Research Article

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# Body Size, Weight Change, and Risk of Colon Cancer

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## Abstract

**Background:** Epidemiologic studies have consistently reported positive associations between obesity and colon cancer risk for men, but the evidence is less consistent for women. Few studies have investigated effects of weight change on colon cancer risk.

**Methods:** Using the Melbourne Collaborative Cohort Study, which recruited men and women mostly in 40 to 69 years of age, we investigated associations between weight and body mass index (BMI) at age 18 years and at study entry and weight change since age 18 years and colon cancer. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated using Cox regression.

**Results:** During follow-up of 16,188 men and 23,438 women for 14 years on average, we ascertained 569 incident colon cancers. Weight and BMI at study entry were positively associated with colon cancer risk for men [HR, 1.12 (95% CI, 1.04-1.21) per 5-kg increment; HR, 1.39 (95% CI, 1.12-1.71) per 5 kg/m$^2$], but not women. Risk of colon cancer was not associated with weight or BMI at age 18 years. Adult weight change was positively associated with colon cancer risk for men (HR, 1.11 per 5-kg increment; 95% CI, 1.03-1.20), but not women (HR, 1.00; 95% CI, 0.94-1.07). Men who gained ≥20 kg from age 18 had an increased risk of colon cancer compared with men whose weight was stable (HR, 1.47; 95% CI, 0.94-2.31).

**Conclusion:** Weight gain during adult life increases men's risk of colon cancer.

**Impact:** Avoiding excessive weight gain might help reduce colon cancer risk for men. *Cancer Epidemiol Biomarkers Prev; 19(11); 2978–86. ©2010 AACR.*

## Introduction

Several large prospective cohort (1-11) and case-control studies (12, 13) have reported positive associations between colon cancer risk and weight or body mass index (BMI) for men, but the evidence is inconsistent for women (1, 3, 7, 8, 11-17).

The effect of weight change on colon cancer risk has been less widely studied, particularly for women. Positive associations between adult weight gain and colon cancer risk have been reported by some prospective cohort studies (6, 18) and case-control studies (13, 19, 20) for men but only weak or null associations for women (13, 19-22). One study reported that this relationship was stronger for older men (6). Others have reported that women but not men with excessive adult weight gain have an increased risk of colon cancer (23, 24). Weight gain since age 18 was positively associated with risk of colon adenomas in a case-control study (25). The Harvard Alumni Health Study reported that men who remained overweight throughout adulthood had higher risk of colon cancer compared with men whose BMI remained in the lowest quintile during early and late adulthood (26).

We investigated prospectively the relationship between BMI, weight, and adult weight change and risk of colon cancer, including by subsite, using recalled weight at age 18 to 21 years and measured weight and height at recruitment to a cohort study.

## Materials and Methods

### The cohort

The Melbourne Collaborative Cohort Study is a prospective cohort study of 41,514 people (17,045 men, 24,469 women) ages 27 to 80 years at baseline, 99.3% of whom were ages 40 to 69 years. Recruitment occurred between 1990 and 1994. The study protocol was approved by The Cancer Council Victoria's Human Research Ethics Committee. Southern European migrants to Australia (including 5,411 Italians and 4,525 Greeks) were oversampled to extend the range of lifestyle exposures and to increase genetic variation.

Subjects were recruited via the Electoral Rolls (registration to vote is compulsory for adults in Australia), advertisements, and community announcements in local media. Comprehensive lists of Italian and Greek surnames were

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also used to target southern European migrants in phonebooks and Electoral Rolls. Passive follow-up has been conducted by record linkage to Electoral Rolls, electronic phonebooks, and the Victorian Cancer Registry and death records until December 31, 2007. Of the original cohort, 57 (0.3%) men have left Australia and 2,516 (14.8%) have died, compared with 51 (0.2%) and 1,926 (7.9%) of women.

### Subjects

We excluded from the analysis 98 men and 97 women because of colorectal cancer diagnosis before study entry and 410 men and 460 women who were missing weight or height at study entry or recalled weight at age 18 to 21 years. A further two men were excluded from the analysis: one had an unknown primary cancer before study entry, and the other reported a cancer diagnosis 8 years after leaving Australia and his diagnosis could not be verified. Those with missing values for any of the confounders were excluded from the analysis, as were those who reported extreme values (top or bottom percentile) of total energy intake (347 men and 474 women). Altogether, data from 16,188 men and 23,438 women were available for analysis.

### Measurements

Each participant's height and weight were measured at study entry according to written protocols based on standard procedures (27). Weight was measured to 100 g using digital electronic scales and height to 1 mm using a stadiometer.

### Questionnaire measures

At study entry, participants were asked their weight between 18 and 21 years of age (weight at 18). Information was also obtained on country of birth, highest level of education, smoking status, and alcohol consumption. Questions were asked relating to frequency of walking, vigorous exercise (exercise "making you sweat or feel out of breath, and includes such activities as swimming, tennis, netball, athletics, and running"), and less vigorous exercise (exercise "which did not make you sweat or feel out of breath and includes such activities as bike riding, dancing, etc.") over the last 6 months. The reported frequencies were coded as follows: 0 (none), 1.5 (one or two times per week), and 4 (three or more times per week). Walking and less vigorous exercise frequencies were summed along with twice the frequency of vigorous exercise to generate a physical activity score for each person. Subjects also completed a 121-item food frequency questionnaire.

Women were asked about their reproductive history. Postmenopausal women were identified as those reporting cessation of periods either naturally for at least the past 12 months or due to a hysterectomy, oophorectomy, or other unspecified reasons. Women who still had periods at baseline were identified as premenopausal. Additionally, women were asked to report their use of hormone replacement therapy (HRT) and oral contraceptives (OC).

### Identification of incident colon cancer cases

All subjects gave written consent allowing access to their medical records to confirm diagnoses. Cases were identified from notifications to the Victorian Cancer Registry and to the National Cancer Statistics Clearing House, of diagnoses of adenocarcinoma of the colon (International Classification of Diseases 10th revision rubric C18.0, C18.2-C18.9). Only subjects with invasive or metastatic colon cancer were counted as cases. Tumors arising in the cecum (C18.0), ascending colon (C18.2), hepatic flexure (C.18.3), and the transverse colon (C18.4) were defined as proximal, whereas tumors in the descending (C18.6) and sigmoid colon (C18.7) were defined as distal. For the analysis by tumor subsite, tumors arising in the splenic flexure (C18.5), with overlapping subsites (C18.8), or with unknown subsite (C18.9) were censored at date of diagnosis.

### Statistical analysis

Follow-up began at study entry and continued until date of diagnosis of colon or rectal cancer, date of diagnosis of cancer of unknown primary, date of death, date last known to be in Australia, or December 31, 2007 (the date that ascertainment of colon cases was complete), whichever came first.

Cox proportional hazards regression models were fitted, with age as the time axis (28), to estimate the hazard ratios (HR) and 95% confidence intervals (CI) for colon cancer associated with each anthropometric measure (weight and BMI at age 18 and at study entry and adult weight change). These included two-way interaction terms between sex and each variable in the model and were stratified by sex. In sex-specific analyses, we investigated whether age modified the association between weight change and colon cancer risk for two follow-up age groups chosen according to the median age of diagnosis of colon cancer cases ($\leq$70 and >70 years). We compared HRs for these two age groups by fitting a Cox model with two-way interactions between age group and each variable in the model, stratifying by age group.

In sex-specific analyses, competing risk models were fitted using the data duplication method (29) with two end points (proximal and distal colon cancer) to estimate the HRs and 95% CIs for proximal and distal colon cancer associated with adult weight change. Subjects who developed the competing end point were censored at the time of occurrence of that end point. To test for heterogeneity in the HRs by tumor subsite, we included two-way interaction terms between subsite and each variable in the model, stratifying by subsite.

BMI was calculated as weight in kilograms divided by the square of height in meters. Height measured at study entry was used in the BMI calculation at age 18 years. BMI at age 18 years was categorized as <18.5 kg/m$^2$,

18.5 to <23 kg/m$^2$ (referent category), 23 to <25 kg/m$^2$, or ≥25 kg/m$^2$, and BMI at study entry was categorized as <23 kg/m$^2$, 23 to <25 kg/m$^2$ (referent category), 25 to <30 kg/m$^2$, or ≥30 kg/m$^2$. Weight at age 18 years and at study entry were categorized into approximate sex-specific quartiles based on the analysis sample [cut points used: at age 18 years, 61, 67, and 73 kg (men) and 50, 54, and 59 kg (women); at study entry, 73.0, 79.8, and 87.6 kg (men) and 59.8, 66.3, and 74.7 kg (women)]. The lowest quartile was used as the referent category.

Weight change since age 18 was the difference between measured weight at study entry and recalled weight at age 18. Weight change was categorized as weight loss (≤−3 kg), stable weight (up to a 3-kg loss or gain), low (3 to <10 kg), moderate (10 to <20 kg), or high weight gain (≥20 kg). The cutoff used to define stable weight (referent category) was chosen to ensure that at least 10% of our subjects were in this group.

To estimate linear trends on the log hazard scale, each anthropometric variable was fitted as a pseudo-continuous covariate (using the median value in each anthropometric category). Nonlinear associations of weight change with colon cancer risk were explored using second-degree fractional polynomials for selected models. Multivariate models that included fractional polynomial terms with or without a linear term for weight change were compared with multivariate models that included only a linear term for weight change to determine model of best fit.

Given our definition of stable weight, our weight loss group was small, so we conducted additional analyses of association between any weight loss and colon cancer risk using different weight change groups: any weight loss and tertiles of weight gain. The first tertile of weight gain (a gain of up to 9.7 kg for men and 9.3 kg for women) was used as the referent group. Corresponding weight gain cutoffs for the second tertile were 9.7 to ≤17.7 kg for men and 9.3 to ≤17.7 kg for women.

The following were considered potential confounders: country of birth (Australia, Greece, Italy, United Kingdom); highest level of education (primary school, some high/technical school, completed high/technical school, and completed tertiary degree/diploma); current physical activity (0, >0 to <4, ≥4 to <6, ≥6); total dietary energy intake (kJ/d); meat (red, fresh, or processed; times per week), fruit (times per day), vegetable (times per day), and cereal intake (times per week); calcium (mg/d), fat (g/d), and saturated fat (g/d) intake; multivitamin supplements (yes/no); current alcohol consumption (lifetime abstainers, ex-drinkers, low intake, medium intake, high intake); and smoking status (never, current, former). Additionally, for women, we considered as potential confounders: age at menarche (<12, 12, 13, ≥14 years old); parity and age at first birth (nulliparous, 1 child and <25 years, >1 child and <25 years, 1 child and ≥25 years, >1 child and ≥25 years); duration of lactation (never, up to 6 months, 7-12 months, 13-24 months, >24 months); OC use (never, ever); HRT use (never, ever); and menopausal status (premenopausal, naturally postmenopausal, postmenopausal due to other reasons). All potential confounders were initially included in each model (full model). Backward stepwise elimination was then done with each covariate being removed if the HRs of the anthropometric measures changed by <5% compared with the full model (30). Potential confounders changing the estimate for any anthropometric HR by >5% were education, processed and fresh meat consumption, fruit and vegetable consumption, fat intake, daily energy intake, smoking status, and alcohol consumption; thus, these were included in all the final models. All models were also adjusted for country of birth (Australia, United Kingdom, Greece, Italy). Models with weight change as the exposure variable were also adjusted for weight at age 18 years (to adjust for regression to the mean) and height (to adjust for body size). Models with weight at age 18 years or weight at study entry as the exposure variable were also adjusted for height.

Statistical analyses were done using STATA/SE 10.1 (Stata Corp.). $P < 0.05$ (two-sided) was considered statistically significant. Tests based on Schoenfeld residuals showed no evidence of violation of the proportional hazards assumption. All analyses were repeated excluding the first 2 years of follow-up to eliminate the possibility that the observed relationships were distorted by preexisting disease.

## Results

We identified 569 incident colon cancer cases (277 in men and 292 in women) over an average of 14.0 person-years of follow-up (range, 0.02-17.1 person-years) between 1990 and 2007. In men, 138 cases occurred in the proximal colon and 123 in the distal colon; corresponding numbers for women were 170 and 101. The mean age at diagnosis was 68 years (range, 41-85 years). Demographic and anthropometric characteristics of the study sample are shown in Table 1. More than a third of participants had gained between 10 and 20 kg since age 18, and about a quarter had gained ≥20 kg. Only ~11% remained within 3 kg of their weight at age 18. A trend of increasing weight gain with decreasing weight at age 18 years was evident—those with the largest weight gain were the lightest at age 18 (Table 1).

Table 2 shows the HRs for colon cancer associated with weight and BMI at age 18 and at study entry. Using each anthropometric variable as a pseudo-continuous measure, we observed significant positive linear trends in the HRs for weight and BMI at study entry for men ($P < 0.01$) but not for women. There was a significant difference in the HRs by sex for BMI at study entry (test of heterogeneity for linear trend, $P = 0.02$).

Significantly higher HRs were observed for men whose weight at study entry was in the third (79.8-87.6 kg; HR, 1.56; 95% CI, 1.08-2.28) or fourth quartiles (≥87.6 kg; HR, 1.81; 95% CI, 1.22-2.68) compared with those in the lowest quartile (<73 kg). A significantly elevated HR was found for men with BMI ≥30 kg/m$^2$ at study entry (HR, 1.51; 95% CI, 1.00-2.28) compared with men with

**Table 1.** Distribution of demographic and anthropometric characteristics by weight change

| | Weight change since age 18 (kg) | | | | |
|---|---|---|---|---|---|
| | ≤−3 | >−3 to <3 | 3 to <10 | 10 to <20 | ≥20 |
| Men ($n$ = 16,188) | | | | | |
| No. participants, $n$ (%) | 631 (4) | 1,717 (11) | 4,093 (25) | 5,846 (36) | 3,901 (24) |
| Age at study entry, mean (SD) | 56.8 (9.2) | 56.1 (9.1) | 55.2 (9.0) | 55.5 (8.7) | 56.2 (8.5) |
| Weight change (kg), mean (SD) | −7.9 (5.8) | 0.4 (1.6) | 6.7 (2.0) | 14.6 (2.8) | 27.7 (7.3) |
| Weight at 18 y (kg), mean (SD) | 78.9 (13.4) | 70.8 (9.1) | 68.6 (8.2) | 66.7 (8.4) | 63.8 (9.7) |
| Weight at study entry (kg), mean (SD) | 71.0 (11.3) | 71.3 (9.2) | 75.3 (8.3) | 81.4 (8.6) | 91.5 (11.7) |
| Height at study entry (cm), mean (SD) | 172.6 (7.5) | 172.1 (7.4) | 172.1 (7.3) | 172.5 (7.3) | 173.1 (7.4) |
| BMI at 18 y (kg/m$^2$), mean (SD) | 26.4 (4.0) | 23.9 (2.7) | 23.2 (2.3) | 22.4 (2.4) | 21.3 (2.8) |
| BMI at study entry (kg/m$^2$), mean (SD) | 23.8 (3.3) | 24.1 (2.7) | 25.4 (2.4) | 27.4 (2.5) | 30.6 (3.6) |
| Country of birth, $n$ (%) | | | | | |
| Australia | 474 (75) | 1,211 (71) | 2,833 (69) | 3,833 (66) | 2,311 (59) |
| United Kingdom | 45 (7) | 166 (10) | 351 (9) | 487 (8) | 294 (8) |
| Italy | 60 (10) | 182 (11) | 517 (13) | 888 (15) | 614 (16) |
| Greek | 52 (8) | 158 (9) | 392 (10) | 638 (11) | 682 (18) |
| Education, $n$ (%) | | | | | |
| ≤Primary | 87 (14) | 233 (14) | 620 (15) | 1,028 (18) | 950 (24) |
| Some high/technical | 212 (34) | 517 (30) | 1,147 (28) | 1,838 (31) | 1,325 (34) |
| Completed high/technical | 161 (26) | 409 (24) | 1,046 (26) | 1,503 (26) | 955 (25) |
| Degree/diploma | 171 (27) | 558 (33) | 1,280 (31) | 1,477 (25) | 671 (17) |
| Women ($n$ = 23,438) | | | | | |
| No. participants, $n$ (%) | 1,198 (5) | 2,633 (11) | 6,068 (26) | 7,950 (34) | 5,589 (24) |
| Age at study entry, mean (SD) | 55.0 (9.1) | 54.1 (9.2) | 54.1 (8.7) | 55.2 (8.5) | 55.9 (8.0) |
| Weight change (kg), mean (SD) | −7.4 (4.7) | 0.5 (1.6) | 6.6 (2.0) | 14.6 (2.8) | 28.6 (8.1) |
| Weight at 18 y (kg), mean (SD) | 64.4 (10.9) | 57.6 (7.7) | 54.9 (6.9) | 53.6 (7.1) | 53.5 (8.0) |
| Weight at study entry (kg), mean (SD) | 57.0 (9.1) | 58.1 (7.6) | 61.5 (7.0) | 68.2 (7.6) | 82.1 (11.7) |
| Height at study entry (cm), mean (SD) | 160.3 (6.7) | 160.5 (6.7) | 160.1 (6.7) | 159.8 (6.7) | 160 (6.5) |
| BMI at 18 y (kg/m$^2$), mean (SD) | 25.1 (4.0) | 22.4 (2.8) | 21.4 (2.5) | 21.0 (2.6) | 21.0 (2.9) |
| BMI at study entry (kg/m$^2$), mean (SD) | 22.2 (3.3) | 22.6 (2.8) | 24.0 (2.7) | 26.8 (3.0) | 32.3 (4.6) |
| Country of birth, $n$ (%) | | | | | |
| Australia | 936 (78) | 2,048 (78) | 4,619 (76) | 5,679 (71) | 3,528 (63) |
| United Kingdom | 93 (8) | 205 (8) | 426 (7) | 510 (6) | 335 (6) |
| Italy | 81 (7) | 213 (8) | 578 (10) | 959 (12) | 947 (17) |
| Greek | 88 (7) | 167 (6) | 445 (7) | 802 (10) | 779 (14) |
| Education, $n$ (%) | | | | | |
| ≤Primary | 159 (13) | 314 (12) | 875 (14) | 1,567 (20) | 1,582 (28) |
| Some high/technical | 491 (41) | 1,066 (41) | 2,530 (42) | 3,598 (45) | 2,468 (44) |
| Completed high/technical | 231 (19) | 520 (20) | 1,169 (19) | 1,387 (17) | 887 (16) |
| Degree/diploma | 317 (27) | 733 (28) | 1,494 (25) | 1,398 (18) | 652 (12) |

NOTE: Percentages may not add up to 100% due to rounding.

BMI between 23 and <25 kg/m$^2$. For women, no consistent associations were found with weight or BMI either at age 18 years or at study entry.

Table 3 shows the HRs for colon cancer associated with weight change. Using weight change as a pseudo-continuous measure, we observed a significant positive linear trend in the HRs for men ($P < 0.01$), but not women ($P = 0.95$). For men, the fractional polynomial models showed no evidence of a departure of linearity for weight change on a log hazard scale. There was a significant difference in the HRs by sex (test of heterogeneity for linear trend, $P = 0.04$).

An elevated HR was found for men having an adult weight gain of ≥20 kg (HR, 1.47; 95% CI, 0.94-2.31) compared with those whose weight remained within 3 kg of their weight at age 18, although this was not statistically significant. The HRs were below unity for both men and women with weight loss of ≥3 kg, but the corresponding CIs included unity and were wide. There was no association between high adult weight gain and colon cancer risk for women.

In separate analyses for men and women, we observed elevated HRs for weight change for both younger (≤70 years,

HR, 1.18 per 5-kg increment; 95% CI, 1.06-1.31) and older men (>70 years, HR, 1.05 per 5-kg increment; 95% CI, 0.94-1.16). The difference in HRs by age was not significant (test of heterogeneity, $P = 0.12$; data not shown). There was no association between weight change and colon cancer for either younger or older women and no significant difference in the HRs by age (test of heterogeneity for linear trend for women, $P = 0.58$).

Using our alternative definition for weight change groups, no relationship was found between weight loss and colon cancer risk compared with those in the first tertile of gain. Men with weight gain of >17.7 kg since age 18 years had a HR of 1.53 (95% CI, 1.11-2.10) compared with those in the first tertile of weight gain (data not shown).

In sex-specific analyses, we observed a significant positive linear trend in the HRs for proximal colon cancer in men ($P < 0.01$) and a weaker nonsignificant positive trend for distal colon cancer ($P = 0.14$) (Table 4). The differences in the HRs by subsite were not significant for men or women (test of heterogeneity, $P = 0.59$ and $P = 0.72$, respectively).

For proximal colon cancer, elevated HRs were found for men having an adult weight gain of 3 kg or more compared with those whose weight remained within 3 kg of their weight at age 18 (Table 4), but these were only statistically significant for weight gain ≥20 kg (HR, 2.12; 95% CI, 1.10-4.10). There was no association between adult weight change and risk of distal colon cancer for men, and no association for women for either subsite.

**Table 2.** HRs and 95% CIs for colon cancer in relation to weight and BMI

| | Men | | Women | |
|---|---|---|---|---|
| | Cases (PY) | HR (95% CI)* | Cases (PY) | HR (95% CI)* |
| Weight at age 18 y (quartiles) | | | | |
| <61 kg/<50 kg | 73 (56,370) | 1.00 | 60 (72,766) | 1.00 |
| 61 to <67 kg/50 to <54 kg | 61 (58,551) | 0.79 (0.55-1.11) | 81 (80,481) | 1.24 (0.88-1.73) |
| 67 to <73 kg/54 to <59 kg | 70 (52,479) | 1.00 (0.70-1.41) | 62 (85,169) | 0.93 (0.64-1.34) |
| ≥73/≥59 kg | 73 (54,206) | 1.05 (0.72-1.51) | 89 (94,561) | 1.25 (0.88-1.79) |
| Linear model (per 5 kg)† | 277 (221,606) | 1.03 (0.94-1.12) | 292 (332,977) | 1.03 (0.94-1.14) |
| *P* for trend (linear model) | | 0.54 | | 0.50 |
| Weight at study entry (quartiles) | | | | |
| <73.0 kg/<59.8 kg | 50 (55,504) | 1.00 | 67 (83,762) | 1.00 |
| 73.0 to <79.8 kg/59.8 to <66.3 kg | 63 (55,853) | 1.23 (0.84-1.80) | 81 (83,009) | 1.24 (0.89-1.72) |
| 79.8 to <87.6 kg/66.3 to <74.7 kg | 78 (55,662) | 1.56 (1.08-2.28) | 61 (83,311) | 0.93 (0.65-1.33) |
| ≥87.6 kg/≥74.7 kg | 86 (54,587) | 1.81 (1.22-2.68) | 83 (82,896) | 1.32 (0.93-1.86) |
| Linear model (per 5 kg)† | 277 (221,606) | 1.12 (1.04-1.21) | 292 (332,977) | 1.04 (0.98-1.11) |
| *P* for trend (linear model) | | <0.01 | | 0.22 |
| BMI at age 18 y | | | | |
| <18.5 kg/m$^2$ | 18 (11,012) | 1.46 (0.89-2.40) | 28 (42,291) | 0.79 (0.53-1.18) |
| 18.5 to <23 kg/m$^2$ (reference) | 135 (118,562) | 1.00 | 180 (205,695) | 1.00 |
| 23 to <25 kg/m$^2$ | 70 (53,675) | 1.08 (0.81-1.45) | 53 (50,366) | 1.18 (0.87-1.61) |
| ≥25 kg/m$^2$ | 54 (38,358) | 1.21 (0.88-1.67) | 31 (34,625) | 1.07 (0.73-1.58) |
| Linear model (per 5 kg/m$^2$)† | 277 (221,606) | 1.05 (0.80-1.37) | 292 (332,977) | 1.19 (0.93-1.52) |
| *P* for trend (linear model) | | 0.73 | | 0.16 |
| BMI at study entry | | | | |
| <23 kg/m$^2$ | 13 (22,766) | 0.60 (0.32-1.13) | 64 (75,853) | 0.95 (0.67-1.36) |
| 23 to <25 kg/m$^2$ (reference) | 38 (38,972) | 1.00 | 59 (63,349) | 1.00 |
| 25 to <30 kg/m$^2$ | 160 (118,719) | 1.31 (0.91-1.87) | 102 (121,574) | 0.84 (0.61-1.17) |
| ≥30 kg/m$^2$ | 66 (41,150) | 1.51 (1.00-2.28) | 67 (72,201) | 1.00 (0.70-1.44) |
| Linear model (per 5 kg/m$^2$)† | 277 (221,606) | 1.39 (1.12-1.71) | 292 (332,977) | 1.01 (0.86-1.18) |
| *P* for trend (linear model) | | <0.01 | | 0.90 |

Abbreviation: PY, person-years.

*Models adjusted for country of birth, education, processed and fresh meat consumption, fruit and vegetable consumption, fat intake, daily energy intake, smoking status, and alcohol consumption and stratified by sex. Models with weight at age 18 y or weight at study entry were also adjusted for height at study entry.

†Test for heterogeneity in the HRs between men and women, for weight at age 18 y ($P = 0.92$), weight at study entry ($P = 0.12$), BMI at age 18 y ($P = 0.49$), and BMI at study entry ($P = 0.02$).

**Table 3.** HRs and 95% CIs for colon cancer in relation to weight change

| Weight change category | Men | | Women | |
|---|---|---|---|---|
| | Cases (PY) | HR (95% CI)* | Cases (PY) | HR (95% CI)* |
| ≤−3 kg | 8 (8,370) | 0.68 (0.31-1.50) | 17 (16,651) | 0.90 (0.50-1.62) |
| >−3 to <3 kg (reference) | 29 (23,271) | 1.00 | 37 (36,968) | 1.00 |
| 3 to <10 kg | 58 (56,260) | 0.92 (0.59-1.44) | 73 (86,306) | 0.88 (0.59-1.31) |
| 10 to <20 kg | 94 (80,478) | 1.05 (0.68-1.60) | 91 (113,454) | 0.81 (0.55-1.20) |
| ≥20 kg | 88 (53,228) | 1.47 (0.94-2.31) | 74 (79,598) | 0.96 (0.64-1.44) |
| Linear model (per 5 kg)† | 277 (221,606) | 1.11 (1.03-1.20) | 292 (332,977) | 1.00 (0.94-1.07) |
| *P* for trend (linear model) | | <0.01 | | 0.95 |

*Adjusted for country of birth, weight at age 18 and height at study entry, education, processed and fresh meat consumption, fruit and vegetable consumption, fat intake, daily energy intake, smoking status, and alcohol consumption and stratified by sex.
†Test for heterogeneity in the HRs for weight change between men and women ($P = 0.04$).

Additional analyses excluding the first 2 years of follow-up did not substantially change the HRs.

## Discussion

We found a positive association between adult weight change and colon cancer risk for men, but not for women. For men, there was weak evidence that the association was stronger for the proximal colon.

We had virtually complete follow-up in this prospective study, as the identification of incident colon cancers was done by record linkage to the Australian population-based cancer registries that have complete coverage of the cohort participants. Only 0.3% of participants left Australia during follow-up, so it is unlikely that we have missed many cases. Our study has limitations. First was the use of the long-term recall of body weight at age 18 years. Previous validation studies of self-reports of past body weight over a similar period to that used in our study show moderate to strong correlations with measured weight in the range of 0.64 to 0.95 (31-35). These studies have shown that long-term recall of past weight is influenced by sex and current weight. However, its accuracy is generally supported in epidemiologic studies (31, 33, 34). Second, the number of cases was small for some of our analyses, particularly for the weight loss group; thus, some associations may not have been detected because of low statistical power.

Although physical activity, dietary factors, and, for women, reproductive factors could possibly have confounded the observed relationships, adjusting for these factors did not change HRs by >5%. Information on potential confounding variables was only collected at study entry and might not be relevant to the time period we studied.

Weight loss is a clinical feature of colon cancer (36), and although we were not able to differentiate between intentional and unintentional weight loss, the null association we observed between weight loss and colon cancer risk, using the two different weight loss categories (weight loss of 3 kg or more and any weight loss), remained evident in additional analyses excluding the first 2 years of follow-up.

A recent review and meta-analysis of obesity and colorectal cancer concluded that men with BMI ≥30 kg/m$^2$ had a relative risk for colon cancer of 1.53 (95% CI, 1.33-1.75) compared with those with BMI <25 kg/m$^2$ (after correcting for publication bias; ref. 37), which is similar to the relative risk reported in our study. They reported a relative risk of 1.09 (95% CI, 0.93-1.28) for women.

We are aware of only one other study that formally tested for sex differences in the association between weight change and colon cancer or adenoma risk (38). Sedjo et al. (38) reported a nonsignificant weight change by sex interaction in their study of colorectal adenoma risk and recent weight change; thus, results were presented for men and women combined. Other studies have fit separate models for men and women or stratified by sex (11, 13, 19, 23-25, 39, 40).

Studies investigating associations between adult weight change and incident colon cancer risk have used recalled weight between ages 18 to 25 years, which is consistent with our study. Our findings for men are comparable with those from other prospective cohort (6, 18) and case-control studies (13, 19, 20, 25) that examined weight gain since early adulthood. The Health Professionals Study reported weight gain to be positively associated with colon cancer risk; men gaining >7.5 kg per 10 years have a HR of 1.41 (18). One case-control study (13) reported a relative risk of 1.77 for men who gained >20 kg since age 20 years, whereas a pooled analysis of several case-control studies (including the aforementioned study) gave a relative risk of 1.5 for weight gain of >20 kg since age 20 (20). Another case-control study reported a relative risk of 1.6 for men who gained >14 kg since age 25 (19). Lubin et al. (25) reported a positive linear relationship between weight gain since age 18 and colorectal adenomas and a >2-fold excess risk (sexes combined) for those gaining >11 kg. In contrast to ours, these studies

reported that even moderate adult weight gain increased colon cancer risk for men. Nomura et al. (6) reported a positive association between weight gain since age 25 years and colon cancer risk, which was stronger for men older than 55 years. Our results suggest that the association between weight change and colon cancer risk is not modified by age.

Consistent with other prospective (21, 22) and case-control (13, 19, 20) studies, we found no significant association between women's adult weight gain and colon cancer risk.

Inconsistent results have been reported for change in BMI. The Harvard Alumni Health Study reported a 2.5-fold increase in colon cancer risk for men who were overweight both at college entry (1916-1950) and at follow-up (1962 or 1966) compared with their lightest peers (26). In contrast to our findings on weight gain, the Japan Collaborative Cohort Study (23) reported obesity and high weight gain since age 20 years to be associated with increased risk of colon cancer mortality for Japanese women but not men. A population-based case-control study (24) investigated changes in BMI at different times in adulthood and reported a positive association between change in BMI (>10 kg/m$^2$) between both the 20s and the 30s decade and the study recruitment period and colon cancer risk for women, but not men. Slightly weaker, nonsignificant associations were reported for men and women with moderate BMI changes (5-10 kg/m$^2$) over this period.

We are aware of only one other study that has investigated the association between weight change and risk of colon cancer by tumor subsite (11). In contrast to our findings for men, Laake et al. (11) reported a relative risk for distal colon cancer of 1.87 (95% CI, 0.93-3.75) for weight gain ≥10 kg but only 1.02 (95% CI, 0.47-2.18) for proximal colon cancer in a Norwegian, population-based cohort study. They found relative risks of 0.91 (95% CI, 0.43-1.94) and 1.46 (95% CI, 0.83-2.56), respectively, for women. In the Norwegian study, participants were ~40 years old at baseline and weight change was measured (prospectively) over a much shorter period compared with our study.

We can only speculate about possible reasons for sex differences in colon cancer risk associated with weight change. One possibility is differences in body fat distribution between the sexes. With aging, the distribution of body fat tends to shift from peripheral to central sites, and particularly for men, there is a tendency toward abdominal obesity and this is a stronger risk factor than weight or BMI (41). For men, weight gain is more likely to be associated with an increase in waist circumference compared with women (42) and this might partly explain the sex difference in risk. It is possible that increases in abdominal obesity over adulthood could convey higher risks than those we have observed for weight increases. To our knowledge, only one study examined the relationship between change in waist circumference or waist-hip ratio and risk of colorectal adenomas, but they reported

**Table 4.** HRs and 95% CIs for colon cancer in relation to weight change by tumor subsite

| Weight change category | Men | | Women | |
|---|---|---|---|---|
| | Cases | HR (95% CI)* | Cases | HR (95% CI)* |
| Proximal | | | | |
| ≤−3 kg | 5 | 1.04 (0.35-3.08) | 9 | 0.72 (0.32-1.59) |
| >−3 to <3 kg (reference) | 11 | 1.00 | 24 | 1.00 |
| 3 to <10 kg | 31 | 1.37 (0.69-2.71) | 39 | 0.73 (0.44-1.20) |
| 10 to <20 kg | 50 | 1.63 (0.85-3.10) | 54 | 0.73 (0.46-1.18) |
| ≥20 kg | 41 | 2.12 (1.10-4.10) | 44 | 0.86 (0.53-1.40) |
| Linear model (per 5 kg)† | 138 | 1.14 (1.03-1.25) | 170 | 1.01 (0.92-1.10) |
| *P* for trend (linear model) | | <0.01 | | 0.89 |
| Distal | | | | |
| ≤−3 kg | 2 | 0.36 (0.09-1.53) | 7 | 1.31 (0.49-3.52) |
| >−3 to <3 kg (reference) | 15 | 1.00 | 11 | 1.00 |
| 3 to <10 kg | 24 | 0.69 (0.36-1.32) | 29 | 1.17 (0.59-2.33) |
| 10 to <20 kg | 41 | 0.78 (0.42-1.44) | 30 | 0.92 (0.46-1.82) |
| ≥20 kg | 41 | 1.11 (0.58-2.11) | 24 | 1.07 (0.53-2.18) |
| Linear model (per 5 kg)† | 123 | 1.09 (0.97-1.22) | 101 | 0.98 (0.88-1.10) |
| *P* for trend (linear model) | | 0.14 | | 0.72 |

*Adjusted for country of birth, weight at age 18 and height at study entry, education, processed and fresh meat consumption, fruit and vegetable consumption, fat intake, daily energy intake, smoking status, and alcohol consumption and stratified by tumor subsite.

†Test for heterogeneity in the HRs for weight change between proximal and distal subsite: $P = 0.59$ (men) and $P = 0.72$ (women).

no associations between 5- or 10-year change in either measure of abdominal obesity (38).

A recent review concluded that colon cancer risk is related to determinants of the metabolic syndrome (obesity, abdominal obesity, and physical inactivity), its clinical consequences (type 2 diabetes and hypertension), its plasma or serum components (hypertriglyceridemia, hyperglycemia, and low high-density lipoprotein cholesterol), and markers of hyperinsulinemia or insulin resistance (insulin and C-peptide; ref. 43). Evidence from both human and animal studies suggests that hyperinsulinemia might play a more direct role for colon cancer risk than other factors associated with insulin resistance, but this is not conclusive (43). Weight change and obesity (particularly abdominal) are associated with hyperinsulinemia (44); this might induce changes in the insulin-like growth factor system (45, 46), which could have implications for the development and progression of cancer (45, 46). Visceral abdominal fat (VAF), not subcutaneous or total body fat, seems to be a stronger risk factor for colon cancer risk (47). Women tend to accumulate less VAF with weight gain than men (48). Higher VAF in men leads to increased insulin and a decrease in insulin sensitivity (49), whereas improved insulin sensitivity has been reported in women with a peripheral fat distribution (50, 51). Thus, the propensity for men to develop abdominal obesity might partly explain the sex differences in colon cancer risk. Higher circulating leptin levels in the obese are also associated with colon cancer (52), and a recent cohort study has shown that leptin was associated with increased risk of colorectal cancer for men, but not women (53).

Androgens are converted to estrogen by adipose tissue in postmenopausal women (54). In men, testosterone levels decrease with obesity (particularly abdominal; refs. 55, 56), whereas the reverse is true for women (57, 58). Estrogen supplementation increases insulin resistance in men, but not women, and as the estrodial/testosterone ratio increases, so do the plasma glucose and insulin levels (59, 60). Therefore, we would expect the estrodial/testosterone ratio to be higher in obese men compared with women, and this might partly explain the observed sex difference in the relationship with weight gain and colon cancer risk.

Our findings, if confirmed by further prospective studies, suggest that weight maintenance, in particular avoiding excessive weight gain, might help reduce colon cancer risk for men.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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