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ORIGINAL REPORT

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

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

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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 × 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× (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-kg/m^2 increase in body mass index. The risk of all LS-related cancers in obese people was 1.77× (95% CI, 1.06 to 2.96; $P = .03$) greater than for the reference group. In subgroup analysis, obesity was associated with 3.72× (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.

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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

was 1.46 (95% CI, 1.33 to 1.56).[4] There was no evidence of publication bias, and the positive association with obesity was evident for both sexes, several geographic regions, and cancers of colon and rectum.[4] In patients with LS, a prospective cohort study from the Netherlands found that compared with normal weight, there was a statistically significant association between overweight (body mass index [BMI] ≥ 25 kg/m^2) and colorectal adenoma (benign precursor of CRC) risk in men but not in women.[5] These findings are in line with an earlier Canadian case-control study, which reported that men with and without clinically defined familial risk of cancer (LS diagnosed using Amsterdam[6] or Bethesda[7] criteria) were at significantly greater CRC risk if overweight (BMI ≥ 25 kg/m^2) or obese (BMI ≥ 30 kg/m^2) compared with normal weight.[8] As in the Dutch study, there was no relationship between adiposity and LS-related bowel cancer in women.[8] 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.[9]

Table 1. Baseline Characteristics of Participants With LS

Characteristic	Colorectal Adenoma Data Set (n = 746) No. (%)	Colorectal Cancer Data Set (n = 937) No. (%)
Male sex	336 (45.0)	412 (44.0)
Age at cohort entry, years		
Mean	45.2	45.2
SD	10.8	11.0
Median	44.9	44.9
Q1-Q3	36.7-53.2	36.3-53.3
Age quartile, years		
21.5-36.25	179 (24.0)	234 (25.0)
36.26-44.85	192 (25.7)	234 (25.0)
44.86-53.32	191 (25.6)	234 (25.0)
≥ 55.33	184 (24.7)	235 (25.0)
Follow-up time, months		
Mean	28.0	55.7
SD	11.2	31.2
Median	25.0	53.1
Q1-Q3	23.4-30.3	29.4-78.3
Time receiving intervention, months		
Mean	29.0	25.0
SD	11.5	13.4
Median	25.3	24.4
Q1-Q3	23.7-33.5	15.9-28.9
BMI, kg/m^2		
Mean	25.8	25.9
SD	4.7	4.8
Median	25.1	25.2
Interquartile range	22.5-28.2	22.7-28.4
BMI category, kg/m^2		
Underweight (< 18.5)	12 (1.6)	14 (1.5)
Normal weight (18.5-24.9)	341 (47.7)	418 (44.6)
Overweight (25.0-29.9)	254 (34.1)	321 (34.3)
Obese (≥ 30)	112 (15.1)	143 (15.3)
Missing	27 (3.6)	41 (4.4)
MMR gene mutation		
Clinical diagnosis	132 (17.7)	163 (17.4)
MLH1	358 (48.0)	464 (49.5)
MSH2	235 (31.5)	284 (30.3)
MSH6	21 (2.82)	26 (2.8)
Clinical center (geographic region)		
Northern Europe	334 (44.8)	423 (45.1)
United Kingdom	218 (29.2)	277 (29.6)
Other	194 (26.0)	237 (25.3)
Intervention		
Aspirin		
Placebo	343 (46.0)	434 (46.3)
Aspirin	350 (46.9)	427 (45.6)
Not randomly assigned	53 (7.1)	76 (8.1)
Resistant starch		
Placebo	369 (49.5)	455 (48.6)
Resistant starch	358 (48.0)	463 (49.4)
Not randomly assigned	19 (2.5)	19 (2.0)

Abbreviations: BMI, body mass index; LS, Lynch syndrome; MMR, mismatch repair; Q, quartile; SD, standard deviation.

Table 2. HRs for Developing Colorectal Adenoma by BMI Category Stratified by Sex in Participants With LS

Variable	Unadjusted HR HR (95% CI)	Adjusted HR* HR (95% CI)
Participants with adenoma of total participants	117 of 719	117 of 719
BMI, kg/m^2 (continuous variable HR per unit BMI)	1.03 (0.99 to 1.06)	1.02 (0.98 to 1.06)
Under- and normal weight (< 25)	1.00	1.00
Overweight (25-29.99)	1.05 (0.70 to 1.58)	0.98 (0.65 to 1.48)
Obese (≥ 30)	1.39 (0.85 to 2.29)	1.28 (0.77 to 2.12)
Women	56 of 389	56 of 389
BMI, kg/m^2 (continuous variable)	1.04 (0.99 to 1.08)	1.03 (0.99 to 1.07)
Under- and normal weight (< 25)	1.00	1.00
Overweight (25-29.99)	1.18 (0.65 to 2.16)	1.23 (0.66 to 2.28)
Obese (≥ 30)	1.46 (0.73 to 2.93)	1.38 (0.67 to 2.83)
Men	61 of 330	61 of 330
BMI, kg/m^2 (continuous variable)	0.99 (0.93 to 1.07)	0.99 (0.93 to 1.07)
Under- and normal weight (< 25)	1.00	1.00
Overweight (25-29.99)	0.89 (0.51 to 1.55)	0.82 (0.47 to 1.46)
Obese (≥ 30)	1.24 (0.61 to 2.51)	1.17 (0.56 to 2.43)
MLH1 mutation	55 of 339	55 of 339
Under- and normal weight (< 25)	1.00	1.00
Overweight (25-29.99)	0.70 (0.38 to 1.29)	0.67 (0.36 to 1.25)
Obese (≥ 30)	1.25 (0.59 to 2.65)	1.21 (0.55 to 1.11)
MSH2 mutation	30 of 232	30 of 232
BMI, kg/m^2 (continuous variable)	1.04 (0.96 to 1.12)	1.02 (0.94 to 1.11)
Under- and normal weight (< 25)	1.00	1.00
Overweight (25-29.99)	0.76 (0.31 to 1.86)	0.64 (0.25 to 1.62)
Obese (≥ 30)	1.64 (0.70 to 3.88)	1.29 (0.53 to 3.15)
Clinical diagnosis	30 of 127	30 of 127
BMI, kg/m^2 (continuous variable)	1.04 (0.99 to 1.10)	1.04 (0.99 to 1.10)
Under- and normal weight (< 25)	1.00	1.00
Overweight (25-29.99)	2.32 (1.03 to 5.20)†	2.53 (1.10 to 5.83)†
Obese (≥ 30)	1.17 (0.40 to 3.45)	1.32 (0.42 to 4.13)

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.
†Significant at $P = .02$.

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.[10,11] In addition, the gut microbiome may mediate both increased adiposity and greater CRC risk.[12,13] 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 (Colorectal Adenoma/Carcinoma Prevention Programme 2) study, a randomized controlled trial of effects of intervention with aspirin and/or resistant starch (RS) using a 2 × 2 factorial design.[1,14,15]

PATIENTS AND METHODS

Between January 1999 and March 2005, 937 LS carriers started intervention in the CAPP2 study.[14,16] Eligible patients were proven carriers of DNA MMR mutation or members of a family that met the Amsterdam diagnostic criteria[6] 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.[14] 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, 53.1; Q1 to Q3, 29.4 to 78.3 months).[1]

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/m^2).[17] 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/m^2) as the reference group.

Statistical Analysis

The analysis was based on time to first event using life-table methods and Cox proportional hazards. The life-table analysis used the end of follow-up for each participant as the time of first event, if affected; for those unaffected, the last recorded contact date at which the clinical status of the participant was known was used. The analysis considered the following events: adenoma occurrence (this analysis considered data from intervention time period only); CRC incidence during both intervention and follow-up phases (those without diagnosis of CRC were considered unaffected at this last clinical contact); and LS cancer (same as for CRC incidence but including all cancers within syndrome). The analysis strategy was designed to test the hypothesis that BMI increases the risk of neoplasia in those with LS. Cox proportional hazards models were used to estimate crude and adjusted hazard ratios (HRs) and 95% CIs for the association between BMI and risk of LS-related neoplasia (adenoma and cancer), adjusting for age, sex, geographic region, MMR gene mutation, and intervention (aspirin or RS). The analyses were repeated for sex and MMR gene mutation subgroups separately. All analyses used STATA software (version 10; STATA, College Station, TX).

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

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

Variable	CRC Incidence Adjusted HR (95% CI)*	Incidence of Other LS-Related Cancers (excluding CRC) Adjusted HR (95% CI)*	Incidence of All LS-Related Cancers Adjusted HR (95% CI)*
Participants with cancer diagnosis of total participants with follow-up	54 of 896	43 of 896	95 of 896
BMI, kg/m^2 (quantitative variable)	1.07 (1.02 to 1.13)†	1.02 (0.96 to 1.08)	1.05 (1.01 to 1.09)‡
Under- and normal weight (< 25)	1.00	1.00	1.00
Overweight (25-29.99)	1.09 (0.57 to 2.11)	0.59 (0.26 to 1.31)	0.87 (0.53 to 1.44)
Obese (≥ 30)	2.34 (1.17 to 4.67)‡	1.23 (0.58 to 2.63)	1.81 (1.08 to 3.03)§
Women	25 of 494	36 of 494	60 of 494
BMI, kg/m^2 (quantitative variable)	1.06 (0.99 to 1.13)	1.03 (0.97 to 1.09)	1.04 (0.99 to 1.09)
Under- and normal weight (< 25)	1.00	1.00	1.00
Overweight (25-29.99)	0.66 (0.20 to 2.13)	0.80 (0.33 to 1.93)	0.74 (0.37 to 1.50)
Obese (≥ 30)	2.36 (0.91 to 6.20)	1.58 (0.68 to 3.66)	1.77 (0.93 to 3.37)
Men	29 of 402	7 of 402	35 of 402
BMI, kg/m^2 (quantitative variable)	1.12 (1.02 to 1.24)‡	0.84 (0.65 to 1.08)	1.08 (0.98 to 1.18)
Under- and normal weight (< 25)	1.00	1.00	1.00
Overweight (25-29.99)	1.45 (0.61 to 3.43)	0.16 (0.02 to 1.39)	1.01 (0.47 to 2.18)
Obese (≥ 30)	2.41 (0.85 to 6.81)	0.31 (0.03 to 3.32)	1.71 (0.67 to 4.37)

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/m^2; 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 χ^2 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.[18] 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).

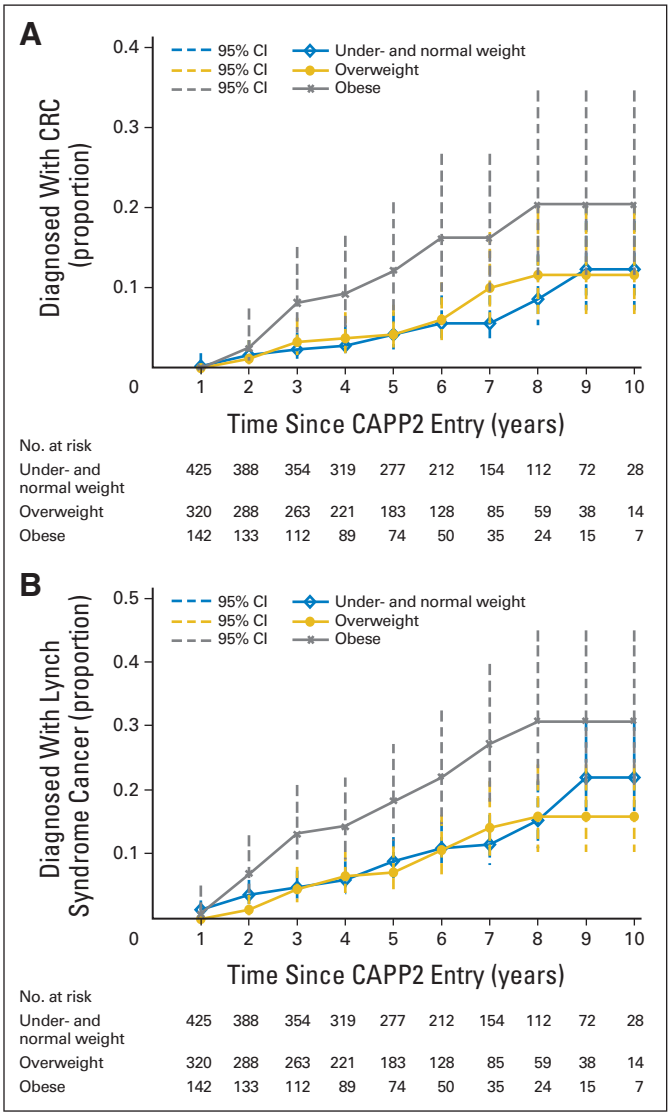

Fig 1. Time to first (A) colorectal cancer (CRC) and (B) Lynch syndrome cancer in participants stratified by body mass index category.

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 ($P =$

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

Variable	CRC Incidence Adjusted HR (95% CI)*	Incidence of Other LS-Related Cancers (excluding CRC) Adjusted HR (95% CI)*	Incidence of All LS-Related Cancers Adjusted HR (95% CI)*
MLH1 mutation	28 of 438	22 of 438	50 of 438
BMI, kg/m^2 (quantitative variable)	1.12 (1.04 to 1.21)†	0.95 (0.86 to 1.05)	1.05 (0.99 to 1.12)
Under- and normal weight (< 25)	1.00	1.00	1.00
Overweight (25-29.99)	1.19 (0.47 to 3.01)	0.39 (0.13 to 1.14)	0.75 (0.37 to 1.48)
Obese (≥ 30)	3.72 (1.41 to 9.81)‡	0.64 (0.19 to 2.19)	1.76 (0.85 to 3.65)
MSH2 mutation	20 of 276	16 of 276	35 of 276
BMI, kg/m^2 (quantitative variable)	1.01 (0.91 to 1.12)	1.09 (1.00 to 1.20)§	1.04 (0.97 to 1.11)
Under- and normal weight (< 25)	1.00	1.00	1.00
Overweight (25-29.99)	1.26 (0.44 to 3.60)	1.21 (0.30 to 4.92)	1.33 (0.58 to 3.06)
Obese (≥ 30)	1.59 (0.47 to 5.44)	4.34 (1.15 to 16.4)	2.02 (0.84 to 4.85)

Abbreviations: BMI, body mass index; CRC, colorectal cancer; HR, hazard ratio; LS, Lynch syndrome; MMR, mismatch repair.
*Adjusted for age, sex, starch, aspirin, and geographic region.
†Significant at $P = .002$.
‡Significant at $P = .008$.
§Significant at $P = .05$.

.01), suggesting that aspirin changes the relationship between BMI and CRC risk, with no evidence of any association for those receiving aspirin.

DISCUSSION

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 ($P = .02$) than those of normal weight, and there was a linear increase in HR for CRC with increasing BMI. The greater CRC risk associated with each 1-kg/m^2 increase in BMI seemed to be stronger for men (HR, 1.12; 95% CI, 1.02 to 1.24; $P = .02$) than for women (HR, 1.06; 95% CI, 0.99 to 1.13; 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[8] 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[5] 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.[4] 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).[4] This observation of sex-dependent

Table 5. HRs for Developing Cancer by BMI Category Stratified by Aspirin Treatment in Participants With LS

Variable	CRC Incidence Adjusted HR (95% CI)*	Incidence of Other LS-Related Cancers (excluding CRC) Adjusted HR (95% CI)*	Incidence of All LS-Related Cancers Adjusted HR (95% CI)*
Placebo	36 of 485	28 of 485	62 of 485
BMI, kg/m^2 (quantitative variable)	1.10 (1.03 to 1.17)†	1.03 (0.96 to 1.10)	1.06 (1.02 to 1.11)‡
Under- and normal weight (< 25)	1.00	1.00	1.00
Overweight (25-29.99)	1.46 (0.63 to 3.78)	0.46 (0.16 to 1.29)	0.91 (0.49 to 1.70)
Obese (≥ 30)	2.75 (1.12 to 6.75)§	1.33 (0.51 to 3.52)	1.91 (1.00 to 3.69)‖
Aspirin	18 of 411	15 of 411	33 of 411
BMI, kg/m^2 (quantitative variable)	1.00 (0.90 to 1.12)	0.99 (0.89 to 1.10)	1.00 (0.93 to 1.08)
Under- and normal weight (< 25)	1.00	1.00	1.00
Overweight (25-29.99)	0.74 (0.22 to 3.46)	0.89 (0.21 to 3.77)	0.87 (0.36 to 2.10)
Obese (≥ 30)	2.00 (0.61 to 6.70)	1.14 (0.30 to 4.27)	1.58 (0.66 to 3.81)

Abbreviations: BMI, body mass index; CRC, colorectal cancer; HR, hazard ratio; LS, Lynch syndrome.
*Adjusted for age, sex, starch, mismatch repair gene status, and geographic region.
†Significant at $P = .001$.
‡Significant at $P = .006$.
§Significant at $P = .03$.
‖Significant at $P = .05$.

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/m^2 increase in BMI, CRC risk increased by 7% (95% CI, 4% to 10%).[19] Importantly, among those with LS in our study, each 1-kg/m^2 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 instability (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.[20] In a population-based case-control study, Slattery et al[21] found that increased BMI was associated with greater risk of microsatellite-stable tumors but not of tumors exhibiting MSI. This observation is supported 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,[5] there was a trend (not significant) 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/m^2. 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 homologues, the MLH1 protein forms a heterodimer with PMS2, which leads to the initiation of MMR.[24] Because all MMR proteins are necessary for successful DNA repair, the mechanistic basis for the seemingly 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 definitive 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.[27] 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.

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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

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Appendix

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

Reference	Study Design	Outcome	Sex	BMI (kg/m^2)	Risk Estimate (95% CI)	
					OR	HR
Diergaarde et al*†	Case control	CRC	Both	< 23.2	1 (referent)	
				> 25.5	0.90 (0.4 to 1.8)	
Campbell et al[8]‡	Case control	CRC	M	18.5-24.99	1 (referent)	
				25-29.99	1.25 (0.97 to 1.61)	
				≥ 30	1.83 (1.33 to 2.51)	
			F	18.5-24.99	1 (referent)	
				25-29.99	1.03 (0.80 to 1.33)	
				≥ 30	0.85 (0.62 to 1.16)	
Win et al[9]§‖	Retrospective	CRC	Both	< 18.5		1.04 (0.00 to 1.64)
				18.5-24.99		1 (referent)
				25.0-29.99		1.12 (0.78 to 1.62)
				≥ 30		2.35 (1.30 to 4.23)
Botma et al[5]§	Prospective (incident cohort)	Adenomatous polyps	M	< 25		1 (referent)
				≥ 25		5.19 (1.30 to 20.80)
			F	< 25		1 (referent)
				≥ 25		0.78 (0.20 to 3.05)
	Prospective (prevalent cohort)	Adenomatous polyps	M	< 25		1 (referent)
				≥ 25		1.00 (0.42 to 2.38)
			F	< 25		1 (referent)
				≥ 25		0.91 (0.29 to 2.91)

Abbreviations: BMI, body mass index; CRC, colorectal cancer; HR, hazard ratio; LS, Lynch syndrome; OR, odds ratio.
*Diergaarde B et al: Clin Gastroenterol Hepatol 5:736-742, 2007.
†Both mismatch repair gene mutation carriers (n = 73) and untested individuals suspected of having LS (n = 175).
‡Clinically defined familial risk of cancer (according to Amsterdam or revised Bethesda criteria for LS).
§Known carriers of germline mutations in mismatch repair genes.
‖Estimated from self-reported height and weight at approximately age 20 years.