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Associations Between Obesity and Changes in Adult BMI Over Time and Colon Cancer Risk

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Abstract

Obesity has been associated with increased colon cancer risk in epidemiological studies; however, the specific time periods during which obesity may be most relevant as well as how changes in adult body size over time affect colon cancer risk have not been well explored. We evaluated potential associations between BMI in each age decade (20s, 30s, 40s, 50s, and 2 years before study recruitment ("recruitment period")) and in BMI changes over time and colon cancer risk in a population-based case–control study comprising 438 cases and 491 controls. We found that obese (BMI ≥ 30.0 kg/m^2) compared to normal (BMI ≥ 18.5 to <25.0 kg/m^2) body size at the recruitment period was associated with increased colon cancer risk (odds ratio (OR) = 1.54; 95% confidence interval (CI) = 1.03–2.31; P = 0.03). No associations were observed for obese body size in the other age decades. An increased risk was found for changes in BMI between the 30s decade and the recruitment period of 5–10 kg/m^2 (OR = 1.54; 95% CI = 1.02–2.34; P = 0.04) and >10 kg/m^2 (OR = 2.40; 95% CI = 1.23–4.66; P = 0.01) (P trend = 0.01). Stratification by gender revealed that BMI changes >10 kg/m^2 increased risk in women but not men. Similar results were found for BMI changes between the 20s decade and the recruitment period but effect sizes were smaller. Our results provide additional support for obesit's role in colon cancer and suggest large body size increases exceeding 10 kg/m^2 may potentially be more important after age 30, particularly among women; however, prospective studies with sex hormone, growth factor, and pro-inflammatory biomarkers are needed to provide insights to the underlying biological mechanism(s).

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DISCLOSURE

The authors declared no conflict of interest.

INTRODUCTION

Colorectal cancer is the third most common nonskin cancer and the third leading cause of cancer death among men and women in the United States (1). Although many risk factors have been postulated, obesity, which is a result of chronic positive energy balance and typically defined as having a BMI of ≥30.0 kg/m^2 (2), has been associated with colon cancer in epidemiological studies (3–8). Most of these studies, however, have examined only obesity one to a few years before diagnosis or interview, leaving potentially important earlier periods and changes over time much less explored.

Interestingly, the association between obesity and colon cancer development has been reported to be stronger and generally more consistent in men than in women (9). Moreover, colon cancer mortality appears to be greater among obese men compared to obese women (5). The mechanisms underlying these apparent differential effects by gender, however, are not well understood but thought to involve sex steroid hormone differences (10). If the hormonal milieu in adipocytes plays a role in colon cancer through either direct and/or indirect actions of androgens and/or estrogens (10), examination of changes in body fat or its surrogates (e.g., BMI) over time, particularly over periods of major but gradually occurring hormonal shifts, is warranted.

In this study, we evaluated potential associations between obese (BMI ≥ 30.0 kg/m^2) and overweight (BMI ≥ 25.0 to <30.0 kg/m^2) compared to normal (BMI ≥ 18.5 to <25.0 kg/m^2) body size in each age decade (20s, 30s, 40s, 50s, and 2 years before study recruitment ("recruitment period")) as well as changes in adult BMI over time and colon cancer in a population-based case–control study comprising 438 colon cancer cases and 491 controls. Because of probable differences by gender, we also examined potential associations in men and women, separately.

METHODS AND PROCEDURES

Study population

The study population consisted of 438 incident colon cancer cases and 491 population controls. All subjects were recruited between July, 2003 and April, 2006. Eligible cases were identified using the Kentucky Cancer Registry, which covers all residents living in the State of Kentucky at the time of their diagnosis. The Kentucky Cancer Registry is part of the National Cancer Institute's Surveillance, Epidemiology, and End Results and the Centers for Disease Control and Prevention's National Program of Cancer Registries.

The Kentucky Cancer Registry database was queried every 3 months and all histopathologically confirmed incident primary colon cancer cases were identified and contacted within 6 months of diagnosis. Potential cases identified were sent an introductory letter explaining the study and contacted by phone ~3 weeks later for a screening interview to determine eligibility. Cases with known inflammatory bowel diseases, family history of familial adenomatous polyposis, and hereditary nonpolyposis colorectal cancer were not eligible.

Random digital dialing was used to identify and recruit controls living in the State of Kentucky per a protocol similar to that described above for cases. To generate the telephone list, the area codes and exchanges of the case subjects were used with random number generation of the past four digits. Controls were screened by telephone interview and were required to be at least 40 years of age and to have no personal history of cancer other than skin cancer. In addition, potential controls with known inflammatory bowel diseases, familial adenomatous polyposis, and hereditary nonpolyposis colorectal cancer were excluded. Recruitment was not conducted if a business was reached.

Eligible cases and controls were sent a self-administered lifestyle risk factor questionnaire developed by the National Cancer Institute Colon Cancer Familial Cancer Registry (http://epi. grants.cancer.gov/CFR/about_questionnaires.html) to complete and return in a prepaid envelope. A 72.2% of cases and 62.5% of controls who answered the phone and allowed us to determine their eligibility agreed to participate. Of these, 86.5% of cases and 91.3% of controls actually completed the study. The study was approved by the Institutional Review Boards of the University of Kentucky, Lexington, and Case Western Reserve University/ University Hospitals of Cleveland. All participants provided informed written consent.

BMI and other lifestyle factors

Self-reported height and self-reported usual weight was used to calculate BMI in each age decade (20s, 30s, 40s, and 50s) and 2 years before study recruitment ("recruitment period"). Subjects were classified as obese (BMI ≥ 30.0 kg/m^2), overweight (BMI ≥ 25.0 to < 30.0 kg/m^2), or normal (BMI ≥ 18.5 to < 25.0 kg/m^2) body size per the criteria set forth by the World Health Organization (2).Family history of colorectal cancer was defined as reporting colorectal cancer in one or more first-degree relatives. Smoking and alcohol variables were classified as "ever" or "never" based on self-reported cigarette smoking of at least one cigarette per day for 3 months or longer and consuming any form of alcoholic beverage for at least once a week for 6 months or longer, respectively. Nonsteroidal anti-inflammatory drug use was defined as using anti-inflammatory medicines, such as Advil, Motrin, Nupren, or Medipren, for at least twice a week for 6 months or longer. Recreational physical activity could only be assessed using intensity because information on frequency and duration were not available, and we determined physical activity intensity by first assigning a metabolic equivalent value to the activity (11) and, then, categorizing intensity into either light (1 to <3 metabolic equivalents), moderate (3–6 metabolic equivalents), or vigorous (>6 metabolic equivalents) activity similar to Gerrior *et al.* (12).

Statistical analysis

We used unconditional logistic regression modeling to evaluate the potential associations between overweight and obesity compared to normal body size and colon cancer risk in each decade (20s, 30s, 40s, 50s, and "recruitment period"). In addition, we conducted stratified analyses to evaluate potential associations among men and women, separately. We adjusted all analyses for potential confounding by other known colon cancer risk factors including age, race, education, income, physical activity, family history of colon cancer, smoking, alcohol and nonsteroidal anti-inflammatory drug use. In regression models examining changes in BMI over time, we additionally adjusted for BMI in the recruitment period (e.g.,

when examining BMI changes between the 30s age decade and the recruitment period, we included BMI in the recruitment period in the model). All *P* values are from two-sided tests. All analyses were undertaken using SAS (Version 8.2, SAS Institute, Cary, NC).

RESULTS

Characteristics of the study population are provided in **Table 1**. Cases and controls were predominantly white. Controls were also slightly younger, tended to be consisted of more women and reported having higher education and income than that of cases. Smoking and alcohol use were similar between cases and controls but family history of colorectal cancer was more common among cases and the use of nonsteroidal anti-inflammatory drugs greater among controls.

We evaluated potential associations between overweight (BMI ≥ 25.0 to <30.0 kg/m^2) and obese (BMI ≥ 30.0 kg/m^2) compared to normal (BMI ≥ 18.5 to <25.0 kg/m^2) body size and colon cancer risk in several decades over a lifetime (20s, 30s, 40s, 50s, and 2 years before study recruitment ("recruitment period")) (**Table 2**). We found that obesity in the "recruitment period" increased colon cancer risk (odds ratio (OR) = 1.54; 95% confidence interval (CI) = 1.03–2.31; *P* = 0.03). When we stratified by gender, the effect size among obese men and obese women remained similar to that observed in the total population; however, neither of these associations was statistically significant. We did not observe any statistically significant associations between obese or overweight status in any of the other age decades examined.

We next evaluated potential associations between changes in adult BMI between the 20s, 30s, 40s, and 50s age decades and the "recruitment period" and colon cancer risk adjusting for BMI in the "recruitment period" in addition to the other potential confounders (**Table 3**). When examining changes in BMI between the 30s age decade and the "recruitment period", we observed statistically significant positive associations between "moderate" BMI changes of 5–10 kg/m^2 (OR = 1.54; 95% CI = 1.02–2.34; *P* = 0.04) and "large" BMI changes exceeding 10 kg/m^2 (OR = 2.40; 95% CI = 1.23–4.66; *P* = 0.01) compared to "small" BMI changes <5 kg/m^2 and colon cancer (*P* trend = 0.01). Between the 20s age decade and the "recruitment period," "large" (OR = 2.36; 95% CI = 1.29–4.32; *P* = 0.01) but not "moderate" changes in body size were associated with increased colon cancer risk. No statistically significant associations were observed when examining "moderate" or "large" changes in BMI between the 40s and the "recruitment period" and between the 50s and the "recruitment period." When we stratified by gender, the associations for BMI changes between the 20s and 30s age decades and the "recruitment period" were generally stronger and only remained statistically significant in women (**Table 3**). Specifically, "large" body size changes between the 30s age decade and the "recruitment period" resulted in a markedly increased effect size in women (OR = 4.20; 95% CI = 1.85–9.53; *P* = 0.01) but this association was not observed in men. Similarly, a "large" change in body size between the 20s age decade and the "recruitment period" was positively associated with colon cancer among women (OR = 2.74; 95% CI = 1.27–5.92; *P* = 0.01) but not men; however, the effect size in women was only slightly greater than that observed in the total population. No other statistically significant associations were observed when stratifying by gender. When

examining changes in BMI over time, adjusting for BMI in the younger age decade (i.e., the 20s, 30s, 40s, or 50s) vs. adjusting for BMI in the "recruitment period" produced similar results in the total study population and among men and women (data not shown).

DISCUSSION

We found that obesity in the "recruitment period" (2 years before study recruitment) was associated with increased colon cancer risk. Moreover, changes in body size between the 30s age decade and the "recruitment period" of "moderate" (BMI change of 5–10 kg/m^2) and "large" (BMI change >10 kg/m^2) magnitude were independently associated with colon cancer risk in a "dose-dependent" manner. However, when we stratified by gender, the associations remained statistically signifi-cant in women but not in men. To help put our findings into the perspective of body weight gain, a one unit increase in BMI is approximately equal to an increase in weight of 5 lbs. Therefore, changes in BMI of 5 and 10 kg/m^2 correspond to weight gains of ~25 and 50 lbs, respectively.

The association between obesity and colon cancer has been well studied (3–8) but changes in body size over a lifetime have been much less explored. Some evidence suggests the association between obesity and colon cancer may be more consistent and stronger among men than women (9). In our study, we did not observe any differences by gender in the association between obesity in the "recruitment period" and colon cancer; however, we did observe significantly stronger associations among women with "large" changes in body size (BMI change >10 kg/m^2) between the "recruitment period" and the 30s age decade. In a recent study conducted in the Insulin Resistance Atherosclerosis multiethnic cohort, the association between obesity at the time of colonoscopy and diagnosis of colorectal adenomas (potential colon cancer precursor lesions), was stronger in women than in men (13). They (13) also found that subjects gaining >4 lbs in the 10 years before colonoscopy had a higher colorectal adenoma risk compared to those who maintained their weight but the authors did not report any differences in this association by gender. In an earlier study, Lubin *et al.* (14) observed that a lifetime (age 18 to the study period) weight gain of >11 kg (~24.2 lbs) compared to a weight gain of <4 kg (~8.8 lbs) was associated with an increased risk of colorectal adenomas but the authors did not report any differences by gender. Interestingly, the approximately twofold increase in risk reported in both of these studies (13,14) was similar to the effect size we observed in our population for a change in BMI > 10 kg/m^2, which corresponds to a weight gain of ~50 lbs, between the 30s and the "recruitment period"; while smaller changes in BMI of 5–10 kg/m^2, which correspond to a weight gain between ~25–50 lbs, resulted in a 1.5-fold colon cancer risk.

In the United States, women tend to have a higher frequency of obesity than men and this difference appears to peak during the 40s and 50s age decades, with 38.8% of women and 34.8% of men between the ages of 40–59 are being obese according to the 2003– 2004 National Health and Nutrition Examination Survey (15). Furthermore, 7.9% of women between the ages of 40–59 but only 2.9% of men are extremely obese (BMI ≥ 40 kg/m^2) (15). In our study population, we also observed differences in body size by gender. We found that 9.0% of females without colon cancer (and 19.3% females with colon cancer) while only 5.5% of males without colon cancer (and 6.7% males with colon cancer) had

"large" increases in body size (BMI change > 10 kg/m^2 or weight gain of more than ~50 lbs) between their 30s and the "recruitment period." Moreover, we observed that in women but not in men, "large" changes in body size (BMI > 10 kg/m^2 or weight gain of >50 lbs) resulted in approximately fourfold increase in risk of colon cancer whereas "moderate" changes (BMI of 5–10 kg/m^2 or weight gain of ~25–50 lbs) resulted in approximately twofold increase in colon cancer risk.

Carcinogenesis is generally believed to depend on the processes of initiation and promotion where initiation is associated with heritable and/or somatic mutagenic changes in the DNA and promotion is associated with a variety of factors favoring cell growth and proliferation. Colon cancer cells, in particular, have been shown to encompass highly frequent somatic changes in tumor suppressor genes (p53), oncogenes (kras, apc), and in the phosphatidylinositol 3-kinase gene, a critical protein in the insulin signaling pathway that may play a key role in cellular proliferation (16). Thus, the increased risk of colon cancer we observed with obesity and "moderate" and "large" changes in BMI between the 30s age and the "recruitment period" decade may be attributed, in part, to excess adiposity which may provide energy and growth factors to drive the progression of an initiated colon cancer cell (17,18). Sex steroid hormones, such as estrogen, may also play a role in obesity-associated colon cancer (11), particularly among women because estrogen can increase the size and number of subcutaneous adipocytes, attenuate lipolysis, and upregulate the enzyme 11β-hydroxysteroid dehydrogenase type 1, which converts inactive cortisone to active cortisol (19). Furthermore, cytokines released from adipocytes (adipokines) may invoke a pro-inflammatory response and increase oxidative stress (20), leading to oxidative base lesions and potentially mutations in the DNA. Although it is plausible that excess adiposity could be involved in cancer initiation and/or progression, our results appear more consistent with the latter because obesity during the "recruitment period" was the only individual time period statistically significantly associated with colon cancer. Nevertheless, our findings of increased colon cancer risk with "moderate" and "large" changes in BMI among women between the 30s age decade and the "recruitment period" are intriguing and warrant further prospective biomarker studies to better understand the mechanism(s) involved.

Weaknesses of our study include potential information bias from the case–control study design and use of self-reported height and weight to calculate BMI—which is only a surrogate measure of total body fat. However, correlations between self-reported and measured weight are generally quite high (21) and self-reported weight has been shown to be accurately recalled up to 28 years prior in elderly subjects (22). Recent studies also indicate that overweight and obese non-Hispanic European American women in the United States tend to underestimate their weight (23); therefore, the associations we observed between changes in BMI over time and colon cancer in women are more likely to have been under (not over) estimated. Another limitation of our study is the modest participation rate of controls which were recruited through random digit dialing. Although random digit dialing was the most feasible option for obtaining a control sample representative of the entire State of Kentucky (the case source population), we cannot exclude the possibility of selection bias. We did, however, adjust all analyses for well-established risk factors including education and income using very finely defined categories. In addition, other associations observed in this study population have effect sizes consistent with those well-

documented from other population-based colon cancer studies (24) including the inverse association of nonsteroidal anti-inflammatory drugs (OR = 0.51; 95% CI = 0.71–1.00; P = 0.05) and the positive association of family history of colorectal cancer (OR = 2.15; 95% CI = 1.46–3.11; $P < 0.001$). Although we performed several statistical tests, we did not adjust for multiple comparisons because the intent of our study was to generate hypotheses about changes in body size over time and colon cancer risk; and, applying such statistical penalties in "hypothesis generating" may inhibit discovery (25). As a result, additional studies are needed to validate our initial findings.

In summary, we found that obesity in the "recruitment period" was positively associated with colon cancer; and, adult BMI increases of 5–10 kg/m^2 and >10 kg/m^2 between the 30s age decade and the "recruitment period" increased colon cancer risk in a dose-dependent manner. Stratification by gender revealed that effects only remained statistically significant in women. Our results emphasize the importance of considering changes in adult body size over time in colon cancer; and, suggest that body size increases >10 kg/m^2, particularly among women, may be more important after age 30. However, additional prospective biomarker studies are needed to assess how estrogen and other sex steroid hormones as well as how pro-inflammatory and growth factors change over time relative to body size to better understand the underlying biological mechanism(s). Given the dramatic rise in obesity over the past three decades among US adults (26) and that the mean BMI in women in the United States has now surpassed men (27), such studies should be prioritized.

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Table 1

Characteristics of the Kentucky Colon Cancer Case-Control Study population

Characteristic	Cases (*N* = 438)	Controls (*N* = 491)	*P* value[a]
Age (years)	62.8 (10.6)[b]	58.3 (11.1)[b]	<0.001
Gender			
Male	216 (49.5%)	185 (37.9%)	<0.001
Female	220 (50.5%)	305 (62.1%)	–
Race			
White	413 (94.7%)	458 (93.3%)	0.48
African American	17 (3.9%)	21 (4.3%)	–
Other	6 (1.4%)	12 (2.4%)	–
Education			
<8 Years	28 (6.4%)	8 (1.6%)	<0.001
8–11 Years	42 (9.7%)	46 (9.4%)	–
High school (HS) diploma	135 (31.0%)	131 (26.8%)	–
Some post-HS training	134 (30.9%)	158 (32.3%)	–
Bachelor's degree	38 (8.7%)	63 (12.9%)	–
Graduate degree	58 (13.3%)	83 (17.0%)	–
Income			
<$15,000	56 (13.0%)	58 (12.0%)	0.02
$15,000–$29,000	110 (25.6%)	119 (24.6%)	–
$30,000–$44,000	92 (21.4%)	79 (16.4%)	–
$45,000–$69,000	90 (20.9%)	93 (19.3%)	–
≥$70,000	67 (15.6%)	115 (23.8%)	–
Refused	15 (3.5%)	19 (3.9%)	–
Smoker (ever vs. never)	236 (54.4%)	267 (54.8%)	0.32
Drank alcohol (yes vs. no)	95 (25.3%)	92 (25.3%)	0.17
Family history of colorectal cancer	114 (26.2%)	77 (15.7%)	<0.001
Physical activity			
Light intensity[c]	167 (38.4%)	209 (42.6%)	0.34
Moderate intensity[c]	153 (35.2%)	153 (31.1%)	–
Vigorous intensity[c]	115 (26.4%)	129 (26.3%)	–
NSAIDs use (yes vs. no)	266 (62.4%)	328 (68.5%)	0.06

NSAID, Nonsteroidal anti-inflammatory drug.

[a] P value for *t*-test or χ^2-test with *k* (number of groups)-1 degrees of freedom.

[b] Mean and s.d. of the mean in parentheses.

[c] Light intensity: 1 to <3.0 metabolic equivalents (METs); moderate intensity: ≥3.0 to ≤6.0 METs; vigorous intensity: >6.0 METs.

Table 2

Odds ratios (ORs) for BMI and colon cancer by age, decade, and gender[a]

	Total population				Males				Females			
	Cases/controls	**OR (95% CI)**	***P***	***P*** *	**Cases/controls**	**OR (95% CI)**	***P***	***P*** *	**Cases/controls**	**OR (95% CI)**	***P***	***P*** *
BMI in the "recruitment period"[b]												
Normal[c]	109/159	1.00 (Referent)	–	–	45/45	1.00 (Referent)	–	–	64/114	1.00 (Referent)	–	–
Overweight	145/170	1.08 (0.73–1.60)	0.70	–	78/77	1.13 (0.62–2.07)	0.69	–	67/93	0.97 (0.57–1.67)	0.92	–
Obese	166/143	1.54 (1.03–2.31)	0.03	0.03	85/60	1.63 (0.87–3.04)	0.13	0.12	81/83	1.51 (0.86–2.64)	0.15	0.16
BMI in the 50s												
Normal[c]	196/278	1.00 (Referent)	–	–	84/91	1.00 (Referent)	–	–	112/187	1.00 (Referent)	–	–
Overweight	134/113	1.21 (0.84–1.74)	0.31	–	77/53	1.22 (0.70–2.13)	0.49	–	57/60	1.15 (0.69–1.92)	0.60	–
Obese	90/81	1.31 (0.86–2.01)	0.21	0.18	47/38	1.16 (0.61–2.21)	0.65	0.59	43/43	1.48 (0.81–2.72)	0.21	0.21
BMI in the 40s												
Normal[c]	254/272	1.00 (Referent)	–	–	105/78	1.00 (Referent)	–	–	149/194	1.00 (Referent)	–	–
Overweight	104/123	0.89 (0.60–1.30)	0.54	–	68/66	0.86 (0.51–1.46)	0.59	–	36/57	0.86 (0.47–1.58)	0.63	–
Obese	62/77	0.85 (0.52–1.39)	0.52	0.44	35/38	0.71 (0.36–1.42)	0.33	0.32	27/39	1.04 (0.51–2.03)	0.91	0.92
BMI in the 30s												
Normal[c]	298/328	1.00 (Referent)	–	–	122/94	1.00 (Referent)	–	–	176/234	1.00 (Referent)	–	–
Overweight	87/97	0.87 (0.58–1.31)	0.51	–	65/64	1.01 (0.60–1.71)	0.96	–	22/33	0.64 (0.31–1.33)	0.23	–
Obese	35/47	0.88 (0.46–1.67)	0.69	0.51	21/24	0.91 (0.37–2.22)	0.83	0.90	14/23	1.01 (0.39–2.59)	0.99	0.57
BMI in the 20s												
Normal[c]	346/379	1.00 (Referent)	–	–	155/129	1.00 (Referent)	–	–	191/250	1.00 (Referent)	–	–
Overweight	56/71	0.71 (0.44–1.15)	0.16	–	41/45	0.87 (0.47–1.59)	0.65	–	15/26	0.67 (0.29–1.59)	0.37	–
Obese	18/22	0.69 (0.31–1.55)	0.37	0.13	12/8	1.31 (0.40–4.29)	0.65	0.81	6/14	0.42 (0.12–1.44)	0.17	0.11

[a] Adjusted for age, race, gender, education, income, physical activity, smoking, alcohol, nonsteroidal anti-inflammatory drugs use, and family history of colorectal cancer.

[b] Recruitment period: 2 years before recruitment/interview.

[c] Normal: ≥18.5 to <25 kg/m^2; overweight: ≥25 to <30 kg/m^2; obese: ≥30 kg/m^2.

* *P* value for trend.

Table 3

Odds ratios (ORs) for changes in BMI over time and colon cancer by gender[a]

	Total population				Males				Females			
	Cases/controls	**OR (95% CI)**	***P***	***P*** *	**Cases/controls**	**OR (95% CI)**	***P***	***P*** *	**Cases/controls**	**OR (95% CI)**	***P***	***P*** *
BMI change: "recruitment period"[b]–30s[c]												
<5 kg/m^2 [d]	261/348	1.00 (Referent)	–	–	141/144	1.00 (Referent)	–	–	120/204	1.00 (Referent)	–	–
5-10 kg/m^2	104/88	1.54 (1.02-2.34)	0.04	–	53/28	1.45 (0.77-2.74)	0.25	–	51/60	1.68 (0.94-3.00)	0.08	–
>10 kg/m^2	55/36	2.40 (1.23-4.66)	0.01	0.01	14/10	0.64 (0.20-2.07)	0.46	0.85	41/26	4.20 (1.85-9.53)	0.01	0.01
BMI change: "recruitment period"[b]–20s[c]												
<5 kg/m^2 [d]	195/255	1.00 (Referent)	–	–	107/105	1.00 (Referent)	–	–	88/150	1.00 (Referent)	–	–
5-10 kg/m^2	133/153	1.33 (0.91-1.96)	0.14	–	69/58	1.49 (0.83-2.69)	0.18	–	64/95	1.10 (0.65-1.89)	0.73	–
>10 kg/m^2	92/64	2.36 (1.29-4.32)	0.01	0.01	32/19	1.09 (0.41-2.87)	0.87	0.47	60/45	2.74 (1.27-5.92)	0.01	0.01

[a] Adjusted for age, race, gender, education, income, physical activity, smoking, alcohol, nonsteroidal anti-inflammatory drugs use, and family history of colorectal cancer.

[b] Recruitment period: 2 years before recruitment/interview.

[c] Analysis additionally adjusted for baseline BMI (BMI in the "recruitment period").

[d] <5 kg/m^2 (weight gain of approximately <25 lbs); 5-10 kg/m^2 (weight gain of ~25-50 lbs) and >10 kg/m^2 (weight gain exceeding 50 lbs).

* *P* value for trend.