Obesity and colon and rectal cancer risk: a meta-analysis of prospective studies1–3

Susanna C Larsson and Alicja Wolk

ABSTRACT

Background: Whereas obesity has been associated with an increased risk of colon cancer in men, a weak or no association has been observed in women. Results for rectal cancer have also been inconsistent.

Objective: The objective was to perform a meta-analysis to summarize the available evidence from prospective studies on the associations of overall and abdominal obesity with the risk of colon and rectal cancer.

Design: We searched MEDLINE (1966–April 2007) and the reference lists of pertinent articles to search for more studies. Study-specific relative risks (RRs) were pooled by using a random-effects model.

Results: Thirty prospective studies were included in the meta-analysis of body mass index (BMI; in kg/m²). Overall, a 5-unit increase in BMI was related to an increased risk of colorectal cancer in both men (RR: 1.30; 95% CI: 1.25, 1.35) and women (RR: 1.12; 95% CI: 1.07, 1.18), but the association was stronger in men (P < 0.001). BMI was positively associated with rectal cancer in men (RR: 1.12; 95% CI: 1.09, 1.16) but not in women (RR: 1.03; 95% CI: 0.99, 1.08). The difference in RRs between cancer sites was statistically significant (P < 0.001 in men and P = 0.04 in women). Colon cancer risk increased with increasing waist circumference (per 10-cm increase) in both men (RR: 1.33; 95% CI: 1.19, 1.49) and women (RR: 1.16; 95% CI: 1.09, 1.23) and with increasing waist-hip ratio (per 0.1-unit increase) in both men (RR: 1.43; 95% CI: 1.19, 1.71) and women (RR: 1.20; 95% CI: 1.08, 1.33).


KEY WORDS Body mass index, colorectal cancer, meta-analysis, obesity, prospective studies

INTRODUCTION

Colorectal cancer is the third most common cancer worldwide (1). Incidence rates vary by 25-fold between countries, with the highest rates observed in North America, Australia, and Western Europe and the lowest rates in Africa and Asia (1). Nutritional-related factors are considered to play a major role in colorectal cancer development (2). A mounting body of evidence indicates that insulin resistance and resulting hyperinsulinemia may be responsible for many of the associations of nutritional factors with colorectal cancer risk and for the high incidence of this malignancy in Westernized countries (3, 4). Obesity, especially abdominal obesity, is related to insulin resistance and hyperinsulinemia (5, 6). Although body mass index (BMI), as a measure of overall obesity, is positively associated with the risk of colon cancer in men, a weaker or no association has been observed in women (6). Findings for rectal cancer have also been inconsistent. We therefore undertook a meta-analysis of prospective studies to quantitatively assess the relations between BMI and the risk of colon and rectal cancer in men and women. In addition, we conducted a meta-analysis to summarize the prospective data relating waist circumference and waist-hip ratio, indicators of abdominal adiposity, to colon and rectal cancer risk.

METHODS

Literature search

We searched MEDLINE (US National Library of Medicine, National Institutes of Health, Bethesda, MD) for studies published in any language from 1966 to April 2007 using the search terms obesity, body mass index, or BMI combined with colorectal cancer, colon cancer, or rectal cancer. The search was restricted to studies of human participants. We also reviewed the reference lists of pertinent articles to search for more studies.

Inclusion criteria

To be included in this meta-analysis, studies had to have a prospective study design; contain data on colon or rectal cancer incidence or mortality or both; report relative risks (RRs) with corresponding 95% CIs for ≥3 categories of exposure (BMI, waist circumference, or waist-hip ratio); or provide an RR per unit increase in exposure. We did not include studies that only reported estimates that combined colon and rectal cancer or men and women. When there were multiple published reports from the same study population, we included the one that had the longest follow-up.

Data extraction

We extracted the following information from each study: first author’s last name, year of publication, country where the study was conducted, and study population characteristics. We also recorded the outcome variables, exposure variables, and methods used for data analysis. We used a random-effects model to pool study-specific relative risks (RRs) and corresponding 95% confidence intervals (CIs) for overall and abdominal obesity.

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was performed, sample size, age range of the participants at baseline, assessment of anthropometric measures (self-reported compared with measured), duration of follow-up, covariates adjusted for in the analysis, and RRs with corresponding 95% CIs for every exposure category or per unit increase in exposure. From each study, we extracted the RR estimates that reflected the greatest degree of adjustment for potential confounders.

Statistical analysis

The cutoffs for the lowest and highest exposure categories varied between studies included in this meta-analysis. Therefore, to place studies on a common scale, we calculated, for each study, the RR per unit increase in the anthropometric measures: a 5-unit increase for BMI, a 10-cm increase for waist circumference, and a 0.1-unit increase for waist-to-hip ratio. This was done by relating the natural log of RRs for different exposure categories to the midpoint of the corresponding category. We used the method described by Greenland et al (7, 8), which takes into account that the level-specific risk estimates are correlated. This method requires that the number of cases and total subjects (or person-time) for each category are known. For studies that did not provide this information, we estimated the dose-response slopes using variance-weighted least-squares regression analysis. For open-ended categories (eg, BMI ≥ 30), we estimated the midpoint using data from the Cohort of Swedish Men (9) and the Swedish Mammography Cohort (10) or obtained the values from the authors (for studies conducted in Asia; 11–13). Summary RR estimates were obtained from random-effects models applied to the study-specific dose-response slopes (14).

Statistical heterogeneity among studies was tested with the Q statistic, and inconsistency was quantified with the I² statistic (15). Besides analyses of cancer site and sex, we conducted analyses of BMI stratified by subsite in the colon (proximal versus distal colon) and geographic region. To assess for publication bias, funnel plots (ie, plots of study results against precision) were constructed and the Egger’s regression test was used to test funnel plot asymmetry (16). The potential influence that unpublished studies could have on the summary RR estimates was examined by using trim and fill analysis, which is a method based on the addition of studies to the funnel plot so that it becomes symmetrical (17). P < 0.05 was considered statistically significant. All statistical analyses were performed by using STATA (version 9.0; StataCorp, College Station, TX).

RESULTS

Our search strategy and inclusion criteria resulted in a total of 31 articles (with data from 30 prospective studies) being included in our analyses of BMI (9–13, 18–43) (Figure 1). Two additional studies (44, 45) were included in the analyses of waist circumference or waist-to-hip ratio; these 2 studies were not included in the analyses of BMI because more recent data were available (29). The characteristics of the included studies are summarized in Table 1. Most of the studies were conducted in the United States (n = 12) or Europe (n = 11). The outcome was colon or rectal cancer mortality in 5 studies (25, 26, 31, 34, 35) and incidence of these cancers in all of the other studies.

Body mass index

The estimated RRs of colon cancer per 5-unit increase in BMI for each study, separately for men and women, are shown in Table 2. The studies combined involved 3,128,274 men (22,546 cases) from 24 studies and 2,419,875 women (22,231 cases) from 21 studies. In a meta-analysis, a 5-unit increase in BMI was associated with a 30% increased risk of colon cancer in men and with a 12% increased risk in women (Figure 2). This sex difference for BMI was statistically significant (P < 0.001). BMI was statistically significantly positively related to proximal colon cancer risk among men and with distal colon cancer in both sexes (Table 2). Although the association between BMI and risk of colon cancer was observed between studies conducted in both North America and Europe (Table 2), the summary estimates were higher in North American studies (P = 0.01 for differences among men; P = 0.004 for differences among women). Increased BMI was also associated with colon cancer risk among carried out in Asia, but the association was statistically significant in men only (Table 2). The summary estimates were nonsignificantly lower for the studies in which weight and height had been measured (men, RR: 1.27; 95% CI: 1.23, 1.32; women, RR: 1.07; 95% CI: 1.01, 1.15) than for those that relied on self-reporting (men, RR: 1.36; 95% CI: 1.27, 1.46; women, RR: 1.17; 95% CI: 1.08, 1.26).

Physical activity is potentially the most likely confounder of the positive relation between BMI and risk of colon cancer. When we restricted the meta-analysis to studies that controlled for physical activity, the results were similar to those of the overall analyses for 10 studies in men (RR: 1.33; 95% CI: 1.24, 1.43) and for 8 studies in women (RR: 1.16; 95% CI: 1.07, 1.25).

The studies on BMI and rectal cancer risk involved 2,616,503 men (13,830 cases) from 15 studies and 1,802,320 women (8,878 cases) from 13 studies. Overall, BMI was statistically significantly positively related to rectal cancer risk in men (12% increase per 5-unit higher BMI) but not in women (Figure 3: P = 0.002 for difference in association between men and women). A formal test for differences in the association with BMI between cancer sites showed that the RR was statistically significantly higher for colon cancer than for rectal cancer (P < 0.001 in men and P = 0.01 in women). Among

FIGURE 1. Flow diagram of study selection. *Two additional studies were included in the analyses of waist circumference, waist-to-hip ratio, or both. (These studies were excluded from the analyses of BMI because more recent data were available.)

Figure 2. The studies combined involved 3,128,274 men (22,546 cases) from 24 studies and 2,419,875 women (22,231 cases) from 21 studies. In a meta-analysis, a 5-unit increase in BMI was associated with a 30% increased risk of colon cancer in men and with a 12% increased risk in women (Figure 2). This sex difference for BMI was statistically significant (P < 0.001). BMI was statistically significantly positively related to proximal colon cancer in men and with distal colon cancer in both sexes (Table 2). Although the association between BMI and risk of colon cancer was observed between studies conducted in both North America and Europe (Table 2), the summary estimates were higher in North American studies (P = 0.01 for differences among men; P = 0.004 for differences among women). Increased BMI was also associated with colon cancer risk among carried out in Asia, but the association was statistically significant in men only (Table 2). The summary estimates were nonsignificantly lower for the studies in which weight and height had been measured (men, RR: 1.27; 95% CI: 1.23, 1.32; women, RR: 1.07; 95% CI: 1.01, 1.15) than for those that relied on self-reporting (men, RR: 1.36; 95% CI: 1.27, 1.46; women, RR: 1.17; 95% CI: 1.08, 1.26).

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TABLE 1
Characteristics of prospective studies of obesity and colon cancer (CC) and rectal cancer (RC) risk

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country, study name</th>
<th>Study participants</th>
<th>No. of case subjects</th>
<th>Years of follow-up</th>
<th>Assessment of anthropometric measures</th>
<th>Adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bostick et al, 1994 (19)</td>
<td>United States, Iowa Women’s Health Study</td>
<td>35,215 women aged 55–69 y</td>
<td>212 CC</td>
<td>1986–1990 (4.8)</td>
<td>Self-reported</td>
<td>Age, height, parity, vitamin A supplement use, intakes of energy and total vitamin E</td>
</tr>
<tr>
<td>Giovannucci et al, 1995 (21)</td>
<td>United States, Nurses’ Health Study</td>
<td>31,055 men aged 40–75 y</td>
<td>117 CC</td>
<td>1987–1992</td>
<td>Self-reported</td>
<td>Age, history of endoscopy, family history, smoking, physical activity, aspirin, intakes of red meat, alcohol, fiber, folate, methionine, and energy intake</td>
</tr>
<tr>
<td>Martinez et al, 1997 (23)</td>
<td>United States, Nurses’ Health Study</td>
<td>52,687 women aged 30–55 y</td>
<td>161 CC</td>
<td>1986–1992</td>
<td>Self-reported</td>
<td>Age, family history, smoking, physical activity, PMH use, intakes of red meat and alcohol</td>
</tr>
<tr>
<td>Singh and Fraser, 1998 (24)</td>
<td>United States, Adventist Health Study</td>
<td>32,051 men and women aged ≥25 y</td>
<td>59 CC (M) 83 CC (F)</td>
<td>1976–1982 (5.6)</td>
<td>Self-reported</td>
<td>Age, family history</td>
</tr>
<tr>
<td>Murphy et al, 2000 (27)</td>
<td>United States, Cancer Prevention Study II</td>
<td>379,167 men and 496,239 women aged ≥30 y</td>
<td>1792 CC (M) 1616 CC (F)</td>
<td>1982–1994 (8.8)</td>
<td>Self-reported</td>
<td>Age, race, education, family history, smoking, exercise, PMH use (women), aspirin, intakes of fat, vegetables, and fiber</td>
</tr>
<tr>
<td>Terry et al, 2001 (28)</td>
<td>Sweden, Swedish Mammography Cohort</td>
<td>61,463 women aged 40–76 y</td>
<td>291 CC 159 RC</td>
<td>1987–1998 (9.6)</td>
<td>Self-reported</td>
<td>Age, education, intakes of energy, red meat, alcohol, fat, folate, vitamin D, vitamin C, and calcium</td>
</tr>
<tr>
<td>Shimizu et al, 2003 (31)</td>
<td>Japan</td>
<td>13,392 men and 15,659 women aged ≥30 y</td>
<td>104 CC (M) 58 RC (M) 89 CC (F) 41 RC (F)</td>
<td>1993–2000 (7.1)</td>
<td>Self-reported</td>
<td>Age, education, height, smoking, physical activity, alcohol</td>
</tr>
<tr>
<td>Wei et al, 2004 (33)</td>
<td>United States, Nurses’ Health Study</td>
<td>86,857 women aged 30–55 y</td>
<td>672 CC 204 RC</td>
<td>1980–2000</td>
<td>Self-reported</td>
<td>Age, family history, height, smoking, physical activity, intakes of red meat, alcohol, calcium, and folate</td>
</tr>
<tr>
<td>Moore et al, 2004 (34)</td>
<td>United States, Framingham Study cohort</td>
<td>33,456 men and 42,211 women aged 30–79 y</td>
<td>140 CC (M) 166 CC (F)</td>
<td>1948–1999 (23.1)</td>
<td>Measured</td>
<td>Age, education, height, smoking, physical activity, alcohol</td>
</tr>
<tr>
<td>Tamakoshi et al, 2004 (35)</td>
<td>Japan, Japan Collaborative Cohort</td>
<td>43,171 men and 58,775 women aged 40–79 y</td>
<td>127 CC (M) 122 CC (F)</td>
<td>1988–1999 (10.0)</td>
<td>Self-reported</td>
<td>Age, family history, smoking, exercise, intakes of meat, vegetables, and alcohol</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Reference</th>
<th>Country, study name</th>
<th>Study participants</th>
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<th>Years of follow-up</th>
<th>Assessment measures</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Lin et al, 2004 (33)</td>
<td>United States, Women’s Health Study</td>
<td>37 671 women aged ≥45 y</td>
<td>158 CC, 40 CC</td>
<td>1993–2003 (8.7)</td>
<td>Self-reported</td>
<td>Age, family history, history of colon polyps, aspirin, PMH use, smoking, physical activity, intakes of red meat and alcohol</td>
</tr>
<tr>
<td>Kuriyama et al, 2005 (12)</td>
<td>Japan</td>
<td>12 485 men and 15 054 women aged ≥40 y</td>
<td>88 CC (M), 72 CC (F), 42 RC (F), 22 CC</td>
<td>1984–1992 (9)</td>
<td>Self-reported</td>
<td>Age, smoking, intakes of meat, fish, fruits, vegetables, and alcohol</td>
</tr>
<tr>
<td>Eichholzer et al, 2005 (34)</td>
<td>Switzerland, Basel Cohort Study</td>
<td>2974 men aged 20–79 y</td>
<td>22 CC</td>
<td>1971–1990</td>
<td>Measured</td>
<td>Age, smoking</td>
</tr>
<tr>
<td>Rapp et al, 2005 (36)</td>
<td>Austria, Vorarlberg Health Monitoring and Promotion Program Study</td>
<td>67 447 men and 78 484 women aged 19–94 y</td>
<td>260 CC (M), 271 CC (F), 133 RC (F), 22 CC</td>
<td>1985–2001 (9.9)</td>
<td>Measured</td>
<td>Age, occupational group, smoking</td>
</tr>
<tr>
<td>Engeland et al, 2005 (37)</td>
<td>Norway</td>
<td>962 901 men and 1 037 077 women aged 20–74 y</td>
<td>13805 CC (M), 9182 RC (M), 16638 CC (F), 7492 RC (F)</td>
<td>1963–2002 (23)</td>
<td>Measured</td>
<td>Age, birth cohort</td>
</tr>
<tr>
<td>Otani et al, 2005 (11)</td>
<td>Japan, Japan Public Health Center-based Prospective Study</td>
<td>45 158 men and 53 791 women aged 40–69 y</td>
<td>424 CC (M), 202 RC (M), 229 RC (F), 131 RC (F), 73 CC (M), 58 RC (M), 76 CC (F), 31 RC (F)</td>
<td>1990–2001 (9.4)</td>
<td>Self-reported</td>
<td>Age, smoking, Public Health Center areas, refraining from salty foods and animal fats, and intakes of miso soup and alcohol</td>
</tr>
<tr>
<td>Pischon et al, 2006 (40)</td>
<td>Europe, European Prospective Investigation into Cancer and Nutrition</td>
<td>129 731 men and 238 546 women aged 20–70 y</td>
<td>421 CC (M), 295 RC (M), 563 CC (F), 291 RC (F)</td>
<td>1992–2004 (6.1)</td>
<td>Measured</td>
<td>Age, center, education, smoking, physical activity, and intakes of red meat, processed meat, fish, fruit, vegetables, fiber, and alcohol</td>
</tr>
<tr>
<td>Larsson et al, 2006 (9)</td>
<td>Sweden, Cohort of Swedish Men</td>
<td>45 906 men aged 45–79 y</td>
<td>309 CC, 190 RC</td>
<td>1998–2005 (7.1)</td>
<td>Self-reported</td>
<td>Age, family history, education, aspirin, smoking, diabetes, physical activity</td>
</tr>
<tr>
<td>MacInnis et al, 2006 (43)</td>
<td>Australia, Melbourne Collaborative Cohort Study</td>
<td>16 867 men and 24 247 women aged 27–75 y</td>
<td>134 RC (M), 95 RC (F)</td>
<td>1990–2003 (10.4)</td>
<td>Measured</td>
<td>Age, country of birth</td>
</tr>
</tbody>
</table>

1 OC, oral contraceptives; PMH, postmenopausal hormones.
2 Mean or median duration of follow-up in parenthesis.
3 Nested case-control study within a prospective cohort.
men, the association between BMI and rectal cancer was similar among studies conducted in Europe and Asia; only one study in men from North America precluded calculation of a summary RR. Among women, there was a statistically significant positive association between BMI and rectal cancer risk among studies from North America, but not among studies from Europe or Asia ($P = 0.02$ for difference in association between geographic regions). Among men, the summary estimate was similar for studies in which weight and height had been measured (RR: 1.12; 95% CI: 1.09, 1.15) and for studies that relied on self-reporting (RR: 1.16; 95% CI: 1.01, 1.34), whereas among women, the summary estimate was lower from studies based on measured weight and height (RR: 1.01; 95% CI: 0.98, 1.03) than from those based on self-reporting.

**FIGURE 2.** Relative risk of colon cancer per 5-unit increase in BMI (in kg/m²).
(RR: 1.16; 95% CI: 1.06, 1.24; 7 studies) \( (P = 0.003 \text{ for difference}) \). Because physical activity is not associated with rectal cancer risk (46), it is not a potential confounder of the association between BMI and rectal cancer.

There was no evidence of publication bias in the literature on BMI and colon cancer in men or on BMI and rectal cancer in men or women (Egger’s test: \( P > 0.2 \text{ for all} \)). For BMI and colon cancer in women, the funnel plot showed some asymmetry (data not shown), which reflected the relative deficit of small studies showing no association or an inverse association (Egger’s test: \( P = 0.001 \)). According to trim and fill analysis, 4 such studies may have been missing. When those potentially missing studies were added to the meta-analysis, the summary RR of colon cancer per 5-unit increase in BMI among women was 1.10 (95% CI: 1.05, 1.16).

**Waist circumference and waist-hip ratio**

Overall, both waist circumference and waist-hip ratio was statistically significantly positively associated with risk of colon cancer in both sexes (Figure 4). A statistically significant sex difference was found for waist circumference (stronger association in men than in women, \( P = 0.04 \)) and a nonsignificant sex difference was found for waist-hip-ratio (stronger association in men than in women, \( P = 0.10 \)). We did not detect evidence for publication bias (\( P > 0.3 \)).

Only 3 studies provided results on waist circumference and waist-hip ratio in relation to rectal cancer risk in men (9, 40, 43) and women (40, 43). In a meta-analysis of these studies, the summary RR estimates of rectal cancer per 10-cm increase in waist circumference were 1.12 (95% CI: 1.03, 1.22; \( P \text{ for heterogeneity} = 0.93 \)) in men and 1.09 (95% CI: 0.99, 1.20; \( P \text{ for heterogeneity} = 0.86 \)) in women. The corresponding estimates per 0.1-unit increase in waist-hip ratio were 1.22 (95% CI: 0.81, 1.83; \( P \text{ for heterogeneity} = 0.001 \)) in men and 1.15 (95% CI: 0.95, 1.39; \( P \text{ for heterogeneity} = 0.22 \)) in women.

**DISCUSSION**

This meta-analysis of prospective studies indicates that the association between obesity and risk of colorectal cancer varies by sex and cancer site. Although colon cancer risk increased with increasing BMI, waist circumference, and waist-hip-ratio in both men and women, the associations were stronger in men. The relation between BMI and colon cancer was similar for proximal and distal colon cancer. With regard to rectal cancer, the risk increased with increasing BMI in men, whereas no overall association was observed in women.

Available epidemiologic evidence suggests that abdominal obesity (as reflected by high waist circumference and waist-hip ratio) may be more predictive of colon cancer risk than overall obesity (high BMI). Of the studies that provided results for both abdominal and overall obesity in relation to risk of colon cancer (9, 19, 30, 32, 39, 40, 44, 45), most showed that abdominal obesity was more strongly related to increased colon cancer risk than was overall obesity (30, 32, 39, 40). Furthermore, these studies found that the positive association of waist circumference or waist-hip ratio with colon cancer remained after adjustment for BMI (30, 32, 40, 44), whereas the relation between BMI and colon cancer was attenuated, and generally not statistically significant, after adjustment for waist or waist-hip ratio (30, 32, 40).

The exact biologic mechanisms underlying the association between obesity and increased risk of colorectal cancer are not fully understood, but certainly involve alterations in the metabolism of endogenous hormones, including insulin, insulin-like growth factors (IGFs), sex steroids, and possibly adipocyte-derived factors such as leptin and adiponectin. Obesity, particularly abdominal obesity, is linked to insulin resistance, to hyperinsulinemia, and to the development of type 2 diabetes (5, 6). Epidemiologic evidence indicates that high circulating concentrations of insulin and C-peptide (a marker of pancreatic insulin secretion) (24, 47–51) as well as diabetes (52) are associated with a greater risk of colorectal cancer. IGF binding protein-1 (IGFBP-1) concentrations decrease with increasing adiposity (53), which may lead to elevated concentrations of free and bioavailable IGF-I (3). IGFBP-1 concentrations have been shown to be inversely related to risk of colon cancer (48), whereas IGF-I concentrations, particularly relative to IGFBP-3, have been shown to be positively associated with risk of colon or colorectal cancer in prospective studies (24, 28, 54–56).

### TABLE 2

<table>
<thead>
<tr>
<th>Relative risk (95% CI)</th>
<th>Heterogeneity/M (P)</th>
<th>Heterogeneity/M (I²)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal colon</td>
<td>1.29 (1.17, 1.42)</td>
<td>0.41</td>
</tr>
<tr>
<td>Distal colon</td>
<td>1.35 (1.22, 1.48)</td>
<td>0.75</td>
</tr>
<tr>
<td>North America</td>
<td>1.39 (1.31, 1.48)</td>
<td>0.61</td>
</tr>
<tr>
<td>Europe</td>
<td>1.27 (1.12, 1.32)</td>
<td>0.29</td>
</tr>
<tr>
<td>Asia</td>
<td>1.27 (1.08, 1.49)</td>
<td>0.13</td>
</tr>
<tr>
<td>Rectal cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>— —</td>
<td>— —</td>
</tr>
<tr>
<td>Europe</td>
<td>1.12 (1.09, 1.15)</td>
<td>0.69</td>
</tr>
<tr>
<td>Asia</td>
<td>1.16 (1.05, 1.28)</td>
<td>0.46</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon cancer</td>
<td>1.13 (0.93, 1.36)</td>
<td>0.02</td>
</tr>
<tr>
<td>Rectal cancer</td>
<td>1.17 (1.05, 1.31)</td>
<td>0.47</td>
</tr>
</tbody>
</table>

1 \( I^2 \) is interpreted as the proportion of total variation across studies that is due to heterogeneity rather than chance.

2 Because there was only one study of rectal cancer in men in North America, a summary relative risk could not be calculated.
is also positively associated with serum leptin but inversely associated with adiponectin concentrations (57). In prospective studies, high leptin (47, 58, 59) and low adiponectin (60) concentrations have been related to an increase in colon or colorectal cancer risk.

The reasons for the apparent sex difference in associations for BMI, waist circumference, and waist-hip ratio are unclear but might be related to differences between men and women in the association between adiposity and testosterone concentrations. Adiposity is inversely related to testosterone concentrations in men (61–63) but positively related to testosterone concentrations in women (64, 65). Several clinical trials have shown that testosterone therapy decreases adiposity and improves insulin sensitivity (66–69), whereas androgen deprivation increases adiposity and insulin resistance in men (70, 71). Moreover, a meta-analysis found that high testosterone concentrations were associated with a lower risk of type 2 diabetes in men but with a higher risk in women (72). If insulin resistance is one of the mechanisms linking obesity to risk of colon and rectal cancer, an obesity-induced reduction in testosterone concentrations in men may be one reason for the stronger association of obesity with colon and rectal cancer risk in men than in women.

Other potential explanations for the sex difference in association with adiposity might be related to a counteracting beneficial effect of obesity on colorectal cancer risk in women or to postmenopausal hormone use. BMI is positively associated with circulating concentrations of estradiol in postmenopausal women and men (63–65, 73). Exogenous estrogens (in the form of postmenopausal hormone therapy) have been associated with a decreased risk of colorectal cancer in observational and intervention studies (74–76). Results of a recent large prospective cohort study showed that abdominal adiposity was positively related to risk of colon cancer only in women who did not use postmenopausal hormones (40). Likewise, a smaller prospective cohort study found that BMI was significantly positively associated with the risk of colorectal cancer in never users of postmenopausal hormones but not in current users (33). Some (10, 27) but not all (30) prospective studies have found that BMI is positively related to risk of colorectal cancer in premenopausal women but not in postmenopausal women.

Results from this meta-analysis indicate that the association between BMI and cancer risk is stronger for colon cancer than for rectal cancer. Similarly, another meta-analysis showed that increased leisure-time physical activity, which is related to improved insulin sensitivity (77, 78), was associated with a reduced risk of colon cancer but not of rectal cancer (46). This may suggest that insulin resistance, hyperinsulinemia, and other factors related to obesity are stronger risk factors for colon cancer.
than for rectal cancer. Indeed, several prospective studies reported that circulating C-peptide (24, 28, 47, 51) and leptin (47, 58) concentrations were more strongly positively associated with risk of colon cancer than with overall colorectal cancer or rectal cancer.

As with any meta-analysis of observational studies, our study has limitations. First, the possibility that the observed relation between obesity and colorectal cancer risk was due to unmeasured or residual confounding should be considered. The most likely confounder of the obesity-colon cancer relation is physical activity, which is inversely associated with colon cancer risk (46). However, a positive association between BMI and risk of colon cancer in both men and women persisted when we restricted the meta-analysis to studies that controlled for physical activity. Second, half of the studies in this meta-analysis relied on self-reported anthropometric measures, which may have led to some underestimation of the true associations. The summary RR estimate for the studies that had measured weight and height was lower than that for studies that relied on self-reporting. Finally, in a meta-analysis of published studies, it is possible that an observed association is the result of publication bias, because studies with null results tend not to be published. There was an indication of publication bias in the literature relating BMI to colon cancer risk in women. Nevertheless, the positive association remained when we controlled for potential unpublished studies.

In summary, the results of this meta-analysis showed that obesity was significantly positively associated with colon cancer risk in both men and women and with rectal cancer risk in men. The association between obesity and risk of colon cancer was stronger in men than in women. Moreover, increased BMI was more strongly related to risk of colon cancer than to risk of rectal cancer. The mechanisms accounting for the sex and cancer site differences need further investigation. This meta-analysis provides further support to public health efforts aiming to lower the prevalence of overweight and obesity to reduce the incidence of cancer and other chronic diseases (79).

The authors’ responsibilities were as follows—SCL and AW: study concept and design, data collection, interpretation of results, critical revision of manuscript, and review of the final manuscript; SCL: statistical analyses and writing of the manuscript. None of the authors had any personal or financial conflicts of interest.

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