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Prospective weight change and colon cancer risk in male US health professionals

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Abstract

Epidemiological studies are remarkably consistent, especially among men, in showing that overweight and obesity [body mass index (BMI) >25] are associated with increased risk of colon cancer. However, no prospective studies address the influence of weight change in adulthood on subsequent colon cancer risk. In this study, we investigated whether weight change influences colon cancer risk utilizing prospectively collected weight data. We included 46,349 men aged 40–75 participating in the Health Professionals Follow-Up Study. Questionnaires including items on weight were completed every second year during follow-up from 1986 to 2004. Updated weight change between consecutive questionnaires during follow-up and recalled weight gain since age 21 was evaluated. All eligible men were cancer-free at baseline. Proportional hazard and restricted spline regression models were implemented. Over an 18-year period, we documented 765 cases of colon cancer. Cumulative mean BMI >22.5 was associated with significantly increased risk of colon cancer. The short-term weight change in the prior 2 to 4 years was positively and significantly associated with risk [HR = 1.14 (95% confidence interval, 1.00–1.29) for 4.54 kg (10 pounds) increment, $p = 0.04$ for overall trend]. Weight gain per 10 years since age 21 was associated with significantly increased risk [HR = 1.33 (1.12–1.58) for 4.54 kg increase per 10 years, $p = 0.001$]. We estimated that 29.5% of all colon cancer cases was attributable to BMI above 22.5. Our results add support that overweight and obesity are modifiable risk factors for colon cancer among men and suggest that weight has an important influence on colon cancer risk even in later life.

Keywords

colonic neoplasms/epidemiology; weight gain; weight loss

Globally, colorectal cancer is the fourth most common cancer among men and third most common among women.[1] During the last 2 decades, large prospective studies[2–7] and

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population-based case-control studies[8,9] have supported increased risk of colon cancer among overweight and obese persons [body mass index (BMI) >25 m^2/kg], most consistently observed among men.[10] The increasing prevalence of overweight and obesity in the developed and developing world[11,12] could therefore greatly influence future incidence of colon cancer.

Although strong epidemiologic evidence indicates that high BMI increases colon cancer incidence, whether weight change influences the risk of colon cancer, especially in middle-aged and older individuals, is unknown. Previous studies of weight change and risk of colon adenoma and cancer[13–21] showed inconsistent results. Weight gain was associated with greater risk of adenoma in 4 case-control studies,[18–21] while weight change during adult life was unrelated with colon cancer risk in 2 prospective studies among women.[14,15] Among men older than 55 years, weight gain during adult life was associated with increased risk of colon cancer, [13] while weight gain appeared to increase risk among women but not men in another study.[17] All previous prospective studies used recalled information on past weight.

In the Health Professionals Follow-Up Study (HPFS), a large prospective cohort study of male health professionals repeated assessments of current weight were available over a long follow-up period. Such information is useful, because recalled weight may have greater measurement error than repeated reports of current weight, and is perhaps susceptible to differential bias in case-control studies. Also, latency can be studied more directly when data are prospectively collected. Thus, in this cohort, in which every participant received biannual questions on current weight during 18 years of follow-up, we prospectively investigated the relation of weight and weight change to risk of colon cancer. For comparison with previous studies, we also utilized recalled past weight at age 21 and 5 years before baseline.

Material and methods

Study design and population

Participants were members of the HPFS, an ongoing prospective cohort study of 51,129 men aged 40–75 years at enrollment in 1986. At baseline, the men returned a questionnaire inquiring about their medical history and lifestyle factors, including a 131-item food frequency questionnaire (FFQ).[22] Information on medical history and lifestyle factors was updated every second year and dietary information was updated every fourth year. Deaths were reported by family members, the postal system or were identified through the National Death Index, which we estimate to have a sensitivity of more than 98%.[23]

Men who on their FFQs reported very high or very low intakes (*i.e.*, <800 or >4,200 kcal/day) or who had left more than 70 items blank were excluded from this study. Men with a history of ulcerative colitis or cancer (except for nonmelanoma skin cancer) before 1986 were also excluded and, finally, men with missing data on BMI in 1986 were excluded. After these exclusions, 46,349 men formed our baseline population. The Human Subjects Committee of the Harvard School of Public Health approved this study.

Exposure information

Weight information was collected every second year, when the participants were asked about their current weight measured in pounds (1 pound = 0.454 kg), which we term prospective weight information. In a validation study in the HPFS cohort, Rimm *et al.*[24] found self-reported weight to be highly accurate when compared to standardized measurements. Trained technicians visited randomly selected Boston-area cohort members of similar age distribution as the entire cohort twice, approximately 6 months apart, to

measure current weight. The Pearson correlation coefficient of the mean of the technicians' 2 measurements and the self-reported weight was 0.97 and the men underestimated their weight by 1.0 kg compared to the technicians' measurements.

To assess the influence of weight, we used the mean of all available information on current weight up to the beginning of each 2-years follow-up cycle, which we call the cumulative mean weight. This time-varying variable combined with height reported in 1986 was utilized to calculate cumulative mean BMI (kg/m^2).

When analyzing weight change, we used prospective weight information by evaluating updated weight change between 2 consecutive weight measures during follow-up. This way updated weight change combines data on weight change between 2 consecutive questionnaires (*e.g.* weight change 1986–1988) in relation to the risk over the next 2 years (colon cancer risk 1988–1990), and weight change from 1988 to 1990 in relation to risk from 1990 to 1992, etc. Each 2-year risk interval was evaluated as a new short term follow-up study and the information obtained on all these intervals was pooled statistically as described by Cupples *et al*.[25] This method thereby assume no influence of previous weight change, which is a standard assumption when including updated exposure information.[25] Weight loss was categorized as 1.1–4 kg, and more than 4 kg, while weight gain was categorized as 1.1–4, 4.1–7 and more than 7 kg. The reference group was stable weight ± 1 kg.

Weight loss is a clinical feature of colon cancer[26,27] and occult disease may create reverse causation. We therefore examined latency time between updated weight change and colon cancer risk by lagging the follow-up by 2–4 years, *i.e.*, updated weight change lagged 2–4 years would include weight change 1986–88 in relation to colon cancer risk 1990–92, weight change 1988–90 in relation to risk 1992–94, etc.

On the 1986 questionnaire information on weight at age 21 was ascertained by recall. In a validation study among nurses, the correlation between recalled and measured weight from physical examinations at college or nursing school entrance was 0.87[15] and weight was slightly underreported (mean difference 1.4 kg). The same result was supported by other studies.[28–30] Reported weight at age 21 was used to evaluate the influence of weight change during adult life by comparing weight at age 21 with updated weight during follow-up. We calculated weight change per 10 years to take account of different time periods from age 21 to age during follow-up and adjusted the analysis for BMI at age 21.

Obesity seems to be a factor in adenoma growth rather than adenoma formation,[31] and although time for an adenoma to grow to cancer is unclear, 5–15 years is proposed.[32,33] On this background, it is of interest to simultaneously examine the influence of weight change from age 21 to 10 years before follow-up and weight change in the prior 10 years to follow-up. We approximated this by utilizing recalled weight change 5 years before baseline to calculate weight in 1981. We lagged the analyses by 2–4 years. The follow-up for this analysis was 1992–2004.

Our study population consisted of men with valid information on weight in 1986. On average 80% of the surviving population completed the questions on current weight on each of the subsequent follow-up cycles. When valid information on weight was available 2 years before and 2 years after one missing weight value, we imputed weight as the mean of these 2 measures (7.2%). For all other missing weight values, we eliminated the intervals with missing exposure information (10.6%).

Confounders

We considered confounding by other variables shown previously to be associated with colon cancer. We examined alcohol intake, physical activity, folate, methionine and vitamin D intake, calcium use, total calorie intake, processed and red meat intake, smoking habit, multivitamin use, aspirin use, endoscopic screening and family history of colorectal cancer. All variables were included as potential confounders in the above analyses. To be certain that confounders were not intermediate variables between weight change and colon cancer diagnosis, we included time varying confounders measured before weight change. We also adjusted for BMI before weight change to assess the independent influence of weight change. Finally, we conducted analyses stratified by BMI before weight change and tested for interaction between binary BMI (below and above 25 kg/m^2) and weight change (treated as a continuous variable) using a log likelihood test with 1 degree of freedom.

Outcome

We requested consent to review medical records for men who indicated a recent diagnosis of colorectal cancer on their biannual follow-up questionnaires. Study investigators reviewed those medical records and extracted information on histology, anatomic location and stage of colorectal cancer. For this analysis, we only included adenocarcinomas of the colon. Rectal cancer cases were not included because obesity has not been consistently associated with this malignancy.[5,7,10] Participants with rectal cancer diagnosis were censored at month of diagnosis. A total of 643 colon cancer cases were identified from 1986 to January 31, 2004. We also included 122 colorectal cancer cases with missing information on anatomic site, since the majority of colorectal cancer cases were colon cancer cases. The influence of updated weight change did not differ when excluding these cases (not shown). Of those 765 cases, 655 cases (86%) were confirmed by medical records and the remaining cases were confirmed by corroborating information on cancer treatment and diagnosis from participants (*e.g.*, telephone interviews). When studying updated weight change lagged 2–4 years, we excluded cases before 1990 (140 cases) and when studying cumulative mean BMI and recalled weight change lagged 2–4 years, we excluded cases before 1988 (72 cases). For analysis by colon cancer subsites, colon cancers located in the cecum, ascending colon, or transverse colon were defined as proximal colon cancers, whereas colon cancers located in the descending or sigmoid colon were defined as distal colon cancers.

Statistical methods

Follow-up time began at the month during which the baseline questionnaire was returned and ended at the month during which colon cancer was diagnosed, the month during which death occurred, or the end of the study period (January 31, 2004), whichever came first. We directly computed age-standardized mean values and proportions for potential confounders by categories of weight change using the age-distribution of the entire cohort. Cox proportional hazards regression was performed to estimate the age-adjusted and multivariate hazard ratio (HR) and 95% confidence intervals (95% CI) of colon cancer by considering weight change included categorically, while taking either age or the aforementioned potential confounders into account. Because age was a strong predictor for colon cancer, the analyses were stratified by age in 1-year groups. We also conducted analyses using weight change as a continuous variable because weight change is measured continuously and such analysis had more statistical power. We also examined the possibly nonlinear relation between weight change and HR of colon cancer nonparametrically with restricted cubic splines.[34] Risk estimates for weight change modeled continuously were reported per 10 pounds (4.54 kg). Tests for nonlinearity used the likelihood ratio test, comparing the model with only the linear term to the model with the linear and the cubic spline terms. To evaluate the population level influence of BMI and weight gain, we calculated the population

attributable risk percent (PAR%) for high BMI and weight gain.[35,36] All tests of significance were 2-sided. We used SAS/STAT software version 9.

Results

Age and weight change from 1986 to 1988 were inversely related as mean age was highest among those losing weight and lowest among those gaining weight (Table I). Vitamin D and folate intakes were positively related with weight change, while a U-shaped relationship was observed for smoking prevalence, BMI and methionine intake and weight change. The mean age at baseline was 54.3 with standard deviation of 9.7.

During follow-up, the mean weight of the cohort steadily increased from 0.21 kg to 0.60 kg per 2 years interval. Furthermore, an increasing standard deviation and wider gap between the lower and upper quartiles indicated that the weight distribution became wider during follow-up. The correlation between consecutive weight measures was above 0.93 and became lower for greater time spans; the correlation was lowest for weight 1986 and 2002 (r = 0.83). The correlation between change in 2 consecutive intervals was negative, *e.g.*, the correlation between change in weight 1990–92 and change 1992–94 was −0.28, while there was no or only weak correlation between weight change separated by one or more 2-year intervals.

Prospective weight information

Cumulative mean BMI above 22.5 was associated with significantly increased risk of colon cancer compared to BMI of 20–22.5 (Table II). The multivariate adjusted HR for BMI of 30.1–35 was 2.29 (95% CI, 1.58–3.31) and for BMI >35 was HR = 2.29 (95% CI, 1.23–4.26). A nonsignificant increased risk for BMI below 20 was observed (1.69: 0.83–3.44). A test for nonlinearity by spline regression was significant (p = 0.03), which supported that the association deviates from linearity. The risk estimates for baseline BMI (1986) were slightly lower for all categories compared to cumulative mean BMI, *e.g.*, baseline BMI of 30.1–35 had HR = 2.02 (95% CI, 1.43–2.86) (not shown).

Two-year weight change lagged 2–4 years was positively associated with colon cancer risk, and the linear association was significant [HR = 1.14 (95% CI, 1.00–1.29) for a 4.54 kg increment, p = 0.04]. The test for nonlinearity was not significant (p = 0.71). Weight loss was associated with lower risk, but this was not significant (for weight loss >4 kg HR = 0.82, 95% CI = 0.57–1.17) (Table III).

Two-year weight change without allowing any time lag showed nonsignificantly increased risk for weight loss and lower risk for weight gain >7 kg (HR = 0.33: 95% CI,0.12–0.89). The linear association was significant and negative [HR = 0.85 (0.76–0.94) for 4.54 kg increase, p = 0.003]. This analysis is likely to be biased by an influence of undiagnosed colon cancer on weight loss.

When stratified by BMI (below and above BMI of 25), 2-year weight change was only significantly associated with risk among men with BMI ≤ 25, but an interaction test between BMI strata and weight change was nonsignificant (p = 0.11).

Site-specific analyses showed a significant positive association between 2-year weight change and proximal colon cancer risk [HR = 1.39 (1.14–1.68) for 4.54 kg increase, p < 0.001], while weight change was not associated with distal colon cancer risk [HR = 0.96 (0.79–1.17) for 4.54 kg increase, p = 0.66].

Weight change from age 21

Change in weight from age 21 to weight at the start of a 2-year interval was positively associated with risk of colon cancer [HR = 1.17 (0.99–1.38) for 4.54 kg increase per 10 year, $p = 0.06$]. When allowing 2–4 years of lag time for weight change, the association became stronger [HR = 1.33 (1.12–1.58) for 4.54 kg increase per 10 years, $p = 0.001$] (Table IV).

A significant linear association between BMI at age 21 and colon cancer risk during follow-up was observed with significantly increased risk for the highest quintile compared to lowest quintile (HR = 1.34, 95% CI = 1.05–1.70). When we jointly classified BMI at age 21 and updated BMI into tertiles, the influence of BMI at age 21 was not consistently positive within tertiles of updated BMI, while updated BMI showed a clear positive association within all tertiles of BMI at age 21. A log-likelihood test did not support that BMI at age 21 (quintiles) was associated with risk conditional on updated weight ($p = 0.72$).

When including both change from age 21 to 10 years prior to follow-up and weight change from 10 years prior to start of follow-up (lagged 2–4 years), the influence of both weight changes had the same magnitude, HR (weight change age 21 to 10 years prior) = 1.08 (95% CI,1.03–1.14) for 4.54 kg increase and HR (weight change 10 years prior) = 1.05 (95% CI, 0.97–1.13) for 4.54 kg increase.

The PAR% for cumulative mean BMI >25 *vs*. ≤25 was 14.2% (95%CI,6.1–22.2%) and for BMI >22.5 *vs*. ≤22.5 was 29.5% (10.4–44.9%) meaning that BMI >22.5 contributes to 29.5% of the colon cancers. The PAR% for long-term weight change from age 21 to updated weight lagged 2–4 years (>1 kg per 10 years *vs*. <= 1 kg per 10 years) was 21.9% (9.2–33.3%) and for updated weight change lagged 2–4 years was 5.0% (−1.5–11.7%).

Discussion

In this study, which to our knowledge is the first to examine prospectively collected weight change data in relation to risk of colon cancer, we observed a significant positive association between updated weight change during follow-up and colon cancer risk. Furthermore, weight gain since age 21 and weight change during the last 10 years conditional on prior weight change from age 21 were both positively associated with colon cancer risk. BMI at age 21 was not associated with risk conditional on BMI during follow-up. Taken together, these findings suggest that weight during later life has an important influence on colon cancer.

Previous epidemiologic studies of weight and BMI on risk of colon cancer have been remarkably consistent, especially among men, in showing that overweight and obesity (BMI>25) were associated with moderately increased risk of colon cancer (generally with risk estimates below 2).[2–10] We add that BMI of 22.6–25 is associated with increased risk compared to BMI of 20–22.5 and by including repeated measures of BMI during follow-up we observed stronger risk estimates than studies using only baseline information.

We found that approximately one third of all colon cancer cases was attributable to BMI >22.5. Previous studies using BMI of 25 as a cutpoint reported PAR% around 10%,[4] which we also observed in our cohort (PAR% = 14.2%). These findings point out that a greater proportion of colon cancer cases are attributable to excess weight than previously reported.

From such results it may not directly be inferred that weight change modify colon cancer risk. Previous studies on weight change and colon cancer and adenomas showed inconsistent results.[13–21] In two[18,19] of the 3 case-control studies, information on weight change was retrospectively collected, *i.e*., after diagnosis for cases, while in a Japanese adenoma case-

control study of endoscopic screened military personnel, information on weight 10 years before screening was collected from records of biannual health check-up.[20] In some of the prospective cohort studies, information on weight change was collected by subtracting recalled weight at some earlier time point in life from weight at baseline, where after the cohorts were prospectively followed for cancer outcomes.[13,15,17] French *et al*.[14] analyzed weight from 5 times through adult life, but reported at baseline. These results may be influenced by differential information bias in case-control studies if disease diagnosis influences recall of previous weight and in the prospective studies, imperfect memory may cause nondifferential misclassification when utilizing recalled past weight. When utilizing purely prospective weight information, as was done in this study, the influence of information bias and random error probably was lower compared previous studies. Other strengths of this study included long follow-up period, repeated assessment of confounders, detailed information on most known risk factors for colon cancer, validation studies of current weight and several confounders, and high follow-up rate.

Our results suggested that by lagging follow-up time by 2–4 years the influence of preexisting disease diminished. This strong temporal modification was not evaluated in previous prospective studies on weight change in that follow-up in these studies began at baseline without any lag.[13–17] Our results using recalled weight at age 21 suggested that unlagged risk estimates for colon cancer may be biased toward no association because weight change since age 21 became stronger when allowing 2–4 years of lag time. When including updated weight change during follow-up without any lag, the short-term influence of weight loss was associated with increased risk and weight gain was associated with decreased risk. This result probably was biased, because weight loss has been reported as 1 of the cardinal clinical feature of colon cancer.[26,27]

Obesity and weight change are closely associated with many metabolic abnormalities related to insulin resistance.[37] An increasing body of evidence indicates that colon cancer risk is associated with determinants of the insulin resistance syndrome (obesity, central adiposity, physical inactivity), its metabolic consequences (type 2 diabetes, hypertriglyceridemia, hyperglycemia), and its plasma or insulin markers (insulin, C-peptide).[37] The mechanisms underlying these associations with colon cancer are unclear, but may involve direct effects of insulin, the resultant increase of free or bioavailable IGF-1, or increase in bile acids, some of which are potentially toxic to the colonic mucosa. In a recent animal model, only hyperinsulinemia, but not other factors associated with insulin resistance, independently enhanced colorectal epithelial proliferation. [38]

In our analysis, the associations were primarily observed for proximal colon cancer. This result could have been because of chance, and needs confirmation, but an increasing body of evidence suggests that important differences exist in the etiology between distal and proximal colon cancers.[39] The proximal colon may be more strongly exposed to fecal bile acids emptying from the small bowel. Cholecystectomy, which changes the profile of bile acids, has been generally associated with risk of proximal colon cancer,[40] and polymorphisms in the cholesterol 7α-hydroxylase (CYP7A1), the rate limiting enzyme producing bile acids from cholesterol, have been associated with risk of proximal colon cancer and adenoma.[41,42] Although not entirely consistently observed, in some studies associations with hyperinsulinemia or the metabolic syndrome have been observed only for proximal colon cancer or adenoma,[43,44] or the associations were stronger in the proximal colon.[45,46] Future studies of obesity and weight change should examine potential subsite differences.

Our results may not be directly generalizable to women, where other studies have shown less consistent findings on weight change and colon cancer[14–17] and generally the risk

estimates for BMI among women are lower. Also, relationships between weight change and risk of colon cancer should be examined in other ethnic groups, which may have greater degree of insulin resistance.[47]

Our findings using prospectively collected weight data suggest that both cumulative mean BMI above 22.5 and long- and short-term weight gain increase colon cancer risk. Our results support that later life weight and weight change have important influence on colon cancer risk. An elevated risk of colon cancer was primarily attributable to attained weight during follow-up, whereas weight at age 21 had no independent influence on risk. These results add further evidence that overweight and obesity are important modifiable risk factors for colon cancer and support public health interventions to avoid weight gain for prevention of colon cancer.

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References

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin. 2005; 55:74–108. [PubMed: 15761078]
2. Moller H, Mellemgaard A, Lindvig K, Olsen JH. Obesity and cancer risk: a Danish record-linkage study. Eur J Cancer A. 1994; 30:344–350. [PubMed: 8204357]
3. Martinez ME, Giovannucci E, Spiegelman D, Hunter DJ, Willett WC, Colditz GA. Leisure-time physical activity, body size, and colon cancer in women. J Natl Cancer Inst. 1997; 89:948–955. [PubMed: 9214674]
4. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med. 2003; 348:1625–1638. [PubMed: 12711737]
5. Giovannucci E. Diet, body weight, and colorectal cancer: a summary of the epidemiologic evidence. J Womens Health (Larchmt). 2003; 12:173–182. [PubMed: 12737716]
6. Batty GD, Shipley MJ, Jarrett RJ, Breeze E, Marmot MG, Davey Smith G. Obesity and overweight in relation to organ-specific cancer mortality in London (UK): findings from the original Whitehall study. Int J Obes. 2005; 29:1267–1274.
7. Pischon T, Lahmann PH, Boeing H, Friedenreich C, Norat T, Tjønneland A, Halkjaer J, Overvad K, Clavel-Chapelon F, Boutron-Ruault MC, Guernec G, Bergmann MM, et al. Body size and risk of colon and rectal cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC). J Natl Cancer Inst. 2006; 98:920–931. [PubMed: 16818856]
8. Kune GA, Kune S, Watson LF. Body weight and physical activity as predictors of colorectal cancer risk. Nutr Cancer. 1990; 13:9–17. [PubMed: 2300499]
9. Caan BJ, Coates AO, Slattery ML, Potter JD, Quesenberry CP Jr, Edwards SM. Body size and the risk of colon caner in a large case-control study. Int J Obes. 1998; 22:178–184.
10. Potter, JD.; Hunter, D. Colorectal cancer. In: Adami, HO.; Hunter, D.; Trichopoulus, D., editors. Textbook in cancer epidemiology. Oxford: Oxford University Press; 2001. p. 201
11. Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among U.S. adults, 1999–2000. JAMA. 2000; 288:1723–1727. [PubMed: 12365955]
12. Prentice AM. The emerging epidemic of obesity in developing countries. Int J Epidemiol. 2006; 35:93–99. [PubMed: 16326822]
13. Nomura A, Heilbrun LK, Stemmermann GN. Body mass index as a predictor of cancer in men. J Natl Cancer Inst. 1985; 74:319–323. [PubMed: 3856045]

14. French SA, Folsom AR, Jeffery RW, Zheng W, Mink PJ, Baxter JE. Weight variability and incident disease in older women: the Iowa Women's Health Study. Int J Obes. 1997; 21:217–223.
15. Colditz GA, Coakley E. Weight, weight gain, activity, and major illnesses: the Nurses Health Study. Int J Sports Med. 1997; 18:S162–S170. [PubMed: 9272843]
16. Parker ED, Folsom AR. Intentional weight loss and incidence of obesity-related cancers: the Iowa Women's Health Study. Int J Obes. 2003; 27:1447–1452.
17. Tamakoshi K, Wakai K, Kojima M, Watanabe Y, Hayakawa N, Toyoshima H, Yatsuya H, Kondo T, Tokudome S, Hashimoto S, Suzuki K, Ito Y, et al. A prospective study of body size and colon cancer mortality in Japan: the JACC study. Int J Obes Relat Metab Disord. 2004; 28:551–558. [PubMed: 14968128]
18. Lubin F, Rozen P, Arieli B, Farbstein M, Knaani Y, Bat L, Farbstein H. Nutritional and lifestyle habits and water-fiber interaction in colorectal adenoma etiology. Cancer Epidemiol Biomarkers Prev. 1997; 6:79–85. [PubMed: 9037557]
19. Bird CL, Frankl HD, Lee ER, Haile RW. Obesity, Weight gain, large weight changes, and adenomatous polyps of the left colon and rectum. Am J Epidemiol. 1998; 147:670–680. [PubMed: 9554606]
20. Kono S, Handa K, Hayabuchi H, Kiyohara C, Inoue H, Marugame T, Shinomiya S, Hamada H, Onuma K, Koga H. Obesity, weight gain and risk of colon adenomas in Japanese men. Jpn J Cancer Res. 1999; 90:805–811. [PubMed: 10543250]
21. Sedjo RL, Byers T, Levin TR, Haffner SM, Saad MF, Tooze JA, D'Agostino RB Jr. Changes in body size and the risk of colorectal adenomas. Cancer Epidemiol Biomarkers Prev. 2007; 16:526–531. [PubMed: 17372248]
22. Rimm EB, Giovannucci EL, Willett WC, Colditz GA, Ascherio A, Rosner B, Stampfer MJ. Prospective study of alcohol consumption and risk of coronary disease in men. Lancet. 1991; 338:464–468. [PubMed: 1678444]
23. Stampfer MJ, Willett WC, Speizer FE, Dysert DC, Lipnick R, Rosner B, Hennekens CH. Test of the national death index. Am J Epidemiol. 1984; 119:837–839. [PubMed: 6720679]
24. Rimm EB, Stampfer MJ, Colditz GA, Chute CG, Litin L, Willett WC. Validity of self-reported waist and hip circumferences in men and women. Epidemiology. 1990; 1:466–473. [PubMed: 2090285]
25. Cupples LA, D'Agostino RB, Anderson K, Kannel WB. Comparison of baseline and repeated measure covariate techniques in the Framingham Heart Study. Stat Med. 1988; 7:205–218. [PubMed: 3353604]
26. Hamilton W, Round A, Sharp D, Peters TJ. Clinical features of colorectal cancer before diagnosis: a population-based case-control study. Br J Cancer. 2005; 93:399–405. [PubMed: 16106247]
27. Laviano A, Meguid MM, Inui A, Muscaritoli M, Rossi-Fanelli F. Therapy insight: cancer anorexia-cachexia syndrome-when all you can eat is yourself. Nat Clin Pract Oncol. 2005; 2:158–165. [PubMed: 16264909]
28. Must A, Willett WC, Dietz WH. Remote recall of childhood height, weight, and body built by elderly subjects. Am J Epidemiol. 1993; 138:56–64. [PubMed: 8333427]
29. Tamakoshi K, Yatsuya H, Kondo T, Hirano T, Hori Y, Yoshida T, Toyoshima H. The accuracy of long-term recall of past weight in Japanese adult men. Int J Obes. 2003; 27:247–252.
30. Troy LM, Hunter DJ, Manson JE, Colditz GA, Stampfer MJ, Willett WC. The validity of recalled weight among younger women. Int J Obes Relat Metab Disord. 1995; 19:570–572. [PubMed: 7489028]
31. Almendingen K, Hofstad B, Vatn MH. Does high body fatness increase the risk of presence of growth of colorectal adenomas followed up in situ for 3 years? Am J Gastroenterol. 2001; 96:2238–2246. [PubMed: 11467659]
32. Kozuka S, Nogaki M, Ozeki T, Masumori S. Premalignancy of the mucosal polyp in the large intestine. II. Estimation of the periods required for malignant transformation of mucosal polyps. Dis Colon Rectum. 1975; 6:494–500. [PubMed: 1181151]
33. Levine JS, Ahnen DJ. Adenomatous polyps of the colon. N Engl J Med. 2006; 355:2551–2557. [PubMed: 17167138]

34. Durrleman S, Richard S. Flexible regression models with cubic splines. Stat Med. 1989; 8:551–561. [PubMed: 2657958]
35. Wacholder S, Benichou J, Heineman EF, Hartge P, Hoover RN. Attributable risk: advantages of a broad definition of exposure. Am J Epidemiol. 1994; 140:303–309. [PubMed: 8059765]
36. Platz EA, Willett WC, Colditz GA, Rimm EB, Spiegelman D, Giovannucci E. Proportion of colon cancer risk that might be preventable in a cohort of middle-aged US men. Cancer Causes Control. 2000; 11:579–588. [PubMed: 10977102]
37. Giovannucci E. Insulin, insulin-like growth factors and colon cancer: a review of the evidence. J Nutr. 2001; 131:3109S–3120S. [PubMed: 11694656]
38. Tran TT, Naigamwalla D, Oprescu AI, Lam L, McKeown-Eyssen G, Bruce WR, Giacca A. Hyperinsulinemia, but not other factors associated with insulin resistance, acutely enhances colorectal epithelial proliferation in vivo. Endocrinology. 2006; 147:1830–1837. [PubMed: 16410309]
39. Gervaz P, Bucher P, Morel P. Two colons-two cancers: paradigm shift and clinical implications. J Surg Oncol. 2004; 88:261–266. [PubMed: 15565587]
40. Giovannucci E, Colditz GA, Stampfer MJ. A meta-analysis of cholecystectomy and risk of colorectal cancer. Gastroenterology. 1993; 105:130–141. [PubMed: 8514030]
41. Tabata S, Yin G, Ogawa S, Yamaguchi K, Mineshita M, Kono S. Genetic polymorphism of cholesterol 7alpha-hydroxylase (CYP7A1) and colorectal adenomas: Self Defense Forces Health Study. Cancer Sci. 2006; 97:406–410. [PubMed: 16630139]
42. Hagiwara T, Kono S, Yin G, Toyomura K, Nagano J, Mizoue T, Mibu R, Tanaka M, Kakeji Y, Maehara Y, Okamura T, Ikejiri K. Genetic polymorphism in cytochrome P450 7A1 and risk of colorectal cancer: the Fukuoka Colorectal Cancer Study. Cancer Res. 2005; 65:2979–2982. [PubMed: 15805302]
43. Limburg PJ, Anderson KE, Johnson TW, Jacobs DR Jr. Lazovich D, Hong CP, Nicodemus KK, Folsom AR. Diabetes mellitus and subsite-specific colorectal cancer risks in the Iowa Women's Health Study. Cancer Epidemiol Biomarkers Prev. 2005; 14:133–137. [PubMed: 15668486]
44. Wei EK, Ma J, Pollak MN, Rifai N, Fuchs CS, Hankinson SE, Giovannucci E. A prospective study of C-peptide, insulin-like growth factor-I, insulin-like growth factor binding protein-1, and the risk of colorectal cancer in women. Cancer Epidemiol Biomarkers Prev. 2005; 14:850–855. [PubMed: 15824155]
45. Morita T, Tabata S, Mineshita M, Mizoue T, Moore MA, Kono S. The metabolic syndrome is associated with increased risk of colorectal adenoma development: the Self-Defense Forces health study. Asian Pac J Cancer Prev. 2005; 6:485–489. [PubMed: 16435997]
46. Hu FB, Manson JE, Liu S, Hunter D, Colditz GA, Michels KB, Speizer FE, Giovannucci E. Prospective study of adult onset diabetes mellitus (type 2) and risk of colorectal cancer in women. J Natl Cancer Inst. 1999; 91:542–547. [PubMed: 10088625]
47. Shai I, Jiang R, Manson JE, Stampfer MJ, Willett WC, Colditz GA, Hu FB. Ethnicity, obesity, and risk of type 2 diabetes in women: a 20-year follow-up study. Diabetes Care. 2006; 29:1585–1590. [PubMed: 16801583]

TABLE I

Age-standardized baseline characteristics (1986) of study cohort according to weight change from 1986 to 1988

Characteristic	Weight change 1986–1988					
	Loss > 4 kg	Loss 1.1–4 kg	Stable ± 1 kg	Gain 1.1–4 kg	Gain 4.1–7 kg	Gain >7 kg
Participants, *n*	2,861	7,347	17,090	11,097	3,035	868
Mean age (years)	55.8	55.4	54.8	53.2	52.5	51.7
Alcohol intake (g/day)	11.4	11.2	11.4	11.6	11.7	10.6
Past and current smoker (%)	45.6	41.8	40.0	42.5	43.1	50.0
Mean body mass index (kg/m^2)	27.9	25.7	24.9	25.3	26.1	26.8
Mean waist circumference (cm)	98.1	93.7	92.5	94.6	98.6	104.0
Mean physical activity (METS/week)[1]	16.3	20.8	22.2	21.3	19.1	21.2
Regular use of aspirin (%)	30.6	29.9	28.6	29.6	30.2	29.2
Multivitamin use (%)	38.9	41.5	41.9	41.6	41.3	42.2
Colonoscopy (%)[2]	13.7	12.2	11.9	11.5	13.9	13.7
Sigmoidoscopy (%)[2]	58.9	50.6	52.0	48.3	54.3	54.4
Colon polyps diagnosis 1980–86 (%)	1.7	1.6	1.6	1.7	2.2	1.6
Family history of colorectal cancer (%)	7.8	8.4	8.7	8.4	8.9	10.1
Mean daily intakes						
Folate (μg/day)	468	476	481	481	478	501
Methionine (gm/day)	2.21	2.16	2.17	2.18	2.24	2.31
Vitamin D (IU/day)	390	402	406	406	413	439
Calcium (mg/day)	890	901	895	901	900	944
Red meat (servings/day)	1.24	1.16	1.10	1.13	1.18	1.26
Processed meat (servings/day)	0.19	0.18	0.17	0.17	0.18	0.19

[1] MET-hours, sum of average time/week spent in each activity times MET value of each activity.

[2] Information on colonoscopy and sigmoidoscopy was collected in 1988.

TABLE II

Body mass index and colon cancer risk from 1988 to 2004

	Cumulative mean body mass index (lagged 2–4 years)					
	≤20	**20.1–22.5**	**22.6–25**	**25.1–30**	**30.1–35**	**>35**
Cases/person-years	9/7,713	50/79,815	205/226,256	341/305,046	75/48,981	13/9,164
Age-adjusted HR[1]	1.73 (0.85–3.53)	1.00 (ref)	1.44 (1.06–1.96)	1.75 (1.30–2.36)	2.52 (1.75–3.62)	2.54 (1.38–4.69)
Multivariate adjusted HR[2]	1.69 (0.83–3.44)	1.00 (ref)	1.40 (1.03–1.92)	1.64 (1.21–2.22)	2.29 (1.58–3.31)	2.29 (1.23–4.26)

[1] HR, hazard ratio. Numbers in parentheses are 95% confidence interval.

[2] Adjusted for cumulative average physical activity, alcohol intake, folate, methionine, vitamin D, calcium, calorie intake, processed and red meat and updated information on smoking habit, multivitamin use, aspirin use, endoscopic screening and family history of colorectal cancer. All confounders were lagged 2 years.

TABLE III

Weight change and risk of colon cancer from 1990 to 2004

	Updated weight change (lagged 2–4 years)[1]						Increase 4.54 kg	*p*-value
	< −4 kg	−4 to −1.1 kg	−1 to 1 kg	1.1–4 kg	4.1–7 kg	>7 kg		
Cases/person-years	38/35,709	98/87,410	212/200,702	137/131,925	40/37,148	15/11,048	540/503,942	
Age-adjusted HR[2]	0.98 (0.69–1.38)	0.97 (0.76–1.23)	1.00 (ref)	1.11 (0.89–1.38)	1.19 (0.85–1.68)	1.70 (1.00–2.87)	1.12 (0.99–1.28)	0.08
Multivariate adjusted HR[3]	0.82 (0.57–1.17)	0.90 (0.71–1.15)	1.00 (ref)	1.07 (0.86–1.33)	1.05 (0.75–1.49)	1.46 (0.86–2.50)	1.14 (1.00–1.29)	0.04

[1] Weight change between two consecutive weight measures two years apart on risk of colon cancer 2–4 years later, *i.e.*, weight change between 1986–1988 on risk of colon cancer 1990–92, weight change 1988–1990 on risk 1992–94, etc.

[2] HR, hazard ratio. Numbers in parentheses are 95% confidence interval.

[3] Adjusted for cumulative average body mass index, physical activity, alcohol intake, folate, methionine, vitamin D, calcium, calories, processed and red meat and updated smoking habit, multivitamin use, aspirin use, endoscopic screening and family history of colorectal cancer. Confounder information was lagged four years, *i.e.*, before weight change.

TABLE IV

Weight change during adult life from age 21 to updated weight lagged 2–4 years, follow-up 1988–2004

	Weight change per 10 years since age 21 years[1]						Increase 4.54 kg	*p*-value
	< −1 kg	−1 to 1 kg	1.1–3 kg	3.1–5 kg	5.1–7.5 kg	>7.5 kg		
Cases / person-years	25/36,564	121/126,379	216/200,385	141/121,497	56/57,590	17/24,060		
Age-adjusted HR[2]	0.95 (0.62–1.47)	1.00 (ref)	1.18 (0.94–1.47)	1.49 (1.16–1.90)	1.55 (1.12–2.14)	1.50 (0.89–2.52)	1.32 (1.12–1.55)	<0.001
Multivariate adjusted HR[3]	0.82 (0.53–1.28)	1.00 (ref)	1.19 (0.95–1.50)	1.49 (1.15–1.94)	1.51 (1.07–2.13)	1.41 (0.83–2.41)	1.33 (1.12–1.58)	0.001

[1] Weight change between weight at age 21 and updated weight on risk of colon cancer 2–4 years later, *i.e.*, weight change between age 21 and 1988 on risk of colon cancer 1990–92, weight change 21 years-1990 on risk 1992–94, etc. Weight change was calculated per 10 years to take account of different time periods from age 21 to age during follow-up.

[2] HR, hazard ratio. Numbers in parentheses are 95% confidence interval.

[3] Adjusted for body mass index at age 21, cumulative average physical activity, alcohol intake, folate, methionine, vitamin D, calcium, calories, processed and red meat and updated smoking habit, multivitamin use, aspirin use, endoscopic screening and family history of colorectal cancer. Confounder information, except body mass index at age 21, was lagged two years, *i.e.* at time of updated weight.