Adiposity and Cancer Risk: A Life Course Approach

The Harvard community has made this article openly available. Please share how this access benefits you. Your story matters.

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Citable link</td>
<td><a href="http://nrs.harvard.edu/urn-3:HUL.InstRepos:16121141">http://nrs.harvard.edu/urn-3:HUL.InstRepos:16121141</a></td>
</tr>
<tr>
<td>Terms of Use</td>
<td>This article was downloaded from Harvard University’s DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at <a href="http://nrs.harvard.edu/urn-3:HUL.InstRepos:flash.current.terms-of-use#LAA">http://nrs.harvard.edu/urn-3:HUL.InstRepos:flash.current.terms-of-use#LAA</a></td>
</tr>
</tbody>
</table>
Adiposity and Cancer Risk: A Life Course Approach

Mingyang Song

A Dissertation Submitted to the Faculty of

The Harvard T.H. Chan School of Public Health

in Partial Fulfillment of the Requirements

for the Degree of Doctor of Science

in the Departments of Nutrition and Epidemiology

Harvard University

Boston, Massachusetts

May, 2015
Adiposity and Cancer Risk: A Life Course Approach

ABSTRACT

Obesity is a risk factor for several cancers, including colorectal cancer (CRC). I and my colleagues investigated adulthood weight change and body fat distribution and its change in relation to CRC risk in the Nurses’ Health Study and Health Professionals Follow-up Study. We also identified distinct trajectories of body fatness across the lifespan using a group-based modeling approach and then compared cancer risk across these trajectories.

We found that weight gain from early adulthood to baseline was associated with an increased risk of CRC, whereas weight loss was associated with a lower risk. The association was stronger in men than in women. High waist circumference, hip circumference and waist-to-hip ratio were all associated with a higher risk of CRC in men, even after adjusting for body mass index. The associations were weaker in women. Ten-year gain of waist circumference, independent of weight change, was positively associated with CRC risk in men, but not in women. We identified 5 distinct adiposity trajectories across the lifespan: lean-stable, lean-moderate increase, lean-marked increase, medium-stable, and heavy-marked increase. Compared to women in the lean-stable group, those in the lean-marked increase and heavy-marked increase groups had a higher risk of esophageal adenocarcinoma and cancers of the colorectum, pancreas, kidney, and endometrium. Postmenopausal breast cancer risk was inversely associated with early-life adiposity, but was positively associated with late-life adiposity. In men, increased body fatness at any life period was associated with a higher risk of esophageal adenocarcinoma and
colorectal cancer; compared to men in the lean-stable group, those in the heavy-marked increase group had a higher risk of pancreatic cancer, but lower risk of advanced prostate cancer. The trajectory-cancer associations were generally stronger for non-smokers and women who did not use menopausal hormone therapy.

In conclusion, weight gain from early to middle adulthood was positively, and weight loss was negatively associated with CRC risk. Abdominal adiposity was positively associated with CRC risk and this association was stronger and independent of overall obesity in men than in women. Adiposity trajectories throughout life were associated with cancer risk and the pattern of associations varied by sex and cancer site.
Table of Contents

List of Figures with Captions ......................................................................................................... vi
List of Tables with Captions ......................................................................................................... vii
Acknowledgements ........................................................................................................................ xi
Introduction ..................................................................................................................................... 1
CHAPTER 1. Weight change and colorectal cancer .............................................................. 5
  Abstract ................................................................................................................................. 6
  Introduction .......................................................................................................................... 8
  Methods ............................................................................................................................... 9
  Results ................................................................................................................................. 12
  Discussion ........................................................................................................................... 27
  References ............................................................................................................................ 31
  Supplementary Materials ................................................................................................. 35
CHAPTER 2. Body fat distribution and colorectal cancer .................................................. 48
  Abstract ............................................................................................................................... 49
  Introduction ........................................................................................................................ 50
  Methods ............................................................................................................................... 51
  Results ................................................................................................................................. 54
  Discussion ........................................................................................................................... 69
  References ............................................................................................................................ 72
  Supplementary Materials ................................................................................................. 76
CHAPTER 3. Trajectory of body fatness and cancer risk ................................................ 90
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abstract</td>
<td>91</td>
</tr>
<tr>
<td>Introduction</td>
<td>93</td>
</tr>
<tr>
<td>Methods</td>
<td>94</td>
</tr>
<tr>
<td>Results</td>
<td>98</td>
</tr>
<tr>
<td>Discussion</td>
<td>115</td>
</tr>
<tr>
<td>References</td>
<td>120</td>
</tr>
<tr>
<td>Supplementary Materials</td>
<td>126</td>
</tr>
<tr>
<td>Concluding Remarks</td>
<td>134</td>
</tr>
</tbody>
</table>
List of Figures with Captions

CHAPTER 2

FIGURE 2.1 Joint association of BMI and waist circumference with risk of colorectal cancer in women (Nurses’ Health Study, 1988-2010) and men (Health Professionals Follow-up Study, 1990-2010) ..........................................................61

FIGURE 2.2 Ten-year waist circumference change in relation to colorectal cancer in women (A) and men (B) .................................................................68

CHAPTER 3

FIGURE 3.1 Trajectories of body fatness by age in women (A) and men (B) ......................100

FIGURE 3.2 Relative risk and 95% confidence interval of cancer according to early-life (●) and late-life (●) body fatness in women (A) and men (B) .........................107
List of Tables with Captions

CHAPTER 1

TABLE 1.1  Age-standardized characteristics of study participants according to weight change from age 18 (women) or 21 (men) years to baseline .........................13

TABLE 1.2  Relative risk of colorectal cancer according to weight change from age 18 (women) or 21 (men) years to baseline ..................................................16

TABLE 1.3  Relative risk of colorectal cancer according to weight change from baseline to present ........................................................................................................19

TABLE 1.4  Relative risk of colorectal cancer according to 4-year weight change during follow-up ........................................................................................................22

TABLE 1.5  Relative risk of colorectal cancer according to premenopausal and postmenopausal weight change .............................................................................25

TABLE S1.1 Relative risk of colorectal cancer by body mass index according to weight change from age 18 (women) or 21 (men) years to baseline .........................39

TABLE S1.2 Relative risk of colorectal cancer by baseline age according to weight change from age 18 (women) or 21 (men) years to baseline ..............................................40

TABLE S1.3 Subsite-specific relative risk of colorectal cancer according to weight change from age 18 (women) or 21 (men) years to baseline ...........................................41
TABLE S1.4  Relative risk of colorectal cancer by current age according to weight change from baseline to present ........................................................................................................43

TABLE S1.5  Relative risk of colorectal cancer by current age according to 4-year weight change during follow-up ........................................................................................................44

TABLE S1.6  Relative risk of colorectal cancer by postmenopausal hormone use according to postmenopausal weight change ..........................................................................................45

CHAPTER 2

TABLE 2.1  Age-standardized characteristics according to waist circumference in women (Nurses’ Health Study) and men (Health Professionals Follow-up Study) ..........55

TABLE 2.2  Risk of colorectal cancer according to quintiles of waist circumference, hip circumference, and waist-to-hip ratio in women (Nurses’ Health Study, 1988-2010) and men (Health Professionals Follow-up Study, 1990-2010) ..........58

TABLE 2.3  Risk of colorectal cancer according to 10-year change of waist circumference, hip circumference, and waist-to-hip ratio in women (Nurses’ Health Study, 1998-2010) and men (Health Professionals Follow-up Study, 1998-2010) ..........65

TABLE S2.1  Risk of colorectal cancer by subsite according to quintiles of waist circumference, hip circumference, and waist-to-hip ratio in women (Nurses’ Health Study, 1988-2010) ........................................................................................................................................78
TABLE S2.2  Risk of colorectal cancer by subsite according to quintiles of waist circumference, hip circumference, and waist-to-hip ratio in men (Health Professionals Follow-up Study, 1990-2010) ................................................................................................80

TABLE S2.3  Risk of colorectal cancer by use of menopausal hormone therapy according to quartiles of waist circumference, hip circumference, and waist-to-hip ratio in women (Nurses’ Health Study, 1988-2010) .............................................................................82

TABLE S2.4  Relative risk (95% confidence interval) of colorectal cancer according to joint classification of use of menopausal hormone therapy and quartiles of waist circumference, hip circumference and waist-to-hip ratio in women (Nurses’ Health Study, 1988-2010) ....................................................................................84

TABLE S2.5  Age-standardized baseline characteristics of participants according to waist circumference change in women (Nurses’ Health Study) and men (Health Professionals Follow-up Study) ........................................................................................................85

TABLE S2.6  Age-adjusted Pearson correlation coefficient among 10-year changes in waist circumference, hip circumference, waist-to-hip ratio and body weight in women (Nurses’ Health Study, in white) and men (Health Professionals Follow-up Study, in gray) ........................................................................................................87
TABLE S2.7 Risk of colorectal cancer by baseline waist circumference according to 10-year change of waist circumference in women (Nurses’ Health Study, 1998-2010) and men (Health Professionals Follow-up Study, 1998-2010) ...................................88

CHAPTER 3

TABLE 3.1 Relative risk of cancer according to trajectories of body fatness in women (Nurses’ Health Study) and men (Health Professionals Follow-up Study)........103

TABLE 3.2 Relative risk of cancer by smoking history according to trajectories of body fatness in women (Nurses’ Health Study) and men (Health Professionals Follow-up Study) ........................................................110

TABLE 3.3 Relative risk of cancer by menopausal hormone therapy (MHT) according to trajectories of body fatness in women (Nurses’ Health Study).........................113

TABLE S3.1 BMI cutoffs for derivation of somatotype categories at ages 50 and 60 years in women and men........................................................................................................130

TABLE S3.2 Basic characteristics of study participants at age 60 years according to trajectories of body fatness in women (Nurses’ Health Study) and men (Health Professionals Follow-up Study)........................................................................................................131
Acknowledgements

I would like to extend my deepest gratitude to my advisor, Dr. Edward Giovannucci, who has been an invaluable friend and mentor, for his caring and academic guidance during my doctoral study. His incredible wisdom, enduring encouragement, and unwavering commitment to the highest standards of research have been an inestimable source of inspiration and motivation for me.

I would also like to thank my dissertation committee members, Drs. Walter Willett, Donna Spiegelman, and Frank Hu for donating their time to thoroughly review my research and contribute their thoughtful comments. Without their support, this work could not have been completed. I’m also grateful to Drs. Andrew T. Chan, Shuji Ogino, and Kana Wu for their excellent mentorship and generous support for my research.

Thanks also to my friends for their support through my doctoral program including Mu Chen, Wenqing Li, Xuehong Zhang, Neha Khandpur, Lindsey Locks, Rachel Blaine, April Bowling, Ming Ding, and Juan Wu.

Thank you to my parents, Hongquan Song and Ruihong Yang, and my sister Mingyan Song, who have been always supporting me, believing in me, and encouraging me to pursue my dreams.

Finally, I want to thank my wife, Ying Chen, who has been always cheering me up and standing by me through the good and bad times. I feel incredibly blessed to have her in my life.
Introduction

The prevalence of overweight and obesity has increased rapidly over the past few decades, creating major public health problems in both developed and developing countries. A growing body of evidence indicates an influence of adiposity in the development of cancer, a leading cause of death worldwide. According to the systematic reviews by the World Cancer Research Fund and American Institute for Cancer Research, obesity is related to an increased risk of cancers of the esophagus (adenocarcinoma only), colorectum, pancreas, breast (after menopause), endometrium, ovaries, prostate (advanced only), kidney, liver, and gallbladder.

In Chapter 1, I examine adulthood weight change in relation to risk of colorectal cancer (CRC), the third most commonly diagnosed cancer and the fourth leading cause of cancer death in the world. Although adulthood weight gain has been associated with an increased risk of CRC, the critical time window during which adiposity influences CRC remains unclear. Moreover, in contrast to weight gain, investigation of weight loss is more challenging and evidence is sparse. Studies are often limited by statistical power due to low prevalence of sustained weight loss among middle-aged adults. Therefore, I and my colleagues investigated the association between adulthood weight change and incidence of CRC in two large U.S. cohort studies, the Nurses’ Health Study (NHS) and Health Professionals Follow-up Study (HPFS).

In Chapter 2, I assess body fat distribution and risk of CRC. Body fat distribution has a profound metabolic influence and may affect CRC development independent of overall obesity. However, in all but two previous studies, only a single measurement of body fat distribution was taken, and therefore neither its long-term influence nor change during adulthood could be examined. Thus, I and my colleagues examined the cumulative average and change in body fat
distribution measures, including waist circumference, hip circumference and waist-to-hip ratio, during adulthood in relation to CRC risk in the NHS and HPFS.

In Chapter 3, I employ a life-course approach to examine the relationship between body fatness and cancer risk. Given that body mass index usually increases with age and obesity during childhood is associated with persistence of obesity into adulthood, a life-course perspective is crucial to better understand the influences of overweight and obesity on cancer development. Previous studies examined body fatness or weight change at one or more time points individually, which made it challenging to separate and interpret the effect of early adiposity from later weight gain because of their high correlation. Therefore, I and my colleagues characterized distinct trajectories of body fatness across the entire lifespan and then compared cancer incidence across these trajectories. Our findings provided the first prospective evidence on the relationship between lifetime adiposity and risk of total and obesity-related cancer.
References


CHAPTER 1. Weight change and colorectal cancer

Title Adulthood weight change and risk of colorectal cancer in the Nurses’ Health Study and Health Professionals Follow-up Study

Authors: Mingyang Song\textsuperscript{1,2}, Frank B. Hu\textsuperscript{1,2,3}, Donna Spiegelman\textsuperscript{1,2,4,5}, Andrew T. Chan\textsuperscript{3,6}, Kana Wu\textsuperscript{1}, Shuji Ogino\textsuperscript{2,3,7,8}, Charles S. Fuchs\textsuperscript{3,7}, Walter C. Willett\textsuperscript{1,2,3}, Edward L. Giovannucci\textsuperscript{1,2,3}

Authors’ affiliations:

\textsuperscript{1}Department of Nutrition, Harvard T.H. Chan School of Public Health;

\textsuperscript{2}Department of Epidemiology, Harvard T.H. Chan School of Public Health;

\textsuperscript{3}Channing Division of Network Medicine, Department of Medicine, Harvard Medical School;

\textsuperscript{4}Department of Biostatistics, Harvard T.H. Chan School of Public Health;

\textsuperscript{5}Department of Global Health and Population, Harvard T.H. Chan School of Public Health;

\textsuperscript{6}Division of Gastroenterology, Massachusetts General Hospital;

\textsuperscript{7}Department of Medical Oncology, Dana-Farber Cancer Institute;

\textsuperscript{8}Department of Pathology, Brigham and Women's Hospital and Harvard Medical School;
Abstract

Obesity is an established risk factor for colorectal cancer (CRC). However, the influence of adulthood weight change, especially weight loss, on CRC incidence remains poorly understood.

We investigated the association between adulthood weight change and CRC risk with 24 to 34 years of follow-up in two large prospective studies, the Nurses’ Health Study and Health Professionals Follow-up Study. The primary exposures included weight change from early adulthood (age=18 years for women, 21 years for men) to baseline cohort enrollment (median age=43 years for women, 52 years for men), and from baseline to present. In the secondary analyses, we also assessed 4-year weight change during follow-up, and during premenopausal (from age 18 years to menopause) and postmenopausal (from menopause to present) periods in women.

Compared to men maintaining their weight from age 21 years to baseline, those who gained 20kg or more were at a higher risk of CRC (relative risk [RR], 1.64; 95% confidence interval [CI], 1.15-2.35, P for trend<0.001), whereas those who lost 8kg or more had a lower risk (RR, 0.61; 95% CI, 0.30-1.22, P for trend=0.003). Similar but weaker associations were found in women. We estimated that 13% (95% CI, 5.7-20.6%) of CRC cases in women and 20% (95% CI, 4.1-35.0%) of cases in men may be attributable to weight gain of 2kg or more from early adulthood to baseline. Weight change from baseline to present was not associated with CRC risk. Four-year weight change during follow-up was positively associated with CRC risk in men (P for trend=0.03) but not in women (P for trend=0.42). In addition, in women, weight change before, but not after, menopause was associated with CRC risk.
In conclusion, weight gain from early to middle adulthood was associated with higher CRC risk, and weight loss was associated with lower risk. A differential association according to timing of weight change warrants further investigation. Our findings provide further scientific rationale for recommendations to maintain a healthy body weight during adulthood.
Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the fourth leading cause of cancer death in the world. Despite the convincing evidence that overweight and obesity increase CRC risk, the influence of weight change on CRC incidence remains poorly understood. Compared to studies of attained body mass index (BMI), investigation of weight change may better capture the effect of excess body fat during adulthood, and help recommendations about weight control.

Adulthood weight gain has been associated with a higher risk of CRC in several previous studies. However, whether the effects of weight gain vary by gender, timing during the lifespan and tumor subsite remain inconclusive. The obesity-CRC association is generally stronger in men than in women, and stronger for colon cancer, in particular distal colon cancer, than for rectal cancer. Although similar patterns were seen for weight gain in some studies, findings from others were inconsistent. In addition, in most studies body weight data were collected at only two time points to calculate weight change, and therefore a more precise assessment of the timing of weight gain on CRC risk could not be determined.

In contrast to weight gain, investigation of weight loss is more challenging and evidence is sparse. Studies are often limited by statistical power due to low prevalence of sustained weight loss among middle-aged adults. In previous studies, weight loss was typically characterized by a single category and a statistically significant inverse association with colon cancer risk was reported in only one study. Thus, detailed dose-response analyses of large prospective studies with repeated weight assessments are needed to elucidate the relationship between weight loss and CRC.
We investigated the association of adulthood weight change with incidence of CRC in two large U.S. cohort studies, the Nurses’ Health Study (NHS) and Health Professionals Follow-up Study (HPFS). In an earlier examination in the HPFS, we observed a positive association between weight gain and colon cancer; however, that analysis was focused on late adulthood weight gain among only men, and did not examine associations with rectal cancer. In the current study, we present results that encompass weight change in both early and late adulthood in both men and women over 24 to 34 years of follow-up.

Methods

Study population

The NHS included 121,701 U.S. registered female nurses who were aged 30-55 years in 1976. The HPFS included 51,529 U.S. male health professionals who were aged 40-75 years in 1986. Details of the two cohorts have been described elsewhere. Briefly, follow-up questionnaires were administered at baseline enrollment and every two years thereafter to collect lifestyle and medical information (Supplementary Materials). The follow-up proportions were 95.4% in the NHS and 95.9% in the HPFS among participants who were alive up to 2010. Among participants who returned baseline questionnaires, we excluded those who had a history of cancer (except non-melanoma skin cancer) or who did not provide information on body weight. This investigation was approved by the Institutional Review Board at the Brigham and Women’s Hospital and the Harvard School of Public Health.

Exposure assessment
We asked participants their current weight in biennial questionnaires. Recalled weight at age 18 years was inquired in 1980 in the NHS, and weight at age 21 years was inquired in 1986 in the HPFS. In our primary analysis, we assessed weight change in two periods: from early adulthood (age 18 years for women and age 21 years for men) to baseline enrollment, and from baseline to present (updated weight in each questionnaire cycle). To evaluate more recent effect of weight change, in the secondary analysis we also assessed 4-year weight change during follow-up, which was calculated and updated using repeated weight assessments 4 years apart, except that in the HPFS the first cycle of weight change was approximated by utilizing the recalled weight change 5 years before baseline (i.e., change in 1981-1986). To capture the influence of sustained weight change during follow-up, we performed a sensitivity analysis by restricting participants to those who remained in the same category of 4-year weight change (i.e., loss ≥2kg, loss or gain <2kg, or gain ≥2kg) for at least two consecutive questionnaire cycles. In women, we additionally assessed premenopausal and postmenopausal weight changes, which were defined as the weight change from age 18 years to menopause and from menopause up to date, respectively.

In a validation study, we compared self-reported weight to the average of two weight measurements taken by technicians approximately six months apart among a sample of 140 women and 123 men drawn from the two cohorts. Self-reported and measured weights were highly correlated (r=0.97). Recalled weight at age 18 years has also been validated in the parallel Nurses’ Health Study II cohort, with a correlation coefficient of 0.87 between recalled weight and weight recorded on college or nursing school records at age 18 years. Although not validated in the HPFS, recalled weight during early adulthood in men has also been shown to be accurate (r=0.80) in other studies.
**Outcome assessment**

In both cohorts, self-reported CRC diagnoses were obtained in biennial questionnaires. We then asked participants for permission to acquire their medical records. We identified deaths through the National Death Index. For all CRC deaths, we requested permission from next-of-kin to review medical records. A study physician reviewed all records to confirm the CRC diagnosis and to extract relevant information, including anatomic location.

**Statistical analysis**

To minimize the influence of reverse causation arising from undiagnosed cancer-induced weight loss, we examined the association between weight change and CRC risk by introducing a lagged follow-up of 2 to 4 years. Therefore, for the analysis of weight change from early adulthood to baseline, person-years were calculated from 4 years after the date of baseline questionnaire return to the date of CRC diagnosis, death, or the end of the study period (June 1, 2010 for the NHS and January 31, 2010 for the HPFS), whichever came first. For the analysis of weight change from baseline to present, person-time started accumulating in 1980 in the NHS and 1990 in the HPFS. For the analysis of 4-year weight change, follow-up started from 1982 in the NHS and 1988 in the HPFS.

We used Cox proportional hazards regression model with age as the time scale to estimate hazard ratio (as an estimate of relative risk [RR]) and 95% confidence interval (CI). We adjusted for several CRC risk factors in the multivariable model (see the footnotes of tables). Test for trend was performed using continuous weight change, and test for trend across weight
loss categories was restricted to participants who maintained or lost weight, excluding those who gained weight.

We calculated the population attributable risk conferred by weight gain (≥2 kg) to estimate the percentage of CRC cases in our cohort that, theoretically, would have been prevented if participants had maintained or lost weight, assuming a causal relationship between weight gain and CRC incidence, holding all other risk-factor distributions constant.

More details of the statistical analysis are provided in the Supplement Materials. We used SAS 9.3 for all analyses (SAS Institute Inc., Cary, NC, USA). All statistical tests were two sided and P<0.05 was considered statistically significant.

Results

Table 1.1 shows the basic characteristics of participants according to categories of weight change from early adulthood to baseline. On average, women gained 6.4 kg from age 18 years to baseline and men gained 7.9 kg from age 21 to baseline. Compared to individuals who gained weight, those who lost or maintained their weight were less likely to take aspirin or non-steroidal anti-inflammatory drugs, and more likely to smoke, take multivitamins, undergo endoscopy, exercise regularly, and tended to have a high BMI at early adulthood and low BMI at baseline. They also consumed more folate, calcium and fiber, and less processed red meat, thus overall having a higher score on the healthy eating indexes.
Table 1.1 Age-standardized characteristics of study participants according to weight change from age 18 (women) or 21 (men) years to baseline\(^a\)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Women (n=79,294)</th>
<th>Men (n=36,180)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Loss ≥8.0 kg</td>
<td>Loss or gain &lt;2.0 kg</td>
</tr>
<tr>
<td>No. of participants (%)</td>
<td>3,177 (4.0)</td>
<td>12,977 (16.4)</td>
</tr>
<tr>
<td>Age, year</td>
<td>41.7 (7.1)</td>
<td>41.0 (7.1)</td>
</tr>
<tr>
<td>Weight change, kg (^b)</td>
<td>-13.4 (5.8)</td>
<td>0.17 (1.0)</td>
</tr>
<tr>
<td>Height, inch</td>
<td>64.7 (2.5)</td>
<td>64.2 (2.4)</td>
</tr>
<tr>
<td>BMI at early adulthood, kg/m(^2) (^b)</td>
<td>27.1 (4.0)</td>
<td>21.3 (2.3)</td>
</tr>
<tr>
<td>BMI at baseline, kg/m(^2) (^c)</td>
<td>22.1 (3.2)</td>
<td>21.4 (2.3)</td>
</tr>
<tr>
<td>Physical activity (^d)</td>
<td>1.4 (2.1)</td>
<td>1.4 (2.1)</td>
</tr>
<tr>
<td>Pack-years of smoking before age 30</td>
<td>4.9 (5.2)</td>
<td>3.1 (4.3)</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>64</td>
<td>42</td>
</tr>
<tr>
<td>Family history of colorectal cancer, % (^e)</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Current multivitamin use, %</td>
<td>22</td>
<td>24</td>
</tr>
<tr>
<td>Regular use of aspirin/NSAIDs, % (^f)</td>
<td>38</td>
<td>35</td>
</tr>
<tr>
<td>History of endoscopy, % (^f)</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Postmenopausal, %</td>
<td>35</td>
<td>31</td>
</tr>
<tr>
<td>Current use of hormones, % (^h)</td>
<td>26</td>
<td>29</td>
</tr>
<tr>
<td>Dietary intake (^i)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol, g/d</td>
<td>7.2 (12.0)</td>
<td>7.1 (10.9)</td>
</tr>
<tr>
<td>Folate, µg/d</td>
<td>359 (264)</td>
<td>370 (285)</td>
</tr>
<tr>
<td>Vitamin D, IU/d</td>
<td>323 (292)</td>
<td>328 (298)</td>
</tr>
<tr>
<td>Calcium, mg/d</td>
<td>748 (319)</td>
<td>735 (312)</td>
</tr>
<tr>
<td>Total fiber, g/d</td>
<td>14.3 (6.3)</td>
<td>14.1 (6.1)</td>
</tr>
</tbody>
</table>
Table 1.1 Age-standardized characteristics of study participants according to weight change from age 18 (women) or 21 (men) years to baseline

<table>
<thead>
<tr>
<th>Variable</th>
<th>Women (n=79,294)</th>
<th>Men (n=36,180)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Loss ≥8.0 kg</td>
<td>Loss or gain &lt;2.0 kg</td>
</tr>
<tr>
<td>Processed red meat, g/d</td>
<td>9.2 (10.2)</td>
<td>9.3 (10.3)</td>
</tr>
<tr>
<td>DASH diet score</td>
<td>24.2 (4.6)</td>
<td>24.0 (4.6)</td>
</tr>
<tr>
<td>AHEI diet score</td>
<td>43.2 (10.0)</td>
<td>42.5 (9.9)</td>
</tr>
</tbody>
</table>

Abbreviations: AHEI, Alternative Healthy Eating Index; BMI, body mass index; DASH, Dietary Approaches to Stop Hypertension; NSAID, nonsteroidal anti-inflammatory drug.

a All variables were assessed in 1976 in women (Nurses’ Health Study) and in 1986 in men (Health Professionals Follow-up Study) unless otherwise specified. Mean (standard deviation) is presented for continuous variables. All variables are age-standardized except age.

b Early adulthood represents age of 18 years in women and age of 21 years in men.


d Physical activity represents the frequency of regular activity per week in 1980 in women, and the Metabolic Equivalent of Task (MET)-hours/week in 1986 in men.

e Defined as having a diagnosis of colorectal cancer among parents or siblings.

f These variables were assessed in 1980 in women.

g Regular users are defined as ≥2 standard (325-mg) tablets of aspirin or ≥ 2 tablets of NSAIDs per week.

h Proportion of current postmenopausal hormone use is calculated among postmenopausal women only.

i Dietary intake was assessed in 1980 in women and in 1986 in men.
Weight change from early adulthood to baseline was associated with CRC risk (P for trend<0.001 in both women and men, Table 1.2), and the association appeared to be stronger in men than in women (P for interaction=0.05 by gender). Compared with individuals who maintained weight, those who gained 20kg or more were at a higher risk (multivariable RR, 1.38; 95% CI, 1.13-1.69 in women; 1.64, 95% CI, 1.15-2.35 in men), whereas those who lost 8kg or more had 20% and 39% lower risk of CRC in women and men, respectively. We estimated that 13% (95% CI, 5.7-20.6%) and 20% (95% CI, 4.1-35.0%) of CRC cases in our population might be attributable to weight gain of 2kg or more since early adulthood in women and men, respectively.

The association of weight change with CRC did not appear to differ according to early adulthood BMI, age at baseline, or anatomical locations of tumors, although a somewhat stronger association was found among leaner and older individuals than among heavy or young individuals, and for distal colon cancer than for proximal colon or rectal cancers (Tables S1.1-S1.3). When stratified by early adulthood BMI, women with initial BMI of ≥21kg/m² who lost weight of at least 8kg had a RR for CRC of 0.75 (95% CI, 0.54-1.05) compared to those who maintained their weight, and the corresponding RR among men with BMI of ≥23kg/m² was 0.59 (0.28-1.25).
Table 1.2 Relative risk of colorectal cancer according to weight change from age 18 (women) or 21 (men) years to baseline

<table>
<thead>
<tr>
<th>Weight change, kg</th>
<th>Median, kg</th>
<th>No. of cases</th>
<th>Person-years</th>
<th>Age-adjusted RR (95% CI)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Multivariable-adjusted RR (95% CI)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss ≥8.0</td>
<td>-11.3</td>
<td>58</td>
<td>83,615</td>
<td>0.83 (0.61-1.13)</td>
<td>0.80 (0.58-1.09)</td>
</tr>
<tr>
<td>Loss 4.0-7.9</td>
<td>-5.4</td>
<td>84</td>
<td>125,438</td>
<td>0.99 (0.76-1.27)</td>
<td>0.96 (0.74-1.24)</td>
</tr>
<tr>
<td>Loss 2.0-3.9</td>
<td>-2.7</td>
<td>75</td>
<td>115,144</td>
<td>1.06 (0.82-1.39)</td>
<td>1.05 (0.81-1.37)</td>
</tr>
<tr>
<td>Loss or gain &lt;2.0</td>
<td>0</td>
<td>208</td>
<td>358,314</td>
<td>1 [referent]</td>
<td>1 [referent]</td>
</tr>
<tr>
<td>Gain 2.0-5.9</td>
<td>4.1</td>
<td>342</td>
<td>505,356</td>
<td>1.12 (0.95-1.34)</td>
<td>1.14 (0.96-1.35)</td>
</tr>
<tr>
<td>Gain 6.0-9.9</td>
<td>8.2</td>
<td>300</td>
<td>381,793</td>
<td>1.20 (1.00-1.43)</td>
<td>1.22 (1.02-1.45)</td>
</tr>
<tr>
<td>Gain 10.0-19.9</td>
<td>13.6</td>
<td>341</td>
<td>410,171</td>
<td>1.16 (0.98-1.38)</td>
<td>1.18 (0.99-1.41)</td>
</tr>
<tr>
<td>Gain ≥20.0</td>
<td>24.9</td>
<td>177</td>
<td>173,694</td>
<td>1.34 (1.09-1.63)</td>
<td>1.38 (1.13-1.69)</td>
</tr>
<tr>
<td><strong>P for trend</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>P for weight loss trend&lt;sup&gt;c&lt;/sup&gt;</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.22</td>
<td>0.21</td>
</tr>
<tr>
<td><strong>Per 5.0 kg gain per 10 years</strong></td>
<td></td>
<td></td>
<td></td>
<td>1.11 (1.04-1.18)</td>
<td>1.13 (1.06-1.20)</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss ≥8.0</td>
<td>-11.3</td>
<td>10</td>
<td>15,858</td>
<td>0.63 (0.32-1.27)</td>
<td>0.61 (0.30-1.22)</td>
</tr>
<tr>
<td>Loss 4.0-7.9</td>
<td>-5.0</td>
<td>18</td>
<td>27,090</td>
<td>0.75 (0.43-1.28)</td>
<td>0.73 (0.43-1.26)</td>
</tr>
<tr>
<td>Loss 2.0-3.9</td>
<td>-2.3</td>
<td>15</td>
<td>22,820</td>
<td>0.79 (0.44-1.40)</td>
<td>0.78 (0.44-1.39)</td>
</tr>
<tr>
<td>Loss or gain &lt;2.0</td>
<td>0</td>
<td>52</td>
<td>67,217</td>
<td>1 [referent]</td>
<td>1 [referent]</td>
</tr>
<tr>
<td>Gain 2.0-5.9</td>
<td>4.5</td>
<td>128</td>
<td>160,644</td>
<td>1.02 (0.74-1.40)</td>
<td>1.02 (0.74-1.41)</td>
</tr>
<tr>
<td>Gain 6.0-9.9</td>
<td>8.2</td>
<td>119</td>
<td>133,685</td>
<td>1.06 (0.77-1.48)</td>
<td>1.06 (0.77-1.47)</td>
</tr>
<tr>
<td>Gain 10.0-19.9</td>
<td>13.6</td>
<td>153</td>
<td>157,842</td>
<td>1.10 (0.80-1.50)</td>
<td>1.09 (0.80-1.51)</td>
</tr>
<tr>
<td>Gain ≥20.0</td>
<td>24.5</td>
<td>79</td>
<td>52,841</td>
<td>1.62 (1.14-2.31)</td>
<td>1.64 (1.15-2.35)</td>
</tr>
<tr>
<td><strong>P for trend</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>P for weight loss trend&lt;sup&gt;c&lt;/sup&gt;</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.004</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Per 5.0 kg gain per 10 years</strong></td>
<td></td>
<td></td>
<td></td>
<td>1.33 (1.15-1.54)</td>
<td>1.35 (1.16-1.57)</td>
</tr>
</tbody>
</table>
Abbreviations: CI, confidence interval; RR, relative risk.

a Adjusted for age, and body weight at age 18 years for women or at age 21 years for men.

b Additionally adjusted for height (continuous), family history of colorectal cancer (yes or no), pack-years of smoking before age of 30 years (0, 1-10, and >10), current smoking status (yes or no), multivitamin use (yes or no), and regular use of aspirin/NSAIDs (yes or no, in men only). In women, postmenopausal status and hormone use were additionally adjusted.

c Calculated among participants who lost weight of ≥2.0kg, or lost or gained weight of <2.0kg.
Table 1.3 presents the association of weight change from baseline to current time with risk of CRC. No statistically significant association was detected in either sex (P for trend=0.60 in women, 0.21 in men). When stratified by age (Table S1.4), a positive association was found between weight gain and CRC risk among individuals younger than 70 years, but not among older individuals, although the difference between age strata was only statistically significant in women (P for interaction=0.03 in women, 0.93 in men).
Table 1.3 Relative risk of colorectal cancer according to weight change from baseline to present

<table>
<thead>
<tr>
<th>Weight change, kg</th>
<th>Median, kg</th>
<th>No. of cases</th>
<th>Person-years</th>
<th>Age-adjusted RR (95% CI)(^a)</th>
<th>Multivariable-adjusted RR (95% CI)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss ≥5.0</td>
<td>-8.2</td>
<td>126</td>
<td>135,680</td>
<td>0.98 (0.71-1.36)</td>
<td>0.97 (0.70-1.34)</td>
</tr>
<tr>
<td>Loss 2.0-4.9</td>
<td>-3.2</td>
<td>200</td>
<td>219,230</td>
<td>1.15 (0.85-1.56)</td>
<td>1.15 (0.85-1.56)</td>
</tr>
<tr>
<td>Loss 1.0-1.9</td>
<td>-1.4</td>
<td>61</td>
<td>78,634</td>
<td>0.87 (0.65-1.16)</td>
<td>0.89 (0.67-1.19)</td>
</tr>
<tr>
<td>Loss or gain &lt;1.0</td>
<td>0</td>
<td>332</td>
<td>602,816</td>
<td>1 [referent]</td>
<td>1 [referent]</td>
</tr>
<tr>
<td>Gain 1.0-5.9</td>
<td>3.2</td>
<td>600</td>
<td>951,912</td>
<td>0.94 (0.71-1.24)</td>
<td>0.94 (0.71-1.25)</td>
</tr>
<tr>
<td>Gain 6.0-11.9</td>
<td>9.1</td>
<td>485</td>
<td>663,412</td>
<td>1.02 (0.77-1.35)</td>
<td>1.00 (0.75-1.33)</td>
</tr>
<tr>
<td>Gain ≥12.0</td>
<td>17.2</td>
<td>406</td>
<td>553,194</td>
<td>1.07 (0.80-1.43)</td>
<td>1.03 (0.77-1.37)</td>
</tr>
<tr>
<td>P for trend</td>
<td></td>
<td></td>
<td></td>
<td>0.16</td>
<td>0.60</td>
</tr>
<tr>
<td>P for weight loss trend(^c)</td>
<td></td>
<td></td>
<td></td>
<td>0.10</td>
<td>0.36</td>
</tr>
<tr>
<td>Per 5.0 kg gain per 10 years</td>
<td>1.00 (0.99-1.02)</td>
<td>1.00 (0.99-1.01)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss ≥5.0</td>
<td>-7.7</td>
<td>37</td>
<td>32,308</td>
<td>0.94 (0.64-1.36)</td>
<td>0.94 (0.65-1.37)</td>
</tr>
<tr>
<td>Loss 2.0-4.9</td>
<td>-3.2</td>
<td>78</td>
<td>75,146</td>
<td>0.93 (0.71-1.23)</td>
<td>0.93 (0.71-1.23)</td>
</tr>
<tr>
<td>Loss 1.0-1.9</td>
<td>-1.4</td>
<td>36</td>
<td>31,104</td>
<td>1.06 (0.73-1.52)</td>
<td>1.07 (0.75-1.55)</td>
</tr>
<tr>
<td>Loss or gain &lt;1.0</td>
<td>0</td>
<td>174</td>
<td>163,328</td>
<td>1 [referent]</td>
<td>1 [referent]</td>
</tr>
<tr>
<td>Gain 1.0-2.9</td>
<td>2.3</td>
<td>106</td>
<td>113,278</td>
<td>0.97 (0.76-1.24)</td>
<td>0.97 (0.76-1.24)</td>
</tr>
<tr>
<td>Gain 3.0-7.9</td>
<td>4.5</td>
<td>126</td>
<td>144,458</td>
<td>1.03 (0.81-1.31)</td>
<td>1.01 (0.80-1.29)</td>
</tr>
<tr>
<td>Gain ≥8.0</td>
<td>11.3</td>
<td>59</td>
<td>66,786</td>
<td>1.18 (0.86-1.63)</td>
<td>1.15 (0.83-1.58)</td>
</tr>
<tr>
<td>P for trend</td>
<td></td>
<td></td>
<td></td>
<td>0.15</td>
<td>0.21</td>
</tr>
<tr>
<td>P for weight loss trend(^c)</td>
<td></td>
<td></td>
<td></td>
<td>0.20</td>
<td>0.27</td>
</tr>
<tr>
<td>Per 5.0 kg gain per 10 years</td>
<td>1.01 (0.99-1.03)</td>
<td>1.01 (0.99-1.03)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RR, relative risk.

\(^a\)Adjusted for age, and body weight at baseline.
Additionally adjusted for height (continuous), family history of colorectal cancer (yes or no), endoscopic screening (yes or no), pack-years of smoking (0, 0-20, 21-40, >40), current smoking (yes or no), multivitamin use (yes or no), physical activity (<6.5, 6.5-16.7, 16.8-30.1, 30.2-53.3, ≥53.4 MET-hours/week), regular use of aspirin/NSAIDs (yes or no), and consumption of alcohol (0-4.9, 5.0-9.9, 10.0-14.9, 15-29.9, ≥30.0 g/d), folate (in quintiles), calcium (in quintiles), fiber (in quintiles), vitamin D (in quintiles) and processed red meat (in quintiles). In women, postmenopausal status and hormone use (never, past or current users) were additionally adjusted.

Calculated among participants who lost weight of ≥1.0kg, or lost or gained weight of <1.0kg.
Table 1.4 shows the association between 4-year weight change during follow-up and risk of CRC. Weight change was associated with CRC in men (P for trend=0.03) but not in women (P for trend=0.42; P for interaction=0.10 by gender). Among men with sustained change, weight gain of ≥8kg was associated with 89% higher risk (95% CI, 16%-208%) and weight loss of ≥7kg associated with 30% lower risk. We did not detect any statistically significant effect modification by age (Table S1.5). To examine whether the weaker association for 4-year weight change in women was due to limited duration of the time interval over which weight change was assessed, we evaluated weight change per 10 years and the results were similar (data not shown).
### Table 1.4 Relative risk of colorectal cancer according to 4-year weight change during follow-up

<table>
<thead>
<tr>
<th>Weight change, kg</th>
<th>Median, kg</th>
<th>Overall</th>
<th>Among stable change&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Age-adjusted RR (95% CI)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Multivariable-adjusted RR (95% CI)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss ≥7.0</td>
<td>-10.0</td>
<td>93</td>
<td>94,404</td>
</tr>
<tr>
<td>Loss 2.0-6.9</td>
<td>-3.6</td>
<td>275</td>
<td>328,248</td>
</tr>
<tr>
<td>Loss 1.0-1.9</td>
<td>-1.4</td>
<td>89</td>
<td>100,280</td>
</tr>
<tr>
<td>Loss or gain &lt;1.0</td>
<td>0</td>
<td>459</td>
<td>634,414</td>
</tr>
<tr>
<td>Gain 1.0-2.9</td>
<td>2.3</td>
<td>248</td>
<td>394,774</td>
</tr>
<tr>
<td>Gain 3.0-7.9</td>
<td>4.5</td>
<td>331</td>
<td>457,124</td>
</tr>
<tr>
<td>Gain ≥8.0</td>
<td>10.4</td>
<td>99</td>
<td>150,272</td>
</tr>
<tr>
<td>P for trend</td>
<td></td>
<td></td>
<td>0.44</td>
</tr>
<tr>
<td>P for weight loss trend&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>0.76</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss ≥7.0</td>
<td>-9.1</td>
<td>24</td>
<td>24,840</td>
</tr>
<tr>
<td>Loss 2.0-6.9</td>
<td>-3.2</td>
<td>92</td>
<td>97,148</td>
</tr>
<tr>
<td>Loss 1.0-1.9</td>
<td>-1.4</td>
<td>28</td>
<td>34,026</td>
</tr>
<tr>
<td>Loss or gain &lt;1.0</td>
<td>0</td>
<td>190</td>
<td>192,200</td>
</tr>
<tr>
<td>Gain 1.0-2.9</td>
<td>1.8</td>
<td>97</td>
<td>110,914</td>
</tr>
<tr>
<td>Gain 3.0-7.9</td>
<td>4.5</td>
<td>120</td>
<td>126,606</td>
</tr>
<tr>
<td>Gain ≥8.0</td>
<td>11.3</td>
<td>26</td>
<td>21,618</td>
</tr>
<tr>
<td>P for trend</td>
<td></td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>P for weight loss trend&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>0.15</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RR, relative risk.

<sup>a</sup>Adjusted for age, and body weight at the start of each time period (continuous).
Additionally adjusted for height (continuous), family history of colorectal cancer (yes or no), endoscopic screening (yes or no), pack-years of smoking (0, 0-20, 21-40, >40), current smoking (yes or no), multivitamin use (yes or no), physical activity (<6.5, 6.5-16.7, 16.8-30.1, 30.2-53.3, ≥53.4 MET-hours/week), regular use of aspirin/NSAIDs (yes or no), and consumption of alcohol (0-4.9, 5.0-9.9, 10.0-14.9, 15-29.9, ≥30.0 g/d), folate (in quintiles), calcium (in quintiles), fiber (in quintiles), vitamin D (in quintiles) and processed red meat (in quintiles). In women, postmenopausal status and hormone use (never, past or current users) were additionally adjusted.

Among participants who remained in the same category of weight change (defined as gain ≥2.0kg, gain or loss <2.0kg, or loss ≥2.0kg) for at least two consecutive questionnaire cycles.

Calculated among participants who lost weight of ≥1.0kg, or lost or gained weight of <1.0kg.
We further investigated whether the association of the timing of weight change in women was related to menopause. As shown in Table 1.5, weight change before, but not after menopause, was associated with risk of CRC (P for trend=0.04 and 0.60, respectively). We also stratified by hormone use among postmenopausal women, and the association of weight change with CRC did not differ according to hormone use (P for interaction=0.45, Table S1.6).
Table 1.5 Relative risk of colorectal cancer according to premenopausal and postmenopausal weight change\(^a\)

<table>
<thead>
<tr>
<th>Weight change, kg</th>
<th>Median, kg</th>
<th>No. of cases</th>
<th>Person-years</th>
<th>Age-adjusted RR (95% CI)(^b)</th>
<th>Multivariable-adjusted RR (95% CI)(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Premenopausal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss ≥8.0</td>
<td>-11.3</td>
<td>61</td>
<td>69,456</td>
<td>1.06 (0.78-1.45)</td>
<td>1.03 (0.75-1.40)</td>
</tr>
<tr>
<td>Loss 4.0-7.9</td>
<td>-5.4</td>
<td>69</td>
<td>94,056</td>
<td>1.10 (0.82-1.47)</td>
<td>1.09 (0.81-1.45)</td>
</tr>
<tr>
<td>Loss 2.0-3.9</td>
<td>-2.7</td>
<td>44</td>
<td>83,726</td>
<td>0.86 (0.61-1.21)</td>
<td>0.85 (0.60-1.19)</td>
</tr>
<tr>
<td>Loss or gain &lt;2.0</td>
<td>0</td>
<td>146</td>
<td>254,822</td>
<td>1 [referent]</td>
<td>1 [referent]</td>
</tr>
<tr>
<td>Gain 2.0-5.9</td>
<td>4.1</td>
<td>261</td>
<td>418,654</td>
<td>1.11 (0.90-1.36)</td>
<td>1.10 (0.90-1.35)</td>
</tr>
<tr>
<td>Gain 6.0-9.9</td>
<td>8.2</td>
<td>297</td>
<td>422,150</td>
<td>1.17 (0.95-1.42)</td>
<td>1.15 (0.94-1.41)</td>
</tr>
<tr>
<td>Gain 10.0-19.9</td>
<td>14.1</td>
<td>539</td>
<td>689,926</td>
<td>1.19 (0.99-1.43)</td>
<td>1.16 (0.96-1.40)</td>
</tr>
<tr>
<td>Gain ≥20.0</td>
<td>27.2</td>
<td>432</td>
<td>511,662</td>
<td>1.23 (1.02-1.49)</td>
<td>1.20 (0.99-1.45)</td>
</tr>
<tr>
<td>P for trend</td>
<td></td>
<td></td>
<td></td>
<td>0.01</td>
<td>0.04</td>
</tr>
<tr>
<td>P for weight loss trend(^d)</td>
<td></td>
<td></td>
<td></td>
<td>0.95</td>
<td>0.87</td>
</tr>
<tr>
<td><strong>Postmenopausal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss ≥8.0</td>
<td>-11.3</td>
<td>90</td>
<td>67,964</td>
<td>1.17 (0.92-1.49)</td>
<td>1.16 (0.91-1.47)</td>
</tr>
<tr>
<td>Loss 4.0-7.9</td>
<td>-5.0</td>
<td>120</td>
<td>113,008</td>
<td>1.07 (0.87-1.31)</td>
<td>1.05 (0.86-1.29)</td>
</tr>
<tr>
<td>Loss 2.0-3.9</td>
<td>-2.7</td>
<td>137</td>
<td>115,010</td>
<td>1.28 (1.05-1.55)</td>
<td>1.25 (1.03-1.52)</td>
</tr>
<tr>
<td>Loss or gain &lt;2.0</td>
<td>0</td>
<td>462</td>
<td>538,248</td>
<td>1 [referent]</td>
<td>1 [referent]</td>
</tr>
<tr>
<td>Gain 2.0-5.9</td>
<td>3.6</td>
<td>398</td>
<td>463,230</td>
<td>0.96 (0.84-1.10)</td>
<td>0.96 (0.83-1.10)</td>
</tr>
<tr>
<td>Gain 6.0-9.9</td>
<td>7.7</td>
<td>240</td>
<td>240,400</td>
<td>1.04 (0.89-1.22)</td>
<td>1.04 (0.88-1.22)</td>
</tr>
<tr>
<td>Gain ≥10.0</td>
<td>13.6</td>
<td>235</td>
<td>220,330</td>
<td>1.09 (0.92-1.28)</td>
<td>1.08 (0.92-1.28)</td>
</tr>
<tr>
<td>P for trend</td>
<td></td>
<td></td>
<td></td>
<td>0.58</td>
<td>0.60</td>
</tr>
<tr>
<td>P for weight loss trend(^d)</td>
<td></td>
<td></td>
<td></td>
<td>0.40</td>
<td>0.55</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RR, relative risk.
\(^a\)Premenopausal weight change was calculated by the weight change from age 18 years up to menopause, and post-menopausal weight change was the weight change from menopause up to date.
\(^b\)Adjusted for age, and body weight at age 18 years (for premenopausal weight change) or at menopause (for postmenopausal weight change).
Additionally adjusted for height (continuous), family history of colorectal cancer (yes or no), pack-years of smoking before age of 30 years (0, 1-10, and >10), current smoking status (yes or no), multivitamin use (yes or no), regular use of aspirin/NSAIDs (yes or no), endoscopic screening (yes or no), postmenopausal hormone use (current, past, and never users), physical activity ( < 6.5, 6.5-16.7, 16.8-30.1, 30.2-53.3, ≥53.4 MET-hours/week), alcohol consumption (0-4.9, 5.0-9.9, 10.0-14.9, 15-29.9, ≥30.0 g/d), and intake of folate (in quartiles), calcium (in quartiles), vitamin D (in quartiles) and processed red meat (in quartiles).

Calculated among women who lost weight of ≥2.0kg, or lost or gained weight of <2.0kg.
Discussion

In the two large prospective cohorts, we found that weight gain from early adulthood to baseline enrollment (median age=43 years for women, 52 years for men) was associated with a higher risk of CRC, whereas weight loss was associated with lower risk. The associations appeared stronger in men than in women. Weight change during late adulthood was not associated with CRC risk. For weight change in the recent 4 years, a statistically significant association was observed in men, but not in women. In women, weight gain before, but not after, menopause was associated with CRC risk.

Substantial evidence from randomized controlled trials indicates that weight loss due to dietary modification and/or exercise is associated with improved profiles of inflammatory markers, insulin sensitivity, adipokines and sex hormones, all of which have been suggested to mediate the relationship between obesity and increased risk of CRC. However, direct epidemiologic evidence on the association of weight loss with CRC has been sparse and inconsistent. Although surgical weight loss has been inversely associated with the risk of CRC in a few studies, the small sample sizes precluded a detailed dose-response analysis. Similarly, the influence of non-surgical weight loss on CRC remains inconclusive in prospective cohort studies, in which weight loss was typically considered only in a single category due to the small number of cases. To our knowledge, our findings provide the first prospective evidence that weight loss during adulthood may be associated with lower risk of CRC.

For weight gain since early adulthood, consistent with previous studies, we found a positive association with CRC risk and the association was stronger in men than in women. Although it is possible that the older ages of men compared to women at cohort enrollment contribute to the larger elevation of CRC risk associated with weight gain, we did not
find strong evidence that the association between weight change and CRC risk varied by age at baseline in either men or women (Table S1.2). On the other hand, our findings are indeed consistent with the notion that obesity has a more marked influence on CRC incidence in men than in women. Although the exact mechanisms remain to be elucidated, sex hormones have been suggested to explain the difference between men and women. In women, ovarian hormone production declines after menopause and adipose tissue becomes the primary organ for estrogen secretion, resulting in a 2-fold or greater level of circulating estrogen in women with high BMI than those with normal weight. Estrogen protects against CRC development, possibly through regulation of gene transcription and modulation of cellular processes involved in cell proliferation, apoptosis and angiogenesis. On the other hand, obese men are characterized by a progressive decrease of testosterone with increasing body weight. Low testosterone has been associated with higher risk of CRC in men, but not in women. Therefore, it is possible that the increased level of circulating estrogen mitigates the detrimental effect of adiposity in postmenopausal women, while the lower testosterone in men elevates the metabolic risk of CRC associated with obesity. These hormonal alterations might collectively contribute to a weaker association of obesity with CRC in women than in women.

Consistent with this hypothesis, we observed that weight gain before, but not after, menopause was associated with higher risk of CRC. This finding aligns with the results of some prior studies, in which a stronger association of weight gain or high BMI with CRC was found among premenopausal women than among postmenopausal women, although the evidence remains inconclusive. Further investigation is needed to elucidate the potential role of hormonal factors in the observed sex difference of the adiposity-CRC relationship.
In contrast to weight change from early to middle adulthood, weight change during late adulthood, as reflected by change from baseline to present, was not associated with CRC risk in the current study. It has been shown that body weight tends to increase, peaking at about 65-70 years, and then decrease with further aging. In addition, body composition changes with aging, with an increase in fat mass and a decrease in muscle mass. These aging-related anthropometric changes pose challenge for investigation of body size change during late adulthood and complicate the interpretation of findings, particularly for weight change as it does not distinguish lean and fat mass. Indeed, we found some evidence that age may modify the relationship between weight change during late adulthood and CRC risk. Weight gain was suggestively associated with a higher risk of CRC among participants younger, but not older, than 70 years.

Although adiposity has been generally regarded as a tumor promoter, the critical period during which excess fatness increases CRC risk has yet to be determined. Our results suggest a sex-specific manner of action in which timing of exposure modifies the association of weight gain with CRC. In men both remote and recent weight gain poses risk for CRC, whereas in women weight gain from early to middle adulthood, but not in recent years, appeared to be critical for CRC development. Consistent with our findings, in the NIH-AARP cohort, weight changes from 18 to 35 years and from 50 years to baseline (approximately 60 years) were both associated with CRC risk in men, while only weight change from 18 to 35 years was associated with the risk in women. In the Norwegian Counties Study, a stronger association between BMI and colon cancer was reported in women with follow-up of ≥10 years than <10 years, while no difference by duration of follow-up was detected in men. Collectively, these results suggest a longer induction period for the tumorigenic effect of obesity in women than in men. This might
be related to the beneficial effect of adipocytes-derived estrogen on obesity-induced
carcinogenesis as discussed above. However, given the sparse evidence, further research is
warranted to better understand the role of adiposity across the life course on CRC risk.

Some limitations of our study should be noted. First, weight information was self-
reported or recalled and thus subject to measurement error. However, robust validity has been
established in previous validation studies within the two cohorts. Second, although the
homogeneity of the study population is a potential limitation, this reduces the likelihood of
uncontrolled confounding, and it is unlikely that the observed relationship between weight
change and CRC differs substantially from the general population. However, our findings should
be confirmed in other populations.

This study also has several strengths, including the two large well-established cohorts,
long-term follow-up, and detailed analysis on weight loss. Furthermore, repeated assessments of
body weight across adulthood provided us a unique opportunity to examine the potential
modification by timing of exposure, and by menopausal status in women.

In conclusion, our results indicate that weight gain from early to middle adulthood is
associated with a higher risk of CRC, whereas weight loss during this period is associated with
lower risk. The associations appear stronger in men than in women. We do not find strong
evidence that weight change during late adulthood affects CRC risk. A potential differential
association according to timing of weight change and menopausal status warrants further
investigation. Our findings provide further scientific rationale for recommendations for adults to
maintain a healthy body weight, especially during early/middle adulthood.
References


Supplementary Materials

Covariate assessment

In both the Nurses’ Health Study (NHS) and Health Professionals Follow-up Study (HPFS), height was queried at baseline. Smoking, endoscopic examination, and regular use of multivitamins, aspirin and non-steroid anti-inflammatory drugs (NSAIDs) were assessed biennially. Physical activity was assessed biennially in the HPFS; and in 1980, 1982, 1986, 1988, 1992, and biennially since 1994 in the NHS. Physical activity was calculated by summing the products of time spent on a variety of recreational or leisure-time activities with the average metabolic equivalent (MET) for that activity, except that in 1980 in the NHS a simple questionnaire was used to inquire regular physical activity without collecting detailed information on specific activities and durations. In women, menopausal status, age at menopause, and postmenopausal hormone (PMH) use were assessed biennially, as previously described. Women were classified as postmenopausal at the first report of natural menopause or surgery with bilateral oophorectomy. Dietary data were collected using the validated food frequency questionnaires (FFQs) in 1980, 1984, 1986 and every 4 years thereafter in the NHS, and in 1986 and every 4 years thereafter in the HPFS.

Statistical analysis

We assessed the proportional hazards assumption by including the product term between time variable and each covariate (including the exposure of interest, weight change) into the Cox proportional hazards model, and testing the statistical significance of the term by Wald test. No deviation from proportional hazards assumption was detected at $\alpha=0.05$ level.
When testing for trend using continuous weight change, to reduce the influence of outliers, we employed a 99% Winsorisation technique by setting weight change below the 0.5th percentile to the 0.5th percentile, and setting weight change above the 99.5th percentile to the 99.5th percentile. We assessed potential nonlinear relationship between weight change and CRC risk using stepwise restricted cubic spline analysis with a P = 0.05 as the criteria for both inclusion and retention in the model. We used a likelihood ratio test to determine the significance of the non-linearity by comparing the model with only the linear term to the model with both the linear and the cubic spline terms. We did not detect any statistically significant nonlinearity for any weight change variable in relation to CRC risk.

Weight change from baseline enrollment to present was calculated as the difference between the weight at baseline and the updated weight in the current questionnaire cycle. In the CRC incidence analysis, we adopted a 2-4-year lag to minimize the influence of reverse causation arising from undiagnosed cancer-induced weight loss, and therefore associated weight change with CRC events that occurred 2-4 years after weight change assessment. For example, weight change from baseline to 1990 was related to the incidence of CRC between 1992 and 1994, and weight change from baseline to 1992 was related to CRC incidence between 1994 and 1996. To minimize the influence of aging on weight change assessment in the elderly, we stopped updating weight change information when a participant reached age of 70 years.

Premenopausal weight change was calculated as the difference between the weight at age 18 years and the updated body weight until menopause. We also allowed for a 2-year lag in the analysis, and therefore follow-up started 2 years after a woman reported being postmenopausal. Weight change after menopause was calculated as the difference between the weight when menopause was first reported and the current body weight among postmenopausal women.
Similarly, follow-up started 2 years after the return date of the questionnaire in which current weight was assessed.

We tested whether the associations varied by cohort (i.e., sex) using the Cochran’s Q statistic. For subsite analysis, we classified CRC cases into proximal colon (cecum, ascending colon, hepatic flexure, transverse colon, and splenic flexure), distal colon (descending colon and sigmoid) and rectal cancers (rectosigmoid and rectum). To examine whether the associations varied by tumor subsites, we fitted subsite-stratified Cox proportional cause-specific hazards regression model using the duplication method and performed the heterogeneity test using a likelihood ratio test, by comparing the model in which the association with exposures was allowed to vary by tumor subsites to the model in which all the associations were held constant.

We conducted stratified analyses to evaluate whether the association between weight change and CRC risk varied by age, body mass index and PMH use. Test for interaction was performed by including the product term between weight change and the stratified variable into the model and testing the statistical significance using Wald test, except that for PMH use, which has 3 categories, we used a likelihood ratio test by comparing the model with the product terms between weight change and PMH use to the model without these terms.

To minimize the influence of unintentional weight loss, as a sensitivity analysis we excluded participants who quit smoking or had a history of weight loss-accompanied conditions at baseline (i.e., liver disease, emphysema, chronic bronchitis, ulcerative colitis, Crohn’s disease, multiple sclerosis, chronic renal failure, tuberculosis, Parkinson’s disease, and amyotrophic lateral sclerosis). In addition, for the analysis of weight change from baseline to present and 4-year weight change during follow-up, we stopped updating weight change information when a participant quit smoking or reported a diagnosis of weight loss-associated illnesses in the past 2
years. The results were essentially unchanged (data not shown). To further exclude the influence of smoking cessation on weight change, we performed all the analyses among never smokers only, and the results were similar (data not shown).
Table S1.1 Relative risk of colorectal cancer by body mass index according to weight change from age 18 (women) or 21 (men) years to baseline

<table>
<thead>
<tr>
<th>Category of weight change, kg</th>
<th>Women</th>
<th></th>
<th></th>
<th>Men</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BMI &lt;21 kg/m² at age of 18 years</td>
<td>BMI ≥21 kg/m² at age of 18 years</td>
<td>BMI &lt;23 kg/m² at age of 21 years</td>
<td>BMI ≥23 kg/m² at age of 21 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No. of cases</td>
<td>Multivariable-adjusted RR (95% CI)</td>
<td>No. of cases</td>
<td>Multivariable-adjusted RR (95% CI)</td>
<td>No. of cases</td>
<td>Multivariable-adjusted RR (95% CI)</td>
</tr>
<tr>
<td>Loss ≥8.0</td>
<td>0</td>
<td>-</td>
<td>58</td>
<td>0.75 (0.54-1.05)</td>
<td>1</td>
<td>1.98 (0.26-14.8)</td>
</tr>
<tr>
<td>Loss 4.0-7.9</td>
<td>16</td>
<td>1.76 (1.03-3.00)</td>
<td>68</td>
<td>0.80 (0.59-1.08)</td>
<td>1</td>
<td>0.54 (0.07-4.06)</td>
</tr>
<tr>
<td>Loss 2.0-3.9</td>
<td>22</td>
<td>1.32 (0.83-2.12)</td>
<td>53</td>
<td>0.91 (0.66-1.26)</td>
<td>2</td>
<td>0.61 (0.14-2.61)</td>
</tr>
<tr>
<td>Loss or gain &lt;2.0</td>
<td>83</td>
<td>1 [referent]</td>
<td>125</td>
<td>1 [referent]</td>
<td>18</td>
<td>1 [referent]</td>
</tr>
<tr>
<td>Gain 2.0-5.9</td>
<td>187</td>
<td>1.33 (1.02-1.72)</td>
<td>155</td>
<td>1.02 (0.81-1.30)</td>
<td>46</td>
<td>0.92 (0.54-1.59)</td>
</tr>
<tr>
<td>Gain 6.0-9.9</td>
<td>175</td>
<td>1.41 (1.08-1.83)</td>
<td>125</td>
<td>1.13 (0.88-1.44)</td>
<td>66</td>
<td>1.28 (0.76-1.15)</td>
</tr>
<tr>
<td>Gain 10.0-19.9</td>
<td>211</td>
<td>1.50 (1.16-1.94)</td>
<td>130</td>
<td>0.97 (0.76-1.24)</td>
<td>94</td>
<td>1.17 (0.70-1.94)</td>
</tr>
<tr>
<td>Gain ≥20.0</td>
<td>86</td>
<td>1.68 (1.24-2.28)</td>
<td>91</td>
<td>1.25 (0.92-1.64)</td>
<td>56</td>
<td>1.88 (1.10-3.22)</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.01</td>
<td>0.002</td>
<td>&lt;0.001</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P for weight loss trend b</td>
<td>0.16</td>
<td>0.15</td>
<td>0.56</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P for interaction c</td>
<td>0.86</td>
<td>0.42</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; CI, confidence interval; RR, relative risk.

* Multivariable model adjusted for age, body weight at age 18 years for women or at age 21 years for men, height (continuous), family history of colorectal cancer (yes or no), pack-years of smoking before age of 30 years (0, 1-10, and >10), current smoking status (yes or no), multivitamin use (yes or no), and regular use of aspirin/NSAIDs (yes or no, in men only). In women, models were additionally adjusted for postmenopausal status and hormone use.

*b Calculated among participants who lost weight of ≥2.0 kg, or lost or gained weight of <2.0 kg.

*c Wald test was used for the product term between weight change (continuous) and BMI (binary).
Table S1.2 Relative risk of colorectal cancer by baseline age according to weight change from age 18 (women) or 21 (men) years to baseline

<table>
<thead>
<tr>
<th>Category of weight change, kg</th>
<th>Women</th>
<th></th>
<th></th>
<th>Men</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age &lt; 45 years</td>
<td>Age ≥ 45 years</td>
<td></td>
<td>Age &lt; 60 years</td>
<td>Age ≥ 60 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No. of cases</td>
<td>Multivariable-</td>
<td>Multivariable-</td>
<td>No. of cases</td>
<td>Multivariable-</td>
<td>Multivariable-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>adjusted RR (95% CI)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>adjusted RR (95% CI)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>adjusted RR (95% CI)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>adjusted RR (95% CI)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Loss ≥2.0</td>
<td>96</td>
<td>0.89 (0.67-1.19)</td>
<td>121</td>
<td>0.99 (0.76-1.29)</td>
<td>28</td>
<td>0.84 (0.50-1.42)</td>
</tr>
<tr>
<td>Loss or gain &lt;2.0</td>
<td>100</td>
<td>1 [referent]</td>
<td>108</td>
<td>1 [referent]</td>
<td>29</td>
<td>1 [referent]</td>
</tr>
<tr>
<td>Gain 2.0-9.9</td>
<td>263</td>
<td>1.17 (0.93-1.47)</td>
<td>379</td>
<td>1.18 (0.95-1.46)</td>
<td>157</td>
<td>1.24 (0.83-1.84)</td>
</tr>
<tr>
<td>Gain 10.0-19.9</td>
<td>95</td>
<td>1.04 (0.79-1.38)</td>
<td>246</td>
<td>1.26 (1.01-1.59)</td>
<td>88</td>
<td>1.34 (0.88-2.04)</td>
</tr>
<tr>
<td>Gain ≥20.0</td>
<td>45</td>
<td>1.19 (0.84-1.70)</td>
<td>132</td>
<td>1.49 (1.15-1.92)</td>
<td>34</td>
<td>1.53 (0.93-2.53)</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.10</td>
<td>&lt;0.001</td>
<td></td>
<td>0.009</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>P for weight loss trend&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.44</td>
<td>0.22</td>
<td></td>
<td>0.07</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>P for interaction&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.38</td>
<td>0.24</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RR, relative risk.

<sup>a</sup>Multivariable model adjusted for age, body weight at age 18 years for women or at age 21 years for men, height (continuous), family history of colorectal cancer (yes or no), pack-years of smoking before age of 30 years (0, 1-10, and >10), current smoking status (yes or no), multivitamin use (yes or no), and regular use of aspirin/NSAIDs (yes or no, in men only). In women, postmenopausal status and hormone use were additionally adjusted.

<sup>b</sup>Calculated among participants who lost weight of ≥2.0kg, or lost or gained weight of <2.0kg.

<sup>c</sup>Wald test was used for the product term between weight change (continuous) and age (binary).
Table S1.3 Subsite-specific relative risk of colorectal cancer according to weight change from age 18 (women) or 21 (men) years to baseline

<table>
<thead>
<tr>
<th>Category of weight change, kg</th>
<th>Proximal colon cancer</th>
<th>Distal colon cancer</th>
<th>Rectal cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases</td>
<td>Age-adjusted RR (95% CI)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Multivariable-adjusted RR (95% CI)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss ≥2.0</td>
<td>118</td>
<td>1.07 (0.82-1.40)</td>
<td>1.04 (0.80-1.37)</td>
</tr>
<tr>
<td>Gain 2.0-9.9</td>
<td>290</td>
<td>1.04 (0.83-1.31)</td>
<td>1.05 (0.84-1.32)</td>
</tr>
<tr>
<td>Gain 10.0-19.9</td>
<td>155</td>
<td>1.04 (0.81-1.34)</td>
<td>1.06 (0.82-1.36)</td>
</tr>
<tr>
<td>Gain ≥20.0</td>
<td>88</td>
<td>1.32 (0.99-1.75)</td>
<td>1.35 (1.01-1.80)</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.12</td>
<td>0.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P for weight loss trend&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.43</td>
<td>0.41</td>
<td>0.23</td>
</tr>
<tr>
<td>P for heterogeneity&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.23</td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss ≥2.0</td>
<td>15</td>
<td>0.65 (0.33-1.28)</td>
<td>0.64 (0.33-1.26)</td>
</tr>
<tr>
<td>Gain 2.0-9.9</td>
<td>78</td>
<td>0.85 (0.52-1.38)</td>
<td>0.85 (0.52-1.39)</td>
</tr>
<tr>
<td>Gain 10.0-19.9</td>
<td>50</td>
<td>0.91 (0.54-1.52)</td>
<td>0.91 (0.54-1.53)</td>
</tr>
<tr>
<td>Gain ≥20.0</td>
<td>25</td>
<td>1.29 (0.71-2.33)</td>
<td>1.31 (0.72-2.38)</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.06</td>
<td>0.05</td>
<td>0.01</td>
</tr>
<tr>
<td>P for weight loss trend&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.05</td>
<td>0.04</td>
<td>0.31</td>
</tr>
<tr>
<td>P for heterogeneity&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.87</td>
<td>0.87</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RR, relative risk.

<sup>a</sup>Adjusted for age, and body weight at age 18 years for women or at age 21 years for men.
Additionally adjusted for height (continuous), family history of colorectal cancer (yes or no), pack-years of smoking before age of 30 years (0, 1-10, and >10), current smoking status (yes or no), multivitamin use (yes or no), and regular use of aspirin/NSAIDs (yes or no, in men only). In women, postmenopausal status and hormone use were additionally adjusted.

Calculated among participants who lost weight of ≥2.0kg, or lost or gained weight of <2.0kg.

Likelihood ratio test was used to compare the model that allows for separate associations across tumor subsites to the model that assumes a common association across subsites.
### Table S1.4 Relative risk of colorectal cancer by current age according to weight change from baseline to present

<table>
<thead>
<tr>
<th>Category of weight change, kg</th>
<th>Women</th>
<th></th>
<th></th>
<th></th>
<th>Men</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age &lt; 70 years</td>
<td>Age ≥ 70 years</td>
<td>Age &lt; 70 years</td>
<td>Age ≥ 70 years</td>
<td>Age &lt; 70 years</td>
<td>Age ≥ 70 years</td>
<td>Age &lt; 70 years</td>
<td>Age ≥ 70 years</td>
</tr>
<tr>
<td></td>
<td>No. of cases</td>
<td>Multivariable-adjusted RR (95% CI)</td>
<td>No. of cases</td>
<td>Multivariable-adjusted RR (95% CI)</td>
<td>No. of cases</td>
<td>Multivariable-adjusted RR (95% CI)</td>
<td>No. of cases</td>
<td>Multivariable-adjusted RR (95% CI)</td>
</tr>
<tr>
<td>Loss ≥5.0</td>
<td>70</td>
<td>1.17 (0.87-1.57)</td>
<td>56</td>
<td>0.94 (0.68-1.31)</td>
<td>16</td>
<td>0.82 (0.46-1.47)</td>
<td>21</td>
<td>1.05 (0.64-1.72)</td>
</tr>
<tr>
<td>Loss 1.0-4.9</td>
<td>146</td>
<td>1.23 (0.98-1.54)</td>
<td>115</td>
<td>1.22 (0.93-1.58)</td>
<td>59</td>
<td>1.15 (0.81-1.62)</td>
<td>55</td>
<td>0.84 (0.60-1.18)</td>
</tr>
<tr>
<td>Loss or gain &lt;1.0</td>
<td>218</td>
<td>1 [referent]</td>
<td>114</td>
<td>1 [referent]</td>
<td>77</td>
<td>1 [referent]</td>
<td>97</td>
<td>1 [referent]</td>
</tr>
<tr>
<td>Gain 1.0-2.9</td>
<td>166</td>
<td>1.16 (0.94-1.44)</td>
<td>66</td>
<td>0.76 (0.56-1.03)</td>
<td>56</td>
<td>0.98 (0.69-1.40)</td>
<td>50</td>
<td>0.97 (0.69-1.37)</td>
</tr>
<tr>
<td>Gain 3.0-7.9</td>
<td>357</td>
<td>1.21 (1.00-1.45)</td>
<td>186</td>
<td>0.90 (0.71-1.15)</td>
<td>80</td>
<td>1.08 (0.78-1.50)</td>
<td>46</td>
<td>0.97 (0.67-1.40)</td>
</tr>
<tr>
<td>Gain ≥8.0</td>
<td>480</td>
<td>1.28 (1.06-1.53)</td>
<td>236</td>
<td>1.00 (0.79-1.26)</td>
<td>44</td>
<td>1.24 (0.83-1.86)</td>
<td>15</td>
<td>1.01 (0.57-1.81)</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.18</td>
<td>0.42</td>
<td>0.28</td>
<td>0.48</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P for weight loss trendb</td>
<td>0.41</td>
<td>0.65</td>
<td>0.28</td>
<td>0.58</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P for interactionc</td>
<td>0.03</td>
<td>0.93</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RR, relative risk.

*Multivariable model adjusted for age, body weight at baseline, height (continuous), family history of colorectal cancer (yes or no), endoscopic screening (yes or no), pack-years of smoking (0, 0-20, 21-40, >40), current smoking (yes or no), multivitamin use (yes or no), physical activity (<6.5, 6.5-16.7, 16.8-30.1, 30.2-53.3, ≥53.4 MET-hours/week), regular use of aspirin/NSAIDs (yes or no), and consumption of alcohol (0-4.9, 5.0-9.9, 10.0-14.9, 15-29.9, ≥30.0 g/d), folate (in quintiles), calcium (in quintiles), fiber (in quintiles), vitamin D (in quintiles) and processed red meat (in quintiles). In women, postmenopausal status and hormone use (never, past or current users) were additionally adjusted.

*Calculated among participants who lost weight of ≥1.0kg, or lost or gained weight of <1.0kg.

*Cald Wald test was used for the product term between weight change (continuous) and age (binary).
Table S1.5 Relative risk of colorectal cancer by current age according to 4-year weight change during follow-up

<table>
<thead>
<tr>
<th>Category of weight change, kg</th>
<th>Women</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>Men</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age &lt; 70 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Age ≥ 70 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No. of cases</td>
<td>Multivariable-adjusted RR (95% CI)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No. of cases</td>
<td>Multivariable-adjusted RR (95% CI)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>No. of cases</td>
<td>Multivariable-adjusted RR (95% CI)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No. of cases</td>
<td>Multivariable-adjusted RR (95% CI)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Loss ≥7.0</td>
<td>30</td>
<td>0.96 (0.63-1.47)</td>
<td>63</td>
<td>1.02 (0.65-1.58)</td>
<td></td>
<td>14</td>
<td>1.23 (0.68-2.22)</td>
<td>10</td>
<td>0.57 (0.29-1.13)</td>
</tr>
<tr>
<td>Loss 2.0-6.9</td>
<td>103</td>
<td>0.88 (0.63-1.24)</td>
<td>172</td>
<td>0.93 (0.64-1.34)</td>
<td></td>
<td>43</td>
<td>1.03 (0.71-1.50)</td>
<td>49</td>
<td>0.81 (0.57-1.16)</td>
</tr>
<tr>
<td>Loss 1.0-1.9</td>
<td>37</td>
<td>0.97 (0.70-1.33)</td>
<td>52</td>
<td>0.98 (0.69-1.40)</td>
<td></td>
<td>10</td>
<td>0.69 (0.36-1.33)</td>
<td>18</td>
<td>0.89 (0.53-1.49)</td>
</tr>
<tr>
<td>Loss or gain &lt;1.0</td>
<td>211</td>
<td>1 [referent]</td>
<td>248</td>
<td>1 [referent]</td>
<td></td>
<td>92</td>
<td>1 [referent]</td>
<td>98</td>
<td>1 [referent]</td>
</tr>
<tr>
<td>Gain 1.0-2.9</td>
<td>122</td>
<td>0.96 (0.69-1.34)</td>
<td>126</td>
<td>0.73 (0.49-1.09)</td>
<td></td>
<td>62</td>
<td>1.13 (0.82-1.57)</td>
<td>35</td>
<td>0.70 (0.47-1.04)</td>
</tr>
<tr>
<td>Gain 3.0-7.9</td>
<td>172</td>
<td>1.10 (0.79-1.51)</td>
<td>159</td>
<td>0.95 (0.64-1.40)</td>
<td></td>
<td>84</td>
<td>1.29 (0.95-1.74)</td>
<td>36</td>
<td>0.87 (0.58-1.29)</td>
</tr>
<tr>
<td>Gain ≥8.0</td>
<td>57</td>
<td>1.07 (0.74-1.55)</td>
<td>42</td>
<td>0.74 (0.41-1.32)</td>
<td></td>
<td>16</td>
<td>1.39 (0.80-2.40)</td>
<td>10</td>
<td>1.54 (0.78-3.04)</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.08</td>
<td>0.29</td>
<td></td>
<td></td>
<td></td>
<td>0.20</td>
<td>0.07</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P for weight loss trend&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.51</td>
<td>0.96</td>
<td></td>
<td></td>
<td></td>
<td>0.95</td>
<td>0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P for interaction&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.06</td>
<td>0.58</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RR, relative risk.

<sup>a</sup>Multivariable model adjusted for age, body weight at the start of each time period (continuous), height (continuous), family history of colorectal cancer (yes or no), endoscopic screening (yes or no), pack-years of smoking (0, 0-20, 21-40, >40), current smoking (yes or no), multivitamin use (yes or no), physical activity (<6.5, 6.5-16.7, 16.8-30.1, 30.2-53.3, ≥53.4 MET-hours/week), regular use of aspirin/NSAIDs (yes or no), and consumption of alcohol (0-4.9, 5.0-9.9, 10.0-14.9, 15-29.9, ≥30.0 g/d), folate (in quintiles), calcium (in quintiles), fiber (in quintiles), vitamin D (in quintiles) and processed red meat (in quintiles). In women, postmenopausal status and hormone use (never, past or current users) were additionally adjusted.

<sup>b</sup>Calculated among participants who lost weight of ≥1.0kg, or lost or gained weight of <1.0kg.

<sup>c</sup>Wald test was used for the product term between weight change (continuous) and age (binary).
<table>
<thead>
<tr>
<th>Category of postmenopausal weight change, kg</th>
<th>Median of weight change, kg</th>
<th>Overall</th>
<th>Among stable change$^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases</td>
<td>Person-years</td>
<td>Age-adjusted RR (95% CI)$^b$</td>
</tr>
<tr>
<td><strong>Never use of PMH</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss ≥ 8.0</td>
<td>-11.3</td>
<td>43</td>
<td>29,908</td>
</tr>
<tr>
<td>Loss 4.0-7.9</td>
<td>-5.0</td>
<td>61</td>
<td>45,092</td>
</tr>
<tr>
<td>Loss 2.0-3.9</td>
<td>-2.3</td>
<td>64</td>
<td>45,648</td>
</tr>
<tr>
<td>Loss or gain &lt; 2.0</td>
<td>0</td>
<td>230</td>
<td>214,070</td>
</tr>
<tr>
<td>Gain 2.0-5.9</td>
<td>3.6</td>
<td>183</td>
<td>162,504</td>
</tr>
<tr>
<td>Gain 6.0-9.9</td>
<td>7.7</td>
<td>95</td>
<td>77,908</td>
</tr>
<tr>
<td>Gain ≥ 10.0</td>
<td>13.6</td>
<td>84</td>
<td>68,996</td>
</tr>
<tr>
<td>P for trend</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P for weight loss trend$^e$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Past use of PMH</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss ≥ 8.0</td>
<td>-11.3</td>
<td>30</td>
<td>20,780</td>
</tr>
<tr>
<td>Loss 4.0-7.9</td>
<td>-5.4</td>
<td>31</td>
<td>33,574</td>
</tr>
<tr>
<td>Loss 2.0-3.9</td>
<td>-2.7</td>
<td>46</td>
<td>32,598</td>
</tr>
<tr>
<td>Loss or gain &lt; 2.0</td>
<td>0</td>
<td>112</td>
<td>134,686</td>
</tr>
<tr>
<td>Gain 2.0-5.9</td>
<td>3.6</td>
<td>107</td>
<td>128,000</td>
</tr>
<tr>
<td>Gain 6.0-9.9</td>
<td>7.7</td>
<td>73</td>
<td>74,024</td>
</tr>
<tr>
<td>Gain ≥ 10.0</td>
<td>14.1</td>
<td>81</td>
<td>74,358</td>
</tr>
<tr>
<td>P for trend</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P for weight loss trend$^e$</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table S1.6 (Continued).

<table>
<thead>
<tr>
<th>Category of weight change, kg</th>
<th>Median of weight change, kg</th>
<th>No. of cases</th>
<th>Person-years</th>
<th>Overall Age-adjusted RR (95% CI)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Multivariable-adjusted RR (95% CI)&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Among stable change&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss ≥8.0</td>
<td>-10.9</td>
<td>16</td>
<td>16,280</td>
<td>1.26 (0.72-2.19)</td>
<td>1.28 (0.73-2.24)</td>
<td>11</td>
</tr>
<tr>
<td>Loss 4.0-7.9</td>
<td>-5.0</td>
<td>26</td>
<td>32,536</td>
<td>1.15 (0.74-1.79)</td>
<td>1.16 (0.75-1.81)</td>
<td>19</td>
</tr>
<tr>
<td>Loss 2.0-3.9</td>
<td>-2.7</td>
<td>26</td>
<td>34,926</td>
<td>1.11 (0.72-1.70)</td>
<td>1.10 (0.72-1.70)</td>
<td>16</td>
</tr>
<tr>
<td>Loss or gain &lt;2.0</td>
<td>0</td>
<td>109</td>
<td>179,574</td>
<td>1 [referent]</td>
<td>1 [referent]</td>
<td>64</td>
</tr>
<tr>
<td>Gain 2.0-5.9</td>
<td>3.6</td>
<td>104</td>
<td>165,370</td>
<td>1.00 (0.76-1.32)</td>
<td>1.02 (0.78-1.34)</td>
<td>57</td>
</tr>
<tr>
<td>Gain 6.0-9.9</td>
<td>7.7</td>
<td>68</td>
<td>84,492</td>
<td>1.20 (0.88-1.64)</td>
<td>1.23 (0.90-1.68)</td>
<td>55</td>
</tr>
<tr>
<td>Gain ≥10.0</td>
<td>13.6</td>
<td>63</td>
<td>73,168</td>
<td>1.23 (0.89-1.70)</td>
<td>1.22 (0.88-1.70)</td>
<td>58</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.47</td>
<td>0.48</td>
<td>0</td>
<td>0.43</td>
<td></td>
<td>0.24</td>
</tr>
<tr>
<td>P for weight loss trend&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0.09</td>
<td>0.16</td>
<td>0</td>
<td></td>
<td></td>
<td>0.24</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; PMH, postmenopausal hormone; RR, relative risk.

<sup>a</sup>P for interaction between weight change and PMH use is 0.45.

<sup>b</sup>Adjusted for age, and body weight at age 18 years (for premenopausal weight change) or at menopause (for postmenopausal weight change).

<sup>c</sup>Additionally adjusted for height (continuous), family history of colorectal cancer (yes or no), pack-years of smoking before age of 30 years (10, 1-10, and >10), current smoking status (yes or no), multivitamin use (yes or no), regular use of aspirin/NSAIDs (yes or no), endoscopic screening (yes or no), postmenopausal hormone use (current, past, and never users), physical activity (<6.5, 6.5-16.7, 16.8-30.1, 30.2-53.3, ≥53.4 MET-hours/week), alcohol consumption (0-4.9, 5.0-9.9, 10.0-14.9, 15-29.9, ≥30.0 g/d), and intake of folate (in quartiles), calcium (in quartiles), vitamin D (in quartiles) and processed red meat (in quartiles).

<sup>d</sup>Among participants who remained in the same category of weight change (defined as gain ≥2.0kg, gain or loss <2.0kg, or loss ≥2.0kg) for two consecutive questionnaire cycles.

<sup>e</sup>Calculated among women who lost weight of ≥2.0kg, or lost or gained weight of <2.0kg.
References


CHAPTER 2. Body fat distribution and colorectal cancer

**Title** Long-term status and change of body fat distribution, and risk of colorectal cancer: a prospective cohort study

**Authors:** Mingyang Song\(^{1,2}\), Frank B. Hu\(^{1,2,3}\), Donna Spiegelman\(^{1,2,4,5}\), Andrew T. Chan\(^{3,6}\), Kana Wu\(^{1}\), Shuji Ogino\(^{2,3,7,8}\), Charles S. Fuchs\(^{3,7}\), Walter C. Willett\(^{1,2,3}\), Edward L. Giovannucci\(^{1,2,3}\)

**Authors’ affiliations:**

1Department of Nutrition, Harvard T.H. Chan School of Public Health;

2Department of Epidemiology, Harvard T.H. Chan School of Public Health;

3Channing Division of Network Medicine, Department of Medicine, Harvard Medical School;

4Department of Biostatistics, Harvard T.H. Chan School of Public Health;

5Department of Global Health and Population, Harvard T.H. Chan School of Public Health;

6Division of Gastroenterology, Massachusetts General Hospital;

7Department of Medical Oncology, Dana-Farber Cancer Institute;

8Department of Pathology, Brigham and Women's Hospital and Harvard Medical School;
Abstract

Although obesity has been linked to an increased risk of colorectal cancer (CRC), the risk associated with long-term status or change of body fat distribution has not been fully elucidated.

Using repeated anthropometric assessments in the Nurses’ Health Study (NHS) and Health Professionals Follow-up Study (HPFS), we prospectively investigated cumulative average waist circumference, hip circumference and waist-to-hip ratio, as well as their 10-year changes over adulthood, in relation to CRC risk up to 2010. Waist and hip circumferences were assessed in 1986, 1996 and 2000 in the NHS, and in 1987 and 1996 in the HPFS. We used Cox proportional hazards models to calculate the relative risk (RR) and 95% confidence interval (CI).

High waist circumference, hip circumference and waist-to-hip ratio were all associated with a higher risk of CRC in men, even after adjusting for body mass index. The associations were weaker in women. 10-year gain of waist circumference was positively associated with CRC risk in men (P for trend=0.03), but not in women (P for trend=0.34). Compared with men who maintained their waist circumference, the RRs of CRC were 1.59 (95% CI, 1.01-2.49) for men gaining waist circumference by 10 cm or more, and 0.76 (95% CI, 0.47-1.21) for men losing 2 cm or more. These associations were independent of weight change.

In conclusion, abdominal adiposity is associated with high risk of colorectal cancer. This association is stronger in men than in women, and is independent of overall obesity. Our findings, to our knowledge, also provide the first prospective evidence that waist circumference gain during adulthood is associated with higher risk of colorectal cancer in men, thus highlighting the importance of maintaining a healthy waist for colorectal cancer prevention.
Introduction

Overall obesity, as measured by high body mass index (BMI), increases colorectal cancer (CRC) risk, with more consistent evidence in men than in women. Despite these compelling data, several limitations of BMI has been noted, including its inability to distinguish between fat mass and lean mass, and to capture the variation of body fat distribution. On the other hand, accumulating evidence suggests that abdominal fat distribution, measured by high waist circumference or waist-to-hip ratio (WHR), is a better indicator of the metabolic disturbances that may subsequently influence CRC risk.

High waist circumference and WHR have been associated with a higher risk of CRC in many prospective studies. However, in all but two studies, only a single measurement was taken, and therefore neither the long-term influence nor any changes in body fat distribution during adulthood could be examined.

The objective of this study was to investigate the cumulative average and change in body fat distribution measures, including waist circumference, hip circumference and WHR, during adulthood in relation to CRC risk in two large cohort studies, the Nurses’ Health Study (NHS) and Health Professionals Follow-up Study (HPFS). In earlier examinations in the two cohorts, we observed a positive association of baseline waist circumference and WHR with risk of colon cancer; however, those analyses were limited by the short duration of follow-up (5-6 years), and a lack of data on rectal cancer and change in body fat distribution. In the current study, we present results that encompass both the long-term status and change in body fat distribution among men and women over 23 to 24 years of follow-up.
Methods

Study population

Details about the NHS and HPFS have been described elsewhere \cite{18,19}. In brief, the NHS included 121,701 U.S. registered female nurses who were aged 30-55 years in 1976. The HPFS included 51,529 U.S. male health professionals who were aged 40-75 years in 1986. In both cohorts, participants completed a detailed questionnaire inquiring about their medical history and lifestyle factors at baseline, and every two years thereafter. Among participants who were alive up to 2010, the follow-up rates were 95.4% in the NHS and 95.9% in the HPFS. This investigation was approved by the Institutional Review Board at the Brigham and Women’s Hospital and the Harvard School of Public Health.

Exposure measurement

In both cohorts, height and weight were self-reported at baseline. Participants were also asked about their current weight on biennial questionnaires. In 1987 in the HPFS, we enclosed a tape measure in an optional questionnaire and directed participants to measure their waist at the umbilicus and their hips at the largest circumference between their waist and thighs. Participants were instructed to take measurements while standing and avoid measuring over bulky clothing. Waist and hip circumference information was updated using the same procedure in 1996. In the NHS, women were asked to report their waist and hip circumferences using a tape measure in 1986, 1996 and 2000. In both cohorts, circumference measurements were recorded to the nearest one-quarter inch, and WHRs were calculated for each set of circumferences.
The validity of self-reported anthropometric measurements has been evaluated in a sample of 123 men and 140 women drawn from the NHS and HPFS, with similar age distribution as the entire cohorts. A trained technician visited participants twice during the study, spaced approximately six months apart to incorporate seasonal variability, and measured current weight and waist and hip circumferences using the standard protocol. After adjusting for random within-person variability, the Pearson correlation coefficients between self-report and technician measurements in women and men were 0.89 and 0.95 for waist circumference, 0.84 and 0.88 for hip circumference, and 0.70 and 0.69 for WHR, respectively.

Outcome ascertainment

In both cohorts, self-reported diagnoses of CRC were obtained on biennial questionnaires, and participants who reported a diagnosis of CRC were asked for permission to acquire their medical records and pathologic reports. We identified deaths through the National Death Index and next-of-kin. For all CRC deaths, we requested permission from next-of-kin to review medical records. A study physician, blinded to anthropometric information, reviewed records to confirm the CRC diagnosis and to extract relevant information, including anatomic location.

Statistical analysis

All the analyses were performed separately in women and men. To capture the long-term body fat distribution, we calculated the cumulative averages of waist circumference, hip circumference and WHR for each participant using the repeated assessments. We also calculated the approximately 10-year change of measurements from 1986 to 1996 in the NHS, and from 1987 to 1996 in the HPFS. In all the analyses, a 2-to-3-year lag of follow-up was adopted to
minimize the influence of reverse causation arising from undiagnosed cancer-induced change in body size. Therefore, for the cumulative average analysis, we calculated person-time of follow-up for each participant from the age at the date when the 1988 (NHS) or 1990 (HPFS) questionnaire was returned until the age at the date of death, CRC diagnosis, or end of follow-up (June 1, 2010 for the NHS, January 31, 2010 for the HPFS), whichever came first. Similarly, for the analysis of change in anthropometric measurements, follow-up started from the date when the 1998 questionnaires were returned.

For each analysis, we excluded participants who had missing anthropometric data or had cancer other than nonmelanoma skin cancer at the beginning of follow-up. Cox proportional hazards regression was used to calculate hazard ratio (as an estimate of relative risk [RR]) and 95% confidence interval (CI) of CRC associated with body size measurements. In multivariable analysis, we adjusted for several potential confounders (see footnotes of Tables 2.2 and 2.3). Details regarding covariate assessment are provided in the Supplementary Materials. We assessed a potential nonlinear relationship using stepwise restricted cubic spline analysis with a P = 0.05 as the criteria for both inclusion and retention in the model.

For the cumulative average analysis, we corrected for measurement error in self-reported anthropometric data using technician-measured data from the validation study of the two cohorts. We used a risk set regression calibration method, which recalibrates the measurement error model for time-varying exposures within each risk set of the Cox regression model.

Given previous evidence about effect modification by menopausal hormone therapy (MHT) on the obesity-CRC relationship, we also stratified by MHT and tested for the significance of the interaction using likelihood ratio test by comparing the model with the product terms between exposure and MHT use to the model without these terms. We also grouped participants
according to the combined categories of BMI and waist circumference, and tested the joint association and interaction of the two measures with CRC risk.

Additional details regarding statistical analyses are provided in the Supplementary Materials. We used SAS 9.3 for all analyses (SAS Institute Inc., Cary, NC, USA). All statistical tests were two sided and P < 0.05 was considered statistically significant.

Results

For the cumulative average analysis, we identified 1,884 incident CRC cases (1,125 women; 759 men) over 20-22 years, encompassing 1,979,428 person-years of follow-up (1,283,396 in the NHS and 696,032 in the HPFS). As shown in Table 2.1, participants with a large waist circumference were less physically active, had more lifetime tobacco exposure, and tended to take aspirin or non-steroidal anti-inflammatory drugs. In contrast, participants with a low waist circumference were more likely to use multivitamins, undergo endoscopic examination, and consume more folate, calcium, vitamin D and fiber, and less red meat.
Table 2.1 Age-standardized characteristics according to waist circumference in women (Nurses’ Health Study) and men (Health Professionals Follow-up Study)\(^a\)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Quintile 1</td>
<td>Quintile 3</td>
</tr>
<tr>
<td>Age, year (year)</td>
<td>63.1 (9.3)</td>
<td>65.5 (9.2)</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>68.5 (3.9)</td>
<td>80.9 (3.5)</td>
</tr>
<tr>
<td>Hip circumference, cm</td>
<td>93.4 (5.8)</td>
<td>100.8 (6.8)</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.74 (0.17)</td>
<td>0.81 (0.08)</td>
</tr>
<tr>
<td>Height, cm (cm)</td>
<td>162 (6)</td>
<td>164 (6)</td>
</tr>
<tr>
<td>Body mass index, kg/m(^2)</td>
<td>21.3 (2.0)</td>
<td>24.1 (2.5)</td>
</tr>
<tr>
<td>Physical activity, MET-hours/week</td>
<td>22.7 (21.8)</td>
<td>17.1 (16.4)</td>
</tr>
<tr>
<td>Pack-years of smoking</td>
<td>12.2 (18.6)</td>
<td>12.7 (19.3)</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>13.4</td>
<td>11.1</td>
</tr>
<tr>
<td>Family history of colorectal cancer, %</td>
<td>16.3</td>
<td>17.7</td>
</tr>
<tr>
<td>Current multivitamin use, %</td>
<td>61.5</td>
<td>59.3</td>
</tr>
<tr>
<td>Regular use of aspirin/NSAIDs, %(^b)</td>
<td>46.1</td>
<td>52.1</td>
</tr>
<tr>
<td>History of colonoscopy/sigmoidoscopy, %</td>
<td>57.8</td>
<td>58.1</td>
</tr>
<tr>
<td>Postmenopausal, %</td>
<td>91.5</td>
<td>91.8</td>
</tr>
<tr>
<td>Current postmenopausal hormone use, %(^c)</td>
<td>38.2</td>
<td>34.6</td>
</tr>
<tr>
<td>Alcohol consumption, g/d</td>
<td>6.3 (8.5)</td>
<td>6.3 (9.1)</td>
</tr>
<tr>
<td>Dietary intake</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Folate, (\mu g/d)</td>
<td>475 (197)</td>
<td>453 (187)</td>
</tr>
<tr>
<td>Calcium, mg/d</td>
<td>1,051 (383)</td>
<td>1,016 (356)</td>
</tr>
<tr>
<td>Vitamin D, IU/d</td>
<td>380 (204)</td>
<td>369 (193)</td>
</tr>
<tr>
<td>Total fiber, g/d</td>
<td>18.0 (4.9)</td>
<td>17.4 (4.4)</td>
</tr>
<tr>
<td>Total red meat, g/d</td>
<td>70.0 (37.9)</td>
<td>76.6 (38.3)</td>
</tr>
<tr>
<td>AHEI diet score</td>
<td>46.8 (9.1)</td>
<td>45.0 (8.6)</td>
</tr>
</tbody>
</table>

Abbreviations: AHEI, Alternative Healthy Eating Index; MET: metabolic equivalent; NSAID, nonsteroidal anti-inflammatory drug.

*Updated information throughout follow-up was used to calculate the mean (standard deviation) for continuous variables and percentage for categorical variables. All variables are age-standardized except age.*
bRegular users are defined as ≥2 standard (325-mg) tablets of aspirin or ≥2 tablets of NSAIDs per week.

Proportion of current postmenopausal hormone use is calculated among postmenopausal women only.
In women, cumulative average waist circumference was positively associated with CRC risk in the multivariable-adjusted model (Table 2.2). However, further adjustment for BMI attenuated this association to null. A somewhat inverse association was found between hip circumference and CRC risk after adjusting for BMI. WHR was not associated with CRC incidence.

In men, we found a strong positive association of waist circumference, hip circumference and WHR with CRC risk (Table 2.2). These associations were attenuated after adjusting for BMI and other covariates, but remained at least marginally statistically significant. After correcting for measurement error, the RR per 10-cm increase of waist circumference was 1.27 (95% CI, 1.12-1.43, P for trend<0.001). We detected a statistically significant sex difference in the BMI-adjusted association between waist circumference and CRC risk (P<0.001).
Table 2.2 Risk of colorectal cancer according to quintiles of waist circumference, hip circumference, and waist-to-hip ratio in women (Nurses’ Health Study, 1988-2010) and men (Health Professionals Follow-up Study, 1990-2010)

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>No. of cases</td>
</tr>
<tr>
<td><strong>Waist circumference, cm</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quintile 1</td>
<td>68.6</td>
<td>190</td>
</tr>
<tr>
<td>Quintile 2</td>
<td>75.4</td>
<td>193</td>
</tr>
<tr>
<td>Quintile 3</td>
<td>81.3</td>
<td>220</td>
</tr>
<tr>
<td>Quintile 4</td>
<td>87.6</td>
<td>247</td>
</tr>
<tr>
<td>Quintile 5</td>
<td>99.4</td>
<td>275</td>
</tr>
<tr>
<td><strong>P for trend</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncorrected RR (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per 10-cm increase</td>
<td>1.07</td>
<td>0.02</td>
</tr>
<tr>
<td>Corrected RR (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per 10-cm increase</td>
<td>1.08</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Hip circumference, cm</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quintile 1</td>
<td>91.4</td>
<td>196</td>
</tr>
<tr>
<td>Quintile 2</td>
<td>96.5</td>
<td>224</td>
</tr>
<tr>
<td>Quintile 3</td>
<td>101.0</td>
<td>241</td>
</tr>
<tr>
<td>Quintile 4</td>
<td>106.7</td>
<td>219</td>
</tr>
<tr>
<td>Quintile 5</td>
<td>115.1</td>
<td>243</td>
</tr>
<tr>
<td><strong>P for trend</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncorrected RR (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per 10-cm increase</td>
<td>1.03</td>
<td>0.32</td>
</tr>
<tr>
<td>Corrected RR (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per 10-cm increase</td>
<td>1.04</td>
<td>0.25</td>
</tr>
<tr>
<td><strong>Waist-to-hip ratio</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quintile 1</td>
<td>0.72</td>
<td>169</td>
</tr>
<tr>
<td>Quintile 2</td>
<td>0.76</td>
<td>223</td>
</tr>
<tr>
<td>Quintile 3</td>
<td>0.80</td>
<td>226</td>
</tr>
</tbody>
</table>
### Table 2.2 (Continued).

| Quintile | Median | No. of cases | Age-adjusted RR (95% CI)* | Multivariable-adjusted RR (95% CI)† | Multivariable + BMI-adjusted RR (95% CI)‡ | P for trend | Uncorrected RR (95% CI) per 0.1-unit increase | Corrected RR (95% CI) per 0.1-unit increase¹ | Abbreviations: CI, confidence interval; RR, relative risk.  
  
  *Age-adjusted estimates were calculated from Cox proportion hazards regression using age as the underlying time variable and stratified by calendar year of the current questionnaire cycle.  
  
  †Multivariable models were based on age-adjusted models with additional adjustment for height (continuous), family history of colorectal cancer (yes or no), pack-years of smoking (continuous), multivitamin use (yes or no), physical activity (in women: 0-2.9, 3.0-8.9, 9.0-17.9, 18.0-26.9, and ≥27.0 MET-hours/week; in men: <6.5, 6.5-16.7, 16.8-30.1, 30.2-53.3, and ≥53.4 MET-hours/week), endoscopic screening (yes or no), regular use of aspirin/NSAIDs (yes or no), alcohol consumption (<5.0, 5.0-9.9, 10.0-14.9, 15.0-29.9, and ≥30.0 g/day), calcium intake (in quartiles), and AHEI score (in quartiles). In women, postmenopausal status (yes or no) and hormone use (never, current, and past users) were additionally adjusted.  
  
  ‡Further adjusted for body mass index (continuous).  
  
  §RR and 95% CI were corrected for measurement error in anthropometric assessments. |  |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quintile 4</td>
<td>0.84</td>
<td>223</td>
<td>1.03 (0.84-1.27)</td>
<td>0.98 (0.80-1.21)</td>
<td>0.91 (0.74-1.12)</td>
<td>0.02</td>
<td>1.10 (1.02-1.19)</td>
<td>1.17 (1.02-1.34)</td>
<td></td>
</tr>
<tr>
<td>Quintile 5</td>
<td>0.91</td>
<td>280</td>
<td>1.25 (1.03-1.51)</td>
<td>1.17 (0.96-1.42)</td>
<td>1.05 (0.86-1.29)</td>
<td>0.09</td>
<td>1.07 (0.99-1.16)</td>
<td>1.11 (0.96-1.27)</td>
<td></td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quintile 4</td>
<td>0.97</td>
<td>175</td>
<td>1.27 (0.99-1.62)</td>
<td>1.23 (0.96-1.58)</td>
<td>1.14 (0.89-1.47)</td>
<td>&lt;0.001</td>
<td>1.29 (1.13-1.48)</td>
<td>1.51 (1.16-1.96)</td>
<td></td>
</tr>
<tr>
<td>Quintile 5</td>
<td>1.01</td>
<td>199</td>
<td>1.57 (1.23-2.00)</td>
<td>1.50 (1.18-1.92)</td>
<td>1.33 (1.03-1.71)</td>
<td>0.002</td>
<td>1.25 (1.09-1.43)</td>
<td>1.42 (1.10-1.84)</td>
<td></td>
</tr>
</tbody>
</table>

*P for trend*
Figure 2.1 shows the joint association of BMI and waist circumference with risk of CRC. No distinct pattern was detected in women; compared to women with low BMI and low waist circumference, only those high in both measures were at a statistically significantly higher risk of CRC (RR, 1.28; 95% CI, 1.06-1.54). In men, increasing waist circumference was associated with a higher risk of CRC within each BMI group, whereas the association between BMI and CRC risk within each tertile of waist circumference was less striking. The RR was 1.78 (95% CI, 1.40-2.26) comparing men high in BMI and waist circumference to those low in both measures. P for interaction between BMI and waist circumference was 0.74 in women and 0.97 in men.

No statistically significant heterogeneity was detected according to tumor subsite. (Tables S2.1-S2.2)
Figure 2.1 Joint association of BMI and waist circumference with risk of colorectal cancer in women (Nurses’ Health Study, 1988-2010) and men (Health Professionals Follow-up Study, 1990-2010)
Abbreviation: BMI, body mass index.

The multivariable Cox proportion hazards regression models were used, as described in the footnote of Table 2.2.
As shown in Table S2.3, we did not find any statistically significant interaction between body size measures and PMH use, although the positive associations of waist circumference and WHR with CRC risk were restricted to women who never used PMH (P for trend=0.02 and 0.04, respectively). We also classified women jointly according to PMH use and body fat distribution measures (Table S2.4). The risk of CRC was generally low among current users of PMH and did not appreciably change with waist or hip measures, while the highest risk of CRC were found in women who never used PMH and had the highest waist or hip measurements.

During the 10-year period in adulthood, waist circumference, on average, increased 8 cm in women and 3.1 cm in men; hip circumference increased 1.7 cm in women and 1.5 cm in men. Table S2.5 shows the baseline characteristics among participants who lost, maintained or gained waist circumference. Changes in waist circumference were positively correlated with changes in hip circumference, WHR and body weight (r ranged from 0.25 to 0.78; Table S2.6).

Table 2.3 presents the associations with CRC risk for changes in waist circumference, hip circumference and WHR. We did not find any statistically significant association in women. In contrast, gain of waist circumference was associated with an increased CRC risk in men (P for trend=0.03; P for heterogeneity by sex=0.15). Compared to men who maintained their waist circumference, the RR of CRC were 1.59 (95% CI, 1.01-2.49) for those who gained waist circumference ≥10 cm, and 0.76 (95% CI, 0.47-1.21) for those losing waist circumference ≥2 cm.

Hip circumference change was also associated with CRC risk in men (RR per 10-cm gain: 1.34, 95% CI, 0.99-1.81, P for trend=0.06, Table 2.3), whereas no association was found for WHR change (P for trend=0.73). To further examine whether the association for change in body fat distribution is independent of body weight change, we adjusted for weight change during the same period in the multivariable model in men. The association between waist circumference...
change and CRC did not appreciably change (RR per 10-cm gain: 1.38, 95% CI, 0.99-1.92, P for trend=0.06), whereas the association of hip circumference change with CRC risk was attenuated (RR per 10-cm gain: 1.28, 95% CI, 0.91-1.80, P for trend=0.16, data only shown in the text).
### Table 2.3 Risk of colorectal cancer according to 10-year change of waist circumference, hip circumference, and waist-to-hip ratio in women (Nurses’ Health Study, 1998-2010) and men (Health Professionals Follow-up Study, 1998-2010)

<table>
<thead>
<tr>
<th>Category of change</th>
<th>Median</th>
<th>No. of cases</th>
<th>Age-adjusted RR (95% CI)</th>
<th>Multivariable-adjusted RR (95% CI)</th>
<th>Category of change</th>
<th>Median</th>
<th>No. of cases</th>
<th>Age-adjusted RR (95% CI)</th>
<th>Multivariable-adjusted RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Waist change, cm</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss ≥3.0</td>
<td>-5.1</td>
<td>15</td>
<td>0.97 (0.54-1.74)</td>
<td>0.87 (0.48-1.57)</td>
<td>Loss ≥2.0</td>
<td>-4.4</td>
<td>28</td>
<td>0.90 (0.57-1.43)</td>
<td>0.76 (0.47-1.21)</td>
</tr>
<tr>
<td>Loss or gain &lt;3.0</td>
<td>0.6</td>
<td>59</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
<td>Loss or gain &lt;2.0</td>
<td>0.0</td>
<td>58</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Gain 3.0-7.9</td>
<td>5.1</td>
<td>58</td>
<td>0.93 (0.65-1.34)</td>
<td>0.94 (0.65-1.35)</td>
<td>Gain 2.0-4.9</td>
<td>3.2</td>
<td>39</td>
<td>1.00 (0.66-1.50)</td>
<td>1.03 (0.69-1.55)</td>
</tr>
<tr>
<td>Gain 8.0-15.9</td>
<td>11.4</td>
<td>58</td>
<td>1.06 (0.74-1.52)</td>
<td>1.04 (0.72-1.49)</td>
<td>Gain 5.0-9.9</td>
<td>6.4</td>
<td>43</td>
<td>0.95 (0.64-1.41)</td>
<td>0.92 (0.62-1.37)</td>
</tr>
<tr>
<td>Gain ≥16.0</td>
<td>21.6</td>
<td>49</td>
<td>1.22 (0.83-1.80)</td>
<td>1.18 (0.80-1.74)</td>
<td>Gain ≥10.0</td>
<td>12.1</td>
<td>30</td>
<td>1.65 (1.05-2.58)</td>
<td>1.59 (1.01-2.49)</td>
</tr>
<tr>
<td>Per 10-cm gain</td>
<td></td>
<td></td>
<td>1.07 (0.93-1.24)</td>
<td>1.07 (0.93-1.24)</td>
<td>Per 10-cm gain</td>
<td></td>
<td></td>
<td>1.27 (0.97-1.67)</td>
<td>1.34 (1.03-1.74)</td>
</tr>
<tr>
<td><strong>Hip change, cm</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss ≥2.0</td>
<td>-5.1</td>
<td>53</td>
<td>0.97 (0.67-1.40)</td>
<td>0.90 (0.62-1.30)</td>
<td>Loss ≥1.0</td>
<td>-3.2</td>
<td>53</td>
<td>1.13 (0.71-1.80)</td>
<td>1.03 (0.65-1.65)</td>
</tr>
<tr>
<td>Loss or gain &lt;2.0</td>
<td>0.0</td>
<td>62</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
<td>Loss or gain &lt;1.0</td>
<td>0.0</td>
<td>28</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Gain 2.0-3.9</td>
<td>2.5</td>
<td>45</td>
<td>1.37 (0.93-2.00)</td>
<td>1.38 (0.94-2.03)</td>
<td>Gain 1.0-1.9</td>
<td>1.3</td>
<td>22</td>
<td>1.25 (0.72-2.19)</td>
<td>1.29 (0.74-2.25)</td>
</tr>
<tr>
<td>Gain 4.0-7.9</td>
<td>5.1</td>
<td>45</td>
<td>1.11 (0.76-1.63)</td>
<td>1.09 (0.74-1.60)</td>
<td>Gain 2.0-5.9</td>
<td>3.8</td>
<td>62</td>
<td>1.44 (0.92-2.25)</td>
<td>1.43 (0.91-2.24)</td>
</tr>
<tr>
<td>Gain ≥8.0</td>
<td>10.8</td>
<td>33</td>
<td>1.14 (0.73-1.78)</td>
<td>1.10 (0.70-1.72)</td>
<td>Gain ≥6.0</td>
<td>8.3</td>
<td>31</td>
<td>1.40 (0.83-2.36)</td>
<td>1.37 (0.81-2.31)</td>
</tr>
<tr>
<td>Per 10-cm gain</td>
<td></td>
<td></td>
<td>1.11 (0.91-1.36)</td>
<td>1.14 (0.93-1.39)</td>
<td>Per 10-cm gain</td>
<td></td>
<td></td>
<td>1.27 (0.93-1.73)</td>
<td>1.34 (0.99-1.81)</td>
</tr>
<tr>
<td><strong>Waist-to-hip ratio change</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss ≥0.02</td>
<td>-0.04</td>
<td>23</td>
<td>0.86 (0.51-1.45)</td>
<td>0.83 (0.49-1.40)</td>
<td>Loss ≥0.05</td>
<td>-0.07</td>
<td>17</td>
<td>1.09 (0.62-1.90)</td>
<td>0.90 (0.50-1.61)</td>
</tr>
<tr>
<td>Loss or gain &lt;0.02</td>
<td>0.00</td>
<td>49</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
<td>Loss 0.02-0.049</td>
<td>-0.03</td>
<td>31</td>
<td>1.12 (0.72-1.75)</td>
<td>1.06 (0.68-1.66)</td>
</tr>
<tr>
<td>Gain 0.02-0.049</td>
<td>0.03</td>
<td>53</td>
<td>1.15 (0.78-1.70)</td>
<td>1.15 (0.78-1.69)</td>
<td>Loss or gain &lt;0.02</td>
<td>0.00</td>
<td>52</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Gain 0.05-0.09</td>
<td>0.07</td>
<td>44</td>
<td>0.85 (0.56-1.27)</td>
<td>0.84 (0.56-1.26)</td>
<td>Gain 0.02-0.059</td>
<td>0.003</td>
<td>59</td>
<td>1.01 (0.70-1.47)</td>
<td>1.06 (0.73-1.54)</td>
</tr>
<tr>
<td>Gain ≥0.10</td>
<td>0.16</td>
<td>68</td>
<td>1.18 (0.81-1.71)</td>
<td>1.16 (0.80-1.68)</td>
<td>Gain ≥0.06</td>
<td>0.08</td>
<td>37</td>
<td>1.23 (0.80-1.88)</td>
<td>1.32 (0.86-2.03)</td>
</tr>
<tr>
<td>Category of change</td>
<td>Median</td>
<td>No. of cases</td>
<td>Age-adjusted RR (95% CI)*</td>
<td>Multivariable-adjusted RR (95% CI)†</td>
<td>P for trend</td>
<td>Age-adjusted RR (95% CI)*</td>
<td>Multivariable-adjusted RR (95% CI)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------</td>
<td>--------</td>
<td>--------------</td>
<td>----------------------------</td>
<td>-------------------------------------</td>
<td>------------</td>
<td>---------------------------</td>
<td>-------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waist-to-hip ratio change</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P for trend</td>
<td>0.82</td>
<td></td>
<td>0.85</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per 0.1-unit gain</td>
<td>1.02 (0.89-1.16)</td>
<td>1.01 (0.89-1.16)</td>
<td>0.96 (0.81-1.14)</td>
<td>1.03 (0.86-1.24)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RR, relative risk.

*Age-adjusted estimates were calculated from age-stratified Cox proportion hazards regression model.

Multivariable estimates were based on age-adjusted models with additional adjustment for corresponding anthropometric measurements at baseline (continuous), height (continuous), family history of colorectal cancer (yes or no), pack-years of smoking (continuous), multivitamin use (yes or no), physical activity (in quartiles), endoscopic screening (yes or no), regular use of aspirin/NSAIDs (yes or no), alcohol consumption (in quartiles), calcium intake (in quartiles), and AHEI score (in quartiles). In women, postmenopausal status (yes or no) and hormone use (never, current, and past users) were additionally adjusted.
As shown in Figure 2.2, the relationship between waist circumference change and CRC risk appeared to be linear. The association did not appear to differ by baseline waist circumference (P for interaction = 0.79 in women and 0.92 in men; Table S2.7).
Figure 2.2 Ten-year waist circumference change in relation to colorectal cancer in women (A) and men (B)

Abbreviation: CRC, colorectal cancer; RR, relative risk.

Dashed lines represent 95% confidence intervals. Multivariable Cox proportion hazards regression models were used, as described in the footnote of Table 2.3. No statistically significant non-linearity was detected for either of the analyses. The P values for the linear relationship were 0.34 in women and 0.03 in men.
Discussion

In this prospective study over 23 years of follow-up, we found that men with high waist circumference and WHR were at a higher risk of CRC. This finding extends our previous report which was based on only 5 years of follow-up. In line with findings from other studies, we also found that adjusting for BMI attenuated but did not eliminate these associations, suggesting an independent effect on CRC development of abdominal fatness beyond general obesity. At the same time, higher waist circumference was also associated with an increased CRC risk within each BMI group, even among men with BMI of <25kg/m².

Compared to subcutaneous adipose tissue, visceral adipose tissue has been more strongly associated with unfavorable metabolic profiles, including hyperinsulinemia, systemic inflammation, higher leptin level, and lower adiponectin level, all of which have been suggested as potential mechanisms that underlie the association between obesity and CRC. Insulin is an endogenous mitogen and directly increases the risk of tumorigenesis through increased cell proliferation and reduced apoptosis. Hyperinsulinemia also indirectly increases the bioavailability of insulin-like growth factor-1, a key promoter of tumor development. In addition, adipose tissue secretes many signaling proteins and cytokines known as adipokines, which have been implicated in insulin resistance and tumor development.

In contrast to men, the findings in women were less pronounced. The positive association of waist circumference with CRC was attenuated to null after adjusting for BMI. These results are consistent with the notion that obesity poses lesser CRC risk in women than in men. Sex hormones might play a role in the observed sex difference in the strength of the obesity-CRC relationship. Experimental evidence indicates an anti-cancer effect of estrogen through
regulation of gene transcription and modulation of cellular processes involved in colorectal carcinogenesis.\(^{38}\) In postmenopausal women, adipose tissue becomes the primary organ for estrogen production through aromatization of androstenedione to estrone.\(^{39}\) Therefore, it has been hypothesized that a high level of bioavailable estrogen in obese women might counterbalance the detrimental effect of obesity on CRC development.\(^{30}\)

In women, abdominal obesity has been associated with CRC risk in some\(^6,9-13,15\) but not other\(^14,16,17\) studies. In contrast to our results, in the European Prospective Investigation Into Cancer and Nutrition (EPIC) study\(^\text{11}\), a positive association was found between WHR and CRC risk in women even after adjusting for BMI. One possible reason for the discrepant findings might be related to the different composition of premenopausal versus postmenopausal women between the two studies. In our study, over 90% of person-years of follow-up in women were postmenopausal, whereas this figure was approximately 50% in the EPIC study. Obesity has been more consistently associated with CRC risk in premenopausal than postmenopausal women,\(^40,41\) possibly due to the lack of protection from endogenously produced estrogen in adipose tissue prior to menopause. Interestingly, in both the current and EPIC studies,\(^\text{11}\) the positive association of waist circumference and WHR with CRC in postmenopausal women was restricted to those who never used PMH. Given the potential preventive effect of PMH on CRC development,\(^42,43\) it is possible that PMH use mitigates the pro-carcinogenic effect of adiposity in postmenopausal women.

Substantial changes in body composition occur with aging. In particular, lean muscle mass typically peaks in the third to fourth decade of life and then declines steadily with advancing age, whereas fat mass, especially abdominal visceral fat, continuously increases with age.\(^44\) Such changes in the distribution of body weight have been shown to predict the risk of
type 2 diabetes is a high-risk condition for CRC development. However, to our knowledge, no study has yet assessed the potential risk of CRC associated with these changes because of the lack of repeated measurements of waist and hip circumferences over time. In the current study, we showed that in men accumulation of abdominal fat during adulthood, as assessed by increase in waist circumference, was positively related to CRC risk, whereas loss of waist circumference was associated with lower risk of CRC. These associations were independent of changes in body weight. This finding provides further support for the critical role of abdominal adiposity in CRC development in men. In contrast, we did not find any association between change in waist circumference and CRC risk in women. This may either reflect the insignificant impact of obesity on CRC occurrence in women, or be due to the less redistribution of body fat to the abdominal compartment in elderly women compared to men.

We did not find an independent association between change in hip circumference and CRC risk after adjusting for weight change. Because hip circumference not only measures lower-body fatness, but also reflects gluteal muscularity and pelvic width, it is possible that adjustment for weight change explains away the risk of fat accumulation conferred by increased hip girth, while other components captured by hip circumference change have a relatively neutral or even favorable metabolic effect. For WHR change, we did not observe any association with CRC risk, possibly due to the inherent difficulty in interpretation of this composite measure.

Our study has some limitations. First, anthropometric measurements were self-reported or recalled and thus subject to error. However, robust validity has been established in a previous validation study within the two cohorts, and correction for measurement error strengthened the observed associations. Second, only a subset of participants provided repeated data on waist and hip circumference, and thus statistical power was limited for the analysis of change in body fat
distribution. Third, our study participants were all health professionals and thus the findings may not be generalizable to the general population. However, it is unlikely that the observed relationship between body fat distribution and CRC differs substantially from the general population.

This study also has several strengths, including the two large well-established cohorts, long-term follow-up, and detailed lifestyle data. Moreover, repeated measurements of waist and hip circumference provided a unique opportunity to examine the long-term influence of abdominal adiposity and the change of body fat distribution during adulthood on CRC risk.

In conclusion, our results indicate a positive association between abdominal adiposity and risk of CRC. This association appears to be stronger and independent of overall obesity in men compared to women. A potential differential association according to postmenopausal hormone use in women warrants further investigation. Our findings also provide the first prospective evidence that increase in abdominal fatness during adulthood is associated with higher CRC risk in men, thus highlighting the importance of maintaining a healthy waist throughout adulthood for CRC prevention.

References


Supplementary Materials

Covariate assessment

In both the Nurses’ Health Study (NHS) and Health Professionals Follow-up Study (HPFS), we assessed smoking, endoscopic examination, and regular use of multivitamin, aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) on biennial questionnaires. Family history of CRC was ascertained in 1982, 1988, 1992, 1996, and 2000 in the NHS; and in 1986, 1990, 1992, and 1996 in the HPFS. We assessed mainly recreational or leisure-time physical activity using the validated questionnaire in 1980, 1982, 1986, 1988, 1992, and biennially thereafter in the NHS; and every two years in the HPFS. Physical activity was calculated by summing the products of time spent on a variety of activities with the average metabolic equivalent (MET) for that activity. Dietary data were collected using the validated food frequency questionnaires (FFQs) in 1980, 1984, 1986, and every 4 years thereafter in the NHS; and in 1986 and every 4 years thereafter in the HPFS. We assessed menopausal status and PMH use biennially in the NHS, as previously described. To assess the overall dietary pattern, we calculated a summary score ranging from 2.5 (worst) to 87.5 (best) based on individual food intake for each participant according to the Alternate Healthy Eating Index (AHEI), which is designed to target food choices and macronutrient sources associated with reduced chronic disease risk. Adherence to AHEI has been associated with a lower risk of major chronic diseases in the two cohorts.

Statistical analysis

We assessed the proportional hazards assumption by including the product term between time variable and each covariate (including the exposure of interest) into the Cox proportional...
hazards model, and testing the statistical significance of the term by a Wald test. No deviation from proportional hazards assumption was detected at \( \alpha=0.05 \) level.

We tested the sex (i.e., cohort) difference of the associations using the Cochran’s Q statistic. When testing for trend using continuous variables, to reduce the influence of outliers, we employed a 99% Winsorisation technique by setting values below the 0.5th percentile to the 0.5th percentile, and setting values above the 99.5th percentile to the 99.5th percentile. For spline analysis, we used an automatic stepwise procedure to select spline variables according to the \( P = 0.05 \) for both inclusion and retention in the model. We used a likelihood ratio test to determine the significance of the non-linearity by comparing the model with only the linear term to the model with both the linear and the cubic spline terms.

We classified CRC cases according to subsite into proximal colon (cecum, ascending colon, hepatic flexure, transverse colon, and splenic flexure), distal colon (descending colon and sigmoid) and rectal cancers (rectosigmoid and rectum). To examine whether the associations varied by tumor subsite, we fitted subsite-stratified Cox proportional cause-specific hazards regression model using the duplication method. We tested heterogeneity by subsite using a likelihood ratio test, by comparing the model in which the association with exposure was allowed to vary by tumor subsite to the model in which all the associations were held constant.

We assessed the correlation among anthropometric changes within each cohort by Pearson correlation coefficients with adjustment for age. To assess whether the association of waist circumference change with CRC risk differed by baseline measurements, we stratified by baseline waist circumference, and evaluated the interaction between baseline measurements and the measurement change by a Wald test of the product term.
Table S2.1 Risk of colorectal cancer by subsite according to quintiles of waist circumference, hip circumference, and waist-to-hip ratio in women (Nurses’ Health Study, 1988-2010)

<table>
<thead>
<tr>
<th>Waist circumference</th>
<th>Proximal colon cancer</th>
<th>Distal colon cancer</th>
<th>Rectal cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases</td>
<td>Multivariable-adjusted RR (95% CI)*</td>
<td>No. of cases</td>
</tr>
<tr>
<td>Quintile 1</td>
<td>104</td>
<td>1.00 (reference)</td>
<td>47</td>
</tr>
<tr>
<td>Quintile 2</td>
<td>94</td>
<td>0.80 (0.60-1.06)</td>
<td>54</td>
</tr>
<tr>
<td>Quintile 3</td>
<td>114</td>
<td>0.86 (0.65-1.12)</td>
<td>59</td>
</tr>
<tr>
<td>Quintile 4</td>
<td>113</td>
<td>0.80 (0.60-1.05)</td>
<td>69</td>
</tr>
<tr>
<td>Quintile 5</td>
<td>141</td>
<td>1.03 (0.79-1.35)</td>
<td>77</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.15</td>
<td></td>
<td>0.23</td>
</tr>
<tr>
<td>Per 10-cm increase</td>
<td>1.05 (0.98-1.13)</td>
<td></td>
<td>1.06 (0.96-1.17)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hip circumference</th>
<th>Proximal colon cancer</th>
<th>Distal colon cancer</th>
<th>Rectal cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases</td>
<td>Multivariable-adjusted RR (95% CI)*</td>
<td>No. of cases</td>
</tr>
<tr>
<td>Quintile 1</td>
<td>103</td>
<td>1.00 (reference)</td>
<td>47</td>
</tr>
<tr>
<td>Quintile 2</td>
<td>115</td>
<td>1.05 (0.80-1.37)</td>
<td>64</td>
</tr>
<tr>
<td>Quintile 3</td>
<td>129</td>
<td>1.08 (0.83-1.41)</td>
<td>60</td>
</tr>
<tr>
<td>Quintile 4</td>
<td>90</td>
<td>0.84 (0.63-1.12)</td>
<td>66</td>
</tr>
<tr>
<td>Quintile 5</td>
<td>127</td>
<td>1.13 (0.86-1.48)</td>
<td>69</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.11</td>
<td></td>
<td>0.22</td>
</tr>
<tr>
<td>Per 10-cm increase</td>
<td>1.07 (0.98-1.16)</td>
<td></td>
<td>1.07 (0.96-1.20)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Waist-to-hip ratio</th>
<th>Proximal colon cancer</th>
<th>Distal colon cancer</th>
<th>Rectal cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases</td>
<td>Multivariable-adjusted RR (95% CI)*</td>
<td>No. of cases</td>
</tr>
<tr>
<td>Quintile 1</td>
<td>87</td>
<td>1.00 (reference)</td>
<td>42</td>
</tr>
<tr>
<td>Quintile 2</td>
<td>110</td>
<td>1.05 (0.79-1.39)</td>
<td>67</td>
</tr>
<tr>
<td>Quintile 3</td>
<td>115</td>
<td>1.00 (0.76-1.33)</td>
<td>60</td>
</tr>
<tr>
<td>Quintile 4</td>
<td>117</td>
<td>0.94 (0.71-1.25)</td>
<td>55</td>
</tr>
<tr>
<td>Quintile 5</td>
<td>134</td>
<td>1.01 (0.76-1.34)</td>
<td>82</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.84</td>
<td></td>
<td>0.49</td>
</tr>
<tr>
<td>Per 0.1-unit increase</td>
<td>0.99 (0.89-1.10)</td>
<td></td>
<td>1.05 (0.92-1.20)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RR, relative risk.
Multivariable estimates were calculated from Cox proportion hazards regression using age as the underlying time variable and stratified by calendar year of the current questionnaire cycle with additional adjustment for height (continuous), family history of colorectal cancer (yes or no), pack-years of smoking (continuous), multivitamin use (yes or no), physical activity (0-2.9, 3.0-8.9, 9.0-17.9, 18.0-26.9, and ≥27.0 MET-hours/week), endoscopic screening (yes or no), regular use of aspirin/NSAIDs (yes or no), alcohol consumption (<5.0, 5.0-9.9, 10.0-14.9, 15.0-29.9, and ≥30.0 g/day), calcium intake (in quartiles), AHEI score (in quartiles), postmenopausal status (yes or no), and hormone use (never, current, and past users).

\(^b\) \(P_{\text{heterogeneity}}=0.80\) across subsites.

\(^c\) \(P_{\text{heterogeneity}}=0.88\) across subsites.

\(^d\) \(P_{\text{heterogeneity}}=0.35\) across subsites.
<table>
<thead>
<tr>
<th></th>
<th>Proximal colon cancer</th>
<th>Distal colon cancer</th>
<th>Rectal cancer</th>
</tr>
</thead>
</table>
|                      | No. of cases | Multivariable-adjusted RR (95% CI)
|                      |                      |                      |              |
| Waist circumference  |                       |                      |              |
| Quintile 1           | 32 (reference) | 22 (reference) | 25 (reference) |
| Quintile 2           | 36 (0.61-1.61) | 37 (0.93-2.70) | 24 (0.52-1.64) |
| Quintile 3           | 62 (1.05-2.52) | 41 (1.08-3.09) | 35 (0.77-2.24) |
| Quintile 4           | 64 (0.98-2.39) | 66 (1.44-3.93) | 35 (0.64-1.89) |
| Quintile 5           | 74 (1.15-2.81) | 59 (1.35-3.80) | 49 (0.90-2.57) |
| P for trend          | 0.003                | <0.001              | 0.01         |
| Per 10-cm increase   | 1.23 (1.07-1.41) | 1.27 (1.10-1.46) | 1.25 (1.06-1.47) |
| Hip circumference    |                       |                      |              |
| Quintile 1           | 44 (reference) | 34 (reference) | 21 (reference) |
| Quintile 2           | 41 (0.61-1.45) | 36 (0.73-1.90) | 31 (0.93-2.91) |
| Quintile 3           | 57 (0.77-1.73) | 44 (0.78-1.94) | 37 (0.96-2.88) |
| Quintile 4           | 62 (0.95-2.13) | 44 (0.87-2.21) | 29 (0.74-2.39) |
| Quintile 5           | 63 (0.87-2.00) | 67 (1.17-2.84) | 49 (1.14-3.42) |
| P for trend          | 0.08                 | <0.001              | 0.01         |
| Per 10-cm increase   | 1.16 (0.98-1.37) | 1.34 (1.13-1.59) | 1.29 (1.05-1.59) |
| Waist-to-hip ratio   |                       |                      |              |
| Quintile 1           | 28 (reference) | 29 (reference) | 28 (reference) |
| Quintile 2           | 42 (0.81-2.12) | 35 (0.72-1.97) | 30 (0.62-1.78) |
| Quintile 3           | 55 (1.12-2.82) | 61 (1.37-3.40) | 26 (0.54-1.62) |
| Quintile 4           | 66 (1.07-2.66) | 39 (0.62-1.66) | 47 (0.80-2.10) |
| Quintile 5           | 76 (1.28-3.12) | 61 (1.11-2.79) | 36 (0.64-1.78) |
| P for trend          | 0.005               | 0.19                | 0.48         |
| Per 0.1-unit increase| 1.38 (1.10-1.73) | 1.18 (0.92-1.50) | 1.11 (0.83-1.48) |
Abbreviations: CI, confidence interval; RR, relative risk.

*Multivariable models were calculated from Cox proportion hazards regression using age as the underlying time variable and stratified by calendar year of the current questionnaire cycle with additional adjustment for height (continuous), family history of colorectal cancer (yes or no), pack-years of smoking (continuous), multivitamin use (yes or no), physical activity (<6.5, 6.5-16.7, 16.8-30.1, 30.2-53.3, and ≥53.4 MET-hours/week), endoscopic screening (yes or no), regular use of aspirin/NSAIDs (yes or no), alcohol consumption (<5.0, 5.0-9.9, 10.0-14.9, 15.0-29.9, and ≥30.0 g/day), calcium intake (in quartiles), and AHEI score (in quartiles).

^P_{heterogeneity}=0.88 across subsites.

^cP_{heterogeneity}=0.39 across subsites.

^dP_{heterogeneity}=0.49 across subsites.
Table S2.3 Risk of colorectal cancer by use of menopausal hormone therapy according to quartiles of waist circumference, hip circumference, and waist-to-hip ratio in women (Nurses’ Health Study, 1988-2010)\(^a\)

<table>
<thead>
<tr>
<th></th>
<th>Never use</th>
<th>Past use</th>
<th>Current use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases</td>
<td>Multivariable-adjusted RR (95% CI)(^b)</td>
<td>No. of cases</td>
</tr>
<tr>
<td>Waist circumference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quartile 1</td>
<td>73</td>
<td>1.00 (reference)</td>
<td>84</td>
</tr>
<tr>
<td>Quartile 2</td>
<td>85</td>
<td>1.02 (0.74-1.40)</td>
<td>83</td>
</tr>
<tr>
<td>Quartile 3</td>
<td>103</td>
<td>1.03 (0.76-1.41)</td>
<td>100</td>
</tr>
<tr>
<td>Quartile 4</td>
<td>159</td>
<td>1.38 (1.03-1.85)</td>
<td>93</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.02</td>
<td></td>
<td>0.70</td>
</tr>
<tr>
<td>Per 10-cm increase</td>
<td>1.10 (1.02-1.19)</td>
<td></td>
<td>0.98 (0.89-1.08)</td>
</tr>
<tr>
<td>Hip circumference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quartile 1</td>
<td>101</td>
<td>1.00 (reference)</td>
<td>88</td>
</tr>
<tr>
<td>Quartile 2</td>
<td>87</td>
<td>0.88 (0.66-1.18)</td>
<td>79</td>
</tr>
<tr>
<td>Quartile 3</td>
<td>95</td>
<td>0.97 (0.73-1.30)</td>
<td>102</td>
</tr>
<tr>
<td>Quartile 4</td>
<td>137</td>
<td>1.12 (0.85-1.47)</td>
<td>91</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.28</td>
<td></td>
<td>0.56</td>
</tr>
<tr>
<td>Per 10-cm increase</td>
<td>1.05 (0.96-1.15)</td>
<td></td>
<td>1.03 (0.93-1.15)</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quartile 1</td>
<td>60</td>
<td>1.00 (reference)</td>
<td>92</td>
</tr>
<tr>
<td>Quartile 2</td>
<td>93</td>
<td>1.21 (0.87-1.68)</td>
<td>83</td>
</tr>
<tr>
<td>Quartile 3</td>
<td>109</td>
<td>1.23 (0.89-1.70)</td>
<td>76</td>
</tr>
<tr>
<td>Quartile 4</td>
<td>157</td>
<td>1.50 (1.10-2.04)</td>
<td>109</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.04</td>
<td></td>
<td>0.18</td>
</tr>
<tr>
<td>Per 0.1-unit increase</td>
<td>1.13 (1.01-1.26)</td>
<td></td>
<td>0.91 (0.80-1.04)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RR, relative risk.
\(^a\)P for interaction with postmenopausal hormone use: 0.20 for waist circumference, 0.72 for hip circumference, and 0.13 for waist-to-hip ratio.
\(^b\)Multivariable estimates were calculated from Cox proportion hazards regression using age as the underlying time variable and stratified by calendar year of the current questionnaire cycle with additional adjustment for height (continuous), family history of colorectal cancer (yes or no), pack-years of smoking (continuous), multivitamin use (yes or no), physical activity (0-2.9, 3.0-8.9, 9.0-17.9, 18.0-26.9, and ≥27.0 MET-hours/week), endoscopic screening (yes or no),
regular use of aspirin/NSAIDs (yes or no), alcohol consumption (<5.0, 5.0-9.9, 10.0-14.9, 15.0-29.9, and ≥30.0 g/day), calcium intake (in quartiles), and AHEI score (in quartiles).
Table S2.4 Relative risk (95% confidence interval) of colorectal cancer according to joint classification of use of menopausal hormone therapy and quartiles of waist circumference, hip circumference and waist-to-hip ratio in women (Nurses’ Health Study, 1988-2010)

<table>
<thead>
<tr>
<th>Waist circumference</th>
<th>Never use</th>
<th>Past use</th>
<th>Current use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quartile 1</td>
<td>1.00 (reference)</td>
<td>1.12 (0.81-1.54)</td>
<td>0.84 (0.60-1.16)</td>
</tr>
<tr>
<td>Quartile 2</td>
<td>1.04 (0.76-1.42)</td>
<td>0.99 (0.72-1.37)</td>
<td>0.76 (0.54-1.07)</td>
</tr>
<tr>
<td>Quartile 3</td>
<td>1.03 (0.76-1.39)</td>
<td>1.06 (0.78-1.44)</td>
<td>1.05 (0.77-1.44)</td>
</tr>
<tr>
<td>Quartile 4</td>
<td>1.38 (1.04-1.83)</td>
<td>1.00 (0.73-1.36)</td>
<td>0.94 (0.67-1.32)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hip circumference</th>
<th>Never use</th>
<th>Past use</th>
<th>Current use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quartile 1</td>
<td>1.00 (reference)</td>
<td>0.93 (0.70-1.25)</td>
<td>0.66 (0.48-0.90)</td>
</tr>
<tr>
<td>Quartile 2</td>
<td>0.90 (0.67-1.20)</td>
<td>0.82 (0.61-1.11)</td>
<td>0.81 (0.60-1.09)</td>
</tr>
<tr>
<td>Quartile 3</td>
<td>0.99 (0.75-1.32)</td>
<td>1.07 (0.81-1.41)</td>
<td>0.81 (0.60-1.10)</td>
</tr>
<tr>
<td>Quartile 4</td>
<td>1.17 (0.90-1.53)</td>
<td>0.93 (0.70-1.25)</td>
<td>0.98 (0.72-1.32)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Waist-to-hip ratio</th>
<th>Never use</th>
<th>Past use</th>
<th>Current use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quartile 1</td>
<td>1.00 (reference)</td>
<td>1.45 (1.04-2.02)</td>
<td>0.88 (0.62-1.26)</td>
</tr>
<tr>
<td>Quartile 2</td>
<td>1.21 (0.87-1.67)</td>
<td>1.07 (0.76-1.49)</td>
<td>1.13 (0.81-1.57)</td>
</tr>
<tr>
<td>Quartile 3</td>
<td>1.16 (0.84-1.59)</td>
<td>0.89 (0.63-1.25)</td>
<td>0.89 (0.63-1.27)</td>
</tr>
<tr>
<td>Quartile 4</td>
<td>1.43 (1.05-1.93)</td>
<td>1.17 (0.85-1.61)</td>
<td>0.96 (0.68-1.36)</td>
</tr>
</tbody>
</table>

*Multivariable estimates were calculated from Cox proportion hazards regression using age as the underlying time variable and stratified by calendar year of the current questionnaire cycle with additional adjustment for height (continuous), family history of colorectal cancer (yes or no), pack-years of smoking (continuous), multivitamin use (yes or no), physical activity (0-2.9, 3.0-8.9, 9.0-17.9, 18.0-26.9, and ≥27.0 MET-hours/week), endoscopic screening (yes or no), regular use of aspirin/NSAIDs (yes or no), alcohol consumption (<5.0, 5.0-9.9, 10.0-14.9, 15.0-29.9, and ≥30.0 g/day), calcium intake (in quartiles), and AHEI score (in quartiles).
Table S2.5 Age-standardized baseline characteristics of participants according to waist circumference change in women (Nurses’ Health Study) and men (Health Professionals Follow-up Study)\textsuperscript{a}

<table>
<thead>
<tr>
<th>Variable</th>
<th>Women (n=25,069)</th>
<th>Men (n=18,318)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Loss ≥3.0 cm</td>
<td>Loss or gain &lt;3.0 cm</td>
</tr>
<tr>
<td>No. of participants (%)</td>
<td>1,777 (7.1)</td>
<td>6,309 (25.2)</td>
</tr>
<tr>
<td>Age, year</td>
<td>52.6 (7.02)</td>
<td>52.5 (7.0)</td>
</tr>
<tr>
<td>Waist circumference in 1986 or 1987, cm\textsuperscript{b}</td>
<td>85.7 (12.7)</td>
<td>76.9 (10.4)</td>
</tr>
<tr>
<td>Waist circumference in 1996, cm</td>
<td>77.9 (11.6)</td>
<td>77.4 (10.3)</td>
</tr>
<tr>
<td>Waist circumference change, cm</td>
<td>-7.4 (3.9)</td>
<td>0.5 (1.7)</td>
</tr>
<tr>
<td>Height, inch</td>
<td>64.5 (2.4)</td>
<td>64.4 (2.4)</td>
</tr>
<tr>
<td>Body mass index, kg/m\textsuperscript{2}</td>
<td>26.0 (5.0)</td>
<td>23.7 (4.0)</td>
</tr>
<tr>
<td>Physical activity, MET-hours/week</td>
<td>14.0 (19.1)</td>
<td>16.6 (22.0)</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>18.9</td>
<td>15.5</td>
</tr>
<tr>
<td>Family history of colorectal cancer, %</td>
<td>18.0</td>
<td>18.1</td>
</tr>
<tr>
<td>Current multivitamin use, %</td>
<td>41.6</td>
<td>44.1</td>
</tr>
<tr>
<td>Regular use of aspirin/NSAIDs, %\textsuperscript{c}</td>
<td>42.6</td>
<td>40.4</td>
</tr>
<tr>
<td>History of colonoscopy/sigmoidoscopy, %</td>
<td>18.6</td>
<td>19.3</td>
</tr>
<tr>
<td>Postmenopausal, %</td>
<td>66.4</td>
<td>66.2</td>
</tr>
<tr>
<td>Current postmenopausal hormone use, %\textsuperscript{d}</td>
<td>25.2</td>
<td>28.9</td>
</tr>
<tr>
<td>Dietary intake</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol, g/d</td>
<td>6.9 (11.0)</td>
<td>6.5 (9.5)</td>
</tr>
<tr>
<td>Folate, µg/d</td>
<td>383 (189)</td>
<td>393 (185)</td>
</tr>
<tr>
<td>Calcium, mg/d</td>
<td>886 (309)</td>
<td>921 (330)</td>
</tr>
<tr>
<td>Vitamin D, IU/d</td>
<td>324 (207)</td>
<td>335 (200)</td>
</tr>
<tr>
<td>Total fiber, g/d</td>
<td>16.2 (4.5)</td>
<td>16.5 (4.7)</td>
</tr>
<tr>
<td>Total red meat, g/d</td>
<td>90.1 (45.4)</td>
<td>86.2 (44.0)</td>
</tr>
<tr>
<td>AHEI diet score</td>
<td>41.9 (9.1)</td>
<td>43.2 (9.4)</td>
</tr>
</tbody>
</table>

Abbreviations: AHEI, Alternative Healthy Eating Index; MET, metabolic equivalent; NSAID, nonsteroidal anti-inflammatory drug.
\textsuperscript{a}Mean (standard deviation) is presented for continuous variables. All variables are age-standardized except age.
\textsuperscript{b}Assessed in 1986 in women and 1987 in men.
Regular users are defined as ≥2 standard (325-mg) tablets of aspirin or ≥ 2 tablets of NSAIDs per week.

Proportion of current postmenopausal hormone use is calculated among postmenopausal women only.
<table>
<thead>
<tr>
<th></th>
<th>Waist circumference change</th>
<th>Hip circumference change</th>
<th>Waist-to-hip ratio change</th>
<th>Weight change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference change</td>
<td>1</td>
<td>0.25</td>
<td>0.78</td>
<td>0.48</td>
</tr>
<tr>
<td>Hip circumference change</td>
<td>0.47</td>
<td>1</td>
<td>-0.40</td>
<td>0.55</td>
</tr>
<tr>
<td>Waist-to-hip ratio change</td>
<td>0.63</td>
<td>-0.39</td>
<td>1</td>
<td>0.11</td>
</tr>
<tr>
<td>Weight change</td>
<td>0.49</td>
<td>0.40</td>
<td>0.16</td>
<td>1</td>
</tr>
</tbody>
</table>

\*All P values < 0.001.*
### Table S2.7 Risk of colorectal cancer by baseline waist circumference according to 10-year change of waist circumference in women (Nurses’ Health Study, 1998-2010) and men (Health Professionals Follow-up Study, 1998-2010)

<table>
<thead>
<tr>
<th>Category of waist circumference change, cm</th>
<th>Low waist circumference at baseline</th>
<th>High waist circumference at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases</td>
<td>Multivariable-adjusted RR (95% CI)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss ≥3.0</td>
<td>3</td>
<td>0.83 (0.25-2.71)</td>
</tr>
<tr>
<td>Loss or gain &lt;3.0</td>
<td>31</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Gain 3.0-7.9</td>
<td>20</td>
<td>0.64 (0.36-1.12)</td>
</tr>
<tr>
<td>Gain 8.0-15.9</td>
<td>25</td>
<td>1.01 (0.60-1.72)</td>
</tr>
<tr>
<td>Gain ≥16.0</td>
<td>18</td>
<td>0.95 (0.52-1.74)</td>
</tr>
<tr>
<td>P for trend</td>
<td></td>
<td>0.81</td>
</tr>
<tr>
<td>P for interaction&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td>0.79</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss ≥2.0</td>
<td>9</td>
<td>1.28 (0.59-2.77)</td>
</tr>
<tr>
<td>Loss or gain &lt;2.0</td>
<td>23</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Gain 2.0-4.9</td>
<td>22</td>
<td>1.28 (0.71-2.30)</td>
</tr>
<tr>
<td>Gain 5.0-9.9</td>
<td>20</td>
<td>1.08 (0.59-1.98)</td>
</tr>
<tr>
<td>Gain ≥10.0</td>
<td>15</td>
<td>1.96 (1.00-3.82)</td>
</tr>
<tr>
<td>P for trend</td>
<td></td>
<td>0.33</td>
</tr>
<tr>
<td>P for interaction&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td>0.92</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RR, relative risk.

<sup>a</sup>Multivariable estimates were based on age-adjusted Cox models with additional adjustment for waist circumference at baseline (continuous), height (continuous), family history of colorectal cancer (yes or no), pack-years of smoking (continuous), multivitamin use (yes or no), physical activity (in quartiles), endoscopic screening (yes or no), regular use of aspirin/NSAIDs (yes or no), alcohol consumption (in quartiles), calcium intake (in quartiles), and AHEI score (in quartiles). In women, postmenopausal status (yes or no) and hormone use (never, current, and past users) were additionally adjusted.

<sup>b</sup>Wald test was used for the product term between waist circumference change (continuous) and baseline waist circumference (binary).
References


CHAPTER 3. Trajectory of body fatness and cancer risk

Title: Trajectory of body fatness across the lifespan and cancer risk

Authors: Mingyang Song, Walter C. Willett, Frank B. Hu, Donna Spiegelman, Aviva Must, Kana Wu, Andrew T. Chan, Edward L. Giovannucci

Authors’ affiliations:

1Department of Nutrition, Harvard T.H. Chan School of Public Health;
2Department of Epidemiology, Harvard T.H. Chan School of Public Health;
3Channing Division of Network Medicine, Department of Medicine, Harvard Medical School;
4Department of Biostatistics, Harvard T.H. Chan School of Public Health;
5Department of Global Health and Population, Harvard T.H. Chan School of Public Health;
6Department of Public Health and Community Medicine, Tufts University School of Medicine;
7Division of Gastroenterology, Massachusetts General Hospital;
Abstract

Although adulthood obesity has been related to risk of several cancers, the influence of adiposity over life course on cancer risk remains poorly understood.

We used a novel group-based modeling approach to identify distinct subgroups that shared common trajectories of body fatness across the lifespan among 73,581 women from the Nurses’ Health Study and 32,632 men from the Health Professionals Follow-up Study. Participants recalled their body fatness at ages 5, 10, 20, 30, and 40 years using a validated 9-level somatotype. Body mass index at age 50 and 60 years was assessed through questionnaires. After excluding those who had a history of cancer diagnosis before age 60 years, we followed up the remaining participants for a median of approximately 10 years for incidence of total cancer and obesity-related cancer (esophageal adenocarcinoma, and cancers of the colorectum, pancreas, breast [after menopause], endometrium, ovaries, prostate [advanced only], kidney, liver and gallbladder).

We identified 5 distinct adiposity trajectories: lean-stable, lean-moderate increase, lean-marked increase, medium-stable, and heavy-marked increase. Compared with the lean-stable group, trajectories with increased body fatness had a higher risk of total and obesity-related cancer. In women, trajectories of the lean-marked increase and heavy-marked increase were associated with a higher risk of esophageal adenocarcinoma and cancers of the colorectum, pancreas, kidney, and endometrium (relative risk [RR] ranged from 1.36 to 2.56). Postmenopausal breast cancer risk was inversely associated with early-life adiposity, but was positively associated with late-life adiposity. In men, increased body fatness at any life period was associated with a higher risk of esophageal adenocarcinoma and colorectal cancer (RR ranged from 1.23 to 3.01); trajectory of heavy-marked increase was associated with a higher risk
of pancreatic cancer, but lower risk of advanced prostate cancer. The trajectory-cancer associations were generally stronger for non-smokers and women who did not use menopausal hormone therapy.

In conclusion, trajectories of body fatness throughout life were associated with cancer risk and the pattern of association varied by sex and cancer sites. Our findings support a role for lifetime adiposity in carcinogenesis and the clinical significance of long-term trajectories of body fatness in cancer risk assessment.
Introduction

Overweight and obesity have undergone rapid increase in prevalence over the past few decades, and represent major public health problems. In 2013, 42 million children under the age of 5 worldwide were overweight or obese. In 2014, more than 1.9 billion adults, 18 years and older, were overweight, and of these over 600 million were obese. Given that body mass index (BMI) typically increases with age, and obesity during childhood is associated with persistence of obesity into adulthood, a life-course perspective is crucial to better understand health consequences of overweight and obesity, including their influences on cancer development.

According to the systematic reviews by the World Cancer Research Fund (WCRF) and American Institute for Cancer Research (AICR), adulthood obesity has been related with probable or convincing evidence to an increased risk of cancers of the esophagus (adenocarcinoma), colorectum, pancreas, breast (after menopause), endometrium, ovaries, prostate (advanced only), kidney, liver, and gallbladder. Some of the potential mechanisms through which obesity affects cancer development include hyperinsulinemia, excess activation of the insulin-like growth factor (IGF) axis, dysregulated production of sex hormones and adipokines, and chronic low-grade inflammation. Other more organ-specific mechanisms linking obesity to cancer have also been proposed, such as gastroesophageal reflux for esophageal adenocarcinoma, non-alcoholic fatty liver disease for liver cancer, and increased glomerular filtration rate and renal plasma flow for kidney cancer. Despite these compelling data, however, little is known about the relationship between body fatness across the lifespan and cancer risk.
Given the long induction period of carcinogenesis, it is plausible that the effects of adiposity on cancer risk may differ over life course and the critical window during which adiposity influences cancer risk may vary by organ site. There is some evidence suggesting that obesity in childhood or young adulthood is associated with subsequent risk of certain malignancies, including lower risk of breast[15-22] and advanced prostate cancer[25-28] and higher risk of colorectal[29-32] and endometrial cancer[33-38]. However, the findings remain inconclusive[32,35,39-43] and there are little data for other less common cancers. More importantly, these studies examined body fatness or weight change at one or more time points individually, which made it challenging to separate and interpret the association of early adiposity from later weight gain because of their high correlation and the cumulative growth pattern of body weight.

Therefore, in this study, we employed a novel life-course approach to characterize distinct trajectories of body fatness across the entire lifespan. By comparing cancer incidence among these trajectories, our study offers the first prospective evidence on the relationship between lifetime adiposity and risk of total and obesity-related cancer.

Methods

Study population

We used data from two large ongoing U.S. cohort studies, the Nurses’ Health Study (NHS) and Health Professionals Follow-up Study (HPFS). Details about the two studies have been described elsewhere[44,45]. Briefly, the NHS enrolled 121,701 U.S. registered female nurses who were aged 30-55 years in 1976, and the HPFS enrolled 51,529 U.S. male health professionals who were aged 40-75 years in 1986. Follow-up questionnaires were administered
at baseline enrollment and every two years thereafter to collect updated lifestyle and medical information. We also asked participants about their most recent dietary intake using the validated food frequency questionnaires (FFQs) in 1980, 1984, 1986 and every 4 years thereafter in the NHS, and in 1986 and every 4 years thereafter in the HPFS. The follow-up rates of the two cohorts had been 95.4% in the NHS and 95.9% in the HPFS. This investigation was approved by the Institutional Review Board at the Brigham and Women’s Hospital and the Harvard T.H. Chan School of Public Health.

**Assessment of body fatness**

In 1988, participants in both cohorts were requested to recall their body fatness in early and middle life and choose one of 9 pictorial body diagrams (somatotypes) developed by Stunkard et al that best depicted her or his body outline at ages 5, 10, 20, 30, and 40. The validity of this measure of body fatness in early life has been assessed among 181 participants who were aged 71 to 76 years at follow-up within the Third Harvard Growth Study. We compared participants’ recalled body fatness (from somatotypes) with their measured BMI at approximately the same ages. The Pearson correlation coefficients were 0.60 for age 5 years, 0.65 for age 10 years, and 0.66 for age 20 years in women. The corresponding Pearson correlation coefficients in men were 0.36, 0.66, and 0.53, respectively.

In both cohorts, body height and weight were queried at baseline enrollment and updated weight was collected via biennial follow-up questionnaires. We used these data to calculate BMI at age 50 and 60 within each cohort and then converted BMI to the same scale as somatotypes in younger ages. More details about the procedures for rescaling are provided in the

**Supplementary Materials and Table S3.1.**
Outcome ascertainment

In both cohorts, self-reported diagnoses of cancer were obtained on biennial questionnaires, and participants who reported a cancer diagnosis were asked for permission to acquire their medical records and pathologic reports. We identified deaths through the National Death Index and next-of-kin. For cancer deaths, we requested permission from next-of-kin to review medical records. A study physician, blinded to exposure information, reviewed records to confirm cancer diagnosis and to extract relevant information, such as histology, grade, and sublocation. The outcomes of the current study included total cancer and specific cancers that have been related to obesity with probable or convincing evidence by the most recent WCRF/AICR reviews, including cancers of the colorectum, esophagus (adenocarcinoma only), pancreas, kidney, breast (after menopause), endometrium, ovaries, prostate (advanced only), liver, and gallbladder. Because of the small number of cases, liver and gallbladder cancers were not examined individually but only included in the analysis for overall obesity-related cancer. For prostate cancer, we examined advanced cases that were defined as cases with stage T3a or T3b or distant metastases at diagnosis, or death from prostate cancer over follow-up. Lethal prostate cancer was defined as cases with distant metastases at diagnosis or death from prostate cancer over follow-up. In men, we excluded non-advanced prostate cancer from total cancer analysis to avoid the dominance of indolent localized cancer over the results since only advanced prostate cancer was related to obesity by the WCRF/AICR review.

Statistical analysis
We modelled trajectories of body fatness throughout life using somatotype data from age 5 up to 60 years among 84,792 women from the NHS and 37,706 men from the HPFS with somatotype data at 3 or more ages. We used a group-based trajectory modeling approach via SAS Proc Traj to identify subgroups within each cohort that shared a similar underlying trajectory in body fatness. This method represents an application of finite mixture modeling and is designed to identify relatively homogeneous clusters of developmental trajectories within the population. More details on the trajectory modeling process are provided in the Supplementary Materials. Participants were assigned to one of the 5 distinct trajectory groups of body fatness we identified: lean-stable, lean-moderate increase, lean-marked increase, medium-stable, and heavy-marked increase.

Among participants with trajectory group assignment, we excluded those who died or had a history of cancer diagnosis before age 60 years. After exclusion, 73,581 women and 32,632 men were included in the analysis and followed up for cancer incidence. To minimize the influence of reverse causation arising from undiagnosed cancer-induced weight loss, we allowed for a 2-year lag period and thus follow-up time was calculated from age 62 years to the age of cancer diagnosis, death, or the end of the study period (June 1, 2010 for the NHS and January 31, 2010 for the HPFS), whichever came first. We examined the association between trajectory groups of body fatness and cancer risk using a Cox proportional hazards model with age as the time scale. Hazard ratio (as an estimate of relative risk [RR]) and 95% confidence interval (CI) of cancer incidence were estimated by comparing the other trajectories to the “lean-stable” group. We adjusted for several cancer-risk factors in the multivariable model to control for confounding (see the footnotes of Table 3.1). More details about covariate assessment are provided in the Supplementary Materials.
To examine the influence of early-life adiposity on cancer risk, we compared cancer incidence between the two extreme trajectories whose body fatness measurements were similar at age 60 years but substantially different at early ages (i.e., the heavy-marked increase and lean-marked increase groups). We further adjusted for the average adiposity levels from age 40 to 60 years to minimize any difference in late-life body fatness between the two groups. Similarly, for late-life adiposity we compared cancer incidence between the lean-marked increase to the lean-stable groups with further adjustment for the average fatness levels from age 5 to 20 years.

Because smoking is a risk factor for many cancers and also decreases adiposity, we assessed whether the adiposity-cancer relationship was stronger among non-smokers than smokers in a stratified analysis and tested the interaction via a likelihood ratio test by comparing the model with the product terms between smoking and trajectory groups to the model without these terms. Given the prior evidence suggesting that obesity is differentially associated with cancer risk according to use of menopausal hormone therapy (MHT), likely because estrogen is an important factor for some female-related cancers, we also performed the stratified and interaction analysis by MHT use in women.

**Results**

**Figure 3.1** shows the 5 discrete trajectory groups of body fatness from age 5 up to 60 years: 15% women and 16% men maintained a lean body shape across the lifespan (lean-stable group); 22% women and 18% men started lean and then experienced moderate increase in body fatness (lean-moderate increase group); 21% women and 38% men started lean and then experienced marked increase in body fatness (lean-marked increase group); 28% women and 15%
men maintained a medium adiposity level throughout life (medium-stable group); 14% women and 13% men started heavy and then experienced further increase in body fatness (heavy-marked increase group).
Figure 3.1 Trajectories of body fatness by age in women (A) and men (B)
We found distinctive patterns in lifestyle factors among participants across the 5 trajectory groups (Table S3.2). Participants in the lean-stable and medium-stable groups were more likely to exercise, use multivitamins, follow the Alternate Healthy Eating Index, and have colonoscopy or sigmoidoscopy than those in other groups. Women in these two groups also tended to drink alcohol, smoke, and use MHT. In contrast, participants in the lean-marked increase and heavy-marked increase groups had the highest proportion of using aspirin/NSAIDs.

Table 3.1 presents the association between trajectories and cancer risk. In women, compared to those in the lean-stable group, participants in the lean-moderate, lean-marked increase, and heavy-marked groups had an increased risk of total and obesity-related cancer with a RR ranging from 1.06 to 1.39. For individual cancer types, women in the lean-marked increase and heavy-marked increase groups had a higher risk of colorectal, esophageal (adenocarcinoma only), pancreatic, kidney, and endometrial cancer, although the association was not statistically significant for pancreatic cancer and esophageal adenocarcinoma. For postmenopausal breast cancer, an elevated risk was seen in women in the lean-moderate (RR=1.30, 95% CI, 1.17-1.45) and lean-marked increase (RR=1.41, 95% CI, 1.26-1.58) groups. We did not find any association between adiposity trajectories and risk of ovarian cancer.

In men, compared with the lean-stable group, the other 4 groups were at an elevated risk of total and obesity-related cancer. A similar pattern was also observed for colorectal cancer. For esophageal adenocarcinoma, men in the heavy-marked increase group had a 3.01-fold (95% CI, 1.04-9.13) elevated risk compared to the lean-stable group. An increased risk of pancreatic cancer was also seen in the heavy-marked increase group (RR=1.50, 95% CI, 0.92-2.46). In contrast, we found that the risk of advanced prostate cancer was significantly lower in the heavy-
marked increase group than in the lean-stable group (RR=0.67, 95% CI, 0.47-0.95). Similar results were found for lethal prostate cancer. We did not find any association for kidney cancer.

To minimize the influence of reverse causation arising from undiagnosed cancer-induced weight loss, we performed a sensitivity analysis by excluding participants who lost ≥2 kg weight from age 50 to 60 years and the results remained essentially the same (data not shown).
Table 3.1 Relative risk of cancer according to trajectories of body fatness in women (Nurses’ Health Study) and men (Health Professionals Follow-up Study)*

<table>
<thead>
<tr>
<th>Women</th>
<th>Lean-stable</th>
<th>Lean-moderate increase</th>
<th>Lean-marked increase</th>
<th>Medium-stable</th>
<th>Heavy-marked increase</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases (N=11,462)</td>
<td>1,893</td>
<td>2,632</td>
<td>2,345</td>
<td>3,175</td>
<td>1,417</td>
</tr>
<tr>
<td>Incidence rate&lt;sup&gt;b&lt;/sup&gt;</td>
<td>88.8</td>
<td>97.3</td>
<td>106.7</td>
<td>93.5</td>
<td>107.7</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>1.00 (reference)</td>
<td>1.06 (1.00-1.13)</td>
<td>1.16 (1.09-1.24)</td>
<td>1.04 (0.98-1.10)</td>
<td>1.15 (1.07-1.23)</td>
</tr>
<tr>
<td><strong>Obesity-related cancer&lt;sup&gt;c&lt;/sup&gt;</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases (N=6,400)</td>
<td>1,001</td>
<td>1,530</td>
<td>1,434</td>
<td>1,628</td>
<td>807</td>
</tr>
<tr>
<td>Incidence rate&lt;sup&gt;b&lt;/sup&gt;</td>
<td>53.0</td>
<td>59.2</td>
<td>67.6</td>
<td>52.5</td>
<td>63.2</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>1.00 (reference)</td>
<td>1.17 (1.08-1.30)</td>
<td>1.39 (1.27-1.50)</td>
<td>1.03 (0.95-1.12)</td>
<td>1.28 (1.17-1.41)</td>
</tr>
<tr>
<td><strong>Colorectal cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases (N=1,131)</td>
<td>191</td>
<td>250</td>
<td>233</td>
<td>299</td>
<td>158</td>
</tr>
<tr>
<td>Incidence rate&lt;sup&gt;b&lt;/sup&gt;</td>
<td>9.7</td>
<td>9.2</td>
<td>10.4</td>
<td>9.2</td>
<td>11.9</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>1.00 (reference)</td>
<td>0.97 (0.80-1.17)</td>
<td>1.22 (1.00-1.49)</td>
<td>1.02 (0.85-1.22)</td>
<td>1.40 (1.13-1.74)</td>
</tr>
<tr>
<td><strong>Esophageal adenocarcinoma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases (N=38)</td>
<td>4</td>
<td>6</td>
<td>13</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Incidence rate&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.2</td>
<td>0.2</td>
<td>0.6</td>
<td>0.2</td>
<td>0.6</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>1.00 (reference)</td>
<td>1.02 (0.29-3.63)</td>
<td>2.56 (0.82-8.03)</td>
<td>1.04 (0.30-3.57)</td>
<td>2.19 (0.63-7.70)</td>
</tr>
<tr>
<td><strong>Pancreatic cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases (N=324)</td>
<td>49</td>
<td>76</td>
<td>69</td>
<td>88</td>
<td>42</td>
</tr>
<tr>
<td>Incidence rate&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2.6</td>
<td>2.9</td>
<td>3.2</td>
<td>2.8</td>
<td>3.3</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>1.00 (reference)</td>
<td>1.18 (0.82-1.69)</td>
<td>1.36 (0.93-1.98)</td>
<td>1.15 (0.81-1.63)</td>
<td>1.39 (0.91-2.12)</td>
</tr>
<tr>
<td><strong>Kidney cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases (N=212)</td>
<td>27</td>
<td>46</td>
<td>57</td>
<td>46</td>
<td>36</td>
</tr>
<tr>
<td>Incidence rate&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.4</td>
<td>1.8</td>
<td>2.7</td>
<td>1.5</td>
<td>2.8</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>1.00 (reference)</td>
<td>1.26 (0.78-2.04)</td>
<td>1.89 (1.19-3.03)</td>
<td>1.05 (0.65-1.69)</td>
<td>1.92 (1.15-3.21)</td>
</tr>
<tr>
<td><strong>Postmenopausal breast cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases (N=3,454)</td>
<td>536</td>
<td>898</td>
<td>767</td>
<td>887</td>
<td>366</td>
</tr>
<tr>
<td>Incidence rate&lt;sup&gt;b&lt;/sup&gt;</td>
<td>29.0</td>
<td>35.9</td>
<td>37.1</td>
<td>29.7</td>
<td>29.4</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>1.00 (reference)</td>
<td>1.30 (1.17-1.45)</td>
<td>1.41 (1.26-1.58)</td>
<td>1.05 (0.94-1.17)</td>
<td>1.11 (0.97-1.28)</td>
</tr>
<tr>
<td><strong>Endometrial cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases (N=664)</td>
<td>95</td>
<td>125</td>
<td>167</td>
<td>144</td>
<td>133</td>
</tr>
<tr>
<td>Incidence rate&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5.0</td>
<td>4.83</td>
<td>7.8</td>
<td>4.7</td>
<td>10.5</td>
</tr>
<tr>
<td>Condition</td>
<td>No. of cases (N)</td>
<td>Incidence rate</td>
<td>RR (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>-----------------</td>
<td>----------------</td>
<td>-------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ovarian cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases (N=476)</td>
<td>92</td>
<td>4.8</td>
<td>1.00 (reference)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence rate</td>
<td>107</td>
<td>4.1</td>
<td>0.99 (0.75-1.29)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>95</td>
<td>4.4</td>
<td>1.57 (1.21-2.03)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>130</td>
<td>3.3</td>
<td>0.94 (0.73-1.22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>52</td>
<td>4.1</td>
<td>2.08 (1.59-2.73)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases (N=4,976)</td>
<td>751</td>
<td>108.4</td>
<td>1.00 (reference)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence rate</td>
<td>1,078</td>
<td>118.5</td>
<td>1.06 (0.96-1.16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>1,889</td>
<td>115.9</td>
<td>1.07 (0.98-1.16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>706</td>
<td>110.5</td>
<td>1.04 (0.94-1.15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>552</td>
<td>123.3</td>
<td>1.22 (1.09-1.36)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Obesity-related cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases (N=1,832)</td>
<td>267</td>
<td>33.8</td>
<td>1.00 (reference)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence rate</td>
<td>431</td>
<td>42.4</td>
<td>1.17 (1.00-1.37)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>689</td>
<td>37.4</td>
<td>1.09 (0.95-1.26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>262</td>
<td>37.0</td>
<td>1.13 (0.95-1.34)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>183</td>
<td>35.0</td>
<td>1.17 (0.97-1.42)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Colorectal cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases (N=592)</td>
<td>79</td>
<td>10.1</td>
<td>1.00 (reference)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence rate</td>
<td>141</td>
<td>14.2</td>
<td>1.36 (1.03-1.80)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>222</td>
<td>12.3</td>
<td>1.23 (0.95-1.60)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>85</td>
<td>11.9</td>
<td>1.26 (0.92-1.72)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>65</td>
<td>13.0</td>
<td>1.47 (1.05-2.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Esophageal adenocarcinoma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases (N=60)</td>
<td>5</td>
<td>0.7</td>
<td>1.00 (reference)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence rate</td>
<td>13</td>
<td>1.3</td>
<td>1.90 (0.67-5.34)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>25</td>
<td>1.4</td>
<td>2.09 (0.80-5.48)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>1.0</td>
<td>1.53 (0.48-4.84)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>2.1</td>
<td>3.01 (1.04-9.13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pancreatic cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases (N=231)</td>
<td>34</td>
<td>4.5</td>
<td>1.00 (reference)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence rate</td>
<td>39</td>
<td>4.0</td>
<td>0.85 (0.54-1.35)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>94</td>
<td>5.4</td>
<td>1.20 (0.81-1.78)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>34</td>
<td>4.9</td>
<td>1.12 (0.70-1.80)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>6.2</td>
<td>1.50 (0.92-2.46)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Kidney cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases (N=202)</td>
<td>33</td>
<td>4.4</td>
<td>1.00 (reference)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence rate</td>
<td>46</td>
<td>4.7</td>
<td>1.05 (0.67-1.64)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>72</td>
<td>4.1</td>
<td>0.94 (0.63-1.43)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>32</td>
<td>4.6</td>
<td>1.07 (0.66-1.74)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>3.9</td>
<td>0.93 (0.53-1.64)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Advanced prostate cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases (N=694)</td>
<td>112</td>
<td>14.6</td>
<td>1.00 (reference)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence rate</td>
<td>182</td>
<td>18.1</td>
<td>1.16 (0.91-1.47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>259</td>
<td>14.4</td>
<td>0.97 (0.78-1.21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>96</td>
<td>13.9</td>
<td>1.00 (0.76-1.32)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>8.8</td>
<td>0.67 (0.47-0.95)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RR, relative risk.
Follow-up started at age of 62 years old. RRss were estimated from Cox proportional hazards model with adjustment for height (continuous), race (non-white or white), pack-years of smoking (women: 0, 1-5, 6-20, or >20; men: 0, 1-4, 5-25, 26-45, or >45), family history of cancer (yes or no), history of lower gastrointestinal endoscopy (yes or no; for analysis of total cancer and colorectal cancer), multivitamin use (yes or no), regular aspirin/NSAID use (yes or no), history of physical exam (yes and for screening, yes and for symptoms, or no), mammography (women only: yes and for screening, yes and for symptoms, or no; for total cancer and breast cancer), prostate-specific antigen test (men only: yes or no), menopausal hormone therapy (women only: past use, current use, or no), physical activity (in quintiles), alcohol consumption (women: 0-0.49, 0.5-1.9, 2.0-7.9, or ≥8.0 g/d; men: 0-5.0, 5.0-9.9, 10.0-14.9, 15.0-29.9, or ≥30.0 g/d), and AHEI dietary score (in quintiles).

Incidence rate per 100,000 person-years.

Including cancers of the colorectum, esophagus (adenocarcinoma only), pancreas, kidney, breast (postmenopause), endometrium, ovaries, liver, and gallbladder.

Excluding non-advanced prostate cancer.

Including cancers of the colorectum, esophagus (adenocarcinoma only), pancreas, kidney, prostate (advanced cancer only), liver, and gallbladder.

Advanced prostate cancer defined as stage T3a or T3b at diagnosis, distant metastases at diagnosis or death from prostate cancer over follow-up.
Next, to further investigate the timing effect of adiposity on cancer risk, we compared the extreme trajectory groups whose body fatness measurements were similar at either early or late life but substantially different at the other end of life. As shown in Figure 3.2A, compared to the lean-marked increase group, the heavy-marked increase group had a significantly lower risk of total and obesity-related cancer, suggesting a protective effect of early-life adiposity on cancer development. This inverse association appeared to be driven by postmenopausal breast cancer, for which a RR of 0.80 (95% CI, 0.70-0.92) was detected. In contrast, as reflected by the elevated risk in the lean-marked increase group compared to the lean-stable group, late-life adiposity was positively associated with the risk of total and obesity-related cancer, especially esophageal adenocarcinoma and cancers of the kidney, endometrium, breast, pancreas and colorectum. The RR ranged from 1.25 to 3.80.

In men (Figure 3.2B), early-life adiposity was inversely associated with the risk of advanced prostate cancer (RR=0.64, 95% CI, 0.45-0.92); whereas body fatness in late life was positively associated with risk of obesity-related cancer, especially esophageal adenocarcinoma and cancers of the pancreas and colorectum, although the association did not achieve statistical significance.
Figure 3.2 Relative risk and 95% confidence interval of cancer according to early-life (●) and late-life (○) body fatness in women (A) and men (B)

(A)
For early-life body fatness, we compared risks in the heavy-marked increase to lean-marked increase groups in multivariable model (see footnote of Table 3.1) with further adjustment for average body diagram from ages of 40 to 60 years. Similarly, for late-life body fatness, we compared risks in the lean-marked increase to lean-stable groups with further adjustment for average body diagram from ages of 5 to 20 years. *For total cancer in men, we excluded non-advanced prostate cancer.
We then examined whether smoking modified the trajectory-cancer association. As shown in Table 3.2, adiposity trajectories tended to be more strongly associated with cancer risk among never smokers than among ever smokers, with a statistically significant interaction for total cancer in women and for pancreatic cancer in men (P for interaction=0.005 and 0.03, respectively).
Table 3.2 Relative risk of cancer by smoking history according to trajectories of body fatness in women (Nurses’ Health Study) and men (Health Professionals Follow-up Study)\textsuperscript{a}

<table>
<thead>
<tr>
<th></th>
<th>Lean-stable</th>
<th>Lean-moderate increase</th>
<th>Lean-marked increase</th>
<th>Medium-stable</th>
<th>Heavy-marked increase</th>
<th>P for interaction\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever smokers (N=7,082)</td>
<td>1.00 (reference)</td>
<td>0.99 (0.92-1.07)</td>
<td>1.07 (0.99-1.16)</td>
<td>1.00 (0.93-1.07)</td>
<td>1.00 (0.92-1.10)</td>
<td>0.005</td>
</tr>
<tr>
<td>Never smokers (N=4,380)</td>
<td>1.00 (reference)</td>
<td>1.22 (1.10-1.34)\textsuperscript{c}</td>
<td>1.35 (1.22-1.50)</td>
<td>1.14 (1.03-1.26)</td>
<td>1.46 (1.30-1.64)\textsuperscript{c}</td>
<td></td>
</tr>
<tr>
<td><strong>Obesity-related cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever smokers (N=3,591)</td>
<td>1.00 (reference)</td>
<td>1.14 (1.03-1.27)</td>
<td>1.33 (1.19-1.48)</td>
<td>0.97 (0.88-1.08)</td>
<td>1.15 (1.02-1.31)</td>
<td>0.08</td>
</tr>
<tr>
<td>Never smokers (N=2,809)</td>
<td>1.00 (reference)</td>
<td>1.23 (1.08-1.39)</td>
<td>1.48 (1.30-1.68)</td>
<td>1.12 (0.99-1.27)</td>
<td>1.50 (1.30-1.74)\textsuperscript{d}</td>
<td></td>
</tr>
<tr>
<td><strong>Colorectal cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever smokers (N=675)</td>
<td>1.00 (reference)</td>
<td>0.97 (0.76-1.23)</td>
<td>1.25 (0.97-1.61)</td>
<td>0.97 (0.77-1.22)</td>
<td>1.26 (0.95-1.67)</td>
<td>0.54</td>
</tr>
<tr>
<td>Never smokers (N=456)</td>
<td>1.00 (reference)</td>
<td>0.98 (0.72-1.33)</td>
<td>1.20 (0.87-1.65)</td>
<td>1.11 (0.82-1.51)</td>
<td>1.68 (1.19-2.37)</td>
<td></td>
</tr>
<tr>
<td><strong>Pancreatic cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever smokers (N=179)</td>
<td>1.00 (reference)</td>
<td>1.09 (0.67-1.78)</td>
<td>1.60 (0.98-2.61)</td>
<td>1.09 (0.69-1.73)</td>
<td>1.11 (0.61-2.00)</td>
<td>0.25</td>
</tr>
<tr>
<td>Never smokers (N=145)</td>
<td>1.00 (reference)</td>
<td>1.31 (0.76-2.26)</td>
<td>1.13 (0.63-2.05)</td>
<td>1.25 (0.72-2.15)</td>
<td>1.84 (1.00-3.40)</td>
<td></td>
</tr>
<tr>
<td><strong>Kidney cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever smokers (N=120)</td>
<td>1.00 (reference)</td>
<td>1.20 (0.65-2.22)</td>
<td>1.78 (0.97-3.27)</td>
<td>1.03 (0.57-1.88)</td>
<td>1.59 (0.81-3.14)</td>
<td>0.85</td>
</tr>
<tr>
<td>Never smokers (N=92)</td>
<td>1.00 (reference)</td>
<td>1.41 (0.66-3.03)</td>
<td>2.17 (1.03-4.56)</td>
<td>1.10 (0.50-2.41)</td>
<td>2.57 (1.16-5.66)</td>
<td></td>
</tr>
<tr>
<td><strong>Postmenopausal breast cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever smokers (N=1,951)</td>
<td>1.00 (reference)</td>
<td>1.21 (1.05-1.39)</td>
<td>1.30 (1.12-1.51)</td>
<td>0.94 (0.81-1.07)</td>
<td>0.99 (0.83-1.18)</td>
<td>0.10</td>
</tr>
<tr>
<td>Never smokers (N=1,503)</td>
<td>1.00 (reference)</td>
<td>1.47 (1.24-1.75)</td>
<td>1.60 (1.34-1.92)\textsuperscript{c}</td>
<td>1.25 (1.05-1.49)\textsuperscript{d}</td>
<td>1.33 (1.08-1.65)\textsuperscript{c}</td>
<td></td>
</tr>
<tr>
<td><strong>Endometrial cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever smokers (N=324)</td>
<td>1.00 (reference)</td>
<td>1.17 (0.79-1.72)</td>
<td>1.62 (1.10-2.39)</td>
<td>1.15 (0.79-1.66)</td>
<td>2.25 (1.51-3.34)</td>
<td>0.48</td>
</tr>
<tr>
<td>Never smokers (N=340)</td>
<td>1.00 (reference)</td>
<td>0.84 (0.58-1.22)</td>
<td>1.50 (1.06-2.13)</td>
<td>0.77 (0.53-1.11)</td>
<td>1.97 (1.36-2.86)</td>
<td></td>
</tr>
<tr>
<td><strong>Ovarian cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever smoking (N=271)</td>
<td>1.00 (reference)</td>
<td>0.86 (0.59-1.25)</td>
<td>0.81 (0.54-1.22)</td>
<td>0.95 (0.68-1.34)</td>
<td>0.83 (0.52-1.31)</td>
<td>0.50</td>
</tr>
<tr>
<td>Never smoking (N=205)</td>
<td>1.00 (reference)</td>
<td>0.91 (0.59-1.39)</td>
<td>1.06 (0.69-1.63)</td>
<td>0.76 (0.49-1.18)</td>
<td>0.86 (0.50-1.47)</td>
<td></td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever smokers (N=3,235)</td>
<td>1.00 (reference)</td>
<td>0.96 (0.85-1.08)</td>
<td>1.03 (0.93-1.15)</td>
<td>0.98 (0.86-1.11)</td>
<td>1.17 (1.02-1.34)</td>
<td>0.11</td>
</tr>
<tr>
<td>Never smokers (N=1,741)</td>
<td>1.00 (reference)</td>
<td>1.20 (1.03-1.40)\textsuperscript{c}</td>
<td>1.09 (0.94-1.25)</td>
<td>1.13 (0.95-1.34)</td>
<td>1.16 (0.96-1.41)</td>
<td></td>
</tr>
<tr>
<td><strong>Obesity-related cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever smokers (N=1,125)</td>
<td>1.00 (reference)</td>
<td>1.04 (0.86-1.27)</td>
<td>1.07 (0.89-1.28)</td>
<td>0.99 (0.79-1.23)</td>
<td>1.05 (0.82-1.34)</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>Lean-stable</td>
<td>Lean-moderate increase</td>
<td>Lean-marked increase</td>
<td>Medium-stable</td>
<td>Heavy-marked increase</td>
<td>P for interaction</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>-------------</td>
<td>------------------------</td>
<td>----------------------</td>
<td>---------------</td>
<td>-----------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td><strong>Never smokers (N=707)</strong></td>
<td>1.00 (ref.)</td>
<td>1.40 (1.10-1.79)c</td>
<td>1.12 (0.88-1.41)</td>
<td>1.38 (1.05-1.82)c</td>
<td>1.38 (1.01-1.88)</td>
<td></td>
</tr>
<tr>
<td><strong>Colorectal cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever smokers (N=359)</td>
<td>1.00 (ref.)</td>
<td>1.25 (0.87-1.79)</td>
<td>1.21 (0.86-1.69)</td>
<td>1.08 (0.72-1.64)</td>
<td>1.55 (1.02-2.35)</td>
<td>0.55</td>
</tr>
<tr>
<td>Never smokers (N=233)</td>
<td>1.00 (ref.)</td>
<td>1.51 (0.98-2.35)</td>
<td>1.26 (0.83-1.91)</td>
<td>1.57 (0.97-2.53)</td>
<td>1.33 (0.76-2.34)</td>
<td></td>
</tr>
<tr>
<td><strong>Pancreatic cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever smokers (N=148)</td>
<td>1.00 (ref.)</td>
<td>0.62 (0.34-1.12)</td>
<td>1.18 (0.73-1.89)</td>
<td>0.97 (0.54-1.74)</td>
<td>0.90 (0.46-1.75)</td>
<td>0.03</td>
</tr>
<tr>
<td>Never smokers (N=83)</td>
<td>1.00 (ref.)</td>
<td>1.27 (0.60-2.70)</td>
<td>1.04 (0.51-2.10)</td>
<td>1.34 (0.59-3.05)</td>
<td>2.68 (1.24-5.80)c</td>
<td></td>
</tr>
<tr>
<td><strong>Kidney cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever smokers (N=130)</td>
<td>1.00 (ref.)</td>
<td>1.04 (0.60-1.80)</td>
<td>0.83 (0.49-1.40)</td>
<td>0.81 (0.43-1.55)</td>
<td>1.01 (0.52-1.95)</td>
<td>0.26</td>
</tr>
<tr>
<td>Never smokers (N=72)</td>
<td>1.00 (ref.)</td>
<td>0.93 (0.43-2.03)</td>
<td>1.08 (0.54-2.13)</td>
<td>1.53 (0.71-3.26)</td>
<td>0.46 (0.13-1.64)</td>
<td></td>
</tr>
<tr>
<td><strong>Advanced prostate cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever smokers (N=398)</td>
<td>1.00 (ref.)</td>
<td>1.00 (0.73-1.37)</td>
<td>0.93 (0.69-1.24)</td>
<td>0.93 (0.65-1.32)</td>
<td>0.49 (0.30-0.81)</td>
<td>0.18</td>
</tr>
<tr>
<td>Never smokers (N=296)</td>
<td>1.00 (ref.)</td>
<td>1.40 (0.97-2.03)</td>
<td>1.03 (0.72-1.47)</td>
<td>1.13 (0.73-1.74)</td>
<td>1.04 (0.63-1.73)c</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RR, relative risk.

aFollow-up started at age of 62 years old. RRs were estimated from Cox proportional hazards model with adjustment for the same set of covariates as in Table 3.1.

bGlobal likelihood ratio test with 4 degrees of freedom was used to compare the model with the product terms of smoking (never or ever) and trajectory groups to the model without these terms.

cP for interaction≤0.05, >0.01 by individual Wald test.

dP for interaction≤0.01, >0.001 by individual Wald test.

eP for interaction≤0.001, >0.0001 by individual Wald test.

fIncluding cancers of the colorectum, esophagus (adenocarcinoma only), pancreas, kidney, breast (postmenopause), endometrium, ovaries, liver, and gallbladder.

gExcluding non-advanced prostate cancer.

hIncluding cancers of the colorectum, esophagus (adenocarcinoma only), pancreas, kidney, prostate (advanced cancer only), liver, and gallbladder.

iAdvanced prostate cancer defined as stage T3a or T3b at diagnosis, distant metastases at diagnosis or death from prostate cancer over follow-up.
Finally, we examined the trajectory-cancer association according to MHT use in women (Table 3.3). The increased risk associated with trajectories of the lean-moderate, lean-marked increase and heavy-marked increase was more pronounced among never MHT users than among ever users for all cancers under study except ovarian cancer. The P for interaction was <0.001 for total and obesity-related cancer as well as endometrial cancer. Interestingly, for ovarian cancer, we found a statistically significant lower risk in the medium-stable group among never, but not ever users of MHT (P for interaction=0.008).
<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Group</th>
<th>Lean-stable</th>
<th>Lean-moderate increase</th>
<th>Lean-marked increase</th>
<th>Medium-stable</th>
<th>Heavy-marked increase</th>
<th>P for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total cancer</strong></td>
<td>Ever used MHT (N=6,834)</td>
<td>1.00 (ref)</td>
<td>1.03 (0.96-1.12)</td>
<td>1.10 (1.02-1.20)</td>
<td>1.04 (0.97-1.12)</td>
<td>1.06 (0.97-1.17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Never used MHT (N=4,594)</td>
<td>1.00 (ref)</td>
<td>1.12 (1.02-1.23)</td>
<td>1.26 (1.14-1.39)</td>
<td>1.04 (0.94-1.14)</td>
<td>1.27 (1.14-1.42)</td>
<td></td>
</tr>
<tr>
<td><strong>Obesity-related cancer</strong></td>
<td>Ever used MHT (N=3,776)</td>
<td>1.00 (ref)</td>
<td>1.10 (0.99-1.21)</td>
<td>1.25 (1.12-1.39)</td>
<td>1.01 (0.92-1.12)</td>
<td>1.12 (0.98-1.27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Never used MHT (N=2,606)</td>
<td>1.00 (ref)</td>
<td>1.32 (1.15-1.51)</td>
<td>1.64 (1.43-1.87)</td>
<td>1.07 (0.93-1.23)</td>
<td>1.57 (1.35-1.82)</td>
<td></td>
</tr>
<tr>
<td><strong>Colorectal cancer</strong></td>
<td>Ever used MHT (N=572)</td>
<td>1.00 (ref)</td>
<td>0.95 (0.73-1.24)</td>
<td>1.14 (0.86-1.51)</td>
<td>1.00 (0.78-1.28)</td>
<td>1.45 (1.07-1.97)</td>
<td>0.92</td>
</tr>
<tr>
<td></td>
<td>Never used MHT (N=556)</td>
<td>1.00 (ref)</td>
<td>0.97 (0.73-1.29)</td>
<td>1.30 (0.98-1.72)</td>
<td>1.03 (0.78-1.35)</td>
<td>1.36 (0.99-1.85)</td>
<td></td>
</tr>
<tr>
<td><strong>Pancreatic cancer</strong></td>
<td>Ever used MHT (N=196)</td>
<td>1.00 (ref)</td>
<td>1.06 (0.68-1.65)</td>
<td>1.11 (0.69-1.78)</td>
<td>0.97 (0.63-1.49)</td>
<td>1.23 (0.72-2.09)</td>
<td>0.79</td>
</tr>
<tr>
<td></td>
<td>Never used MHT (N=127)</td>
<td>1.00 (ref)</td>
<td>1.43 (0.75-2.72)</td>
<td>1.85 (0.97-3.51)</td>
<td>1.54 (0.83-2.86)</td>
<td>1.76 (0.87-3.59)</td>
<td></td>
</tr>
<tr>
<td><strong>Kidney cancer</strong></td>
<td>Ever used MHT (N=117)</td>
<td>1.00 (ref)</td>
<td>0.92 (0.50-1.69)</td>
<td>1.77 (0.99-3.16)</td>
<td>0.91 (0.51-1.61)</td>
<td>1.53 (0.78-3.00)</td>
<td>0.36</td>
</tr>
<tr>
<td></td>
<td>Never used MHT (N=94)</td>
<td>1.00 (ref)</td>
<td>2.20 (0.95-5.13)</td>
<td>2.38 (1.02-5.55)</td>
<td>1.48 (0.62-3.54)</td>
<td>2.96 (1.24-7.10)</td>
<td></td>
</tr>
<tr>
<td><strong>Postmenopausal breast cancer</strong></td>
<td>Ever used MHT (N=2,137)</td>
<td>1.00 (ref)</td>
<td>1.25 (1.10-1.43)</td>
<td>1.33 (1.15-1.54)</td>
<td>1.04 (0.91-1.18)</td>
<td>0.98 (0.82-1.17)</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>Never used MHT (N=1,307)</td>
<td>1.00 (ref)</td>
<td>1.41 (1.17-1.70)</td>
<td>1.58 (1.31-1.91)</td>
<td>1.09 (0.90-1.32)</td>
<td>1.36 (1.09-1.68)</td>
<td></td>
</tr>
<tr>
<td><strong>Endometrial cancer</strong></td>
<td>Ever used MHT (N=390)</td>
<td>1.00 (ref)</td>
<td>0.77 (0.56-1.06)</td>
<td>0.93 (0.66-1.29)</td>
<td>0.87 (0.65-1.17)</td>
<td>1.41 (1.00-1.99)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Never used MHT (N=273)</td>
<td>1.00 (ref)</td>
<td>2.19 (1.23-3.90)</td>
<td>4.50 (2.59-7.79)</td>
<td>1.42 (0.78-2.59)</td>
<td>5.25 (2.99-9.23)</td>
<td></td>
</tr>
<tr>
<td><strong>Ovarian cancer</strong></td>
<td>Ever used MHT (N=297)</td>
<td>1.00 (ref)</td>
<td>0.84 (0.58-1.21)</td>
<td>0.91 (0.62-1.35)</td>
<td>1.11 (0.80-1.53)</td>
<td>0.85 (0.53-1.35)</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td>Never used MHT (N=178)</td>
<td>1.00 (ref)</td>
<td>0.91 (0.58-1.41)</td>
<td>0.92 (0.58-1.45)</td>
<td>0.49 (0.30-0.80)</td>
<td>0.79 (0.46-1.34)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RR, relative risk.

a Follow-up started at age of 62 years old. RRs were estimated from Cox proportional hazards model with adjustment for the same set of covariates as in Table 3.1.

b Global likelihood ratio test with 4 degrees of freedom was used to compare the model with the product terms of MHT use (never or ever) and trajectory groups to the model without these terms.

c P for interaction ≤0.05, >0.01 by individual Wald test.
\(^d\)P for interaction ≤ 0.01, > 0.001 by individual Wald test.

\(^e\)P for interaction ≤ 0.001, > 0.0001 by individual Wald test.

\(^f\)P for interaction ≤ 0.0001 by individual Wald test.

\(^g\)Including cancers of the colorectum, esophagus (adenocarcinoma only), pancreas, kidney, breast (postmenopause), endometrium, ovaries, liver, and gallbladder.
Discussion

In the two large cohort studies, we identified 5 heterogeneous subgroups of participants with similar body fatness evolution over age using a group-based trajectory modeling approach. By comparing cancer risk among these subgroups, we found that compared to participants who were lean throughout life, those with increased body fatness at any life period had an overall higher risk of developing cancer. When individual cancer types were examined, we found distinct patterns of association between trajectory groups and cancer risk depending on sex and the organ where cancer arose. Our findings extend the knowledge about obesity and cancer and support a role of adiposity across the lifespan in carcinogenesis.

Building upon the substantial data on adulthood adiposity, some studies have related adiposity in early life to subsequent cancer risk. The most compelling evidence is on breast cancer which demonstrates a dual relationship with adiposity: while recent obesity and adulthood weight gain have been associated with an increased risk of postmenopausal breast cancer, high body fatness in childhood or adolescence has been related to a lower risk. This is consistent with our results that women in the lean-moderate increase and lean-marked increase groups had the highest risk of developing postmenopausal breast cancer. The observation that women who were heavy in early life and gained more weight in later life did not experience an increased risk is probably due to the opposing effects of early obesity and subsequent weight gain on breast cancer incidence. While high levels of adipose tissue-derived estrogen after menopause has been suggested as the predominant mediator for the increased risk of breast cancer associated with current obesity, the mechanism for potential protective effect of early adiposity remains speculative. Several explanations have been proposed, including excess adipose tissue-induced
slower pubertal growth, earlier differentiation of mammary gland cells, and greater frequency of irregular menstrual cycles and ovulatory infertility in adulthood, although the last theory has not been supported by more recent data. Further mechanistic investigation is needed to resolve this perplexing link between adiposity and breast cancer.

Early-life adiposity has also been assessed for risk of endometrial cancer. In most studies, the positive association between early-life adiposity and endometrial cancer risk disappeared after concurrently adjusting for current BMI, suggesting a predominant importance of cumulative fatness. This is in accordance with our results that women with significant body fatness increase since early adulthood had a higher risk, regardless of their adiposity in childhood or adolescent. For colorectal cancer, a stronger and more consistent positive association with obesity, including that in adolescence or early adulthood, has been reported in men than in women, possibly as a result of obesity-related change in sex hormones. In this study, we found that in women only the lean-marked increase and heavy-marked increase groups were at a higher risk of colorectal cancer, while in men those who exhibited elevated adiposity in any life period had a higher risk, indicating a more pronounced influence of body fatness across the lifespan on colorectal cancer in men compared to women.

Obesity has also been associated with an increased risk of esophageal adenocarcinoma and kidney and pancreatic cancer. However, the timing effect of adiposity has yet to be determined. In this study, we found a substantially increased risk of esophageal adenocarcinoma in relation to late-life adiposity, but little evidence for early-life adiposity. For kidney cancer, some studies but not all have noted a stronger positive association with obesity in women than in men. Consistent with this notion, we found that adiposity trajectories were only associated with kidney cancer in women, but not in men; and this association appeared to be
driven by late-life adiposity. For pancreatic cancer, we found a positive association with a marked increase in body fatness since early adulthood in both men and women, suggesting a more proximate effect of adiposity on promotion of pancreatic carcinogenesis.

For prostate cancer, despite the conflicting data, greater body fatness at diagnosis has been recognized as a probable cause of advanced prostate cancer according to the most recent WCRF/AICR review. In contrast, obesity earlier in life (age 10-30) has been inversely associated with adulthood risk in some studies, especially for advanced and lethal prostate cancer, possibly due to delayed puberty and prostate maturation, although the evidence remains inconclusive. In the current study, we found that men who were lean in early life and experienced moderate increase in body fatness were at a suggestively higher risk of advanced and lethal prostate cancer; whereas men who were heavy throughout life had a lower risk. When the timing of adiposity was examined, early-life adiposity was associated with a lower risk of advanced and lethal prostate cancer, while no association was found for late-life adiposity. Our results indicate a predominant benefit of early-life body fatness over a potential adverse effect of adiposity in later life, and provide the first line of evidence on the association of lifelong obesity with prostate cancer.

In agreement with the notion that smoking may dampen the obesity-cancer association, we found that trajectories were more strongly associated with cancer risk among never smokers. In particular, given the substantial influence of smoking on pancreatic cancer, we found that the positive association between lifelong obesity and pancreatic cancer risk in men was restricted to never smokers. MHT use in women has also been suggested to modify cancer risk associated with obesity. In the current study, we observed a stronger association of adiposity trajectories with risk of total and obesity-related cancer, especially endometrial cancer, among never users of
MHT compared to ever users. This is consistent with previous evidence that MHT use attenuates the association between obesity and endometrial cancer likely due to the central role of unopposed estrogen therapy in endometrial cancer that overwhelms the effect of adipose tissue-derived estrogen. Interestingly, we found that among never users of MHT, medium-stable trajectory was associated with a significantly lower risk of ovarian cancer. Previous studies did not find strong evidence that MHT use modifies the obesity-ovarian cancer association. Therefore, our results should be interpreted with caution, especially considering the limited number of cases in each stratum and similar associations for other trajectories between users and nonusers.

Our study has several strengths. First, we applied an innovative statistical method to examine patterns of body fatness across the entire lifespan in two large, well-established cohort studies, which represents a substantial advantage over previous studies that examined body fatness at select ages. This method has only recently been employed in chronic disease epidemiology. For example, a trajectory assessment of blood pressure across adulthood provided additional information for future risk for cardiovascular disease. Second, the high follow-up rate of the cohorts with ascertainment for cancer outcomes over 24-34 years provided us a unique opportunity to systematically investigate the association of adiposity with cancer risk in a longitudinal framework. Third, we collected detailed data on a range of lifestyle and health-related factors that allowed us to control for confounding and to examine the potential modification by smoking and MHT use.

Some limitations of the study need to be noted. First, we grouped participants into certain trajectories that may not accurately reflect each individual’s profile of body fatness. However, good performance of our model indicates that the identified trajectories can summarize the
distinctive features of lifetime adiposity in a parsimonious fashion without significant loss of information. Second, recalled body fatness by somatotypes in early life is subject to measurement error. However, our validation study has shown that the recalled data can provide a reasonable estimate. Third, although the homogeneity of our study population is a potential limitation, it minimizes the likelihood of uncontrolled confounding; given that our prior associations of overall adiposity and cancer risk have been largely validated in other populations, it is unlikely that the observed relationship between body fatness and cancer risk differs substantially from the general population. Nonetheless, our findings should be confirmed in other populations.

In conclusion, we identified several heterogeneous subgroups of body fatness trajectories over life course and found distinct patterns of associations with cancer risk across these subgroups. While early-life adiposity was inversely associated with risk of postmenopausal breast cancer, and advanced and lethal prostate cancer, late-life adiposity was positively associated with risk of esophageal adenocarcinoma and cancers of the breast, endometrium, colorectum, pancreas, and kidney (in women only). Our results extend the knowledge that obesity is related to risk of several cancer types and suggest an influence of adiposity across the lifespan on carcinogenesis.
References


Supplementary Materials

Rescaling of BMI at age 50 and 60 years

To reduce the effect of random error, we assessed the average BMI from ages of 47 to 53 years as the BMI at age of 50 years, and average BMI from ages 57 to 63 years as the BMI at age of 60 years. We then divided BMI at these two ages into 9 categories, consistent with the grouping of somatotypes (ranging from 1 to 9) at younger ages. The cutoff points for each category were calculated as the mean BMI of this category at age of 40 years plus a constant to account for weight gain from age 40 to 50 or 60 years. For example, in women the mean BMIs at age 40 years for the 4th and 5th category of somatotypes were 23.3 and 26.1 kg/m², respectively, and the mean increment of BMI from age 40 to 50 years was 1.5 kg/m². Therefore, the lower cutoff of BMI for the 5th category of somatotypes at age 50 years would be 23.3+1.5=24.8 kg/m² and the upper cutoff would be 26.1+1.5=27.6 kg/m². Similar categorizations were conducted for other categories as well as in men. The BMI cutoffs used to derive somatotype categories at ages of 50 and 60 years for both cohorts were summarized in Table S3.1.

Covariate assessment

In the baseline and biennial follow-up questionnaires, we inquired about potential risk factors for cancer, including family history of cancer, smoking, colonoscopy/sigmoidoscopy examination, physical activity, multivitamin use, and use of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs). Physical activity was calculated by summing the products of time spent on a variety of recreational or leisure-time activities with the average metabolic equivalent (MET) for that activity except that in 1980 in the NHS a simple questionnaire was
used to inquire regular physical activity without collecting detailed information on specific activities and durations. In women, we additionally assessed physical and mammographic examination, menopausal status, and use of menopausal hormone therapy (MHT) in the questionnaires. Prostate-specific antigen test was queried biennially in men. Through administration of the FFQs, we calculated alcohol consumption and a summary dietary score, the Alternate Healthy Eating Index (AHEI), to represent the overall dietary pattern based on individual food intake. AHEI is designed to target food choices and macronutrient sources associated with reduced chronic disease risk. Adherence to AHEI has been associated with a lower risk of major chronic diseases in the two cohorts.

Statistical analysis

Trajectory modeling

In contrast to traditional methods for analyzing developmental trajectories such as hierarchical modeling and latent growth curve modeling that are designed to describe how patterns of growth vary continuously throughout the population, the group-based trajectory modeling strategy provides a flexible and easily applied approach to identify distinctive clusters of individual trajectories within the population. It fits longitudinal data as a discrete mixture of two or more latent trajectories via maximum likelihood using SAS Proc Traj. In this study, we used a censored normal model as a polynomial function of the time scale (i.e., age). The optimal number of groups and shapes of trajectories were selected for best fit to the data using a two-stage approach, as assessed by change in the Bayesian Information Criterion (BIC). The first stage was to determine the number of groups using a quadratic form for all trajectory groups.
Given the data we had, we considered up to 5 groups and compared the BIC to that with 4, 3, 2, and 1, respectively. Once we had identified that the model with 5 groups fit best, we then determined in the second stage the order of the polynomial function specifying the shape of each trajectory. We compared the BIC of the 5-group models with different functional forms and found that the model with all groups with up to cubic order terms demonstrated the best fit to the data. Therefore, estimation of body fatness trajectory throughout life was carried out in the final model using a cubic function of age for each of the 5 trajectories. We then named the trajectory groups to describe their visual patterns (i.e., lean-stable, lean-moderate increase, lean-marked increase, medium-stable, and heavy-marked increase).

From the final model, we calculated the posterior predicted probability for each individual of being a member of each of the 5 trajectories. Participants were assigned into the trajectory group to which their posterior membership probability was largest. We then assessed the adequacy of our final model by calculating the average posterior probability of assignment for each group. Using ≥0.70 as the recommended criteria, our model demonstrated good discrimination in classifying individuals into distinctive trajectory groups: the average posterior probability for each trajectory group was 0.92, 0.86, 0.90, 0.95, and 0.92 in women; and 0.85, 0.92, 0.88, 0.84, and 0.90 in men, respectively. We also calculated the odds of correct classification (OCC), which is the ratio of the odds of correct classification on the basis of the maximum probability classification rule to the odds of correct classification based on random assignment. The OCC for each trajectory group was 100.4, 43.1, 21.4, 23.2, and 66.4 in women; and 28.0, 51.3, 12.5, 29.0, and 55.7 in men, respectively. Using OCC>5.0 for all groups as the recommended criteria, our model had high assignment accuracy.
Association analysis

We assessed the proportional hazards assumption by including the product term between age and each covariate (including trajectory groups) to the multivariable model and then tested the statistical significance of the product term via a likelihood ratio test. No deviation from proportional hazards assumption was detected at $\alpha=0.05$ level.
<table>
<thead>
<tr>
<th>Category</th>
<th>Women</th>
<th></th>
<th></th>
<th>Men</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BMI range at age 50 years, kg/m^2</td>
<td>BMI range at age 60 years, kg/m^2</td>
<td>BMI range at age 50 years, kg/m^2</td>
<td>BMI range at age 60 years, kg/m^2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>≤20.9</td>
<td>≤22.1</td>
<td>≤21.1</td>
<td>≤21.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>&gt;20.9, ≤21.6</td>
<td>&gt;22.1, ≤22.8</td>
<td>&gt;21.1, ≤22.4</td>
<td>&gt;21.4, ≤22.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>&gt;21.6, ≤23.0</td>
<td>&gt;22.8, ≤24.2</td>
<td>&gt;22.4, ≤23.4</td>
<td>&gt;22.7, ≤23.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>&gt;23.0, ≤24.8</td>
<td>&gt;24.2, ≤26.0</td>
<td>&gt;23.4, ≤24.6</td>
<td>&gt;23.7, ≤24.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>&gt;24.8, ≤27.6</td>
<td>&gt;26.0, ≤28.8</td>
<td>&gt;24.6, ≤26.3</td>
<td>&gt;24.9, ≤26.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>&gt;27.6, ≤31.1</td>
<td>&gt;28.8, ≤32.3</td>
<td>&gt;26.3, ≤28.7</td>
<td>&gt;26.6, ≤29.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>&gt;31.0, ≤35.1</td>
<td>&gt;32.3, ≤36.3</td>
<td>&gt;28.7, ≤32.1</td>
<td>&gt;29.0, ≤32.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>&gt;35.1, ≤38.4</td>
<td>&gt;36.3, ≤39.6</td>
<td>&gt;32.1, ≤36.0</td>
<td>&gt;32.4, ≤36.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>&gt;38.4</td>
<td>&gt;39.6</td>
<td>&gt;36.0</td>
<td>&gt;36.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index.
Table S3.2  Basic characteristics of study participants at age 60 years according to trajectories of body fatness in women (Nurses’ Health Study) and men (Health Professionals Follow-up Study)*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lean-stable</th>
<th>Lean-moderate increase</th>
<th>Lean-marked increase</th>
<th>Medium-stable</th>
<th>Heavy-marked increase</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of participants</td>
<td>13,183</td>
<td>18,405</td>
<td>18,217</td>
<td>23,288</td>
<td>11,699</td>
</tr>
<tr>
<td>Body diagram at age 5 years</td>
<td>1.7 (0.9)</td>
<td>1.0 (0.1)</td>
<td>1.7 (0.8)</td>
<td>3.0 (1.2)</td>
<td>4.0 (1.2)</td>
</tr>
<tr>
<td>Body diagram at age 10 years</td>
<td>1.9 (1.0)</td>
<td>1.1 (0.3)</td>
<td>2.1 (0.9)</td>
<td>3.3 (1.2)</td>
<td>4.5 (1.1)</td>
</tr>
<tr>
<td>Body diagram at age 20 years</td>
<td>2.3 (0.9)</td>
<td>1.8 (0.7)</td>
<td>2.9 (0.8)</td>
<td>3.2 (1.0)</td>
<td>4.4 (1.0)</td>
</tr>
<tr>
<td>Body diagram at age 30 years</td>
<td>2.5 (0.8)</td>
<td>2.5 (0.8)</td>
<td>3.6 (0.8)</td>
<td>3.3 (0.8)</td>
<td>5.0 (1.0)</td>
</tr>
<tr>
<td>Body diagram at age 40 years</td>
<td>2.7 (0.8)</td>
<td>3.2 (0.8)</td>
<td>4.5 (0.9)</td>
<td>3.7 (0.8)</td>
<td>5.7 (1.1)</td>
</tr>
<tr>
<td>BMI at age 50 years, kg/m$^2$</td>
<td>20.3 (1.3)</td>
<td>23.8 (2.1)</td>
<td>28.8 (3.6)</td>
<td>23.3 (1.8)</td>
<td>31.7 (5.3)</td>
</tr>
<tr>
<td>BMI at age 60 years, kg/m$^2$</td>
<td>20.5 (1.2)</td>
<td>25.3 (2.3)</td>
<td>30.7 (3.9)</td>
<td>24.3 (2.0)</td>
<td>33.0 (5.6)</td>
</tr>
<tr>
<td>Height, inch</td>
<td>64.7 (2.5)</td>
<td>64.5 (2.5)</td>
<td>64.3 (2.5)</td>
<td>64.5 (2.4)</td>
<td>64.5 (2.4)</td>
</tr>
<tr>
<td>Physical activity, METs-hours/week b</td>
<td>20.4 (21.6)</td>
<td>16.4 (17.6)</td>
<td>13.6 (15.3)</td>
<td>18.1 (18.5)</td>
<td>12.8 (13.6)</td>
</tr>
<tr>
<td>Alcohol consumption, g/d b</td>
<td>7.6 (10.4)</td>
<td>6.1 (9.1)</td>
<td>4.5 (8.0)</td>
<td>7.2 (10.0)</td>
<td>4.3 (7.9)</td>
</tr>
<tr>
<td>Pack-years of smoking b</td>
<td>14.5 (20.8)</td>
<td>13.1 (19.3)</td>
<td>12.5 (19.3)</td>
<td>15.0 (20.5)</td>
<td>14.7 (20.9)</td>
</tr>
<tr>
<td>Alternative Healthy Eating Index b</td>
<td>45.4 (9.4)</td>
<td>43.8 (8.7)</td>
<td>43.3 (8.3)</td>
<td>45.5 (8.9)</td>
<td>43.7 (8.5)</td>
</tr>
<tr>
<td>Family history of cancer, %</td>
<td>58</td>
<td>60</td>
<td>59</td>
<td>59</td>
<td>58</td>
</tr>
<tr>
<td>Multivitamin use, %</td>
<td>56</td>
<td>52</td>
<td>51</td>
<td>54</td>
<td>52</td>
</tr>
<tr>
<td>Regular aspirin/NSAID use, % c</td>
<td>43</td>
<td>48</td>
<td>56</td>
<td>49</td>
<td>60</td>
</tr>
<tr>
<td>Current use of menopausal hormone therapy, %</td>
<td>39</td>
<td>34</td>
<td>28</td>
<td>37</td>
<td>27</td>
</tr>
<tr>
<td>History of colonoscopy/sigmoidoscopy within the past 2 years, % d</td>
<td>45</td>
<td>44</td>
<td>44</td>
<td>46</td>
<td>42</td>
</tr>
<tr>
<td>History of physical exam within the past 2 years, % d</td>
<td>92</td>
<td>92</td>
<td>93</td>
<td>92</td>
<td>94</td>
</tr>
<tr>
<td>History of mammography within the past 2 years, % d</td>
<td>82</td>
<td>83</td>
<td>82</td>
<td>84</td>
<td>81</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of participants</td>
<td>5,946</td>
<td>6,881</td>
<td>14,225</td>
<td>5,725</td>
<td>4,929</td>
</tr>
<tr>
<td>Body diagram at age 5 years</td>
<td>2.1 (0.9)</td>
<td>1.0 (0.1)</td>
<td>1.8 (0.8)</td>
<td>4.2 (1.1)</td>
<td>4.7 (1.3)</td>
</tr>
</tbody>
</table>

*Numbers may not sum to totals due to missing values.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Lean-stable</th>
<th>Lean-moderate increase</th>
<th>Lean-marked increase</th>
<th>Medium-stable</th>
<th>Heavy-marked increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body diagram at age 10 years</td>
<td>2.3 (0.7)</td>
<td>1.0 (0.1)</td>
<td>2.3 (0.8)</td>
<td>4.5 (1.1)</td>
<td>5.2 (1.1)</td>
</tr>
<tr>
<td>Body diagram at age 20 years</td>
<td>2.6 (0.7)</td>
<td>1.8 (0.7)</td>
<td>3.2 (0.8)</td>
<td>4.0 (0.9)</td>
<td>4.9 (1.0)</td>
</tr>
<tr>
<td>Body diagram at age 30 years</td>
<td>3.0 (0.8)</td>
<td>2.7 (0.9)</td>
<td>4.1 (0.9)</td>
<td>4.3 (0.8)</td>
<td>5.3 (0.9)</td>
</tr>
<tr>
<td>Body diagram at age 40 years</td>
<td>3.3 (0.8)</td>
<td>3.5 (1.0)</td>
<td>4.7 (0.8)</td>
<td>4.4 (0.8)</td>
<td>5.7 (0.9)</td>
</tr>
<tr>
<td>BMI at age 50 years, kg/m²</td>
<td>22.3 (1.4)</td>
<td>24.1 (2.1)</td>
<td>26.9 (2.5)</td>
<td>24.2 (1.5)</td>
<td>29.5 (3.2)</td>
</tr>
<tr>
<td>BMI at age 60 years, kg/m²</td>
<td>22.6 (1.5)</td>
<td>24.8 (2.1)</td>
<td>27.7 (2.7)</td>
<td>24.5 (1.7)</td>
<td>30.1 (3.5)</td>
</tr>
<tr>
<td>Height, inch</td>
<td>70.2 (2.7)</td>
<td>70.3 (2.7)</td>
<td>70.1 (2.6)</td>
<td>70.1 (2.5)</td>
<td>70.0 (2.7)</td>
</tr>
<tr>
<td>Physical activity, METs-hours/week b</td>
<td>29.4 (30.2)</td>
<td>26.3 (25.7)</td>
<td>26.0 (27.6)</td>
<td>31.5 (30.3)</td>
<td>25.2 (26.2)</td>
</tr>
<tr>
<td>Alcohol consumption, g/d b</td>
<td>11.2 (14.5)</td>
<td>11.7 (14.2)</td>
<td>11.8 (15.1)</td>
<td>11.8 (15.0)</td>
<td>10.8 (14.5)</td>
</tr>
<tr>
<td>Pack-years of smoking b b</td>
<td>12.0 (18.9)</td>
<td>14.0 (19.2)</td>
<td>14.8 (20.0)</td>
<td>14.2 (19.8)</td>
<td>17.4 (22.6)</td>
</tr>
<tr>
<td>Alternative Healthy Eating Index b</td>
<td>42.8 (10.2)</td>
<td>41.4 (9.5)</td>
<td>40.6 (9.3)</td>
<td>43.0 (9.7)</td>
<td>41.5 (9.5)</td>
</tr>
<tr>
<td>Family history of cancer, %</td>
<td>37</td>
<td>37</td>
<td>36</td>
<td>37</td>
<td>36</td>
</tr>
<tr>
<td>Multivitamin use, %</td>
<td>51</td>
<td>48</td>
<td>48</td>
<td>51</td>
<td>47</td>
</tr>
<tr>
<td>Regular aspirin/NSAID use, % c</td>
<td>43</td>
<td>49</td>
<td>51</td>
<td>49</td>
<td>55</td>
</tr>
<tr>
<td>History of colonoscopy/sigmoidoscopy within the past 2 years, % d</td>
<td>51</td>
<td>49</td>
<td>50</td>
<td>53</td>
<td>51</td>
</tr>
<tr>
<td>History of physical exam within the past 2 years, % d</td>
<td>83</td>
<td>84</td>
<td>85</td>
<td>84</td>
<td>85</td>
</tr>
<tr>
<td>History of Prostate-Specific Antigen test within the past 2 years, % d</td>
<td>39</td>
<td>37</td>
<td>38</td>
<td>38</td>
<td>37</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; CI, confidence interval; MET, metabolic equivalent of task; NSAID, nonsteroidal anti-inflammatory drug.

*a* All variables are standardized by age at baseline (1976 for the Nurses’ Health Study and 1986 for the Health Professionals Follow-up Study).

*b* Cumulative average measurements from baseline up to age of 60 years.

*c* Regular users are defined as ≥2 standard (325-mg) tablets of aspirin or ≥2 tablets of NSAIDs per week.

*d* Information on these variables was carried forward if an individual ever underwent these tests/examinations during the past two years over follow-up.
References


Concluding Remarks

Obesity and cancer are two major public health problems in the world. Accumulating evidence has indicated a link between the two entities. The work presented here provides further evidence for the importance of obesity in cancer risk.

In Chapter 1, I and my colleagues found that weight gain from early adulthood to baseline was associated with an increased risk of CRC, whereas weight loss was associated with a lower risk. Weight change from baseline to present was not associated with CRC risk. Four-year weight change during follow-up was positively associated with CRC risk in men but not in women. In addition, in women, weight change before, but not after, menopause was associated with CRC risk. Our findings provide further scientific rationale for recommendations to maintain a healthy body weight during adulthood. A potential differential association according to sex and timing of weight change warrants further investigation.

In Chapter 2, I and my colleagues found that high waist circumference, hip circumference and waist-to-hip ratio were all associated with a higher risk of CRC in men, even after adjusting for body mass index. The associations were weaker in women. Ten-year gain of waist circumference was positively associated with colorectal cancer risk in men, but not in women. The association between change in waist circumference and CRC risk were independent of weight change. Our findings provide further support for a positive association between abdominal adiposity and CRC development, thus highlighting the importance of maintaining a healthy waist for colorectal cancer prevention in adults.

In Chapter 2, using a novel group-based modeling approach, I and my colleagues identified five distinct adiposity trajectories across the lifespan. In women, trajectories of the lean-marked increase and heavy-marked increase were associated with a higher risk of
esophageal adenocarcinoma and cancers of the colorectum, pancreas, kidney, and endometrium. Postmenopausal breast cancer risk was inversely associated with early-life adiposity, but was positively associated with late-life adiposity. In men, increased body fatness at any life period was associated with a higher risk of esophageal adenocarcinoma and colorectal cancer; trajectory of heavy-marked increase was associated with a higher risk of pancreatic cancer, but lower risk of advanced prostate cancer. The trajectory-cancer associations were generally stronger for non-smokers and women who did not use menopausal hormone therapy. Our findings provide the first prospective evidence for a role of lifetime adiposity in carcinogenesis and suggest clinical significance of long-term trajectories of body fatness for cancer risk assessment.