

Excess Body Weight and Colorectal Cancer Risk in Canada: Associations in Subgroups of Clinically Defined Familial Risk of Cancer

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Abstract

Overweight and obesity are linked with several chronic diseases, including colorectal cancer, among men, but results among women are equivocal. Previous evidence suggests that menopausal status, postmenopausal hormone use, and family history of cancer may modify the link between adiposity and colorectal cancer. In data from two population-based case-control studies (cases: 1,292 males and 1,404 females; controls: 1,465 males and 1,203 females) in Ontario and Newfoundland, Canada, we examined the link between colorectal cancer and body mass index (BMI) at two reference periods (BMI 2 years prior and BMI at age 20 years), weight gain since age 20 years, and height. Based on recent BMI indices among men, obesity (BMI ≥ 30 kg/m²) was associated with an 80% [95% confidence interval (95% CI), 1.43-2.27] increased risk of colorectal cancer relative to a normal BMI (18.5-24.9 kg/m²). The same comparison for BMI at age 20 years suggested a 94% increased risk of colorectal

cancer (95% CI, 1.19-3.16). Odds ratios were similar among subgroups of men with and without a clinically defined familial risk of cancer (according to the Amsterdam or revised Bethesda criteria for Lynch syndrome). Associations were moderately stronger for cancer of the colon than cancer of the rectum. Among women, BMI and weight gain were not linked with colorectal cancer; the null associations were persistent in subgroups of familial risk of cancer, menopausal status, estrogenic status, and subsite. Tall height (>1.75 m), however, was linked with increased risk of colorectal cancer among women (odds ratio, 2.27; 95% CI, 1.46-3.59) but not among men. This study suggests that obesity is associated with increased risk of sporadic and Lynch syndrome-related colon and rectal cancers among men but not among women, whereas height is directly linked with all such cancers among women but not among men. (Cancer Epidemiol Biomarkers Prev 2007;16(9):1735-44)

Introduction

Obesity is a major cause of cardiovascular disease, type 2 diabetes mellitus, and hypertension (1). Epidemiologic data also show a link between adiposity and colorectal cancer risk in men (2-9), but studies among women have been inconsistent (2, 4-15). Some evidence suggests that the link in women may be modified by menopausal status, with some (13, 16, 17), but not all (7, 18), data supporting a positive association among premenopausal, but not postmenopausal, women. Other evidence suggests that postmenopausal hormones modify the colon cancer risk from obesity (19), but conflicting evidence for that link too has been offered (15).

Recent data indicated that obesity was more strongly linked with colon cancer risk among cases who reported a family history of the disease than among sporadic cases (20). To date, study of this potential heterogeneity was limited to data from one case-control study in the United States (20, 21). Further, some studies suggest a modestly stronger link between obesity and cancer of the colon than the rectum among men (6, 9, 12, 22-26) and women (5, 8, 11, 15, 22, 23, 25, 27), whereas other studies suggest stronger (or similar) associations between obesity and cancer of the rectum than the colon among men (2, 5, 7, 8, 27, 28) and women (2, 6, 7, 9, 13, 16, 26, 28).

In the present study, we examined the risk of colorectal cancer associated with body mass index (BMI), weight gain during adulthood, and adulthood height. We also conducted analyses among strata of familial risk of cancer, estrogen status, menopausal status, and subsite of the colon or rectum.

Materials and Methods

Cases and Controls. In Ontario, the first period of data collection occurred during 1997-2000 and the second period of data collection occurred during 2003-2006. Incident cases were identified in the population-based

Received 12/20/06; revised 5/29/07; accepted 7/3/07.

Grant support: National Cancer Institute, NIH, under RFA CA-96-011 and through cooperative agreements with members of the Colon Cancer Family Registry and Principal Investigators. Data collection in Newfoundland and Labrador was funded by the Canadian Institutes of Health Research, grant CRT 43821. P.T. Campbell was supported by a National Cancer Institute of Canada Doctoral Fellowship (no. 13523), with funds from the Canadian Cancer Society.

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doi:10.1158/1055-9965.EPI-06-1059

Ontario Cancer Registry. In Newfoundland, incident cases diagnosed during 1999-2003 were identified through the population tumor registry maintained by the Newfoundland Cancer Treatment and Research Foundation. Both registries identified newly diagnosed cases of colon or rectal cancer (pathology-confirmed International Classification of Diseases 9th rubric: 153.0-153.9, 154.1-154.3, and 154.8; or International Classification of Diseases 10th rubric: C18x, C19, and C20) ages 20 to 74 years. The median time between diagnosis and completion of the questionnaire was 1.45 years (95% CI, 0.32-3.54 years). Approximately 65% of eligible cases participated in the study.

Controls were a random sample of residents in each province ages 20 to 74 years. Several databases were used to identify potential control subjects. In Ontario, controls were identified through a list of residential phone numbers or from population-based property assessment rolls (owners and occupants). In Newfoundland, controls were identified through random digit dialing. Both registries frequency matched controls to cases on sex and 5-year age strata. Approximately 63% of eligible controls participated in the study.

Case Subgroups

Familial Risk of Cancer. Cancers among relatives were confirmed by medical records or pathology reports wherever possible. Pedigrees were drawn and used to classify subjects according to one of three familial risk categories. High familial risk cases were those who met the Amsterdam criteria for Lynch syndrome (29). The intermediate familial risk cases were those who met the revised Bethesda criteria for Lynch syndrome, which are more inclusive than the stricter Amsterdam criteria (30). Sporadic cases met none of the above criteria. In Ontario, intermediate-risk and high-risk familial cases were over-sampled (100% were invited to participate in the study); due to resource constraints imposed by the relatively large population of Ontario, 25% of sporadic cases were invited to participate. The sampling strategy in Ontario is described in detail elsewhere (31). In Newfoundland, all controls were invited to participate.

Sample Counts. These analyses consisted of 1,292 male and 1,404 female colorectal cancer cases and 1,465 male and 1,203 female controls with available personal history questionnaire data. In the Amsterdam/Bethesda criteria (i.e., the high-risk/intermediate-risk group) and sporadic familial risk strata, 461 and 535 male cases (77% of male cases) and 466 and 665 female cases (80% of female cases), respectively, were linked to the personal history questionnaire data and included in this study. For subsite analyses, 808 male and 976 female colon cancer cases and 478 male and 425 female rectal cancer cases had available subsite and questionnaire information.

Exposure Data. The self-administered personal history questionnaire sought information on an extensive array of medical, demographic, lifestyle, and anthropometric variables. Two measures of body weight were requested: recent weight (i.e., weight ~1 year before participation for controls, or 1 year before colorectal cancer diagnosis for cases) and weight at age ~20 years. Recent BMI (BMI_{recent}) was calculated from recent body weight (kg) divided by height squared (m^2); BMI at age 20 y (BMI_{age20y}) was similarly calculated from body weight

at age 20 y. Both values were categorized as per WHO criteria (32). Other primary exposures of interest included adult weight gain [weight (kg) at age 20 y subtracted from recent weight (kg)] and adulthood height.

Physical activity was evaluated from self-reports of frequency (days per week, weeks per year) and duration (minutes per session) of the most common modes of physical activity in Canada (e.g., walking, swimming, and cycling) during three periods of the life span (20s, 30s-40s, and 50s). Modes of physical activity were converted to metabolic equivalent units, and metabolic equivalent hours were calculated and categorized. Race/ethnicity was not considered as a potential confounder or effect modifier because more than 95% of participants self-reported themselves as White.

Statistical Analyses. Descriptive statistics of all study variables were calculated stratified by sex, case-control status, and province of accrual (Table 1). Age-adjusted odds ratios (OR) and corresponding 95% confidence intervals (95% CI) were estimated from unconditional logistic regression models for the main anthropometric variables, stratified by province, and pooled (Table 2). Because of the lack of heterogeneity between provinces and the lack of confounding from province in pooled analyses, the multivariate and subgroup analyses were done on the pooled data only. Given the strong prior evidence for effect modification by sex on adiposity and colorectal cancer risk, all analyses were stratified by sex.

Multivariable unconditional logistic regression was used to evaluate the association between the anthropometric variables and colorectal cancer risk while simultaneously adjusting for covariates. Potential confounders were assessed in individual logistic regression models that included age and BMI_{recent} . Confounders were identified when the inclusion of a given covariate changed either a parameter estimate for overweight or obesity, with normal BMI as the reference, by 10% or greater (33). Only education and previous diagnosis of high cholesterol/triglycerides met this criteria for confounding. Because controls were matched to cases on age and province, these variables were included in the final multivariable models. Other variables were identified that were related to colorectal cancer risk (listed in Table 1); because these variables may, in combination, account for slight confounding, a few were included in the final multivariable models, as listed in the footnotes of Tables 2 to 5. Analyses and database management procedures were run with SAS software (version 9.1, SAS Institute).

Results

Table 1 shows selected colorectal cancer risk factors stratified by sex, case-control status, and province. As expected, because of the sampling strategy (i.e., Ontario undersampled sporadic cases, who tend to be older), cases in Ontario were younger than cases in Newfoundland. The control groups in both provinces were similarly distributed according to age. Interprovincial comparisons of control groups by sex yielded some significant differences, as indicated in Table 1.

Table 2 shows the pooled results with adjustment for covariates. Among males, relative to normal BMI, overweight and obese BMI categories were associated

Table 1. Distributions of selected covariates by sex, case-control status, and province

	Men				Women			
	Cases		Controls		Cases		Controls	
	ON (n = 871), %	NL (n = 421), %	ON (n = 1,040), %	NL (n = 425), %	ON (n = 1,132), %	NL (n = 272), %	ON (n = 910), %	NL (n = 293), %
Age (y)								
18-29	0.9	0.7	0.3	0.7	0.5	0.0	0.6	0.0
30-39	5.4	0.5	1.0	0.9	4.4	1.8	2.8	2.7
40-49	21.8	9.0	6.8	10.6	17.9	6.3	10.7	7.9
50-59	20.7	23.3	28.1	25.2	21.5	30.2	26.7	33.8
60-69	33.8	37.5	41.2	38.4	35.6	37.9	39.5	39.3
70+	18	29	23	24	20	24	20	16
<i>p</i> *			0.13				0.12	
University graduate	28	8	29	15	18	10	21	15
<i>p</i> *			<0.0001				0.003	
Household income ≥\$30,000, 2 y ago	51	48	53	58	47	38	52	47
<i>p</i> *			0.0001				<0.0001	
Currently married or living as married	86	83	86	84	69	68	67	75
<i>p</i> *			0.88				0.01	
Ever endoscopy screened for CRC	7	7	14	13	7	8	8	14
<i>p</i> *			0.56				0.006	
Diabetes †	10	22	11	14	7	18	6	12
<i>p</i> *			0.009				0.002	
Hypercholesterolemia/ triglyceridemia requiring medication ‡	15	18	21	25	12	18	14	23
<i>p</i> *			0.36				0.0002	
Regular † NSAID use	41	41	51	44	42	33	46	46
<i>p</i> *			0.05				0.88	
Regular † bulk-forming laxative use	15	7	8	3	20	12	13	8
<i>p</i> *			0.001				0.009	
Regular † multivitamin use	31	17	35	17	44	23	41	27
<i>p</i> *			<0.0001				0.0001	
Regular † calcium use	9	6	14	8	44	25	48	40
<i>p</i> *			0.003				0.02	
Ever pregnant					87	89	89	90
<i>p</i> *							0.54	
Peri- or post-menopausal					81	93	84	87
<i>p</i> *							0.14	
Ever use of hormonal contraceptives §					52	42	57	55
<i>p</i> *							0.42	
Ever use of any form of postmenopausal hormones					35	26	44	38
<i>p</i> *							0.22	
Fruit >14 servings/wk, 2 y ago	13	10	12	10	25	15	24	24
<i>p</i> *			0.0006				0.31	
Vegetables >14 servings/wk, 2 y ago	16	17	15	13	36	22	36	30
<i>p</i> *			0.0001				0.01	
Red meat >5 servings/wk, 2 y ago	28	18	22	16	21	17	18	17
<i>p</i> *			0.004				0.03	
Average weekly recreational activity during 20s ≤3 MET-h	25	32	27	30	33	43	36	37
<i>p</i> *			0.33				0.38	
Average alcoholic drinks during 20s >7/wk	42	38	36	42	6	2	7	3
<i>p</i> *			0.0001				0.0001	
Nonsmoker?	35	19	34	29	51	44	49	50
<i>p</i> *			0.08				0.04	

Abbreviations: ON, Ontario; NL, Newfoundland; CRC, colorectal cancer; MET, metabolic equivalent; NSAID, nonsteroidal anti-inflammatory drugs.

**P* value of χ^2 test between provincial control groups.

†Physician diagnosed.

‡At least twice a week for longer than 1 mo.

§For 1 y or longer.

||Did not smoke at least one cigarette a day for 3 mo or longer.

Table 2. Counts and risk estimates for BMI, weight gain, and height in relation to incident CRC, stratified by sex

Measure	Cases, n (%)	Controls, n (%)	Age-adjusted OR (95% CI)	Multivariable adjusted OR (95% CI)*
Women				
BMI 2 y ago (kg/m ²)				
18.5-24.99	616 (43.9)	545 (45.3)	1	1
25-29.99	443 (31.6)	384 (31.9)	1.06 (0.88-1.27)	0.99 (0.83-1.20)
30+	260 (18.5)	224 (18.6)	1.05 (0.85-1.30)	0.94 (0.75-1.18)
BMI at age 20 y (kg/m ²)				
18.5-24.99	996 (70.9)	875 (72.7)	1	1
25-29.99	100 (7.1)	92 (7.7)	0.92 (0.68-1.25)	0.89 (0.65-1.22)
30+	38 (2.7)	27 (2.2)	1.12 (0.68-1.86)	0.97 (0.58-1.64)
Weight gain since age 20 y				
Weight loss				
1-5 kg	107 (7.6)	85 (7.1)	1.19 (0.85-1.67)	1.19 (0.84-1.68)
6-10 kg	258 (18.4)	243 (20.2)	1	1
11-20 kg	228 (16.2)	210 (17.5)	1.04 (0.80-1.34)	1.05 (0.81-1.38)
21+ kg	386 (27.5)	349 (29.0)	1.09 (0.86-1.37)	1.07 (0.85-1.36)
Height (m)	312 (22.2)	258 (21.5)	1.19 (0.93-1.52)	1.13 (0.88-1.46)
<1.55	184 (13.1)	220 (18.3)	1	1
1.65 > height ≥ 1.55	633 (45.1)	528 (43.9)	1.41 (1.12-1.78)	1.47 (1.16-1.87)
1.75 > height ≥ 1.65	497 (35.4)	409 (34.0)	1.43 (1.13-1.81)	1.53 (1.20-1.96)
≥1.75	79 (5.6)	42 (3.5)	2.22 (1.45-3.40)	2.27 (1.46-3.59)
Men				
BMI 2 y ago (kg/m ²)				
18.5-24.99	298 (23.1)	441 (30.1)	1	1
25-29.99	627 (48.5)	738 (50.4)	1.27 (1.06-1.53)	1.29 (1.07-1.56)
30+	322 (24.9)	264 (18.0)	1.83 (1.46-2.29)	1.80 (1.43-2.27)
BMI at age 20 y (kg/m ²)				
18.5-24.99	784 (60.7)	1,022 (69.8)	1	1
25-29.99	295 (22.8)	273 (18.6)	1.34 (1.10-1.62)	1.34 (1.10-1.63)
30+	51 (4.0)	29 (2.0)	1.98 (1.23-3.20)	1.94 (1.19-3.16)
Weight gain since age 20 y				
Weight loss				
1-5 kg	76 (5.9)	86 (5.9)	1.24 (0.86-1.78)	1.14 (0.79-1.65)
6-10 kg	214 (16.6)	296 (20.2)	1	1
11-20 kg	205 (15.9)	269 (18.4)	1.08 (0.83-1.40)	1.06 (0.82-1.39)
21+ kg	352 (27.2)	443 (30.2)	1.20 (0.95-1.51)	1.18 (0.93-1.50)
Height (m)	333 (25.8)	305 (20.8)	1.71 (1.34-2.17)	1.64 (1.28-2.11)
<1.65	53 (4.1)	54 (3.7)	1	1
1.75 > height ≥ 1.65	409 (31.7)	490 (33.5)	0.83 (0.55-1.24)	0.91 (0.60-1.39)
1.85 > height ≥ 1.75	640 (49.5)	739 (50.4)	0.85 (0.57-1.27)	0.97 (0.64-1.47)
≥1.85	170 (13.2)	175 (12.0)	0.91 (0.58-1.41)	1.03 (0.65-1.54)

NOTE: Some counts do not add to totals because of missing and omitted information.

*In men and women, adjusted for age, education, red meat intake, recreational physical activity, province of residence, CRC screening endoscopy, and history of high cholesterol/triglycerides. In women only, additionally adjusted for menopausal status and ever use of postmenopausal hormones.

with ~30% and 80%+ increased colorectal cancer risks, respectively, in both reference periods. There was no association between height and colorectal cancer risk among men; among women, however, height >1.75 m was associated with a greater than doubling of colorectal cancer risk relative to height <1.55 m. Inclusion of BMI_{recent} and BMI_{age20y} in logistic regression models for adult weight gain and height had no material effect on the results for men or women (data not shown).

Table 3 shows associations of anthropometry and colorectal cancer among women stratified by estrogen status: "estrogen positive" were those women who were premenopausal or currently (i.e., as of 1 year before enrollment) using postmenopausal hormones; "estrogen negative" were those women who were postmenopausal and not using postmenopausal hormones. Menopausal status was self-reported in the questionnaire; postmenopausal women had not reported a menstrual period in the last 12 months, excluding amenorrhea due to pregnancy or chemotherapy/radiotherapy. These comparisons were largely in line with results for all women (as shown in Table 2). When risk estimates were

stratified according to menopausal status (premenopausal and postmenopausal), the results were largely consistent with Table 2 (data not shown).

Table 4 shows results for anthropometry and colorectal cancer risk stratified by sex and familial risk of cancer status. Among men and women, associations across familial risk strata were similar and consistent with the unstratified results. Table 5 shows results for anthropometry and colon or rectal cancer risk, separately. Among women, height was more strongly linked with colon (OR, 2.56) than rectal (OR, 1.61) cancer risk; however, the respective confidence intervals largely overlap. Similarly, among men, BMI at both reference periods and weight gain since age 20 y were more strongly linked with colon than rectal cancers; but again, the relevant confidence limits largely include the same range.

Discussion

Our data from a large population based case-control study suggested that, in men, adiposity and adult weight

gain were positively associated with colorectal cancer risk. Relative to normal BMI, recent overweight and obese BMI in men suggested 30% and 80% increased colorectal cancer risks, respectively. Similarly, obesity was linked with about a doubling of colon cancer and a 40% to 60% increased risk of rectal cancer. Our findings are similar to previous reports for associations between BMI and colorectal, colon, and rectal cancers in men from case-control (2, 4, 12, 17, 20, 25, 34) and cohort (3, 5-9, 18, 23, 24, 26-28, 35-40) studies.

Our results for men indicate that weight gain of ≥ 21 kg was associated with $\sim 60\%$, $\sim 80\%$, and $\sim 50\%$ increased risks of colorectal, colon, and rectal cancers, respectively, which is similar to risk estimates from one previous case-control study of colorectal cancer (4) and one cohort study of colorectal cancer (3). That height was not associated with colorectal cancer risk among men was consistent with some (4, 7), but not all

(6, 26, 40), earlier findings. Among men, the influence of adiposity (as assessed by the BMI) and adult weight gain on colorectal/colon cancer risk has been consistent and based on data accumulated in the last three decades in Eastern and Western Europe, Australia, China, Japan, and North America. Subsite analyses suggested moderately stronger associations for colon than rectal cancers, consistent with many (6, 9, 12, 22-26), but not all (2, 5, 7, 8, 27, 28), previous studies that were similarly stratified.

Our findings indicate that men both with and without clinically defined familial risk of cancer were at similar risks of colorectal cancer if overweight or obese. To our knowledge, these are the first data on obesity and colorectal cancer risk among a case series that met the clinical Amsterdam (29) or revised Bethesda (30) criteria for Lynch syndrome. If confirmed in future work, especially from prospective cohort studies, then further

Table 3. Counts and risk estimates among women for BMI, weight gain, and height in relation to incident CRC, stratified by estrogen status

Measure	Cases, <i>n</i> (%)	Controls, <i>n</i> (%)	Age-adjusted OR (95% CI)	Multivariable adjusted OR (95% CI)*
Estrogen-positive women[†]				
BMI 2 y ago (kg/m ²)				
18.5-24.99	260 (51.3)	243 (50.0)	1	1
25-29.99	148 (29.2)	143 (29.4)	1.00 (0.75-1.34)	0.89 (0.66-1.21)
30+	80 (15.8)	86 (17.7)	0.84 (0.59-1.21)	0.67 (0.45-0.98)
BMI at age 20 y (kg/m ²)				
18.5-24.99	351 (69.2)	366 (75.3)	1	1
25-29.99	40 (7.9)	38 (7.8)	1.06 (0.66-1.71)	1.06 (0.64-1.76)
30+	15 (3.0)	14 (2.9)	1.03 (0.49-2.18)	0.74 (0.33-1.67)
Weight gain since age 20 y				
Weight loss	30 (5.9)	41 (8.4)	0.82 (0.48-1.42)	0.86 (0.49-1.50)
1-5 kg	107 (21.1)	116 (23.9)	1	1
6-10 kg	97 (19.1)	89 (18.3)	1.17 (0.79-1.74)	1.16 (0.77-1.74)
11-20 kg	144 (28.4)	139 (28.6)	1.18 (0.82-1.69)	1.09 (0.75-1.58)
21+ kg	102 (20.1)	91 (18.7)	1.25 (0.84-1.85)	1.04 (0.68-1.58)
Height (m)				
<1.55	51 (10.1)	79 (16.3)	1	1
1.65 > height \geq 1.55	226 (44.6)	210 (43.2)	1.62 (1.08-2.42)	1.71 (1.12-2.62)
1.75 > height \geq 1.65	200 (39.5)	179 (36.8)	1.68 (1.11-2.53)	1.84 (1.10-2.84)
≥ 1.75 m	28 (5.5)	18 (3.7)	2.31 (1.15-4.65)	2.54 (1.23-5.25)
Estrogen-negative women[†]				
BMI 2 y ago (kg/m ²)				
18.5-24.99	356 (39.7)	302 (42.1)	1	1
25-29.99	295 (32.9)	241 (33.6)	1.09 (0.86-1.37)	1.08 (0.85-1.37)
30+	180 (20.1)	138 (19.3)	1.12 (0.85-1.48)	1.05 (0.79-1.40)
BMI at age 20 y (kg/m ²)				
18.5-24.99	645 (71.9)	509 (71.0)	1	1
25-29.99	60 (6.7)	54 (7.5)	0.86 (0.58-1.27)	0.81 (0.54-1.21)
30+	23 (2.6)	13 (1.8)	1.15 (0.56-2.35)	1.08 (0.52-2.27)
Weight gain since age 20 y				
Weight loss	77 (8.6)	44 (6.1)	1.44 (0.92-2.25)	1.45 (0.92-2.29)
1-5 kg	151 (16.8)	127 (17.7)	1	1
6-10 kg	131 (14.6)	121 (16.9)	0.96 (0.68-1.36)	1.04 (0.73-1.48)
11-20 kg	242 (27.0)	210 (29.3)	1.02 (0.75-1.39)	1.08 (0.79-1.48)
21+ kg	210 (23.4)	167 (23.3)	1.11 (0.81-1.53)	1.13 (0.82-1.58)
Height (m)				
<1.55	133 (14.8)	141 (19.7)	1	1
1.65 > height \geq 1.55	407 (45.4)	318 (44.4)	1.36 (1.03-1.80)	1.40 (1.05-1.87)
1.75 > height \geq 1.65	297 (33.1)	230 (32.1)	1.35 (1.00-1.81)	1.42 (1.05-1.93)
≥ 1.75	51 (5.7)	24 (3.4)	2.23 (1.29-3.86)	2.31 (1.31-4.07)

NOTE: Some counts do not add to totals because of missing and omitted information.

*Adjusted for age, education, red meat, physical activity, province of residence, CRC screening endoscopy, history of high cholesterol/triglycerides, and hormonal contraceptive use.

[†]Estrogen positive: premenopausal or postmenopausal taking postmenopausal hormone therapy; estrogen negative: postmenopausal, not taking hormone therapy.

Table 4. BMI, weight gain, and height in relation to risk of colorectal cancer, stratified by sex and family history of CRC status

Measure	Cases		Controls <i>n</i> (%)	Case-control		Case-only
	High/Int familial risk	Sporadic risk		High/Int risk	Sporadic risk	High/Int vs sporadic
	<i>n</i> (%)		OR _{adj} (95% CI)*		OR _{adj} (95% CI)*	
Women						
BMI 2 y ago (kg/m ²)						
18.5-24.99	208 (44.6)	283 (42.6)	545 (45.3)	1	1	1
25-29.99	152 (32.6)	225 (33.8)	384 (31.9)	1.03 (0.80-1.33)	0.99 (0.79-1.25)	1.05 (0.78-1.41)
30+	82 (17.6)	112 (16.8)	224 (18.6)	0.85 (0.62-1.16)	0.93 (0.70-1.24)	1.04 (0.72-1.51)
BMI (kg/m ²) at age 20 y						
18.5-24.99	330 (70.8)	483 (72.6)	875 (72.7)	1	1	1
25-29.99	36 (7.7)	43 (6.5)	92 (7.7)	0.90 (0.59-1.37)	0.99 (0.66-1.49)	1.05 (0.63-1.76)
30+	10 (2.2)	13 (2.0)	27 (2.2)	0.81 (0.38-1.72)	1.04 (0.50-2.15)	1.06 (0.43-2.63)
Weight gain since age 20 y						
Weight loss	35 (7.5)	50 (7.5)	85 (7.1)	1.23 (0.76-1.98)	1.09 (0.70-1.68)	0.96 (0.53-1.73)
1-5 kg	80 (17.2)	117 (17.6)	243 (20.2)	1	1	1
6-10 kg	88 (18.9)	103 (15.5)	210 (17.5)	1.31 (0.91-1.88)	1.08 (0.77-1.53)	1.19 (0.76-1.87)
11-20 kg	123 (26.4)	195 (29.3)	349 (29.0)	1.11 (0.79-1.55)	1.03 (0.76-1.39)	1.08 (0.72-1.61)
21+ kg	107 (23.0)	144 (21.7)	258 (21.5)	1.21 (0.85-1.73)	1.05 (0.76-1.44)	1.07 (0.70-1.64)
Height (m)						
<1.55	60 (12.9)	99 (14.9)	220 (18.3)	1	1	1
1.65 > height ≥ 1.55	204 (43.8)	296 (44.5)	528 (43.9)	1.43 (1.02-1.99)	1.35 (1.01-1.79)	1.03 (0.69-1.52)
1.75 > height ≥ 1.65	168 (36.1)	235 (35.3)	409 (34.0)	1.59 (1.12-2.24)	1.47 (1.09-1.99)	1.00 (0.66-1.49)
≥1.75	31 (6.7)	31 (4.7)	42 (3.5)	2.81 (1.61-4.90)	1.90 (1.09-3.30)	1.36 (0.71-2.60)
Men						
BMI 2 y ago (kg/m ²)						
18.5-24.99	104 (22.6)	127 (23.7)	441 (30.1)	1	1	1
25-29.99	215 (46.6)	267 (49.9)	738 (50.4)	1.25 (0.96-1.64)	1.25 (0.97-1.61)	1.08 (0.76-1.52)
30+	117 (25.4)	127 (23.7)	264 (18.0)	1.83 (1.33-2.51)	1.74 (1.28-2.36)	1.18 (0.79-1.74)
BMI at age 20 y (kg/m ²)						
18.5-24.99	280 (60.7)	334 (62.4)	1,022 (69.8)	1	1	1
25-29.99	106 (23.0)	111 (20.8)	273 (18.6)	1.37 (1.04-1.79)	1.35 (1.03-1.76)	1.04 (0.74-1.46)
30+	17 (3.7)	15 (2.8)	29 (2.0)	1.92 (1.02-3.63)	1.78 (0.90-3.53)	1.14 (0.52-2.48)
Weight gain since age 20 y						
Weight loss	25 (5.4)	26 (4.9)	86 (5.9)	1.07 (0.63-1.82)	0.92 (0.55-1.56)	1.05 (0.52-2.12)
1-5 kg	79 (17.1)	81 (15.1)	296 (20.2)	1	1	1
6-10 kg	66 (14.3)	78 (14.6)	269 (18.4)	0.98 (0.67-1.43)	1.05 (0.73-1.52)	1.00 (0.60-1.64)
11-20 kg	121 (26.3)	149 (27.9)	443 (30.2)	1.10 (0.79-1.53)	1.19 (0.86-1.63)	1.08 (0.70-1.67)
21+ kg	130 (28.2)	149 (27.9)	305 (20.8)	1.72 (1.22-2.41)	1.65 (1.18-2.29)	1.11 (0.72-1.71)
Height (m)						
<1.65	19 (4.1)	24 (4.5)	54 (3.7)	1	1	1
1.75 > height ≥ 1.65	138 (29.9)	174 (32.5)	490 (33.5)	0.86 (0.48-1.52)	0.86 (0.51-1.47)	0.92 (0.47-1.80)
1.85 > height ≥ 1.75	239 (51.8)	264 (49.4)	739 (50.4)	1.03 (0.59-1.82)	0.94 (0.55-1.58)	0.95 (0.49-1.84)
≥1.85	55 (11.9)	66 (12.3)	175 (12.0)	0.97 (0.52-1.81)	1.00 (0.55-1.80)	0.80 (0.38-1.70)

NOTE: Some counts do not add to totals because of missing and omitted information.

Abbreviations: OR_{adj}, adjusted odds ratio; High/Int, Amsterdam or Bethesda criteria for family history of CRC.

*Adjusted for age, province, history of hypercholesterolemia/hypertriglyceridemia, education, and history of colon screening endoscopy.

consideration of differential prevention and screening recommendations according to family history of cancer and obesity status may be warranted.

Among women, the influence of adiposity and height on colorectal cancer risk has been less clear. Our findings that BMI and adult weight gain were not associated with colorectal/colon/rectal cancer risk were consistent with several case-control (2, 4, 12) and cohort (7, 18, 23, 26-28, 41) studies. Other case-control (17, 20, 25) and cohort (5, 8, 9, 15, 38, 39, 42, 43) studies reported (usually weak) positive associations between BMI and colorectal, colon, and rectal cancer risks among women. These discordant findings were not likely caused by (a) geographic differences because null and positive reports were offered from within the same country [e.g., the study by Pan et al. (25) and the current study were both conducted in Canada]; (b) BMI cutoff points because both null (7) and positive (8) reports used WHO classifications

for BMI; (c) measurement of height and weight because both self-reported (7, 43) and directly measured (28, 38) BMI indices produced null (7, 28) and positive (38, 43) findings; or (d) any systematic bias between null and positive studies in controlling for potential confounding because within-study comparisons consistently showed similar results in age-only and multivariable-adjusted models (7, 15, 23, 44, 45).

The associations of BMI and weight gain with colorectal cancer risk among women are likely lower than those found among men, or simply nil (2, 4, 6, 7, 12, 17, 18, 23, 25, 26, 28). That height was positively associated with colorectal cancer risk among women in our study was consistent with some (6, 26, 42), but not all (4, 7, 11), previous work. The contrast between men and women for height and adiposity is an interesting finding, and it may suggest different susceptibility periods to cancer development due to positive energy

balance. Among men, both BMI measures were associated with risk whereas no associations were observed among women for the BMI; in contrast, height was associated with cancer risk among women but not among men. These results may indicate that positive energy balance early in life, as indicated by adulthood height, confers risk of colorectal cancer in women, whereas positive energy balance later in life, as indicated by the BMI, is linked with colorectal cancer risk in men.

Similar to previous work (18), our results suggest that adiposity measures are not generally associated with colorectal or colon cancer risk when stratified by menopause or estrogen status. These findings were not in agreement with earlier work (15, 16, 19). Terry et al. (16) reported that obesity in premenopausal women was linked with an almost doubling in colorectal cancer risk. Similarly, Slattery et al. (19) showed that estrogen-

positive women were at ~2.5 times the risk of colon cancer if obese. Conversely, Lin et al. (15) reported that estrogen-negative, but not estrogen-positive, women were at almost 2.5 times the risk of colorectal cancer if obese. Recent work from a large European cohort study reported that obesity was not associated with colon cancer risk among women who were taking postmenopausal hormones (e.g., estrogen-positive women; ref. 26). Publication bias must be also considered in this regard because BMI and colorectal cancer studies that do not find discordance across menopausal or estrogen strata may simply exclude those results from publication or cite them as null and "data not shown," as in the recent work by Otani et al. (7).

Caan et al. (20) provided evidence for effect modification by family history of colon cancer. Among younger participants with a family history of colon cancer (the family history criteria were not explicitly defined), males

Table 5. Counts and risk estimates for BMI, weight gain, and height in relation to incident colon and rectal cancers, stratified by sex

Measure	Cases		Controls <i>n</i> (%)	Colon cancer: case-control	Rectal Cancer: case-control
	Colon cancer <i>n</i> (%)	Rectal cancer <i>n</i> (%)		Multivariable adjusted OR (95% CI)*	
Women					
BMI 2 y ago (kg/m ²)					
18.5-24.99	436 (44.7)	178 (41.9)	545 (45.3)	1	1
25-29.99	304 (31.2)	139 (32.7)	384 (31.9)	0.94 (0.77-1.16)	1.19 (0.91-1.57)
30+	179 (18.3)	80 (18.8)	224 (18.6)	0.91 (0.71-1.16)	1.00 (0.72-1.39)
BMI at age 20 y (kg/m ²)					
18.5-24.99	686 (70.3)	309 (72.7)	875 (72.7)	1	1
25-29.99	68 (7.0)	32 (7.5)	92 (7.7)	0.85 (0.60-1.20)	0.96 (0.61-1.52)
30+	27 (2.8)	11 (2.6)	27 (2.2)	0.98 (0.55-1.73)	0.89 (0.42-1.88)
Weight gain since age 20 y					
Weight loss					
1-5 kg	72 (7.4)	35 (8.2)	85 (7.1)	1.16 (0.79-1.71)	1.27 (0.78-2.07)
6-10 kg	168 (17.2)	88 (20.7)	243 (20.2)	1	1
11-20 kg	161 (16.5)	67 (15.8)	210 (17.5)	1.15 (0.86-1.54)	0.93 (0.63-1.37)
21+ kg	275 (28.2)	111 (26.1)	349 (29.0)	1.15 (0.88-1.49)	0.96 (0.68-1.35)
Height (m)					
<1.55	220 (22.5)	91 (21.4)	258 (21.5)	1.21 (0.92-1.60)	1.00 (0.69-1.45)
1.65 > height ≥ 1.55	134 (13.7)	50 (11.8)	220 (18.3)	1	1
1.75 > height ≥ 1.65	428 (43.9)	203 (47.8)	528 (43.9)	1.38 (1.06-1.79)	1.73 (1.20-2.48)
≥1.75 m	346 (35.5)	150 (35.3)	409 (34.0)	1.50 (1.15-1.96)	1.62 (1.11-2.37)
	61 (6.3)	18 (4.2)	42 (3.5)	2.56 (1.61-4.08)	1.61 (0.83-3.15)
Men					
BMI 2 y ago (kg/m ²)					
18.5-24.99	178 (22.0)	119 (24.9)	441 (30.1)	1	1
25-29.99	394 (48.8)	229 (47.9)	738 (50.4)	1.38 (1.10-1.72)	1.15 (0.88-1.49)
30+	210 (26.0)	111 (23.2)	264 (18.0)	2.04 (1.56-2.66)	1.41 (1.02-1.95)
BMI at age 20 y (kg/m ²)					
18.5-24.99	496 (61.4)	284 (59.4)	1,022 (69.8)	1	1
25-29.99	183 (22.7)	111 (23.2)	273 (18.6)	1.33 (1.06-1.66)	1.35 (1.03-1.77)
30+	33 (4.1)	17 (3.6)	29 (2.0)	2.05 (1.21-3.50)	1.60 (0.83-3.07)
Weight gain since age 20 y					
Weight loss					
1-5 kg	45 (5.6)	30 (6.3)	86 (5.9)	1.16 (0.76-1.79)	1.11 (0.67-1.84)
6-10 kg	129 (16.0)	84 (17.6)	296 (20.2)	1	1
11-20 kg	126 (15.6)	78 (16.3)	269 (18.4)	1.11 (0.81-1.51)	1.00 (0.70-1.45)
21+ kg	224 (27.7)	127 (26.6)	443 (30.2)	1.26 (0.96-1.66)	1.06 (0.76-1.47)
Height (m)					
<1.65	213 (26.4)	118 (24.7)	305 (20.8)	1.77 (1.33-2.37)	1.46 (1.03-2.06)
1.75 > height ≥ 1.65	33 (4.1)	19 (4.0)	54 (3.7)	1	1
1.85 > height ≥ 1.75	247 (30.6)	161 (33.7)	490 (33.5)	0.87 (0.54-1.40)	1.01 (0.56-1.81)
≥1.85	412 (51.0)	224 (46.9)	739 (50.4)	0.96 (0.60-1.54)	0.98 (0.55-1.74)
	107 (13.2)	63 (13.2)	175 (12.0)	0.97 (0.58-1.64)	1.18 (0.63-2.24)

NOTE: Some counts do not add to totals because of missing and omitted information.

*In men and women, adjusted for age, education, red meat intake, recreational physical activity, province of residence, CRC screening endoscopy, and history of high cholesterol/triglycerides. In women only, additionally adjusted for menopausal status and ever use of postmenopausal hormones.

in the highest relative to the lowest tertile of BMI were at a nearly 700% increased risk of colon cancer, and females, 400%, according to the same comparison. Among participants without a family history of colorectal cancer, males and females in the highest relative to the lowest tertile of BMI were at 70% and 50% increased risks of colon cancer, respectively (20).

Several biological mechanisms have been offered to explain this link, including obesity-induced effects on insulin, leptin, chronic inflammation, and steroid hormones (reviewed in refs. 46, 47). The best characterized of these is the concept of insulin resistance and hyperinsulinemia, a common sequela of obesity (48, 49). Animal model and *in vitro* experiments suggest that insulin may exert direct metabolic effects on cancer risk through cell proliferation and apoptosis (50-53) or through indirect metabolic or growth effects on the insulin-like growth factor axis, which is involved in cell signaling, cell differentiation, and apoptosis (54, 55). Leptin, an adipocyte-derived hormone, is an additional plausible link between obesity and colorectal cancer risk. *In vitro* work indicates that leptin may stimulate growth in colon epithelial cells (56) and a cohort study indicated that high-serum leptin was associated with increased risk of colorectal cancer (57). Recent work indicated that another adipose tissue-derived hormone, adiponectin, may be inversely linked with risks of colorectal cancer (58) and adenoma (59), although conflicting evidence (60) for this link too has been offered. Another link between obesity and colorectal cancer is inflammation (61, 62). Inflammation likely initiates or promotes carcinogenesis through formation of reactive oxygen species, which damage DNA, or through nuclear factor κ B-related signaling (63). Our data in men were consistent with these mechanisms.

That BMI was not associated with colorectal cancer risk among women in our study might be explained by the influence of estrogens. Among postmenopausal women, the primary source of endogenous estrogen is through androgen conversion from adipocytes (64). Exogenous estrogens, such as oral contraceptives (65) and postmenopausal hormones (66), are inversely linked with colorectal cancer risk among women, including women with a family history of colorectal cancer (67). In men, however, estrogen supplementation induces insulin resistance (68, 69). Therefore, in women, the protective effects of estrogen derived from adipose tissue may counterbalance the otherwise risk-enhancing effects of obesity.

Alternatively, the weak associations among women may be explained by measurement error in classifying obesity from the BMI. BMI may be more strongly correlated with visceral adipose tissue in men than in women (70); some evidence has further suggested that visceral adipose tissue (usually approximated by waist circumference) is more strongly linked with colorectal cancer risk than is the BMI (18, 40, 41). If BMI is simply a better indicator of visceral adipose tissue in men than in women, and visceral adipose tissue is more strongly associated with disease risk, then the attenuated results among women would reflect misclassification of obesity from the BMI measurement and not a true null effect of obesity. We cannot address this issue because we did not collect data on waist circumference.

That this study relied on self-reported body weight is a limitation because women, more often than men,

underreport body weight (71). If present in the current study, this underreporting may occur about equally between cases and controls, leading to an attenuation of odds. Conversely, differential misclassification would be indicated if cases underreported weight to a greater degree than did controls. Given the consistency in previous studies that used both direct and self-reported measures of body weight, we believe that the influence of this potential limitation is minimal. Long-term recall of body weight and height, as operationalized in the present study with BMI_{age20yr}, has been quite consistently reported as valid with inter-age correlations between measured (at age ~20-30 years) and recalled (at age ~50-70 years) height and weight values ranging between 0.73 and 0.97 (72-76). Strengths of our study include the large sample size, inclusion of data on clinically defined familial risk of cancer, and the broad range of covariates. That familial risk was based on a family history indicative of Lynch syndrome, and not germ-line mutation testing, is a weakness in this study that should be considered for evaluation in future work.

In summary, our data in men indicated that high BMI and adult weight gain were positively associated with risks of colorectal, colon, and rectal cancers. These positive associations persisted among novel subgroup comparisons that included men with and without clinically defined familial risk of cancer. Among women, height only was associated with colorectal and colon cancer risk. These data suggest that sex is a strong modifier for the influence of adiposity on colorectal cancer. Endogenous and exogenous estrogens may explain this effect modification; alternatively, the effect modification may be the result of misclassifying obesity from the BMI in women.

Acknowledgments

We thank Dr. Darshana Daftary, Teresa Mulvenna, and Ontario Familial Colon Cancer Registry/Newfoundland Familial Colon Cancer Registry staff, participants, and investigators for their contributions to this project, and Professors Anthony Hanley, Mary Chipman, Loraine Marrett, and Edward Giovannucci for helpful discussions of this work.

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Cancer Epidemiol Biomarkers Prev 2007;16:1735-1744.

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