Obesity, Aspirin, and Risk of Colorectal Cancer in Carriers of Hereditary Colorectal Cancer: A Prospective Investigation in the CAPP2 Study


Listen to the podcast by Dr Meyerhardt at www.jco.org/podcasts

ABSTRACT

Purpose
In the general population, increased adiposity is a significant risk factor for colorectal cancer (CRC), but whether obesity has similar effects in those with hereditary CRC is uncertain. This prospective study investigated the association between body mass index and cancer risk in patients with Lynch syndrome (LS).

Patients and Methods
Participants with LS were recruited to the CAPP2 study, in which they were randomly assigned to receive aspirin 600 mg per day or aspirin placebo, plus resistant starch 30 g per day or starch placebo (2 x 2 factorial design). Mean intervention period was 25.0 months, and mean follow-up was 55.7 months.

Results
During follow-up, 55 of 937 participants developed CRC. For obese participants, CRC risk was 2.41 x (95% CI, 1.22 to 4.85) greater than for underweight and normal-weight participants (reference group), and CRC risk increased by 7% for each 1-km² increase in body mass index. The risk of all LS-related cancers in obese people was 1.77 x (95% CI, 1.06 to 2.96; P = .03) greater than for the reference group. In subgroup analysis, obesity was associated with 3.72 x (95% CI, 1.41 to 9.81) greater CRC risk in patients with LS with MLH1 mutation, but no excess risk was observed in those with MSH2 or MSH6 mutation (P = .5). The obesity-related excess CRC risk was confined to those randomly assigned to the aspirin placebo group (adjusted hazard ratio, 2.75; 95% CI, 1.12 to 6.79; P = .03).

Conclusion
Obesity is associated with substantially increased CRC risk in patients with LS, but this risk is abrogated in those taking aspirin. Such patients are likely to benefit from obesity prevention and/or regular aspirin.

J Clin Oncol 33:3591-3597. © 2015 by American Society of Clinical Oncology

INTRODUCTION

Lynch syndrome (LS; also known as hereditary nonpolyposis colon cancer) is an autosomal-dominant disease and the commonest cause of hereditary bowel cancer. LS is caused by germline pathogenic variants in DNA mismatch repair (MMR) genes MLH1, MSH2, MSH6, and PMS2. Despite the high penetrance of this condition, treatment with aspirin (600 mg per day for mean of 25 months) halved cancer incidence in LS carriers after a mean of 55.7 months.1 This finding suggests that cancer development in LS may be modulated by exposures, especially those influencing inflammation.

There is substantial evidence that adults with higher adiposity are at greater risk of several common cancers, including colorectal cancer (CRC).2,3 A recent systematic review and meta-analysis identified 41 prospective studies of obesity and 13 studies of central obesity (measured as waist circumference) involving approximately 9 million individuals and 92,481 patient cases of CRC. Overall, the relative risk (RR) of CRC for those in the obese versus normal-weight category was 1.33 (95% CI, 1.25 to 1.42); RR for those in the highest versus lowest category of WC
found that compared with normal weight, there was a statistically significant association between overweight (body mass index [BMI] \( \geq 25 \text{ kg/m}^2 \)) and colorectal adenoma (benign precursor of CRC) risk if overweight (BMI \( \geq 25 \text{ kg/m}^2 \)) or obese (BMI \( \geq 30 \text{ kg/m}^2 \)) compared with normal weight. As in the Dutch study, there was no relationship between adiposity and LS-related bowel cancer in women. In addition, a retrospective analysis of data from participants in the National Cancer Institute Colon Cancer Family Registry with germline MMR mutation showed that increased BMI at age 20 years was associated with subsequent higher CRC risk.

### Table 1. Baseline Characteristics of Participants With LS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Colorectal Cancer</th>
<th>Colorectal Adenoma</th>
<th>Data Set (n = 746)</th>
<th>Data Set (n = 937)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>336 (45.0)</td>
<td>412 (44.0)</td>
<td>No. (%)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>Age at cohort entry, years</td>
<td>45.2</td>
<td>45.2</td>
<td>10.8</td>
<td>11.0</td>
</tr>
<tr>
<td>SD</td>
<td>44.9</td>
<td>44.9</td>
<td>36.7-53.2</td>
<td>36.3-53.3</td>
</tr>
<tr>
<td>Q1-Q3</td>
<td>15.9-28.9</td>
<td>25.0-75.4</td>
<td>15.9-28.9</td>
<td>25.0-75.4</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.7-33.5</td>
<td>15.9-28.9</td>
<td>15.9-28.9</td>
<td>25.0-75.4</td>
</tr>
<tr>
<td>Age quartile, years</td>
<td>23.4-30.3</td>
<td>24.4</td>
<td>24.4</td>
<td>25.0</td>
</tr>
<tr>
<td>Follow-up time, months</td>
<td>24.7</td>
<td>25.0</td>
<td>25.0</td>
<td>25.0</td>
</tr>
<tr>
<td>Time receiving intervention, months</td>
<td>25.0</td>
<td>25.0</td>
<td>25.0</td>
<td>25.0</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.8</td>
<td>25.9</td>
<td>4.7</td>
<td>4.8</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>22.5-28.2</td>
<td>22.7-28.4</td>
<td>22.7-28.4</td>
<td>22.7-28.4</td>
</tr>
<tr>
<td>MMR gene mutation</td>
<td>12 (1.6)</td>
<td>14 (1.5)</td>
<td>341 (47.7)</td>
<td>418 (44.6)</td>
</tr>
<tr>
<td>Clinical diagnosis</td>
<td>132 (17.7)</td>
<td>163 (17.4)</td>
<td>358 (48.0)</td>
<td>464 (49.5)</td>
</tr>
<tr>
<td>MLH1</td>
<td>235 (31.5)</td>
<td>284 (30.3)</td>
<td>21 (2.8)</td>
<td>26 (2.8)</td>
</tr>
<tr>
<td>CLN1</td>
<td>334 (44.8)</td>
<td>423 (45.1)</td>
<td>218 (29.2)</td>
<td>277 (29.6)</td>
</tr>
<tr>
<td>Clinical center (geographic region)</td>
<td>184 (26.0)</td>
<td>237 (25.3)</td>
<td>184 (26.0)</td>
<td>237 (25.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Placebo</th>
<th>Aspirin</th>
<th>Not randomly assigned</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>343 (46.0)</td>
<td>434 (46.3)</td>
<td>76 (8.1)</td>
</tr>
<tr>
<td>Placebo</td>
<td>350 (46.9)</td>
<td>427 (45.6)</td>
<td>65.0 (7.1)</td>
</tr>
<tr>
<td>Clinical diagnosis</td>
<td>30 of 232</td>
<td>30 of 232</td>
<td>30 of 127</td>
</tr>
<tr>
<td>MLH1 mutation</td>
<td>55 of 339</td>
<td>55 of 339</td>
<td>55 of 339</td>
</tr>
<tr>
<td>Under- and normal weight(&lt; 25)</td>
<td>1.00 1.00</td>
<td>1.00 1.00</td>
<td></td>
</tr>
<tr>
<td>Under- and normal weight(\geq 25)</td>
<td>1.32 (0.59 to 2.55)</td>
<td>1.00 1.00</td>
<td></td>
</tr>
<tr>
<td>Overweight (\geq 25-29.99)</td>
<td>0.95 (0.51 to 1.55)</td>
<td>0.82 (0.47 to 1.46)</td>
<td></td>
</tr>
<tr>
<td>Obese (\geq 30)</td>
<td>1.24 (0.61 to 2.51)</td>
<td>1.16 (0.56 to 2.43)</td>
<td></td>
</tr>
<tr>
<td>MSH2 mutation</td>
<td>30 of 232</td>
<td>30 of 232</td>
<td>30 of 127</td>
</tr>
<tr>
<td>Under- and normal weight(&lt; 25)</td>
<td>1.00 1.00</td>
<td>1.00 1.00</td>
<td></td>
</tr>
<tr>
<td>Under- and normal weight(\geq 25)</td>
<td>1.00 1.00</td>
<td>1.00 1.00</td>
<td></td>
</tr>
<tr>
<td>Overweight (\geq 25-29.99)</td>
<td>0.76 (0.31 to 1.68)</td>
<td>0.64 (0.25 to 1.62)</td>
<td></td>
</tr>
<tr>
<td>Obese (\geq 30)</td>
<td>1.43 (0.70 to 2.98)</td>
<td>1.29 (0.53 to 3.15)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Abbreviations: BMI, body mass index; LS, Lynch syndrome; MMR, mismatch repair; Q, quartile; SD, standard deviation.</th>
<th>Unadjusted HR</th>
<th>Adjusted HR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants with adenoma of total participants</td>
<td>117 of 719</td>
<td>117 of 719</td>
</tr>
<tr>
<td>BMI, kg/m² (continuous variable)</td>
<td>HR per unit BMI</td>
<td>Under- and normal weight (&lt; 25)</td>
</tr>
<tr>
<td>Under- and normal weight (&lt; 25)</td>
<td>1.03 (0.99 to 1.06)</td>
<td>1.02 (0.98 to 1.06)</td>
</tr>
<tr>
<td>Under- and normal weight (\geq 25)</td>
<td>1.00 1.00</td>
<td>1.00 1.00</td>
</tr>
<tr>
<td>Under- and normal weight (&lt; 25)</td>
<td>0.96 (0.92 to 1.00)</td>
<td>0.95 (0.91 to 1.00)</td>
</tr>
<tr>
<td>Under- and normal weight (\geq 25)</td>
<td>1.00 1.00</td>
<td>1.00 1.00</td>
</tr>
<tr>
<td>Obese (\geq 30)</td>
<td>1.29 (0.53 to 3.15)</td>
<td>1.29 (0.53 to 3.15)</td>
</tr>
</tbody>
</table>

*Significant at \( P = .02 \).

Abbreviations: BMI, body mass index; HR, hazard ratio; LS, Lynch syndrome. 
*Adjusted for age, starch, aspirin, geographic region, mismatch repair gene, and sex, where appropriate.
Several plausible mechanisms link higher adiposity with greater CRC risk, including those that cause genomic damage (eg, inflammation and oxidative stress), those that promote cell proliferation (eg, raised concentrations of insulin-like growth factors), and those that affect immunosurveillance. In addition, the gut microbiome may mediate both increased adiposity and greater CRC risk. Our hypothesis is that because of their reduced ability to combat DNA damage, overweight or obese patients with LS may be at enhanced cancer risk compared with normal-weight patients with LS. We aimed to test that hypothesis in a prospective study of patients with LS who were enrolled onto the CAPP2 (Colonrectal Adenoma/Carcinoma Prevention Programme 2) study, a randomized controlled trial of effects of aspirin and/or resistant starch (RS) using a 2 × 2 factorial design.

### PATIENTS AND METHODS

Between January 1999 and March 2005, 937 LS carriers started intervention in the CAPP2 study. Eligible patients were proven carriers of DNA MMR mutation or members of a family that met the Amsterdam diagnostic criteria and had a personal history of a cured LS neoplasm but an intact colon. Eligible participants (in 43 centers across 16 countries) were randomly assigned separately in a factorial design to aspirin 600 mg per day and/or RS 30 g per day, with placebo controls. The primary end point was the incidence of bowel neoplasia. The number, size, and histologic status of all colonic adenomas and carcinomas were recorded and compared between treatment and placebo groups. The intervention period lasted a mean of 25.0 months (median, 24.4; quartile [Q] 1 to Q3, 15.9 to 28.9 months), and the study had a preplanned design for 10-year follow-up. At the time of our analysis, the earliest enrolled participants had reached the 10-year threshold, and mean follow-up was 55.7 months (median, 33.1; Q1 to Q3, 29.4 to 78.3 months).

Cancer incidence analysis focused on follow-up of the 937 patients in whom cancer outcome data were recorded from their date of entry into the CAPP2 study until the last known date for which the local center had information with respect to cancer diagnosis. Adenoma incidence was recorded in detail for 746 participants who completed the intervention phase of the study. Outside this group, and beyond the intervention, adenoma incidence was only partially recorded and was excluded from our analysis. At recruitment, participants were asked height and weight. Participant adiposity was determined using the WHO criteria for BMI categories (ie, underweight, < 18.5; normal weight, 18.5 to 24.99; overweight, 25 to 29.99; and obese, ≥ 30 kg/m²).

For analysis purposes in this study, BMI was treated as a quantitative trait, although for clarity, categorical results are also provided, in which the underweight (n = 14) and normal-weight groups (n = 418) were combined (BMI ≤ 24.99 kg/m²) as the reference group.

### RESULTS

Table 1 summarizes the baseline characteristics for participants with LS in the CAPP2 study. The median age at study entry was 44.9 years (Q1 to Q3, 36 to 53 years) in both adenoma and CRC data sets. Women made up 55% and 56% of participants in the adenoma and CRC categories, respectively. Under- and normal-weight groups (n = 432) were combined (BMI 18.5–24.99 kg/m²) as the reference group. Men were slightly older (median age, 45.0 vs. 44.5 years) than women.

Cancer incidence analysis focused on follow-up of the 937 patients in whom cancer outcome data were recorded from their date of entry into the CAPP2 study until the last known date for which the local center had information with respect to cancer diagnosis. Adenoma incidence was recorded in detail for 746 participants who completed the intervention phase of the study. Outside this group, and beyond the intervention, adenoma incidence was only partially recorded and was excluded from our analysis. At recruitment, participants were asked height and weight. Participant adiposity was determined using the WHO criteria for BMI categories (ie, underweight, < 18.5; normal weight, 18.5 to 24.99; overweight, 25 to 29.99; and obese, ≥ 30 kg/m²).

For analysis purposes in this study, BMI was treated as a quantitative trait, although for clarity, categorical results are also provided, in which the underweight (n = 14) and normal-weight groups (n = 418) were combined (BMI ≤ 24.99 kg/m²) as the reference group.

### Table 3. HRs for Developing Cancer by BMI Category Stratified by Sex in Participants With LS

<table>
<thead>
<tr>
<th>Variable</th>
<th>CRC Incidence</th>
<th>Incidence of Other LS-Related Cancers (excluding CRC)</th>
<th>Incidence of All LS-Related Cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted HR (95% CI)</td>
<td>Adjusted HR (95% CI)</td>
<td>Adjusted HR (95% CI)</td>
</tr>
<tr>
<td></td>
<td>n=896</td>
<td>n=896</td>
<td>95 of 896</td>
</tr>
<tr>
<td>Participants with cancer diagnosis of total participants with follow-up</td>
<td>54 of 896</td>
<td>43 of 896</td>
<td>95 of 896</td>
</tr>
<tr>
<td>BMI, kg/m² (quantitative variable)</td>
<td>1.07 (1.02 to 1.13)†</td>
<td>1.02 (0.96 to 1.08)‡</td>
<td>1.05 (1.01 to 1.09)§</td>
</tr>
<tr>
<td>Under- and normal weight (&lt; 25)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Overweight (25-29.99)</td>
<td>1.09 (0.57 to 2.11)</td>
<td>0.59 (0.26 to 1.31)</td>
<td>0.87 (0.53 to 1.44)</td>
</tr>
<tr>
<td>Obese (≥ 30)</td>
<td>2.34 (1.17 to 4.67)§</td>
<td>1.23 (0.58 to 2.63)</td>
<td>1.81 (1.08 to 3.03)§</td>
</tr>
<tr>
<td>Women</td>
<td>25 of 494</td>
<td>36 of 494</td>
<td>60 of 494</td>
</tr>
<tr>
<td>BMI, kg/m² (quantitative variable)</td>
<td>1.06 (0.99 to 1.13)</td>
<td>1.03 (0.97 to 1.09)</td>
<td>1.04 (0.99 to 1.09)</td>
</tr>
<tr>
<td>Under- and normal weight (&lt; 25)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Overweight (25-29.99)</td>
<td>0.66 (0.20 to 1.23)</td>
<td>0.80 (0.33 to 1.93)</td>
<td>0.74 (0.37 to 1.50)</td>
</tr>
<tr>
<td>Obese (≥ 30)</td>
<td>2.36 (0.91 to 6.20)</td>
<td>1.58 (0.68 to 3.66)</td>
<td>1.77 (0.93 to 3.37)</td>
</tr>
<tr>
<td>Men</td>
<td>29 of 402</td>
<td>7 of 402</td>
<td>35 of 402</td>
</tr>
<tr>
<td>BMI, kg/m² (quantitative variable)</td>
<td>1.12 (1.02 to 1.24)†</td>
<td>0.84 (0.65 to 1.08)</td>
<td>1.08 (0.98 to 1.18)</td>
</tr>
<tr>
<td>Under- and normal weight (&lt; 25)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Overweight (25-29.99)</td>
<td>1.45 (0.61 to 3.43)</td>
<td>0.16 (0.02 to 1.39)</td>
<td>1.01 (0.47 to 2.18)</td>
</tr>
<tr>
<td>Obese (≥ 30)</td>
<td>2.41 (0.85 to 6.81)</td>
<td>0.31 (0.03 to 3.32)</td>
<td>1.71 (0.67 to 4.37)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; CRC, colorectal cancer; HR, hazard ratio; LS, Lynch syndrome.

*Adjusted for age, starch, aspirin, geographic region, mismatch repair gene, and sex, where appropriate.
†Significant at P = .007.
‡Significant at P = .02.
§Significant at P = .03.
cancer data sets, respectively. In both data sets, approximately 80% of participants had mutation in MLH1 or MSH2, 34% were overweight, and 15% were obese (BMI ≥ 30 kg/m²; Table 1).

**Obesity and Risk of Colorectal Adenoma**

Of 719 people (of 746 who completed exit colonoscopy from intervention study) for whom BMI data were available, 117 developed colorectal adenoma during the intervention phase (median, 25.3 months; Table 2). Overall, there was a nonsignificant increased risk for colorectal adenoma among obese participants (HR, 1.28; 95% CI, 0.77 to 2.12) compared with the reference group (HR adjusted for age, sex, aspirin and RS intake, geographic region, and MMR gene status; Table 2). A nonsignificant increased risk in obese participants was found for both men (HR, 1.17; 95% CI, 0.56 to 2.43) and women (HR, 1.38; 95% CI, 0.67 to 2.83) and for both MLH1 (HR, 1.21; 95% CI, 0.55 to 2.63) and MSH2 (HR, 1.29; 95% CI, 0.53 to 3.15) gene mutation carriers.

**Obesity and Risk of CRC**

During longer-term follow-up (median, 53.1 months), 55 of the 937 participants in the CAPP2 study developed CRC (Table 3; BMI data were not available for one patient with CRC). Risk of CRC development was 9% higher in the overweight compared with reference group, but the effect was not statistically significant (HR, 1.09; 95% CI, 0.57 to 2.11; P = .8). However, for obese participants, CRC risk was 2.34× (95% CI, 1.17 to 4.67; P = .02), and significantly, greater than for the reference group (HR adjusted for age, sex, aspirin and RS intake, geographic region, and MMR gene status; Table 3; Fig 1A). When the analysis was conducted for each sex separately, CRC risk was 2.41× (95% CI, 0.85 to 6.81) and 2.36× (95% CI, 0.91 to 6.20) greater for obese men and women, respectively, than for the corresponding reference group. With BMI as a continuous variable, CRC risk increased significantly with each unit of BMI in men (HR, 1.12; 95% CI, 1.02 to 1.24; P = .02) but was marginally weaker in women (HR, 1.06; 95% CI, 0.99 to 1.13; P = .09). There was no statistically significant interaction between sex and BMI category in CRC risk (LR χ² with 2 df, 1.37; P = .24; data not shown).

The adjusted HRs for the associations between BMI and CRC risk stratified by MMR gene mutation are listed in Table 4. Obese participants with MLH1 gene mutation had significantly higher CRC risk compared with the reference group (HR, 3.72; 95% CI, 1.41 to 9.81; P = .008). In contrast, CRC risk was not raised significantly in obese participants with MSH2 mutation (HR, 1.59; 95% CI, 0.47 to 5.44).

**Obesity and Risk of LS-Related Cancers**

The secondary analysis considered all LS-related cancers and non-CRC LS cancers, including endometrial, ovarian, and pancreatic cancers and cancers of the brain, small bowel, gallbladder, ureter, stomach, and kidney. After adjustment, there were no significant associations between BMI category and risk of non-CRC LS cancers for men, women, or all participants (Table 3). In addition, there were no significant adjusted associations between BMI category and risk of other LS cancers when stratified by MMR gene mutation (Table 4). Details of individual LS cancer incidence in this study have been reported by Burn et al.1

When CRC was included with all other LS cancers, obesity was a significant risk factor for all LS-related cancer incidence (HR, 2.18; 95% CI, 1.33 to 3.58; P = .002). This effect remained significant (HR, 1.81; 95% CI, 1.08 to 3.03; P = .03) after adjusting for other variables (age, sex, aspirin and RS intake, geographic region, and MMR gene; Table 3; Fig 1B). In addition, among MLH1 gene mutation carriers, obesity increased the risk of all LS-related cancers (HR, 2.77; 95% CI, 1.39 to 5.52; P = .004), but this association became nonsignificant after adjustment for all covariates (HR, 1.76; 95% CI, 0.85 to 3.65; Table 4).

**Effects of Aspirin**

Given the evidence that aspirin treatment reduces cancer risk in patients with LS, we carried out separate analyses of effects of BMI among those randomly assigned to aspirin and those to aspirin placebo in the CAPP2 study (Table 5). In patients with LS randomly assigned to placebo, there was a significant association between increased BMI and CRC risk (HR, 1.10; 95% CI, 1.03 to 1.17; P = .001), whereas there was no evidence of an increased risk among those randomly assigned to aspirin (HR, 1.00; 95% CI, 0.90 to 1.12; nonsignificant). Indeed, these two effect sizes are significantly different (P =
Obesity Increases Cancer Risk in Patients With Lynch Syndrome

In this prospective study, we observed a statistically significant positive association between BMI at baseline and subsequent CRC risk in participants with LS. Those who were obese had 2.34 (95% CI, 1.17 to 4.67) greater risk of CRC (Table 3), although this difference was not statistically significant. This seemingly sex-specific relationship between adiposity and colorectal neoplasia among patients with LS is consistent with previous observations (Appendix Table A1, online only). In a case-control study, Campbell et al reported significantly greater CRC risk in obese men, but not women, with a clinical diagnosis of LS. Similarly, in a short-term prospective study (median follow-up, 20 months) of those with no previous colorectal neoplasia, Botma et al observed that the risk of colorectal adenomatous polyps was increased significantly in overweight and obese men, but not women, who carried germline mutations in MMR genes. In the CAPP2 study, the increased cancer risk with increased BMI in men but not women was restricted to the colorectum (Table 3).

There is substantial evidence that greater adiposity is associated with higher CRC risk in the general population. A recent meta-analysis of 41 prospective studies involving approximately 9 million participants and 85,935 patient cases of CRC revealed an overall RR of 1.33 (95% CI, 1.25 to 1.42) in those in the obese versus normal BMI category. When stratified by sex, CRC risk among obese participants was greater in men (RR, 1.47; 95% CI, 1.36 to 1.58) than in women (RR, 1.15; 95% CI, 1.08 to 1.23). This observation of sex-dependent differences in CRC risk by BMI category is consistent with the studies reported above.

In this study, we observed that increased BMI was associated with increased CRC risk in men but not women. This relationship was stronger for men than for women (Table 3). This observation is consistent with previous studies that have reported sex-dependent differences in CRC risk by BMI category. In a recent meta-analysis of 41 prospective studies involving approximately 9 million participants and 85,935 patient cases of CRC, Botma et al observed that the increased risk of colorectal adenomatous polyps was significantly greater in overweight and obese men, but not women, who carried germline mutations in MMR genes. In the CAPP2 study, the increased cancer risk with increased BMI in men but not women was restricted to the colorectum.

### DISCUSSION

#### Table 4. HRs for Developing Cancer by BMI Category Stratified by MMR Gene in Participants With LS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Incident of Other LS-Related Cancers (excluding CRC) Adjusted HR (95% CI)*</th>
<th>Incident of All LS-Related Cancers Adjusted HR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLH1 mutation</td>
<td>28 of 438</td>
<td>22 of 438</td>
</tr>
<tr>
<td>BMI, kg/m² (quantitative variable)</td>
<td>1.12 (1.04 to 1.21)†</td>
<td>0.95 (0.86 to 1.05)</td>
</tr>
<tr>
<td>Under- and normal weight (&lt; 25)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Overweight (25-29.99)</td>
<td>1.19 (0.47 to 3.01)</td>
<td>0.39 (0.13 to 1.14)</td>
</tr>
<tr>
<td>Obese (≥ 30)</td>
<td>3.72 (1.41 to 9.81)†</td>
<td>0.64 (0.19 to 2.19)</td>
</tr>
<tr>
<td>MSH2 mutation</td>
<td>20 of 276</td>
<td>16 of 276</td>
</tr>
<tr>
<td>BMI, kg/m² (quantitative variable)</td>
<td>1.01 (0.91 to 1.12)</td>
<td>1.09 (1.00 to 1.20)‡</td>
</tr>
<tr>
<td>Under- and normal weight (&lt; 25)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Overweight (25-29.99)</td>
<td>1.26 (0.44 to 3.60)</td>
<td>1.21 (0.30 to 4.92)</td>
</tr>
<tr>
<td>Obese (≥ 30)</td>
<td>1.59 (0.47 to 5.44)</td>
<td>4.34 (1.15 to 16.4)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; CRC, colorectal cancer; HR, hazard ratio; LS, Lynch syndrome; MMR, mismatch repair.

†Significant at P = .05.
‡Significant at P = .01.
§Significant at P = .002.
§§Significant at P = .001.
### Table 5. HRs for Developing Cancer by BMI Category Stratified by Aspirin Treatment in Participants With LS

<table>
<thead>
<tr>
<th>Variable</th>
<th>CRC Incidence Adjusted HR (95% CI)*</th>
<th>Incidence of Other LS-Related Cancers (excluding CRC) Adjusted HR (95% CI)*</th>
<th>Incidence of All LS-Related Cancers Adjusted HR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>36 of 485</td>
<td>28 of 485</td>
<td>62 of 485</td>
</tr>
<tr>
<td>BMI, kg/m² (quantitative variable)</td>
<td>1.10 (1.03 to 1.17)†</td>
<td>1.03 (0.96 to 1.10)</td>
<td>1.06 (1.02 to 1.11)‡</td>
</tr>
<tr>
<td>Under- and normal weight (&lt; 25)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Overweight (25-29.99)</td>
<td>1.46 (0.63 to 3.78)</td>
<td>0.46 (0.16 to 1.29)</td>
<td>0.91 (0.49 to 1.70)</td>
</tr>
<tr>
<td>Obese (≥ 30)</td>
<td>2.75 (1.12 to 6.75)‡</td>
<td>1.33 (0.51 to 3.52)</td>
<td>1.91 (1.00 to 3.69)‡</td>
</tr>
<tr>
<td>Aspirin</td>
<td>18 of 411</td>
<td>15 of 411</td>
<td>33 of 411</td>
</tr>
<tr>
<td>BMI, kg/m² (quantitative variable)</td>
<td>1.00 (0.99 to 1.12)</td>
<td>0.99 (0.89 to 1.10)</td>
<td>1.00 (0.93 to 1.08)</td>
</tr>
<tr>
<td>Under- and normal weight (&lt; 25)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Overweight (25-29.99)</td>
<td>0.74 (0.22 to 3.46)</td>
<td>0.89 (0.21 to 3.77)</td>
<td>0.87 (0.36 to 2.10)</td>
</tr>
<tr>
<td>Obese (≥ 30)</td>
<td>2.00 (0.61 to 6.70)</td>
<td>1.14 (0.30 to 4.27)</td>
<td>1.58 (0.66 to 3.81)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; CRC, colorectal cancer; HR, hazard ratio; LS, Lynch syndrome.

†Significant at P = .05.
‡Significant at P = .006.
§Significant at P = .003.
§§Significant at P = .01.

.01), suggesting that aspirin changes the relationship between BMI and CRC risk, with no evidence of any association for those receiving aspirin.
greater CRC risk among obese men in the general population accords
with our current findings in patients with LS and with reports from
other observational studies (Appendix Table A1, online only). In
addition, in the general population, there is a positive dose-response
relationship between BMI and CRC risk; for each 2-kg/m² increase in
BMI, CRC risk increased by 7% (95% CI, 4% to 10%). Importantly,
among those with LS in our study, each 1-kg/m² increase in BMI was
associated with 7% increased CRC risk (ie, greater adiposity in patients
with LS was associated with twice the excess risk for CRC of that seen
in general population).

The mechanism responsible for the greater cancer risk among
obese patients with LS is not known. However, given the germline loss
of DNA MMR capacity in LS, it may be hypothesized that adverse
sequelae of greater body fatness (eg, chronic low-level inflammation)
have a promoting effect on those stem cells that have accumulated
DNA damage because of this dysfunctional repair system.

Up to 20% of unselected CRC tumors show microsatellite insta-
bility (MSI)—the cardinal feature of loss of MMR function—but in
the vast majority of such tumors, the MMR dysfunction is the result of
epigenetic silencing of the MLH1 gene by promoter methylation. In
a population-based case-control study, Slattery et al found that in-
creased BMI was associated with greater risk of microsatellite-stable
tumors but not of tumors exhibiting MSI. This observation is sup-
ported by findings from patients with stage II or III colon carcinoma
participating in North Central Cancer Treatment Group and National
Surgical Adjuvant Breast and Bowel Project adjuvant chemotherapy
trials, where obesity was associated with a significantly lower rate of
tumors showing deficient MMR.22 A more recent population-based
case-control study reported that the risk of both microsatellite-stable
and MSI-low, but not MSI-high, tumors increased significantly with
increasing BMI.23 In both of these studies, it is probable that MMR
dysfunction in all, or most, CRC tumors was the result of somatic
epigenetic-based loss of MMR; the tumorigenesis stage at which the
loss occurred is unknown. In contrast, in LS, germline loss of MMR
capacity drives tumorigenesis from the earliest stages, and it is possible
that this early MMR dysfunction increases susceptibility to the tumor-
promoting effects of greater adiposity. Interestingly, we found that
CRC risk was increased significantly in obese patients with LS
with germline mutation in MLH1 (HR, 3.72; 95% CI, 1.41 to 9.81; P = .008) but not in those with MSH2 mutation (Table 4). In the short-
term prospective study by Botma et al,3 there was a trend (not signif-
ificant) toward a greater excess of adenomatous polyps in overweight
and obese patients with LS with germline mutation in MLH1 but not
in MSH2 compared with those with BMI < 25 kg/m². A retrospective
analysis of data from participants in the National Cancer Institute
Colon Cancer Family Registry also found a significantly increased HR
with increased BMI for MLH1 mutation carriers (HR, 1.36; 95% CI,
1.04 to 1.77) but not for those with mutation in MSH2, MSH6, or
PMS2.9 After recognition of DNA damage by a pair of MutS homo-
logues, the MLH1 protein forms a heterodimer with PMS2, which
leads to the initiation of MMR.24 Because all MMR proteins are nec-
essary for successful DNA repair, the mechanistic basis for the seem-
ingly greater susceptibility of MLH1 mutation carriers to the adverse
effects of obesity is not known.

Interestingly, our intervention study showed some evidence that
the excess CRC risk in patients with LS is abrogated by regular aspirin
consumption. Data from the Aspirin/Folate Polyp Prevention Study
suggested that aspirin 325 mg per day might be more effective in
preventing advanced colorectal adenomas in those who are obese (RR,
0.44; 95% CI, 0.17 to 1.10) compared with normal-weight individuals
(RR, 1.23; 95% CI, 0.55 to 2.77), but the wide CIs precluded a defini-
tive conclusion.25 In addition, a case-control study of women in the
Australian National Endometrial Cancer Study reported that aspirin
might reduce the risk of endometrial cancer among obese women.26

A limitation of our study is that height and weight (used for BMI
estimation) were self-reported. It is well recognized that height and weight
tend to be over- and underestimated, respectively, so absolute estimates of
obesity can be underestimated. However, the sensitivity and specificity
of self-reported height and weight in detecting obesity are good: 0.83 and
1.00, respectively.27 This suggests that any errors in BMI estimation in our
study were likely to result in conservative estimates of the association
between obesity and increased cancer risk in patients with LS.

In summary, obesity is associated with greater risk of CRC in
patients with LS. The excess risk of CRC with increasing adiposity was
twice as great in patients with LS as has been observed by others for the
general population. However, this increased CRC risk was significant
in men only, and we observed that aspirin abrogated the excess cancer
risk associated with obesity in patients with LS. These findings suggest
that, in addition to recommended bowel surveillance, patients with LS
are likely to benefit substantially from prevention—or effective
treatment—of obesity and from regular aspirin use.

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS
OF INTEREST

Disclosures provided by the authors are available with this article at
www.jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: D. Timothy Bishop, Finlay Macrae, John Burn,
John C. Mathers

Provision of study materials or patients: Jukka-Pekka Mecklin, Annika
Lindblom, Rodney J. Scott

Collection and assembly of data: D. Timothy Bishop, Jukka-Pekka
Mecklin, Gabriela Moeslein, Sylviane Olshchwang, Diana Eccles, D.
Gareth Evans, Eamonn R. Maher, Lucio Bertario, Marie-Luise Bisgaard,
Malcolm G. Dunlop, Judy W.C. Ho, Shirley V. Hodgson, Annika
Lindblom, Jan Lubinski, Patrick J. Morrison, Victoria Murday, Raj S.
Ramesar, Lucy Side, Rodney J. Scott, Huw J.W. Thomas, Hans F. Vasen,
John Burn

Data analysis and interpretation: Mohammad Movahedi, D. Timothy
Bishop, Finlay Macrae, John Burn, John C. Mathers

Manuscript writing: All authors

Final approval of manuscript: All authors

REFERENCES

1. Burn J, Gerdes AM, Macrae F, et al: Long-
term effect of aspirin on cancer risk in carriers of
hereditary colorectal cancer: An analysis from the
CAPP2 randomised controlled trial. Lancet 378:
2081-2087, 2011

2. World Cancer Research Fund, American Insti-
tute for Cancer Research: Food, Nutrition, Physical
Activity, and the Prevention of Cancer: A Global
Perspective. Washington, DC, American Institute
for Cancer Research, 2007

Prospective investigation of body mass index, colorectal
adenoma, and colorectal cancer in the
prostate, lung, colorectal, and ovarian cancer

Affiliations
Mohammad Movahedi, Beheshti University of Medical Sciences, Tehran, Iran; Mohammad Movahedi and Timothy Bishop, University of Leeds, Leeds; Diana Eccles, University of Southampton, Southampton; D. Gareth Evans, St Mary’s Hospital, Manchester; Eamonn R. Maher, University of Birmingham, Birmingham; Malcolm G. Dunlop, Western General Hospital, Edinburgh; Shirley V. Hodgson, St George’s Hospital; Lucy Side, University College London; Huw J.W. Thomas, St Mark’s Hospital, Imperial College, London; Patrick J. Morrison, Queens University Belfast, Belfast City Hospital Health and Social Care Trust, Belfast; Victoria Murday, Yorkhill Hospital, Glasgow; John Burn and John C. Mathers, Newcastle University, Newcastle upon Tyne, United Kingdom; Finlay Macrae, Royal Melbourne Hospital, Melbourne, Victoria; Rodney J. Scott, John Hunter Hospital, New Lambton, New South Wales, Australia; Jukka-Pekka Mecklin, Jyväskylä Central Hospital, Jyväskylä, Finland; Gabriela Moekein, HELIOS St Josefs Hospital, Bochum-Linden, Germany; Sylviane Olschwang, Institut Paoli Calmettes, Marseille, France; Lucio Bertario, Istituto Nazionale per lo Studio e la Curap di Tumori, Milan, Italy; Marie-Luise Bisgaard, University of Copenhagen, Hvidovre, Denmark; Judy W.C. Ho, Queen Mary Hospital, Hong Kong, Special Administrative Region, People’s Republic of China; Annika Lindblom, Karolinska Institutet, Stockholm, Sweden; Jan Lubinski, International Hereditary Cancer Centre, Szczecin, Poland; Raj S. Ramesar, University of Cape Town, South Africa; and Hans F. Vasen, Netherlands Foundation of the Detection of Hereditary Tumours and Leiden University, Leiden, the Netherlands.

GLOSSARY TERMS
Lynch syndrome: hereditary nonpolyposis colorectal cancer (HNPCC). A cancer syndrome characterized by Henry T. Lynch in 1966, this genetic condition has a high risk of colon cancer as well as other cancers including endometrial, ovary, stomach, small intestine, hepatobiliary tract, upper urinary tract, brain, and skin.
Mismatch repair: one of four major pathways of DNA repair in mammalian cells. Mismatch repair recognizes and corrects errors in DNA replication leading to single base-pair mismatches or insertions/deletions in small repetitive tracts of DNA known as microsatellites.
AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Obesity, Aspirin, and Risk of Colorectal Cancer in Carriers of Hereditary Colorectal Cancer: A Prospective Investigation in the CAPP2 Study

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO’s conflict of interest policy, please refer to www.asco.org/rwc or jco.ascopubs.org/site/ifc.

Mohammad Movahedi
No relationship to disclose

D. Timothy Bishop
No relationship to disclose

Finlay Macrae
Research Funding: Pfizer, Bristol-Myers Squibb, Cellgene, AbbieVie, Glutagen, Janssen, Oxidos, Actelion, CSIRO, Amgen

Jukka-Pekka Mecklin
No relationship to disclose

Gabriela Moeslein
Honoraria: Bayer Consultancy, Tillots Consultancy
Consulting or Advisory Role: Tillots Consultancy

Sylviane Olschwang
No relationship to disclose

Diana Eccles
Honoraria: AstraZeneca
Travel, Accommodations, Expenses: AstraZeneca

D. Gareth Evans
No relationship to disclose

Eamonn R. Maher
No relationship to disclose

Lucio Bertario
No relationship to disclose

Marie-Luise Bisgaard
Research Funding: Lundbeck

Malcolm G. Dunlop
No relationship to disclose

Judy W.C. Ho
Research Funding: Fresenius Kabi

Shirley V. Hodgson
No relationship to disclose

Annika Lindblom
No relationship to disclose

Jan Lubinski
No relationship to disclose

Patrick J. Morrison
No relationship to disclose

Victoria Murday
No relationship to disclose

Raj S. Ramesar
No relationship to disclose

Lucy Side
Travel, Accommodations, Expenses: Novartis

Rodney J. Scott
Consulting or Advisory Role: Merck Serono

Huw J.W. Thomas
No relationship to disclose

Hans F. Vasen
No relationship to disclose

John Burn
Employment: QuantuMDx
Leadership: QuantuMDx
Stock or Other Ownership: QuantuMDx
Honoraria: Bayer Pharma
Consulting or Advisory Role: AstraZeneca
Research Funding: Bayer Pharma

John C. Mathers
No relationship to disclose
## Appendix

**Table A1. Outcomes From Previous Studies of Associations Between BMI and Colorectal Neoplasia in Patients With LS**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Design</th>
<th>Outcome</th>
<th>Sex</th>
<th>BMI (kg/m²)</th>
<th>Risk Estimate (95% CI)</th>
<th>OR</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diergaarde et al†</td>
<td>Case control</td>
<td>CRC</td>
<td>Both</td>
<td>&lt; 23.2</td>
<td>1 (referent)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt; 25.5</td>
<td>0.90 (0.4 to 1.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Campbell et al‡</td>
<td>Case control</td>
<td>CRC</td>
<td>M</td>
<td>18.5-24.99</td>
<td>1 (referent)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25-29.99</td>
<td>1.25 (0.97 to 1.61)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥ 30</td>
<td>1.63 (1.33 to 2.51)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>F</td>
<td>18.5-24.99</td>
<td>1 (referent)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25-29.99</td>
<td>1.03 (0.80 to 1.33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥ 30</td>
<td>0.85 (0.62 to 1.16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Win et al§</td>
<td></td>
<td></td>
<td>Retrospective</td>
<td>CRC</td>
<td>Both</td>
<td>&lt; 18.5</td>
<td>1.04 (0.00 to 1.64)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>18.5-24.99</td>
<td>1 (referent)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25.0-29.99</td>
<td>1.12 (0.78 to 1.62)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥ 30</td>
<td>2.35 (1.30 to 4.23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Botma et al§</td>
<td>Prospective (incident cohort)</td>
<td>Adenomatous polyps</td>
<td>M</td>
<td>&lt; 25</td>
<td>1 (referent)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥ 25</td>
<td>5.19 (1.30 to 20.80)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>F</td>
<td>&lt; 25</td>
<td>1 (referent)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥ 25</td>
<td>0.78 (0.20 to 2.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prospective (prevalent cohort)</td>
<td>Adenomatous polyps</td>
<td>M</td>
<td>&lt; 25</td>
<td>1 (referent)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥ 25</td>
<td>1.00 (0.42 to 2.38)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>F</td>
<td>&lt; 25</td>
<td>1 (referent)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥ 25</td>
<td>0.91 (0.29 to 2.91)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; CRC, colorectal cancer; HR, hazard ratio; LS, Lynch syndrome; OR, odds ratio.

† Both mismatch repair gene mutation carriers (n = 73) and untested individuals suspected of having LS (n = 175).
§ Known carriers of germline mutations in mismatch repair genes.
|| Estimated from self-reported height and weight at approximately age 20 years.

**Obesity Increases Cancer Risk in Patients With Lynch Syndrome**