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Association of Obesity With Risk of Early-Onset Colorectal Cancer Among Women

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IMPORTANCE Colorectal cancer (CRC) incidence and mortality among individuals younger than 50 years (early-onset CRC) are increasing. The reasons for such increases are largely unknown, although the increasing prevalence of obesity may be partially responsible.

OBJECTIVE To investigate prospectively the association between obesity and weight gain since early adulthood with the risk of early-onset CRC.

DESIGN, SETTING, AND PARTICIPANTS The Nurses' Health Study II is a prospective, ongoing cohort study of US female nurses aged 25 to 42 years at study enrollment (1989). A total of 85 256 women free of cancer and inflammatory bowel disease at enrollment were included in this analysis, with follow-up through December 31, 2011. Validated anthropomorphic measures and lifestyle information were self-reported biennially. Statistical analysis was performed from June 12, 2017, to June 28, 2018.

EXPOSURES Current body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared), BMI at 18 years of age, and weight gain since 18 years of age.

MAIN OUTCOMES AND MEASURES Relative risk (RR) for incident early-onset CRC.

RESULTS Among the 85 256 women studied, 114 cases of early-onset CRC were documented (median age at diagnosis, 45 years; interquartile range, 41-47 years) during 1 196 452 person-years of follow-up. Compared with women with a BMI of 18.5 to 22.9, the multivariable RR was 1.37 (95% CI, 0.81-2.30) for overweight women (BMI, 25.0-29.9) and 1.93 (95% CI, 1.15-3.25) for obese women (BMI, ≥30.0). The RR for each 5-unit increment in BMI was 1.20 (95% CI, 1.05-1.38; $P = .01$ for trend). Similar associations were observed among women without a family history of CRC and without lower endoscopy within the past 10 years. Both BMI at 18 years of age and weight gain since 18 years of age contributed to this observation. Compared with women with a BMI of 18.5 to 20.9 at 18 years of age, the RR of early-onset CRC was 1.32 (95% CI, 0.80-2.16) for women with a BMI of 21.0 to 22.9 and 1.63 (95% CI, 1.01-2.61) for women with a BMI of 23.0 or greater at 18 years of age ($P = .66$ for trend). Compared with women who had gained less than 5.0 kg or had lost weight, the RR of early-onset CRC was 1.65 (95% CI, 0.96-2.81) for women gaining 20.0 to 39.9 kg and 2.15 (95% CI, 1.01-4.55) for women gaining 40.0 kg or more ($P = .007$ for trend).

CONCLUSIONS AND RELEVANCE Obesity was associated with an increased risk of early-onset CRC among women. Further investigations among men and to elucidate the underlying biological mechanisms are warranted.

Supplemental content

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The overall colorectal cancer (CRC) incidence and mortality rates have decreased by more than 45% since the 1980s,[1,2] in part owing to greater screening uptake among average-risk adults typically starting at 50 years of age[3,4] and favorable changes in some lifestyle risk factors.[5,6] In contrast to the decreasing trends in adults 50 years or older, incidence and mortality of CRC have been increasing among all age groups between 20 and 49 years.[7-9] According to population-based projections, by 2030, colon cancer will increase by 90% among individuals aged 20 to 34 years and by 28% among those aged 35 to 49 years, and rectal cancer will increase by 124% among individuals aged 20 to 34 years and by 46% among those aged 35 to 49 years.[10] Although the incidence of early-onset CRC remains low at approximately 8 per 100 000 population,[11] it represents at least 10% of total CRC that have not been prevented or detected through screening.[12]

The drivers for the increases in incidence of early-onset CRC have not been elucidated.[13] Increasing prevalence of established CRC risk factors, such as obesity,[14] sedentary lifestyle,[15-17] Western diet,[18-20] and diabetes,[21] may contribute. However, these factors were identified in studies that captured CRC predominantly among older individuals. With the emerging evidence that sporadic early-onset CRC may have distinct molecular features[22-26] compared with cancers that arise in older individuals and that these cases are often detected at a more advanced stage[9] with greater years of life lost,[27] there is an urgent and unmet public health and clinical need to identify risk factors of early-onset CRC to develop targeted preventive and detection strategies for younger adults with higher risk.[8,28]

Thus far, few studies[29,30] have prospectively evaluated the association between obesity and risk of early-onset CRC. Because of the parallel increase in obesity[31,32] and early-onset CRC, a thorough examination of the role of current and early-life obesity is among the first steps in our understanding of the increasing burden of early-onset CRC.[7,33,34] We used data from the Nurses' Health Study II (NHSII), a US-based prospective cohort of young women with detailed assessments of body weight, family and endoscopy histories, lifestyle factors, and other potential CRC risk factors to comprehensively examine the association of obesity with CRC diagnosed before 50 years of age.

Key Points

Question Is obesity associated with early-onset colorectal cancer, which may have etiologic differences from late-onset colorectal cancer?

Findings In a prospective cohort study of 85 256 women, those with obesity (body mass index ≥30) had a nearly doubled risk of early-onset colorectal cancer compared with women with a body mass index of 18.5 to 22.9.

Meaning The findings suggest that obesity is associated with an increased risk of early-onset colorectal cancer; further investigations are needed to identify whether this association is causal.

Methods

Study Population

This prospective cohort study included 85 256 women aged 25 to 42 years from the NHSII who were free of cancer and inflammatory bowel disease at enrollment and were followed up from 1989 to December 31, 2011. The NHSII is an ongoing prospective cohort study that began in 1989, when 116 430 female nurses aged 25 to 42 years living in 14 US states provided detailed information on lifestyle and medical history. Participants were followed up every 2 years since inception by self-administered questionnaires on demographics, lifestyle factors, and medical and other health-related information, which were complemented by quadrennial assessments of dietary intake using semiquantitative food frequency questionnaires. The overall active follow-up rate was approximately 90%,[35] and 98% of deaths are documented.[36] We excluded women who reported implausible energy intake (<500 or >3500 kcal/d, n = 2193) and women with a prior diagnosis of cancer or inflammatory bowel disease at baseline (n = 415). Participants who did not report baseline weight or weight at 18 years of age were also excluded (n = 1117). We additionally excluded participants whose baseline body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) was less than 18.5 (n = 2964). Participants with a BMI less than 18.5 in subsequent cycles were skipped (n = 4146). Participants provided written informed consent. Data were deidentified. This study was approved by the institutional review board of the Brigham and Women's Hospital.

Ascertainment of CRC

We requested written permission to acquire medical records and pathology reports from participants who reported having CRC on biennial questionnaires. We also identified unreported, lethal CRC cases through family members, the postal system, and the National Death Index. For all deaths due to CRC, we requested medical records from next of kin. An NHSII study physician masked to exposure information reviewed medical records to verify CRC diagnosis and extracted information on histopathologic findings and anatomical location. Our primary end point was incident CRC diagnosed before 50 years of age.

Assessment of Anthropomorphic Measures

In the NHSII, height and weight were reported at baseline, and weight was updated biennially. In the NHS, the predecessor to the NHSII, self-reported body weight correlated well with measured weight (correlation coefficient, 0.97).[37] We categorized current BMI (BMI according to the immediately preceding questionnaire) based on accepted standards using 18.5 to 20.9, 21.0 to 22.9, 23.0 to 24.9, 25.0 to 29.9, and 30.0 or greater.[38,39] At baseline, participants were asked to recall their body weight at early adulthood (18 years of age). In a prior validation study, we observed a correlation coefficient of 0.87 between recalled weight and weight obtained from school records at 18 years of age.[40] Because participants were generally leaner at 18 years of age, we categorized early adulthood BMI using less than 18.5, 18.5 to 20.9, 21.0 to 22.9, and 23.0 or greater.[39] We calculated weight change as the difference between current weight and weight at 18 years of age. At baseline, we also asked participants to recall their body shapes at 5, 10, and 20 years of age using a validated 9-level pictogram.

Pictograms are graphic representations of body shape, ranging from 1 (most lean) to 9 (most overweight).[35] Body shape reported retrospectively was used as a measurement of body fat and correlated well with measured BMI.[35,41]

Assessment of Covariates

Biennially, we asked participants to report lower gastrointestinal tract endoscopies. The indication for endoscopy, including symptoms (eg, bleeding or abdominal pain), family history of CRC, or routine screening without symptoms, was collected. We assessed total caloric, red meat, fiber, calcium, folate, and alcohol consumption using semiquantitative food frequency questionnaires every 4 years since 1991.[42] Diet quality was assessed using the Alternative Healthy Eating Index 2010, for which a higher score has been consistently associated with reduced risk of cancer, diabetes, and cardiovascular disease.[43,44] Physical activity was self-reported with validated questionnaires every 2 to 4 years.[45] A metabolic equivalent of tasks (MET) score based on energy expenditure was assigned to each type of physical activity, and the amount of total physical activity was calculated by multiplying the MET score by the mean time spent in each activity. Smoking status was updated every 2 years,[46] and pack-years among smokers were derived by multiplying the number of packs smoked daily by the number of years during which that amount was smoked.[46] Participants also updated information on family history of CRC among first-degree relatives, regular use of aspirin, nonaspirin nonsteroidal anti-inflammatory drug use, multivitamin use, diabetes, menopausal status, and use of menopausal hormone therapy regularly.[47-50]

Statistical Analysis

We evaluated the association between current BMI and risk of early-onset CRC as the primary analysis. We also examined the contribution of BMI at 18 years of age, weight gain since 18 years of age, and early-life body shape. Person-time accrued from the return of the baseline questionnaire until the date of CRC diagnosis, death from any cause, 50th birthday, or the end of follow-up, whichever came first.

We used Cox proportional hazards regression models stratified by age (months) and study period (2-year intervals) to estimate multivariable-adjusted hazard ratios and 95% CIs to approximate relative risks (RRs). Covariates were chosen a priori based on established risk factors of CRC and were included in the model on a time-varying basis, including height (continuous), family history of CRC (yes/no), personal history of diabetes (yes/no), screening lower endoscopy within 10 years (yes/no), lower endoscopy for other indications within 10 years (yes/no), smoking pack-years (continuous), physical activity (continuous), alcohol use (continuous), regular use of aspirin (yes/no), nonsteroidal anti-inflammatory drug use (yes/no), multivitamin use (yes/no), menopausal status (premenopausal or postmenopausal), menopausal hormone use (never, past, or current), and dietary intake (total calories, red meat, fiber, folate, calcium, and Alternate Healthy Eating Index 2010, all continuous). For dietary factors, we calculated the cumulative average to represent long-term consumption.[51,52] Tests for linear trend were performed using variables of interest as continuous variables. We examined possible nonlinear associations using restricted cubic splines.[53-55]

We performed sensitivity analyses using cumulative-average BMI. To minimize the possibility that undiagnosed CRC may have contributed to weight change, we introduced a 4-year lag analysis. We also performed subgroup analyses based on tumor site (colon or rectum), year of diagnosis (before or after 2001), smoking status (never or ever), and physical activity (fourth to fifth quintiles or first to third quintiles). We also conducted joint analysis of BMI at 18 years of age and weight change since 18 years of age.

Finally, we examined whether the association between BMI and risk of CRC differed according to age of diagnosis using duplication-method Cox proportional hazards regression modeling.[56] In brief, we followed up women for all incident CRC through 2011 and examined the association of BMI with early-onset CRC and late-onset CRC (CRC diagnosed at 50 years or older). For the analysis of late-onset CRC, early-onset CRC cases were censored at diagnosis. *P* for heterogeneity was calculated assuming a linear association between current BMI vs early-onset or late-onset CRC using a likelihood ratio test. Statistical significance was set as $P \leq .05$ in 2-tailed tests. Analyses were conducted with SAS statistical software, version 9.4 (SAS Institute Inc). Statistical analysis was performed from June 12, 2017, to June 28, 2018.

Results

Among the 85 256 women studied, 114 cases of early-onset CRC were documented (median age at diagnosis, 45 years; interquartile range, 41-47 years) during 1 196 452 person-years of follow-up. The median follow-up duration was 13.9 years. The age-standardized characteristics of person-years according to current BMI are given in **Table 1**. Baseline characteristics in 1989 are given in eTable 1 in the Supplement. Women with higher current BMI were older and more likely to have diabetes. They engaged in less physical activity and consumed more red meat. Current BMI was correlated with BMI at 18 years of age (Pearson correlation coefficient, 0.55).

Obesity was independently associated with an increased risk of early-onset CRC. Compared with women with a BMI of 18.5 to 22.9, women with a BMI of 23.0 to 24.9 had a multivariable RR of 1.33 (95% CI, 0.75-2.36), overweight women (BMI, 25.0-29.9) had an RR of 1.37 (95% CI, 0.81-2.30), and obese women (BMI, ≥30.0) had an RR of 1.93 (95% CI, 1.15-3.25) for early-onset CRC (**Table 2**). This association appears to be linear (Table 2 and the eFigure in the Supplement). Each 5-unit increase in BMI was associated with an RR of 1.20 (95% CI, 1.05-1.38; $P = .01$ for trend). The association between current BMI and risk of early-onset CRC was similar when we restricted the analysis to women with no family history of CRC or to those without lower endoscopy within the past 10 years. When we assessed the cumulative average and 4-year lagged BMI, the association was attenuated but the overall findings were similar (eTable 2 in the Supplement). Although we had limited case numbers, we observed slightly stronger associations for rectal cancer and among women who were past or current smokers (eTable 3 and eTable 4 in the Supplement).

Both BMI at early adulthood and change in weight since early adulthood were associated with risk of early-onset CRC (**Table 3** and the eFigure in the Supplement). Compared with participants

Table 1. Characteristics of Person-Years According to Current BMI Among Women Younger Than 50 Years in the Nurses' Health Study II[a]

Characteristic	Current BMI			
	18.5-22.9	23.0-24.9	25.0-29.9	≥30.0
Age, mean (SD), y	39.7 (5.8)	40.9 (5.6)	41.7 (5.5)	42.4 (5.2)
Person-years, No.	455 250	217 271	296 763	230 169
BMI at 18 y of age, mean (SD)	19.8 (1.9)	20.8 (2.3)	21.8 (2.8)	24.7 (4.5)
Weight change since 18 y of age, mean (SD), kg[b]	3.7 (5.5)	8.4 (6.5)	14.6 (8.3)	29.6 (14.5)
Height, mean (SD), cm	165 (7)	164 (6)	165 (7)	164 (7)
Postmenopausal women	6.1	6.9	7.7	8.8
Current menopausal hormone therapy among postmenopausal women	68.8	71.0	68.8	64.7
Family history of colorectal cancer	5.5	5.4	5.5	5.6
Screening lower endoscopy within past 10 y	3.1	3.1	3.1	3.2
Lower endoscopy for other indications within past 10 y[c]	6.1	6.1	6.8	7.9
History of diabetes	0.7	0.9	1.4	4.6
Ever smokers	32.5	33.6	33.4	33.5
Pack-years among ever smokers, mean (SD)	11.4 (9.2)	12.0 (9.2)	12.6 (9.4)	13.1 (9.7)
Alcohol intake, mean (SD), g/d	4.3 (7.4)	4.0 (7.1)	3.5 (6.9)	2.3 (5.8)
Physical activity, mean (SD), MET h/wk	25.0 (30.9)	22.1 (27.8)	19.4 (25.4)	14.7 (21.1)
Regular aspirin use	10.0	10.3	10.8	12.0
Regular NSAID use	20.8	24.0	27.8	34.6
Current use of multivitamin	47.5	46.1	44.7	41.0
Total energy intake, mean (SD), kcal/d	1789 (537)	1790 (539)	1813 (556)	1862 (582)
Red meat intake, mean (SD), servings per week	5.6 (4.4)	6.1 (4.5)	6.6 (4.8)	7.5 (5.3)
Fiber intake, mean (SD), g/d	19.4 (6.2)	19.1 (5.9)	18.8 (5.6)	18.0 (5.4)
Folate intake, mean (SD), μg/d	537 (300)	530 (302)	524 (301)	494 (294)
Calcium intake, mean (SD), mg/d	1114 (520)	1102 (511)	1094 (507)	1052 (498)
Alternate Healthy Eating Index 2010, mean (SD)	46.6 (11.2)	45.9 (10.8)	45.3 (10.7)	43.4 (10.6)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); MET, metabolic equivalent of tasks; NSAID, nonsteroidal anti-inflammatory drugs.

[a] Data are presented as mean (percentage) of person-years unless otherwise indicated. All values other than age have been directly standardized to age distribution (in 5-year age group) of all the participants.

[b] Weight loss was calculated as a negative value.

[c] Lower endoscopy for indications other than screening (eg, having symptoms, family history of colorectal cancer, follow-up endoscopy, or positive fecal occult blood test result).

Table 2. Current BMI and Risk of Early-Onset Colorectal Cancer

Variable	No. of Cases	No. of Person-Years	Age-Adjusted RR (95% CI)	Multivariable-Adjusted RR (95% CI)[a]
All Participants				
Current BMI				
18.5-22.9	29	455 250	1 [Reference]	1 [Reference]
23.0-24.9	20	217 271	1.27 (0.71-2.24)	1.33 (0.75-2.36)
25.0-29.9	30	296 763	1.32 (0.79-2.22)	1.37 (0.81-2.30)
≥30	35	230 169	1.86 (1.13-3.06)	1.93 (1.15-3.25)
Each 5-unit increase	NA	NA	1.18 (1.04-1.35)	1.20 (1.05-1.38)
P for trend[b]	NA	NA	.01	.01
Participants Without Family History of Colorectal Cancer				
Current BMI				
18.5-22.9	25	429 876	1 [Reference]	1 [Reference]
23.0-24.9	17	205 824	1.22 (0.66-2.27)	1.27 (0.68-2.36)
25.0-29.9	27	280 184	1.36 (0.79-2.36)	1.40 (0.81-2.44)
≥30	30	216 759	1.82 (1.06-3.11)	1.88 (1.07-3.30)
Each 5-unit increase	NA	NA	1.17 (1.01-1.35)	1.18 (1.02-1.38)
P for trend[b]	NA	NA	.03	.03
Participants Without Endoscopy in Past 10 Years				
Current BMI				
18.5-22.9	25	420 262	1 [Reference]	1 [Reference]
23.0-24.9	17	200 095	1.23 (0.66-2.29)	1.28 (0.69-2.38)
25.0-29.9	25	269 644	1.26 (0.72-2.20)	1.30 (0.74-2.29)
≥30	34	205 587	2.01 (1.19-3.40)	2.10 (1.22-3.63)
Each 5-unit increase	NA	NA	1.21 (1.06-1.38)	1.23 (1.07-1.42)
P for trend[b]	NA	NA	.005	.004

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); NA, not applicable; RR, relative risk.

[a] All multivariable-adjusted RRs were adjusted for height (continuous), history of diabetes (yes/no), smoking pack-years (continuous), physical activity (continuous), alcohol intake (continuous), regular use of aspirin (yes/no), nonsteroidal anti-inflammatory drug use (yes/no), multivitamin use (yes/no), menopausal status (premenopausal or postmenopausal), menopausal hormone use (never, past, and current), and dietary intake (total calories, red meat, fiber, folate, calcium, and Alternate Healthy Eating Index 2010, continuous). Analyses among all participants and participants without family history of colorectal cancer were also adjusted for lower endoscopy for screening (yes/no) or for other indications (yes/no) within the past 10 years. Analyses among all participants and participants without endoscopy in past 10 years were also adjusted for family history of colorectal cancer (yes/no).

[b] Calculated using the current BMI as a continuous variable.

Table 3. BMI at 18 Years of Age, Change in Body Weight Since 18 Years of Age, and Risk of Early-Onset Colorectal Cancer

Variable	No. of Cases	No. of Person-Years	Age-Adjusted RR (95% CI)	Multivariable-Adjusted RR (95% CI)[a]	Multivariable-Adjusted RR (95% CI)[a,b]
BMI at 18 Years of Age					
BMI					
<18.5	13	146 589	1.13 (0.60-2.11)	1.06 (0.56-2.00)	1.05 (0.56-1.97)
18.5-20.9	39	512 802	1 [Reference]	1 [Reference]	1 [Reference]
21.0-22.9	27	278 558	1.29 (0.79-2.11)	1.34 (0.82-2.20)	1.32 (0.80-2.16)
≥23	35	258 504	1.72 (1.09-2.72)	1.72 (1.08-2.74)	1.63 (1.01-2.61)
Each 5-point increase	NA	NA	1.09 (0.84-1.42)	1.08 (0.83-1.41)	1.06 (0.81-1.40)
P for trend[c]	NA	NA	.51	.58	.66
Weight Change Since 18 Years of Age[d]					
Loss or gain <5.0 kg[e]	27	373 061	1 [Reference]	1 [Reference]	1 [Reference]
Gain of 5.0-19.9 kg	42	561 417	0.86 (0.53-1.41)	0.86 (0.52-1.42)	0.86 (0.52-1.43)
Gain of 20.0-39.9 kg	34	214 633	1.66 (0.99-2.77)	1.64 (0.96-2.81)	1.65 (0.96-2.81)
Gain ≥40.0 kg	11	47 342	2.25 (1.11-4.59)	2.15 (1.02-4.54)	2.15 (1.01-4.55)
Each 5-kg increase	NA	NA	1.09 (1.03-1.16)	1.09 (1.03-1.16)	1.09 (1.02-1.16)
P for trend[c]	NA	NA	.002	.006	.007

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); NA, not applicable; RR, relative risk.

[a] Additionally adjusted for height (continuous), family history of colorectal cancer (yes/no), history of diabetes (yes/no), screening lower endoscopy within the past 10 years (yes/no), lower endoscopy for other indications within the past 10 years (yes/no), smoking pack-years (continuous), physical activity (continuous), alcohol intake (continuous), regular use of aspirin (yes/no), nonsteroidal anti-inflammatory use (yes/no), multivitamin use (yes/no), menopausal status (premenopausal or postmenopausal), menopausal hormone use (never, past, and current use of menopausal hormones), and dietary intake (total calories, red meat, fiber, folate, calcium, and Alternate Healthy Eating Index 2010, continuous).

[b] For the model for BMI at 18 years of age, we additionally adjusted for weight change since 18 years of age. For the model for weight change since 18 years of age, we additionally adjusted for BMI at 18 years of age.

[c] Calculated using BMI at 18 years of age or weight change since 18 years of age as a continuous variable.

[d] Weight change was calculated as current weight minus weight at 18 years of age.

[e] Two patients with early-onset CRC had weight loss of 5.0 kg or more since 18 years of age. The multivariable-adjusted RR was 0.59 (95% CI, 0.13-2.65) compared with women with weight change within 5.0 kg. Because of the limited number of cases, we combined weight loss of 5.0 kg or more and weight change within 5.0 kg in the same category.

with a BMI of 18.5 to 20.9 at 18 years of age, the RR was 1.63 (95% CI, 1.01-2.61) for participants with a BMI of 23.0 or higher at 18 years of age (*P* = .66 for trend). Compared with women who had lost weight or gained less than 5.0 kg since 18 years of age, the RR was 1.65 (95% CI, 0.96-2.81) for women gaining 20.0 to 39.9 kg and 2.15 (95% CI, 1.01-4.55) for women gaining 40.0 kg or more. The RR for every 5.0-kg increase in weight since 18 years of age was 1.09 (95% CI, 1.02-1.16; *P* = .007 for trend). Women with a BMI of 23.0 or greater at 18 years of age and weight gain of 20.0 kg or more had the highest risk of early-onset CRC (eTable 5 in the Supplement). Body shape during childhood (5 years of age) and adolescence (10 years of age) and change in body shape during early life were not associated with risk of early-onset CRC (eTables 6 and 7 in the Supplement). Body shape during early adulthood (20 years of age) appeared to correlate with the risk of early-onset CRC. Compared with participants with a pictogram of 1 or 2 (leaner) at 20 years of age, the RR was 1.71 (95% CI, 1.01-2.89) for participants with a pictogram of at least 4 (more obese).

We observed that the association between current BMI and risk of CRC differed significantly according to age at onset (*P* = .01 for heterogeneity). Current BMI was associated with risk of early-onset CRC but not CRC diagnosed at 50 years or older (*P* = .38 for trend) (eTable 8 in the Supplement).

Discussion

In this large prospective study of women, we found that higher current BMI, BMI at 18 years of age, and weight gain since early adulthood were associated with increased risk of early-onset CRC. To our knowledge, this study is among the first to investigate prospectively the association between obesity and risk of CRC diagnosed at younger than 50 years. Our additional analyses by age at onset indicate that obesity may play a substantial role in colorectal carcinogenesis among younger people and may contribute to the age-specific differences in CRC trends.[8,57] Our results may help in estimating the contribution of obesity with early-onset CRC trends using simulation studies.[6]

The association between obesity and increased risk of overall CRC diagnosed at a median of over 63 years of age has been well documented, with stronger and more consistent findings among men compared with women.[14,58,59] A recent meta-analysis[60] found a higher risk of colon cancer for each 5-unit increment in BMI of 30% among men and 12% among women. This analysis incorporated findings from the Health Professionals Follow-Up Study[61] and the NHS,[62] 2 large prospective cohorts similar to the NHSII but with participants of older ages and a mean age at CRC diagnosis of 65 years. Early-life body fat, measured by weight or body shape during early adulthood, was also associated with increased risk of overall CRC,[63,64] including in analyses among women in the NHS.[63] However, these studies[63,64] did not examine the associations specifically for early-onset CRC. Little work has been performed to directly evaluate the association between obesity and risk of early-onset colorectal neoplasia in a prospective fashion.[30] A case-control study[29] based in Switzerland and Italy found that BMI at 30 years of age was not associated with risk of CRC at younger than 45 years. In another study,[30] obesity was associated

with increased risk of advanced early-onset colorectal adenoma. Our analyses in a large prospective cohort found that each 5-unit increase in BMI was associated with a 20% increase in risk of early-onset CRC driven by sporadic early-onset CRC. Both BMI at 18 years of age and weight gain since 18 years of age contributed to this association. Moreover, the association between obesity and CRC was stronger for early-onset CRC compared with CRC diagnosed at 50 years or older. Although the study may have been underpowered to fully detect, if any, a weak association between BMI and CRC at 50 years or older,[58] our finding that obesity may be associated with early-onset CRC is in line with a previous meta-analysis[59] in which the association between BMI and CRC was stronger for premenopausal compared with postmenopausal women. Taken together, our findings demonstrate the importance of obesity control during early adulthood as a way to prevent early-onset CRC.

The biological mechanisms underlying the association between obesity and CRC remain unclear.[14] Metabolic syndrome, insulin resistance,[65,66] systemic inflammation, and immunity[67] are important mediators.[68] Microbial dysbiosis may also contribute.[69,70] In addition, obesity can induce mucosal metabolic abnormalities in glycolytic and lipogenic pathways and alter adenosine monophosphate–activated protein kinase and sirtuin function.[71] The positive association observed only with early-onset CRC underscores the need for mechanistic investigations into the interactions among obesity, estrogen, and CRC carcinogenesis in the context of molecular histopathologic profiles.[72] Emerging evidence seems to support the uniqueness of early-onset CRC. For instance, patients with early-onset CRC have a higher rate of long interspersed element 1 hypomethylation and lower frequencies of *BRAF* (OMIM 164757) and *KRAS* (OMIM 190070) mutations, CpG island methylator phenotype, and poorly differentiated foci.[22-26] Elucidating the mediating role of these molecular profiles in obesity-induced colorectal carcinogenesis may provide mechanistic and therapeutic insights.

Apart from direct contributions to colorectal tumorigenesis, obesity could be a surrogate for other established risk factors for CRC.[73] For example, dietary red meat intake and prolonged sedentary time are associated with weight gain[74,75] and risk of CRC.[17,76-78] Metabolic syndrome and diabetes are also correlated with BMI[79] and risk of CRC.[80] Of importance, all these factors have been increasing at the population scale. Taken together, unhealthy diet, sedentary behavior, and resultant excess body weight complicated by metabolic syndrome may independently and collectively increase the risk of early-onset CRC.[33]

Of note, we also observed slightly stronger associations between obesity and rectal cancer compared with cancers of the colon. Rectal cancer incidence rates have been increasing to a greater degree than colon cancer among individuals younger than 50 years.[7] Although the number of patients was limited, our findings suggest that obesity may partially contribute to the comparatively faster increase in early-onset rectal cancer.[7,81] Moreover, our results indicate that the obesity and early-onset CRC association may be stronger among younger women with a history of smoking.

Strengths and Limitations

The strengths of this investigation include the use of a large, well-characterized cohort of younger women. Prospectively collected and validated assessments of weight and other risk factors minimized the influence of residual confounding, recall bias, and measurement errors. Although we could not distinguish whether the findings are the same across all genetic predisposition types, such as familial adenomatous polyposis or Lynch syndrome, our results are generalizable to all persons with early-onset CRC as a group, and the findings were robust when we excluded individuals with family or screening history. Moreover, most early-onset CRC is sporadic; only approximately 7% of cases have confirmed hereditary cancer syndromes.[82] Our robust findings among participants without a family history of CRC and without a lower endoscopy within the past 10 years reassured the role of obesity in sporadic early-onset CRC. We were not able to capture visceral adiposity directly or indirectly because our data on waist and hip measurements were limited. Our study comprised mainly white women. Validations in men and other races/ethnicities are warranted.[8,12]

Conclusions

Obesity and weight gain since early adulthood were associated with increased risk of early-onset CRC in a large, prospective cohort of US women. Given that most of these younger cases are diagnosed symptomatically with more advanced tumors[83] and with a significant influence on years of life lost,[27] our findings reinforce the benefits of maintaining a healthy weight throughout life. Our findings suggest the promise of using body weight to personalize and complement early cancer screening strategies among adults younger than 50 years.[84]

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