Body Mass Index and Risk of Second Obesity-Associated Cancers After Colorectal Cancer: A Pooled Analysis of Prospective Cohort Studies

Todd M. Gibson, Yikyung Park, Kim Robien, Meredith S. Shiels, Amanda Black, Joshua N. Sampson, Mark P. Purdue, Laura E. Beane Freeman, Gabriella Andreotti, Stephanie J. Weinstein, Demetrius Albanes, Joseph F. Fraumeni Jr, Rochelle E. Curtis, Amy Berrington de Gonzalez, and Lindsay M. Morton

See accompanying article on page 3989

Todd M. Gibson, Yikyung Park, Meredith S. Shiels, Amanda Black, Joshua N. Sampson, Mark P. Purdue, Laura E. Beane Freeman, Gabriella Andreotti, Stephanie J. Weinstein, Demetrius Albanes, Joseph F. Fraumeni Jr, Rochelle E. Curtis, Amy Berrington de Gonzalez, Lindsay M. Morton, National Cancer Institute, Bethesda, MD; and Kim Robien, Milken Institute School of Public Health, George Washington University, Washington, DC.

Published online ahead of print at www.jco.org on September 29, 2014.

This research was funded in part by the Intramural program of the National Cancer Institute. The Agricultural Health Study was additionally supported by the National Institute of Environmental Health Sciences (Z01-ES049030) and National Cancer Institute (Z01-CP010119). The Iowa Women's Health Study was funded by National Cancer Institute grant R01 CA39742.

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

Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

Corresponding author: Todd M. Gibson, PhD, St Jude Children's Research Hospital, 262 Danny Thomas Place, Mail Stop 735, Memphis, TN 38105; e-mail: todd.gibson@stjude.org.

© 2014 by American Society of Clinical Oncology

0732-183X/14/3235w-4004w/\$20.00

DOI: 10.1200/JCO.2014.56.8444

ABSTRACT

Purpose

To determine whether prediagnostic body mass index (BMI) is associated with risk of second obesity-associated cancers in colorectal cancer (CRC) survivors, and whether CRC survivors have increased susceptibility to obesity-associated cancer compared with cancer-free individuals.

Patients and Methods

Incident first primary CRC cases (N = 11,598) were identified from five prospective cohort studies. We used Cox proportional hazards regression models to examine associations between baseline (prediagnostic) BMI and risk of second obesity-associated cancers (postmenopausal breast, kidney, pancreas, esophageal adenocarcinoma, endometrium) in CRC survivors, and compared associations to those for first obesity-associated cancers in the full cohort.

Results

Compared with survivors with normal prediagnostic BMI (18.5-24.9 kg/m²), those who were overweight (25-29.9 kg/m²) or obese (30+ kg/m²) had greater risk of a second obesity-associated cancer (n = 224; overweight hazard ratio [HR], 1.39; 95% CI, 1.01 to 1.92; obese HR, 1.47; 95% CI, 1.02 to 2.12; per 5-unit change in BMI HR, 1.12; 95% CI, 0.98 to 1.29). The magnitude of risk for developing a first primary obesity-associated cancer was similar (overweight HR, 1.18; 95% CI, 1.14 to 1.21; obese HR, 1.61; 95% CI, 1.56 to 1.66; per 5-unit change in BMI HR, 1.23; 95% CI, 1.21 to 1.24). Before diagnosis CRC patients were somewhat more likely than the overall cohort to be overweight (44% v 41%) or obese (25% v 21%).

Conclusion

CRC survivors who were overweight or obese before diagnosis had increased risk of second obesity-associated cancers compared with survivors with normal weight. The risks were similar in magnitude to those observed for first cancers in this population, suggesting increased prevalence of overweight or obesity, rather than increased susceptibility, may contribute to elevated second cancer risks in colorectal cancer survivors compared with the general population. These results support emphasis of existing weight guidelines for this high-risk group.

J Clin Oncol 32:4004-4011. © 2014 by American Society of Clinical Oncology

INTRODUCTION

More than 1.1 million people in the United States are living with a colorectal cancer (CRC) diagnosis.¹ Most patients are diagnosed with localized (40%) or regional (36%) disease,¹ which have high 5-year relative survival rates (90% or 70%, respectively), emphasizing the importance of understanding the long-term health of this population.¹ Registry-based studies have shown that CRC survivors have elevated risk of subsequent malignancies compared with the general population,²⁻⁹ which could be due

to genetic susceptibility and/or lifestyle factors. Cancer treatments, particularly radiotherapy, have been linked to elevated risk of subsequent cancers,^{10,11} but are unlikely to account for the majority of these cancers in CRC survivors.¹²

Excess body fatness (overweight/obesity) is a risk factor for primary CRC, as well as breast, endometrial, esophageal, pancreatic, and kidney cancers.¹³ Many of these same cancers occur at elevated rates in CRC survivors compared with the general population,⁴ suggesting obesity may contribute to the observed increases in second cancer risk due to a

combination of increased prevalence of obesity in this population and possibly increased susceptibility to obesity-associated cancers. However, the influence of lifestyle factors and genetic susceptibility on second cancer risk is poorly understood because most registry-based studies lack data on these factors. We therefore examined associations between prediagnosis body mass index (BMI) and risk of second cancers by pooling individual-level data for 11,598 CRC survivors derived from five prospective epidemiologic cohort studies of cancer incidence. Weight loss is a common adverse effect of CRC and subsequent treatments, so prediagnostic BMI may provide a more reliable indicator of long-term weight status. We then compared the association with second cancer risk in CRC survivors to that for first cancer risk in the overall cohort to indirectly address the question of whether survivors have increased genetic susceptibility to obesity-associated cancers.

PATIENTS AND METHODS

Study Population

We identified participants diagnosed with an incident first primary CRC within five large prospective cohort studies: the National Institutes of Health-AARP Diet and Health Study (NIH-AARP)¹⁴; the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO)¹⁵; the Iowa Women's Health Study (IWHS)¹⁶; the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC)¹⁷; and the Agricultural Health Study (AHS).¹⁸ CRC survivors with less than 30 days of follow-up after first cancer diagnosis ($n = 671$), missing BMI at baseline ($n = 445$) or implausible BMI values ($\text{BMI} < 15 \text{ kg/m}^2$ or $\text{BMI} > 50 \text{ kg/m}^2$; $n = 39$) were excluded. We also excluded 95 ($< 1\%$) survivors who were underweight ($\text{BMI} < 18.5 \text{ kg/m}^2$) at baseline to minimize the impact of prevalent disease, resulting in a final analytic cohort of 11,598 CRC survivors. The Institutional Review Boards of the National Cancer Institute and each participating cohort approved this study. All subjects provided written informed consent.

Cancer Ascertainment

Cancers were ascertained via registry linkage (NIH-AARP, IWHS, AHS, ATBC after 1998) or self-report with subsequent medical record verification (PLCO, ATBC before 1999). Ascertainment included all primary cancers, with the exception that PLCO did not record multiple primary cancers at the same topographical site. All cancer diagnoses were translated to the SEER Program Incidence Site Recode based on ICD-O-3.¹⁹ We applied the SEER 2007 Multiple Primary and Histology Coding Rules²⁰ to distinguish new primary malignancies.

Survivors eligible for this analysis had a first primary CRC diagnosis (ICD-O-3 topography codes, colon: C180-189, C260, rectal: C199, C209). Second cancers of interest included the following obesity-associated cancers¹³: postmenopausal breast cancer (C180-C189, C199, C209, C260, with age at diagnosis ≥ 50 years), kidney cancer (C649, C659), pancreatic cancer (C250-C259), endometrial cancer (C540-C549, C559), and esophageal adenocarcinoma (C150-C159 excluding morphology code M8070). Morphology codes M9590-9989 were excluded from all case definitions. Due to lack of ascertainment of same-site multiple primaries in PLCO and potential issues related to recurrence, treatment, and medical surveillance at the site of the first cancer, we censored 184 survivors at diagnosis of a second CRC rather than including them as second obesity-associated cancers.

Exposure Assessment

Data on BMI, participant characteristics, and potential confounders were obtained from questionnaires completed by cohort participants with no prior history of cancer at entry into each study (baseline). BMI was calculated from self-reported height and weight (reported by trained staff for ATBC), and categorized using WHO criteria (normal BMI: 18.5 to 24.9 kg/m^2 ; overweight

BMI: 25.0 - 29.9 kg/m^2 ; obese BMI: $\geq 30.0 \text{ kg/m}^2$).²¹ Original data from each cohort were harmonized to create uniform pooled study variables for race/ethnicity (white, other), CRC stage (local, regional, distant), smoking status (never, former, current), physical activity (low, medium, high, based on relative amounts within each cohort), alcohol use (current use yes/no), and hormone replacement therapy use (never, former, current). Other than BMI, missing data for exposures were included in a separate "missing/unknown" category. This included all PLCO participants for alcohol use and the majority of ATBC cases (52%) for CRC stage. Sensitivity analyses with multivariable models not adjusted for alcohol use or stage yielded results similar to those reported below.

A subset of participants in each cohort provided BMI data on a subsequent follow-up questionnaire, the timing of which varied by cohort. We examined the most recent available post-CRC diagnosis BMI measurement, excluding those occurring after second cancer diagnosis.

Statistical Analysis

We examined associations between prediagnosis BMI and second cancer risk using Cox proportional hazards regression models to determine cause-specific hazard ratios (HRs), with age as the time metric and cohort as a stratification variable. Follow-up started at date of CRC diagnosis and continued until the earliest date of second cancer diagnosis, death, loss to follow-up, or end of cancer ascertainment. Multivariable models included CRC stage and a time-dependent variable for time since CRC diagnosis, as well as sex, race/ethnicity, smoking status, physical activity, alcohol use, and hormone replacement therapy use. Education, time from baseline to CRC diagnosis, parity, age at menarche, and age at menopause did not meaningfully alter HRs and therefore were not included in final models. Addition of an interaction term tested heterogeneity by cohort.

To maximize statistical power, the primary analysis was specified a priori to be risk of any second obesity-associated cancer.¹³ We examined risk of specific second cancers as a secondary analysis due to limited statistical power. Additional secondary analyses included stratification by CRC stage as a proxy for treatment exposures, by duration of follow-up to examine the possible impact of survival, by elapsed time from the baseline questionnaire to CRC diagnosis to assess possible impacts of exposure misclassification, by sex due to differing distributions of obesity-associated cancer types among men and women, and by family history of cancer and young age at CRC diagnosis (≤ 65 years) as proxies for genetic susceptibility to cancer. Interaction terms were used to test for significant differences across strata.

To allow comparison of BMI-cancer associations in the cancer-free cohort population versus CRC survivors, we used Cox proportional hazards regression models to estimate risk of developing first primary obesity-associated cancers (excluding CRC, as in the analysis of second cancers). Analyses of first cancer risk utilized the same multivariable models, but the at-risk group included all cohort participants with no previous cancer diagnosis at baseline and valid BMI data. Follow-up started at cohort entry and continued until the earliest of first cancer diagnosis, death, loss to follow-up, or end of cancer ascertainment.

To investigate death as a potential competing risk in our analyses of BMI and second cancer risk,²²⁻²⁴ we used the Poisson regression method of Fine and Gray²⁵ to evaluate the ratio of subdistribution hazards and plotted the cumulative incidence of overall mortality and second obesity-associated cancers. We further examined associations between prediagnostic BMI categories and risk of all-cause mortality using multivariable Cox regression models with the same covariates described previously. To assess the feasibility of examining changes in BMI over time, we identified a subgroup of participants with follow-up BMI data reported after the initial CRC diagnosis and quantified changes in BMI.

RESULTS

We identified a total of 11,598 first primary CRC survivors (8,470 colon; 3,128 rectum) from five prospective cohorts, of whom 44% were overweight and 25% were obese at baseline (Table 1). The largest

Table 1. Baseline Characteristics of the Pooled Cohort of CRC Survivors, Overall and Stratified by Prediagnostic BMI Categories

Characteristic	Prediagnostic BMI Category								P ^a
	Overall		Normal		Overweight		Obese		
	No.	%	No.	%	No.	%	No.	%	
Total	11,598		3,535	30.5	5,143	44.3	2,920	25.2	
BL age, years†									< .0001
Mean	63.0		63.3		63.1		62.4		
SD	5.6		5.6		5.6		5.6		
Years BL to CRC dx†									< .0001
Mean	6.5		6.9		6.3		6.5		
SD	4.8		5.0		4.7		4.6		
Age at CRC dx, years*									< .0001
Mean	69.4		70.1		69.3		68.8		
SD	6.7		6.6		6.6		6.7		
CRC stage									.35
Local	4,009	34.6	1,208	34.2	1,811	35.2	990	33.9	
Regional	3,691	31.8	1,105	31.3	1,628	31.7	958	32.8	
Distant	1,278	11.0	378	10.7	553	10.8	347	11.9	
Unknown‡	2,620	22.6	844	23.9	1,151	22.4	625	21.4	
First cancer									.04
Colon	8,470	73.0	2,535	71.7	3,760	73.1	2,175	74.5	
Sex									< .0001
Male	6,939	59.8	1,807	51.2	3,419	66.5	1,711	58.6	
Race									.32
White	10,760	92.8	3,293	93.2	4,779	92.9	2,686	92.0	
Smoking status									< .0001
Never	4,154	35.8	1,286	36.4	1,780	34.6	1,088	37.3	
Former	5,172	44.6	1,369	38.7	2,404	46.7	1,399	47.9	
Current	1,928	16.6	787	22.3	799	15.5	342	11.7	
Missing	344	3.0	93	2.6	160	3.1	91	3.1	
Physical activity									< .0001
Low	3,694	31.9	980	27.7	1,555	30.2	1,159	39.7	
Medium	2,160	18.6	607	17.2	985	19.2	568	19.5	
High	4,330	37.3	1,530	43.3	1,957	38.1	843	28.9	
Missing	1,414	12.2	418	11.8	646	12.6	350	12.0	
Alcohol, current									< .0001
Yes	6,850	59.1	2,154	60.9	3,121	60.7	1,575	53.9	
No	2,875	24.8	830	23.5	1,169	22.7	876	30.0	
Missing	1,873	16.2	551	15.6	853	16.6	469	16.1	
HRT use (females only)									< .0001
Never	2,569	55.1	902	52.2	927	53.8	740	61.2	
Former	1,207	25.9	515	29.8	446	25.9	246	20.4	
Current	769	16.5	265	15.3	309	17.9	195	16.1	
Missing	116	2.5	46	2.7	42	2.4	28	2.3	
Family Hx cancer									.09
Yes	5,566	48.0	1,715	48.5	2,408	46.8	1,443	49.4	
No	5,439	46.9	1,647	46.6	2,460	47.8	1,332	45.6	
Missing	593	5.1	173	4.9	275	5.4	145	5.0	

Abbreviations: BL, baseline; BMI, body mass index; CRC, colorectal cancer; dx, diagnosis; Family Hx cancer, first degree relative diagnosed with cancer; HRT, hormone replacement therapy; SD, standard deviation.

*Test for heterogeneity by BMI category; ANOVA for continuous variables, χ^2 test for categorical variables.

†Continuous measures are presented as mean ($\pm$ standard deviation); all others are N (%).

‡CRC stage was not available for 52% of participants from ATBC.

proportion of survivors was from the NIH-AARP study (62%), and the distribution of BMI categories was similar across cohorts (not shown). The mean age of survivors at baseline was 63.0 years, and the mean age at CRC diagnosis was 69.4 years. The majority of CRC cases with specified stage were diagnosed at local or regional stages (86%), and survivors were primarily white (93%) and male (60%). Lifestyle factors differed by prediagnosis BMI category, with normal weight

survivors more likely to be current smokers and to have a high level of physical activity. Obese survivors were less likely to currently consume alcohol or to report use of hormone replacement therapy.

During 128,383 person-years of follow-up after CRC diagnosis (median follow-up = 3.7 years), 224 obesity-associated second cancers were diagnosed (n = 118 postmenopausal breast, n = 43 kidney, n = 34 pancreas, n = 10 esophageal adenocarcinoma, n = 19

endometrium). Compared with survivors who reported being normal weight before CRC diagnosis, those who were overweight had 39% greater risk of a second obesity-associated cancer (HR, 1.39; 95% CI, 1.01 to 1.92), and those who were obese had 47% greater risk (HR, 1.47; 95% CI, 1.02 to 2.12; P_{trend} for categories = .03; Table 2). Across the range of prediagnosis BMI, an increase of 5 BMI units was associated with a 12% nonsignificantly increased risk of second obesity-associated cancers (HR, 1.12; 95% CI, 0.98 to 1.29). There was no evidence of heterogeneity by cohort (P = .99; Appendix Table 1), although second cancer numbers were small for ATBC and AHS (n = 7 for each).

For comparison, risk of developing one of these obesity-associated cancers as a first primary cancer (n = 25,364; n = 15,074 breast, n = 3,440 kidney, n = 2,929 pancreas, n = 931 esophagus, n = 2,990 endometrium) in the pooled population of all individuals was significantly elevated for those who were overweight (HR = 1.18; 95% CI, 1.14 to 1.21) and obese (HR = 1.61; 95% CI, 1.56 to 1.66) at baseline, with a clear dose response trend (P_{trend} for categories < .001; HR = 1.23; 95% CI, 1.21 to 1.24 per 5 BMI units). CRC survivors, before diagnosis, were somewhat more likely than the overall cohort to be overweight (44% v 41%) or obese (25% v 21%).

The most common obesity-associated second cancer among CRC survivors was postmenopausal breast cancer (n = 118; Table 2). The risk estimates for overweight and obesity versus normal weight were suggestive of increased risk, but there were no significant associations or evidence of dose response (overweight HR, 1.36; 95% CI, 0.89 to 2.08; obese HR, 1.17; 95% CI, 0.71 to 1.93). Risk estimates varied by cancer type, and although they were generally elevated for the overweight and obese groups, associations were not statistically significant and 95% CIs were wide due to small case numbers.

Exploratory analyses of prediagnosis BMI and risk of second obesity-associated cancers among subgroups of CRC survivors found no substantial differences by type of first cancer (colon v rectum), stage of CRC, age at CRC diagnosis, family history of cancer, or sex (Table 3). Associations were slightly stronger during the first 5 years of follow-up after CRC and for survivors where baseline BMI was measured within 3 years of CRC diagnosis, but these differences were not statistically significant.

The cumulative incidence of second obesity-associated cancers among CRC survivors was 2% at 5 years postdiagnosis, and was consistently lower in those with normal prediagnostic BMI (1.3% after 5 years) than among those who were overweight (1.7%) or obese (2.1%; Fig 1A). The slightly higher cumulative incidence of second obesity-associated cancers during the first 5 years after CRC diagnosis represented an excess of about eight second cancers per 1,000 survivors. Overall mortality among survivors (n = 3,428 deaths, 65% with CRC as underlying cause) was higher in the obese than normal or overweight groups (5-year cumulative incidence: normal = 29%, overweight = 28%, obese = 32%; Fig 1B), and obesity was associated with increased risk of death in multivariable regression analysis (overweight HR, 0.99; 95% CI, 0.91 to 1.07; obese HR, 1.17; 95% CI, 1.07 to 1.28). In analyses of second obesity-associated cancer risk allowing for death as a competing risk, subdistribution HRs for second obesity-associated cancers in overweight (HR, 1.41; 95% CI, 1.02 to 1.94) and obese (HR, 1.39; 95% CI, 0.96 to 2.00) survivors were similar to the cause-specific HRs in Table 2.

Of the 11,598 CRC survivors in this analysis, 3855 (33%) had BMI data from a follow-up questionnaire ascertained after initial CRC

diagnosis but before second cancer diagnosis or end of follow-up (mean time from CRC diagnosis to questionnaire = 3.9 years). Those with available data during follow-up were younger at CRC diagnosis (mean 68.4 v 70.0 years) and more likely to have local CRC (38% v 25%), be female (46% v 37%), and report never smoking (41% v 33%). Most survivors (n = 2465, 64%) remained within 2 kg/m² of their baseline BMI, with similar numbers reporting increases (17%) or decreases (19%) greater than 2 kg/m². Of all survivors with postdiagnosis BMI, 41% were overweight and 24% were obese. Small numbers of second cancers and limited follow-up time after postdiagnosis BMI measurements precluded examination of associations between weight change and second obesity-associated cancer risk.

DISCUSSION

In this large collaborative study, we provide the first prospective investigation of BMI and subsequent cancer risk in CRC survivors. Our results show that individuals who were overweight or obese before CRC diagnosis had increased risk of subsequent, non-CRC, obesity-associated cancers. The magnitude of the increased risk was similar to that observed for these cancers as first primary malignancies in the cohort. Our results therefore provide evidence that elevated cancer risks in CRC survivors compared with the general population may be related to increased prevalence of overweight or obesity rather than increased susceptibility to obesity-associated carcinogenesis.

Previous registry-based studies have attributed the elevated risk of subsequent cancers in CRC survivors to a likely combination of genetic susceptibility, effects of cancer treatment, and lifestyle factors, but have lacked data on risk factors.⁴ The association between BMI and cancer risk could account for increased risk of second cancers in CRC survivors via a higher prevalence of obesity or enhanced carcinogenic effects of obesity in survivors due to underlying susceptibility. In our pooled cohort study, CRC survivors were more likely than the overall cohort to be overweight or obese before diagnosis, supporting a role for increased prevalence of exposure. However, differences were modest, suggesting a role for other shared risk factors as well. By contrast, comparison of the magnitude of BMI-cancer associations between CRC survivors and the overall cohort population does not support additional susceptibility to obesity-associated carcinogenesis in CRC survivors, though this was an indirect assessment of susceptibility that warrants cautious interpretation.

Overweight and obesity were significantly associated with obesity-associated second cancers as a group, but power was limited to examine associations between BMI and specific second cancers. HRs consistently suggested increased risk for the overweight and obese groups compared with those with normal BMI, but our results demonstrate the need for expanded pooling efforts in future studies of cancer-specific risk factors in cancer survivors.

Compared with CRC survivors with normal prediagnostic BMI, those who were obese had an excess absolute risk 5 years after CRC diagnosis of eight second obesity-associated cancers per 1,000 survivors, suggesting that elevated cancer risks associated with excess body weight remain an important issue after CRC diagnosis. The clinical impact of obesity also extended beyond cancer risk in our cohort of CRC survivors. Those who were obese had significantly greater absolute risk of death (30 deaths per 1,000 survivors after five years). We found a modestly increased risk of overall mortality associated with

Table 2. Associations Between Prediagnostic BMI and Risk of Either a Second Obesity-Associated Cancer Among CRC Survivors or a First Obesity-Associated Cancer Among All Participants at Baseline of the Five Cohort Studies

Type of Cancer	Second Obesity-Associated Cancer Risk							First Obesity-Associated Cancer Risk										
	BMI Category							BMI Category										
	Normal (ref) No.	Overweight			Obese			Normal (ref) No.	Overweight			Obese						
		No.	HR*	95% CI	No.	HR*	95% CI		No.	HR†	95% CI	No.	HR†	95% CI				
All obesity-associated cancers	60	102	1.39	1.01 to 1.92	62	1.47	1.02 to 2.12	1.12	0.98 to 1.29	8,777	9,591	1.18	1.14 to 1.21	6,996	1.61	1.56 to 1.66	1.23	1.21 to 1.24
Breast†	37	52	1.36	0.89 to 2.08	29	1.17	0.71 to 1.93	1.02	0.85 to 1.23	5,922	5,383	1.13	1.09 to 1.17	3,769	1.38	1.32 to 1.44	1.15	1.13 to 1.17
Kidney	9	24	1.57	0.72 to 3.42	10	1.33	0.53 to 3.33	1.26	0.90 to 1.75	843	1,552	1.41	1.29 to 1.53	1,045	2.20	2.01 to 2.42	1.38	1.33 to 1.43
Pancreas	6	16	1.84	0.71 to 4.77	12	2.55	0.93 to 6.96	1.20	0.83 to 1.73	975	1,304	1.10	1.01 to 1.19	650	2.18	1.07 to 1.31	1.05	1.01 to 1.10
Esophagus‡	2	6	1.62	0.33 to 8.12	2	1.23	0.17 to 9.05	0.99	0.44 to 2.23	208	451	1.38	1.17 to 1.63	272	2.01	1.67 to 2.41	1.36	1.26 to 1.46
Endometrium	6	4	0.61	0.17 to 2.21	9	3.19	1.08 to 9.40	1.58	1.02 to 2.43	829	901	1.27	1.16 to 1.40	1260	2.88	2.61 to 3.12	1.57	1.52 to 1.62

Abbreviations: BMI, body mass index; CRC, colorectal cancer; HR, hazard ratio; ref, reference category in regression models.
 *Cause-specific HRs from multivariable Cox regression models adjusted for CRC stage, sex, physical activity, smoking status, alcohol use, and hormone replacement therapy use, and elapsed time since first cancer.
 †Cause-specific HRs from multivariable Cox regression models adjusted for sex, physical activity, smoking status, alcohol use, and hormone replacement therapy use.
 ‡Post-menopausal breast cancer; 1 breast cancer was diagnosed in a male CRC survivor—exclusion of this case did not alter the results.
 §Esophageal adenocarcinoma.

Table 3. Associations Between Prediagnostic BMI and Risk of Second Obesity-Associated Cancers in the Pooled Cohort of CRC Survivors

Characteristic	Second Obesity-Associated Cancer Risk									Pt
	BMI Category									
	Normal (ref) No.	Overweight			Obese			Per 5 BMI Units		
		No.	HR*	95% CI	No.	HR*	95% CI	HR*	95% CI	
CRC survivors	60	102	1.40	1.01 to 1.93	62	1.47	1.02 to 2.12	1.12	0.98 to 1.29	.64
Colon survivors	46	78	1.33	0.92 to 1.93	49	1.48	0.97 to 2.23	1.14	0.98 to 1.33	
Rectum survivors	14	24	1.55	0.78 to 3.06	13	1.45	0.66 to 3.19	1.06	0.78 to 1.44	
CRC stage‡										.65*
Local	23	38	1.40	0.83 to 2.38	26	1.54	0.87 to 2.74	1.07	0.85 to 1.34	
Regional	26	38	1.21	0.73 to 2.02	26	1.48	0.84 to 2.63	1.26	1.02 to 1.57	
Unstaged/Missing	10	24	1.95	0.91 to 4.15	9	1.41	0.56 to 3.55	1.03	0.74 to 1.42	
Follow-up after CRC, years										.42
≤ 5	37	70	1.40	0.93 to 2.11	49	1.46	0.94 to 2.28	1.09	0.93 to 1.29	
> 5	23	32	1.18	0.69 to 2.04	13	0.90	0.45 to 1.82	1.00	0.75 to 1.33	
Time baseline to CRC, years										.28
≤ 3	16	36	1.73	0.95 to 3.15	22	2.11	1.08 to 4.12	1.28	1.01 to 1.62	
> 3	44	66	1.31	0.89 to 1.93	40	1.31	0.84 to 2.03	1.08	0.91 to 1.28	
Age at CRC diagnosis, years										.96
≤ 65	12	20	1.11	0.53 to 2.31	18	1.42	0.66 to 3.03	1.08	0.83 to 1.41	
> 65	48	82	1.44	1.00 to 2.07	44	1.42	0.93 to 2.16	1.13	0.96 to 1.33	
Family history of cancer										.89
Yes	25	56	1.82	1.13 to 2.94	30	1.55	0.90 to 2.68	1.12	0.92 to 1.36	
No	31	41	1.11	0.69 to 1.79	30	1.48	0.88 to 2.48	1.14	0.93 to 1.40	
Sex										.95
Male	12	39	1.73	0.90 to 3.33	15	1.48	0.68 to 3.21	1.17	0.87 to 1.57	
Female	48	63	1.27	0.87 to 1.85	47	1.46	0.96 to 2.22	1.10	0.94 to 1.29	

NOTE. Second obesity-associated cancers included postmenopausal breast, kidney, pancreas, esophageal adenocarcinoma, and endometrium.

Abbreviations: BMI, body mass index; CRC, colorectal cancer; HR, hazard ratio; ref, reference category.

*Cause-specific HRs from multivariable Cox regression models adjusted for CRC stage, sex, physical activity, smoking status, alcohol use, hormone replacement therapy use, and elapsed time since first cancer.

†Test for heterogeneity among the category subgroups.

‡Distant CRC stage not included due to low case numbers (n = 4).

prediagnostic obesity after adjustment for other lifestyle and demographic factors, which was consistent with previous reports from other prospective observational studies,^{22-24,26,27} though these analyses were limited by lack of data on CRC treatment and potential weight change after exposure assessment.²⁸ We similarly were unable to address whether postdiagnostic changes in body weight impact second cancer

risks due to limited availability of longitudinal data. Although those with postdiagnosis BMI in this study may not be representative of all CRC survivors, 65% were overweight or obese, highlighting the need for further research addressing the effectiveness of weight loss as a preventive strategy in this group. Prospective cohort studies have yielded mixed associations between weight loss and first cancer risk,

Fig 1. (A) Cumulative incidence of second obesity-associated cancers in colorectal cancer survivors by prediagnostic body mass index (BMI) category. (B) Cumulative incidence of overall mortality in colorectal cancer survivors by prediagnostic BMI category.

including inverse associations with breast cancer, but no association with colon cancer.²⁹⁻³⁴

This study demonstrates the utility of existing cohorts for examining associations between lifestyle factors and second cancer risk, but also highlights many challenges. In addition to power limitations and limited availability of exposure data collected after CRC diagnosis, we were unable to directly examine the possible impact of treatment for the initial CRC. However, CRC treatment varies by stage,³⁵ with stage I disease primarily treated by surgery alone, whereas patients with more advanced disease receive adjuvant chemotherapy (and radiation therapy for rectal cancer).^{36,37} Thus our similar results stratified by CRC stage indirectly suggest absence of a major impact of treatment differences. Finally, use of existing cohort studies necessitates reliance on exposure collected at baseline of the original cohort study. Notably, prediagnostic BMI may represent “usual BMI” over time and avoids the problem of disease-related weight loss related to assessment of obesity postdiagnosis.

Strengths of this study included pooling of data from prospective studies to identify almost 12,000 CRC survivors, from which second primary malignancies were ascertained primarily using population-based cancer registries. Residual confounding is possible, though we were able to adjust for key potential confounders, including suspected CRC risk factors to address potential collider-stratification bias.^{38,39} Additional limitations included reliance on BMI, which may not always reflect adiposity, and exclusion of second CRCs. Thus we were unable to address whether CRC diagnosis in the context of obesity is associated with elevated risk of cancer in nearby tissues, similar to the concept of field cancerization reported for head/neck cancer and cigarette smoking.⁴⁰

The growing population of cancer survivors has elevated risk of many subsequent cancers compared with the general population, emphasizing the need for effective prevention strategies in this group. Current guidelines advise CRC survivors to maintain a healthy body

weight,⁴¹ but the role of postdiagnostic weight in CRC survival remains unclear,^{22,42} and evidence is lacking regarding obesity and risk of second cancers. We found that overweight and obesity were associated with increased risk of second obesity-associated cancers in CRC survivors, and that the absolute risk of death was highest in obese survivors. These results support application of existing weight guidelines and heightened awareness of obesity-associated cancers among physicians of CRC survivors. They also highlight the need for further research to understand the long-term impact of weight change after CRC diagnosis.

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: Todd M. Gibson, Yikyung Park, Kimberly Robien, Meredith S. Shiels, Amanda Black, Demetrius Albanes, Joseph F. Fraumeni, Amy Berrington de Gonzalez, Lindsay M. Morton

Financial support: Lindsay M. Morton

Administrative support: Demetrius Albanes

Collection and assembly of data: Todd M. Gibson, Yikyung Park, Kimberly Robien, Meredith S. Shiels, Amanda Black, Mark P. Purdue, Laura E. Beane Freeman, Gabriella Andreotti, Stephanie J. Weinstein, Demetrius Albanes, Joseph F. Fraumeni, Lindsay M. Morton

Data analysis and interpretation: Todd M. Gibson, Kimberly Robien, Meredith S. Shiels, Amanda Black, Joshua N. Sampson, Rochelle E. Curtis, Amy Berrington de Gonzalez, Lindsay M. Morton

Manuscript writing: All authors

Final approval of manuscript: All authors

REFERENCES

- Howlader N, Noone A, Krapcho M, et al: SEER Cancer Statistics Review, 1975-2010, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2010/
- Ahmed F, Goodman MT, Kosary C, et al: Excess risk of subsequent primary cancers among colorectal carcinoma survivors, 1975-2001. *Cancer* 107:1162-1171, 2006
- Cluze C, Delafosse P, Seigneurin A, et al: Incidence of second cancer within 5 years of diagnosis of a breast, prostate or colorectal cancer: A population-based study. *Eur J Cancer Prev* 18:343-348, 2009
- Curtis R, Freedman D, Ron E, et al: New Malignancies Among Cancer Survivors: SEER Cancer Registries, 1973-2000. Bethesda, MD, National Cancer Institute, 2006
- Enblad P, Adami HO, Glimelius B, et al: The risk of subsequent primary malignant diseases after cancers of the colon and rectum: A nationwide cohort study. *Cancer* 65:2091-2100, 1990
- Evans HS, Moller H, Robinson D, et al: The risk of subsequent primary cancers after colorectal cancer in southeast England. *Gut* 50:647-652, 2002
- Hemminki K, Li X, Dong C: Second primary cancers after sporadic and familial colorectal cancer. *Cancer Epidemiol Biomarkers Prev* 10:793-798, 2001
- Hoar SK, Wilson J, Blot WJ, et al: Second cancer following cancer of the digestive system in Connecticut, 1935-82. *Natl Cancer Inst Monogr* 68:49-82, 1985
- McCredie M, Macfarlane GJ, Bell J, et al: Second primary cancers after cancers of the colon and rectum in New South Wales, Australia, 1972-1991. *Cancer Epidemiol Biomarkers Prev* 6:155-160, 1997
- Berrington de Gonzalez A, Gilbert E, Curtis R, et al: Second solid cancers after radiation therapy: A systematic review of the epidemiologic studies of the radiation dose-response relationship. *Int J Radiat Oncol Biol Phys* 86:224-233, 2013
- Travis LB, Ng AK, Allan JM, et al: Second malignant neoplasms and cardiovascular disease following radiotherapy. *J Natl Cancer Inst* 104:357-370, 2012
- Berrington de Gonzalez A, Curtis RE, Kry SF, et al: Proportion of second cancers attributable to radiotherapy treatment in adults: A cohort study in the US SEER cancer registries. *Lancet Oncol* 12:353-360, 2011
- World Cancer Research Fund/American Institute for Cancer Research: Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective. Washington, DC, AICR, 2007
- Schatzkin A, Subar AF, Thompson FE, et al: Design and serendipity in establishing a large cohort with wide dietary intake distributions: The National Institutes of Health-American Association of Retired Persons Diet and Health Study. *Am J Epidemiol* 154:1119-1125, 2001
- Prorok PC, Andriole GL, Bresalier RS, et al: Design of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. *Control Clin Trials* 21:273S-309S, 2000
- Sellers TA, Kushi LH, Potter JD, et al: Effect of family history, body-fat distribution, and reproductive factors on the risk of postmenopausal breast cancer. *N Engl J Med* 326:1323-1329, 1992
- The Alpha-Tocopherol, Beta-Carotene Lung Cancer Prevention Study: Design, methods, participant characteristics, and compliance—The ATBC Cancer Prevention Study Group. *Ann Epidemiol* 4:1-10, 1994
- Alavanja MC, Sandler DP, McMaster SB, et al: The Agricultural Health Study. *Environ Health Perspect* 104:362-369, 1996
- Fritz A, Percy C, Jack A, et al: International Classification of Diseases for Oncology, Third Edition. Geneva, Switzerland, World Health Organization, 2000
- Johnson C, Peace S, Adamo P, et al: The 2007 Multiple Primary and Histology Coding Rules. Bethesda, MD, National Cancer Institute, Surveillance, Epidemiology and End Results Program, 2007

21. WHO: Obesity: Preventing and Managing the Global Epidemic. Report of a WHO Consultation. Geneva, Switzerland, World Health Organization, 2000
22. Campbell PT, Newton CC, Dehal AN, et al: Impact of body mass index on survival after colorectal cancer diagnosis: The Cancer Prevention Study-II Nutrition Cohort. *J Clin Oncol* 30:42-52, 2012
23. Doria-Rose VP, Newcomb PA, Morimoto LM, et al: Body mass index and the risk of death following the diagnosis of colorectal cancer in postmenopausal women (United States). *Cancer Causes Control* 17:63-70, 2006
24. Prizment AE, Flood A, Anderson KE, et al: Survival of women with colon cancer in relation to precancer anthropometric characteristics: The Iowa Women's Health Study. *Cancer Epidemiol Biomarkers Prev* 19:2229-2237, 2010
25. Fine J, Gray R: A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 94:496-509, 1999
26. Kuiper JG, Phipps AL, Neuhauser ML, et al: Recreational physical activity, body mass index, and survival in women with colorectal cancer. *Cancer Causes Control* 23:1939-1948, 2012
27. Peller C, Arem H, Pfeiffer RM, et al: Prediagnostic lifestyle factors and survival after colon and rectal cancer diagnosis in the National Institutes of Health (NIH)-AARP Diet and Health Study. *Cancer* 120:1540-1547, 2014
28. Parkin E, O'Reilly DA, Sherlock DJ, et al: Excess adiposity and survival in patients with colorectal cancer: A systematic review. *Obes Rev* 15:434-451, 2014
29. Eliassen AH, Colditz GA, Rosner B, et al: Adult weight change and risk of postmenopausal breast cancer. *JAMA* 296:193-201, 2006
30. Harvie M, Howell A, Vierkant RA, et al: Association of gain and loss of weight before and after menopause with risk of postmenopausal breast cancer in the Iowa women's health study. *Cancer Epidemiol Biomarkers Prev* 14:656-661, 2005
31. Renehan AG: Bariatric surgery, weight reduction, and cancer prevention. *Lancet Oncol* 10:640-641, 2009
32. Renehan AG, Flood A, Adams KF, et al: Body mass index at different adult ages, weight change, and colorectal cancer risk in the National Institutes of Health-AARP Cohort. *Am J Epidemiol* 176:1130-1140, 2012
33. Thygesen LC, Gronbaek M, Johansen C, et al: Prospective weight change and colon cancer risk in male US health professionals. *Int J Cancer* 123:1160-1165, 2008
34. Steins Bisschop CN, van Gils CH, Emaus MJ, et al: Weight change later in life and colon and rectal cancer risk in participants in the EPIC-PANACEA study. *Am J Clin Nutr* 99:139-147, 2014
35. Butler EN, Chawla N, Lund J, et al: Patterns of colorectal cancer care in the United States and Canada: A systematic review. *J Natl Cancer Inst Monogr* 2013:13-35, 2013
36. Benson AB 3rd, Bekaii-Saab T, Chan E, et al: Rectal cancer. *J Natl Compr Canc Netw* 10:1528-1564, 2012
37. Engstrom PF, Arnoletti JP, Benson AB 3rd, et al: NCCN Clinical Practice Guidelines in Oncology: Colon cancer. *J Natl Compr Canc Netw* 7:778-831, 2009
38. Berrington de Gonzalez A, Morton LM: Converting epidemiologic studies of cancer etiology to survivorship studies: Approaches and challenges. *Cancer Epidemiol Biomarkers Prev* 21:875-880, 2012
39. Cole SR, Platt RW, Schisterman EF, et al: Illustrating bias due to conditioning on a collider. *Int J Epidemiol* 39:417-420, 2010
40. Strong MS, Incze J, Vaughan CW: Field cancerization in the aerodigestive tract: Its etiology, manifestation, and significance. *J Otolaryngol* 13:1-6, 1984
41. Meyerhardt JA, Mangu PB, Flynn PJ, et al: Follow-up care, surveillance protocol, and secondary prevention measures for survivors of colorectal cancer: American Society of Clinical Oncology Clinical practice guideline endorsement. *J Clin Oncol* 31:4465-4470, 2013
42. Vrieling A, Kampman E: The role of body mass index, physical activity, and diet in colorectal cancer recurrence and survival: A review of the literature. *Am J Clin Nutr* 92:471-490, 2010

GLOSSARY TERMS

Cox proportional hazards regression model: a statistical model for regression analysis of censored survival data, examining the relationship of censored survival distribution to one or more covariates. This model produces a baseline survival curve, covariate coefficient estimates with their standard errors, risk ratios, 95% CIs, and significance levels.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Body Mass Index and Risk of Second Obesity-Associated Cancers After Colorectal Cancer: A Pooled Analysis of Prospective Cohort Studies

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.

Todd M Gibson

No relationship to disclose

Yikyung Park

No relationship to disclose

Kimberly Robien

No relationship to disclose

Meredith S Shiels

No relationship to disclose

Amanda Black

No relationship to disclose

Joshua N Sampson

No relationship to disclose

Mark P Purdue

No relationship to disclose

Laura E Beane Freeman

No relationship to disclose

Gabriella Andreotti

No relationship to disclose

Stephanie J Weinstein

No relationship to disclose

Demetrius Albanes

No relationship to disclose

Joseph F Fraumeni

No relationship to disclose

Rochelle E Curtis

No relationship to disclose

Amy Berrington de Gonzalez

No relationship to disclose

Lindsay M Morton

No relationship to disclose

Acknowledgment

We thank David Campbell and Leslie Carroll (Information Management Services, Inc, Rockville, MD) for programming support.

Appendix

Table A1. Associations Between Prediagnostic BMI and Risk of Second Obesity-Associated Cancers in Colorectal Cancer Survivors, Stratified by Cohort

Risk of Second Obesity-Associated Cancers										
BMI Category										
Study	Normal (ref) No.	Overweight			Obese			Per 5 BMI Units		Pt
		No.	HR*	95% CI	No.	HR*	95% CI	HR*	95% CI	
Pooled	60	102	1.39	1.01 to 1.92	62	1.47	1.02 to 2.12	1.12	0.98 to 1.29	
NIH-AARP	28	49	1.44	0.89 to 2.31	28	1.47	0.85 to 2.53	1.16	0.96 to 1.41	.99
PLCO	10	14	1.11	0.48 to 2.55	11	1.68	0.69 to 4.06	1.20	0.85 to 1.71	
IWHS	19	32	1.43	0.81 to 2.53	18	1.26	0.65 to 2.45	1.03	0.80 to 1.33	
ATBC	1	4	4.25	0.46 to 39.6	2	6.01	0.51 to 70.7	1.72	0.67 to 4.42	
AHS	2	3	1.93	0.21 to 18.08	2	3.04	0.29 to 31.7	1.16	0.49 to 2.72	

Abbreviations: AHS, Agricultural Health Study; ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; BMI, body mass index; HR, hazard ratio; IWHS, Iowa Women's Health Study; NIH-AARP, National Institutes of Health-AARP Diet and Health Study; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; ref, reference category.

*Cause-specific HRs from multivariable Cox regression models adjusted for colorectal cancer stage, sex, physical activity, smoking status, alcohol use, hormone therapy use, and elapsed time since first cancer.

†Test for heterogeneity by cohort.