than 800). Additional studies with large sample sizes are needed to elucidate how PMH modifies the association between obesity and adenoma risk.

We can only speculate about why postmenopausal PMH users in our study would show a reduced adenoma risk with overweight and obesity, whereas premenopausal women who have high levels of circulating estrogen seem to be at increased risk. This age-dependent discrepancy in risk may indicate differing disease pathologies for younger women versus older women, as suggested independently by Slattery et al. (43) and Potter et al. (44). In other words, whereas young obese women experience an increase in colorectal cancer risk through alterations in the insulin/IGF profile, they do not reap the protective benefit of high estrogen levels as postmenopausal obese PMH-users do. Additional studies will be necessary to explore whether there are differences in estrogen-related risks for different subtypes of colorectal cancer.

Obese cases in this study took PMH, on average, 1 to 2 years longer than obese women in either control group (data not shown). In addition, on average, obese cases who took PMH were postmenopausal 4 years longer than their obese counterparts in both control groups, and 2 to 4 years longer than women not taking PMH (data not shown). However, when compared with obese and overweight colonoscopy controls, obese and overweight cases were less likely to use PMH (data not shown), which is consistent with previous data that suggest a reduction in cancer risk from PMH use (31-35, 45-50). There was no difference PMH use by BMI status among cases and population controls. It is also possible that the observed decrease in adenoma risk among postmenopausal PMH users in our study was a function of the relatively limited sample size of the study and due to chance characteristics of the data set alone.

It has been established that elevated body mass (i.e., BMI >30) is associated with lower progesterone levels, which can lead to amenorrhea (37). As a result, obese women may be more likely to start PMH at an earlier age and to take it for a

longer duration to regulate a perceived onset of menopause. Furthermore, work by Issa et al. (51) suggests that circulating estrogen may be necessary to prevent the age-related hypermethylation of estrogen receptors in colonic tissue, which can lead to deregulated cell growth. Therefore, the inverse association between obesity and adenoma risk among postmenopausal PMH users may be a function of prolonged exposure to exogenous estrogens used to treat perceived menopausal symptoms (i.e., PMH use) and not the result of reduced risk from obesity per se. Furthermore, information on the type of PMH used by postmenopausal women was not available for this analysis. It is possible that differences in PMH formulation (e.g., estrogen + progestin versus estrogen alone) and application could influence the association between obesity and adenoma risk among postmenopausal users. Future studies should address this possibility.

There did not seem to be an overall association between obesity and adenoma size for most women. Obese postmenopausal PMH users had a statistically nonsignificant increased risk of large adenomas and a nonsignificant decreased risk of small adenomas, a pattern not seen in obese nonusers (data not shown). This suggests that postmenopausal PMH use may modify the risk of adenoma growth among obese women who have been found to have an increased risk of large adenomas (52, 53). However, the association of BMI with adenoma size was unreliable due to sample size limitations in analyses according to adenoma type and subsite.

Several biological mechanisms have been hypothesized that could account for the modification of obesity-related colorectal cancer risk by a woman's hormonal status. McMichael and Potter (54) proposed that estrogen may alter the bile acid pool, which is believed to play a role in colon carcinogenesis. In addition, estrogen may alter colorectal cancer risk directly via estrogen receptors in the colonic mucosa (55). Furthermore, changes in the metabolic profile, specifically in the insulin/IGF axis resulting from excess adipose tissue, may also play a role in increasing colorectal cancer risk (36); estrogen is believed to exert a protective effect through the insulin/IGF axis by reducing serum IGF levels (56). In addition, it should be noted that, among postmenopausal women, adipose tissue is the principal source of endogenous estrogen (37). Therefore, the

**Table 3. Adjusted ORs for BMI among colorectal adenoma cases, colonoscopy controls, and population controls; Minnesota Cancer Prevention Unit Case-Control Study, 1991-1994**

BMI* (kg/m <sup>2</sup> )	Colonoscopy controls				Population controls			
	Cases (n)	Controls (n)	OR (95% CI)	P <sub>heterogeneity</sub> <sup>†</sup>	Cases (n)	Controls (n)	OR (95% CI)	P <sub>heterogeneity</sub>
All women								
<25.0 (reference)	93	172	1.00 (—)	0.72	93	127	1.00 (—)	0.28
25.0-30.0	64	131	0.87 (0.58-1.31)		64	63	1.27 (0.80-2.00)	
≥30.0	45	88	0.85 (0.54-1.35)		45	43	1.49 (0.89-2.49)	
Premenopausal women								
<25.0 (reference)	17	68	1.00 (—)	0.20	17	37	1.00 (—)	0.05
25.0-30.0	7	39	0.81 (0.30-2.25)		7	10	1.61 (0.40-6.50)	
≥30.0	11	21	2.09 (0.81-5.41)		11	8	5.18 (1.40-19.32)	
Postmenopausal women								
<25.0 (reference)	75	104	1.00 (—)	0.20	75	90	1.00 (—)	0.90
25.0-30.0	56	92	0.86 <sup>‡</sup> (0.54-1.37)		56	53	1.12 <sup>‡</sup> (0.67-1.86)	
≥30.0	34	69	0.61 <sup>‡</sup> (0.36-1.05)		34	35	1.01 <sup>‡</sup> (0.55-1.84)	
Postmenopausal PMH users								
<25.0 (reference)	42	67	1.00 (—)	0.02	42	58	1.00 (—)	0.68
25.0-30.0	24	62	0.65 (0.35-1.22)		24	25	1.03 (0.49-2.13)	
≥30.0	8	41	0.29 (0.12-0.70)		8	13	0.64 (0.23-1.83)	
Postmenopausal PMH nonusers								
<25.0 (reference)	35	37	1.00 (—)	0.88	35	32	1.00 (—)	0.87
25.0-30.0	34	30	1.19 (0.60-2.38)		34	28	1.19 (0.59-2.41)	
≥30.0	26	28	1.05 (0.50-2.17)		26	22	1.19 (0.56-2.54)	

NOTE: ORs were adjusted for age, family history of colon cancer, family history of polyps, and pack-years of smoking.

\*Categories based on WHO cutoff points.

†Breslow-Day test for heterogeneity of ORs.

‡Additionally adjusted for PMH use.

**Table 4. Adjusted ORs for waist-to-hip ratio among colorectal adenoma cases, colonoscopy controls, and population controls; Minnesota Cancer Prevention Unit Case-Control Study, 1991-1994**

WHR	Cases (n)	Controls (n)	OR (95% CI)	<i>P</i> <sub>heterogeneity*</sub>
<i>Colonoscopy controls</i>				
All women				
<0.765 (reference)	43	98	1.00 (—)	0.23
0.765-<0.818	42	98	0.73 (0.42-1.25)	
0.818-<0.885	66	101	1.05 (0.63-1.74)	
≥0.885	50	97	0.68 (0.40-1.17)	
Premenopausal women				
<0.765 (reference)	12	50	1.00 (—)	0.72
0.765-<0.818	8	33	1.02 (0.35-3.03)	
0.818-<0.885	9	32	1.17 (0.41-3.30)	
≥0.885	6	16	1.96 (0.59-6.54)	
Postmenopausal women				
<0.765 (reference)	30	48	1.00 (—)	0.07
0.765-<0.818	33	67	0.58 <sup>†</sup> (0.30-1.12)	
0.818-<0.885	57	70	0.85 <sup>†</sup> (0.46-1.58)	
≥0.885	44	81	0.48 <sup>†</sup> (0.25-0.91)	
Postmenopausal PMH users				
<0.765 (reference)	20	39	1.00 (—)	0.28
0.765-<0.818	14	49	0.46 (0.20-1.06)	
0.818-<0.885	21	41	0.83 (0.37-1.41)	
≥0.885	18	42	0.62 (0.24-1.41)	
Postmenopausal PMH nonusers				
<0.765 (reference)	12	9	1.00 (—)	0.06
0.765-<0.818	21	19	0.66 (0.21-2.06)	
0.818-<0.885	36	28	0.67 (0.23-1.92)	
≥0.885	26	39	0.30 (0.10-0.88)	
<i>Population controls</i>				
All women				
<0.774 (reference)	54	59	1.00 (—)	0.50
0.774-<0.825	37	58	0.64 (0.36-1.15)	
0.825-<0.879	57	60	0.89 (0.51-1.55)	
≥0.879	53	55	0.85 (0.48-1.51)	
Premenopausal women				
<0.774 (reference)	14	27	1.00 (—)	0.07
0.774-<0.825	6	14	1.31 (0.28-6.12)	
0.825-<0.879	9	9	5.26 (1.17-23.71)	
≥0.879	6	5	6.32 (1.17-34.20)	
Postmenopausal women				
<0.774 (reference)	39	32	1.00 (—)	0.20
0.774-<0.825	30	44	0.50 <sup>†</sup> (0.25-0.98)	
0.825-<0.879	48	51	0.58 <sup>†</sup> (0.30-1.12)	
≥0.879	47	50	0.58 <sup>†</sup> (0.30-1.13)	
Postmenopausal PMH users				
<0.774 (reference)	23	21	1.00 (—)	0.23
0.774-<0.825	14	27	0.41 (0.16-1.02)	
0.825-<0.879	17	23	0.47 (0.18-1.22)	
≥0.879	19	23	0.50 (0.19-1.30)	
Postmenopausal PMH nonusers				
<0.774 (reference)	18	11	1.00 (—)	0.77
0.774-<0.825	18	17	0.66 (0.24-1.84)	
0.825-<0.879	31	28	0.65 (0.26-1.65)	
≥0.879	28	27	0.61 (0.24-1.57)	

NOTE: ORs were adjusted for age, family history of colon cancer, family history of polyps, and pack-years of smoking.

Abbreviation: WHR, waist-to-hip ratio.

\*Breslow-Day test for heterogeneity of ORs.

<sup>†</sup>Additionally adjusted for PMH use.

hypothesis that a woman's risk of colorectal cancer may be affected by her degree of obesity, her hormonal status, and possibly the combination of both factors, is plausible. Clearly, any interrelationship between obesity and estrogen is complex, and, whereas both may play independent roles in the incidence of colorectal cancer, it is also possible that one may modify the association of the other with adenoma and/or cancer risk.

Among the strengths of this study was the use of two control groups. The selection of a control group drawn from the same colonoscopy population as the cases decreases the possibility of misclassification bias. However, use of colonoscopy controls introduces the possibility of selection bias and problems with generalizability to the general population. For these reasons, use of a second, population-based control group

was advantageous, although the possibility of misclassification still exists because the adenoma status of population controls is unknown. These potential biases in relation to both control groups would tend to bias associations toward the null; thus, our findings may underestimate true associations.

Limitations of this study include the potential for bias, as noted above, lack of information on PMH type and formulation, and a relatively small sample size. Evidence for possible misclassification bias was noted as the reported associations were slightly weaker when population controls were used, particularly for BMI among postmenopausal women and PMH users, suggesting that some of the population controls may have had undiagnosed adenomas, an observation we have noted earlier in the first report of the adenoma/PMH association (40). Furthermore, the moderate response rate

(65-68%) for all groups leaves open the possibility that nonrespondents had different patterns of PMH use than did study participants, which could have biased the findings in either direction relative to the null. However, a bias of this nature would require considerably higher PMH use among nonrespondent cases than respondent cases. The small sample sizes, particularly among premenopausal women, explain the wide confidence intervals around the OR estimates and point out the need for caution in interpreting our findings because our results may be due simply to chance. Future studies with larger sample sizes and additional information on PMH use are needed to clarify our results.

In conclusion, the results of this study suggest that obesity is associated with a 2- to 3-fold increased risk of adenomas among young, premenopausal women, which is similar in strength to what has been observed for colorectal cancer risk among men. In contrast, obesity was only weakly associated with adenoma risk among women after menopause, suggesting why most studies have shown no association with obesity among women overall, given that the majority of those studies included mostly postmenopausal women. For reasons yet to be clarified, postmenopausal PMH use seems to decrease adenoma risk with increasing levels of obesity. The effect of obesity and estrogen on the etiology of colorectal cancer in women requires additional study, given the increasing suggestions of risk modification by these factors and the continued high burden of colorectal cancer risk among women.

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## Do Factors Related to Endogenous and Exogenous Estrogens Modify the Relationship between Obesity and Risk of Colorectal Adenomas in Women?

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