Research Article

Cancer Epidemiology, Biomarkers & Prevention

Survival of Women with Colon Cancer in Relation to Precancer Anthropometric Characteristics: the Iowa Women's Health Study

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Abstract

Background: We hypothesized that precancer anthropometric variables are associated with mortality among women who developed colon cancer in a prospective cohort, the Iowa Women's Health Study (IWHS).

Methods: From 1986 to 2005, 1,096 incident cases of colon cancer were identified (mean age at diagnosis, 73 years). Anthropometric characteristics were self-measured before colon cancer diagnosis (in 1986). Cox proportional hazards regression was used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI) for all-cause and colon-cancer mortality, adjusted for age at cancer diagnosis, stage, education, smoking status, and pack-years of smoking.

Results: During the follow-up of up to 20 years, 493 women died; 289 had colon cancer as the underlying cause. The HRs of all-cause death were increased for the highest versus lowest tertile for weight (HR, 1.39; 95% CI, 1.10-1.76; *P* trend = 0.005); waist to hip ratio (WHR; HR, 1.36; 95% CI, 1.08-1.72; *P* trend = 0.008), and waist (HR, 1.45; 95% CI, 1.15-1.82; *P* trend = 0.001). Compared with that for body mass index (BMI) of 18.5 to 24.9 kg/m^2, HRs were increased for BMI ≥30 kg/m^2 (HR, 1.45; 95% CI, 1.14-1.85) and for the few women with BMI <18.5 kg/m^2 (HR, 1.89; 95% CI, 1.01-3.53). Colon cancer mortality was positively associated with WHR and waist: HR, 1.37 (95% CI, 1.02;1.85; *P* trend = 0.04) and 1.34 (95% CI, 1.01-1.80; *P* trend = 0.05), respectively, for the highest versus lowest tertile.

Conclusion: Greater precancer anthropometric measures and BMI <18.5 kg/m^2 predicted poorer survival among colon cancer patients. Higher abdominal adiposity measured by WHR and waist was associated with increased risk of colon cancer death.

Impact: Prediagnostic obesity may be a modifiable risk factor for death in colon cancer patients. *Cancer Epidemiol Biomarkers Prev; 19(9); 2229–37. ©2010 AACR.*

Introduction

About 106,100 people were diagnosed with colon cancer in 2008, making it the third most common cancer in the United States. Five-year relative survival rate is 65% (1, 2). Many studies have shown that the risk of developing colon cancer is associated with general and abdominal obesity, with more consistent associations found for increased waist circumference and waist to hip ratio (WHR) than for body mass index (BMI; refs. 3-6). The Iowa Women's Health Study (IWHS) previously reported that the incidence of colon cancer in postmenopausal women was increased by 70% for those in the highest versus lowest quintile of BMI and by 50% for the highest versus lowest quintile of waist circumference (7).

Many epidemiologic studies have indicated that obesity is related to an elevated mortality from colon cancer but the mortality end point is influenced by both incidence and survival (6, 8, 9). Few studies have specifically investigated the role of obesity in the survival of colon cancer patients (10-14). Among them, only three studies examined cause-specific colon cancer survival in relation to general or abdominal obesity (10-12). It has been suggested that abdominal obesity may better predict all-cause and colorectal cancer mortality than BMI (10, 12).

Thus, although prior research has clearly established that obese people are more likely to get colon cancer and more likely to die from it, little is known about how prediagnostic obesity affects survival in patients newly diagnosed with colon cancer. This is the focus of the present analysis. We hypothesized that increased measures of body size at baseline (i.e., prediagnostic), including weight, waist circumference, WHR, and BMI, are associated with worse prognosis in postmenopausal women with colon cancer. The prediagnostic measurement of several anthropometric characteristics, knowledge

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of underlying causes of death for all cohort members, and the ability to adjust for prognostic risk factors for survival make the IWHS cohort a good resource for examining these relations.

Materials and Methods

The IWHS

A detailed description of the IWHS has been published previously (7). Briefly, in 1986 a mailed questionnaire was sent to 98,030 women ages 55 to 69 years. The 41,836 who completed the questionnaire constituted the cohort. For this study, we excluded women who at baseline self-reported cancer other than nonmelanoma skin cancer (n = 3,830) and women who were premenopausal (n = 547), resulting in 37,459 women at risk for colon cancer. Five follow-up surveys were sent in 1987, 1989, 1992, 1997, and 2004 to update vital status, residence, and exposure information, and high response rates were achieved.

The study population for this analysis included postmenopausal women diagnosed with colon cancer during the period 1986-2005. Incident colon cancer cases were identified through annual linkage to the State Health Registry of Iowa, part of the Surveillance, Epidemiology, and End Results (SEER) Program, using codes 18.0 to 18.9 of the International Classification of Diseases for Oncology, 3rd edition (ICD-O; ref. 15). The registry provided information on tumor location (proximal or distal), extent of cancer at diagnosis, grade (well, moderately, poorly, or undifferentiated), and first course of treatment (surgery, radiation, chemotherapy). Extent of disease (stage) was coded as *in situ* (stage 0, noninvasive), local (stage I, confined to the bowel), regional (stage II, spread through bowel into adjacent organs and/or through lymph nodes), and distant (stage III, metastatic). *In situ* and local cases were combined in this analysis. The number of *in situ* cases was small (n = 42); repeating the analysis after excluding these cases did not substantively change the results.

The annual migration rate from Iowa was <1%, meaning SEER provided very complete follow-up (16). Colon cancer patients were excluded if they had cancer other than colon cancer as their first cancer (n = 113). As a result, our analytical cohort consisted of 1,096 colon cancer patients followed from the date of diagnosis until death or December 31, 2005, whichever came first. Of note, we did not include rectal cancer cases because the mechanism between obesity and the incidence or mortality from colon and rectal cancer has not been clearly established, meta-analyses have indicated stronger associations of obesity with the incidence of colon cancer than of rectal cancer (4, 5), and several studies have indicated that BMI does not predict overall mortality or rectal cancer recurrence in women with rectal cancer (11, 17).

Participants' deaths in Iowa were ascertained through the State Health Registry of Iowa. Deaths in nonrespondents and emigrants from Iowa were found through the National Death Index. It has been estimated that 99% of deaths in the cohort were identified (16). The underlying causes of deaths were coded by State nosologists. Death from colon cancer was defined by an underlying cause of death from colon cancer: 18.0-18.9 (9th Revision ICD-9) or C91.0-95.9 (10th Revision ICD-10).

Exposure assessment

Self-measured height and weight at baseline as well as self-measured weight at each follow-up were used to calculate BMI (kg/m^2). WHR at baseline was calculated using waist (1 inch above umbilicus) and hips (maximal protrusion) measured by a friend with a tape sent to participants (18). The anthropometric measures in IWHS have been shown to be valid (interclass correlation coefficient in comparison with measurements by a trained technician, $r \geq 0.84$ in 87 women) and reliable (intraclass correlation of two self-measures taken 2 months apart by 41 women, $r \geq 0.85$; ref. 19).

The baseline questionnaire also collected information on sociodemographic characteristics and lifestyle behaviors such as education level, smoking status, number of pack-years, usual alcohol intake within the last year, multivitamin use, and physical activity level. Self-reported information on history of hormone replacement therapy (HRT) use, diabetes mellitus, hypertension, and heart disease was collected at baseline and at each follow-up.

The IWHS was conducted under a protocol approved for human subjects research by the University of Minnesota Institutional Review Board. The return of baseline and follow-up questionnaires was considered a subject's consent.

Statistical analysis

Weight, waist circumference, and WHR in 1986 were categorized in tertiles, and BMI (in 1986) was categorized by standard cut points (underweight, <18.5 kg/m^2; normal, 18.5-24.9 kg/m^2; overweight, 25-29.9 kg/m^2; and obese, ≥30 kg/m^2). All-cause mortality and colon cancer mortality among women with colon cancer across BMI categories and WHR tertiles were compared using Kaplan-Meier plots and log rank tests. Lifestyle behaviors, and demographic and treatment characteristics of women at baseline and follow-up were compared across BMI and WHR categories using χ^2 or Fisher's exact tests in the case of categorical variables and using general linear model for continuous variables.

Cox proportional hazard regression was used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI) for risk of all-cause and colon cancer death using SAS software. Survival time was calculated from the diagnosis of colon cancer until death or the end of follow-up. For the analysis of all-cause mortality, subjects who were alive on December 31, 2005 were censored at that point. For the analysis of colon cancer mortality, those who had died from causes other than colon cancer were censored at their date of death and subjects who were alive on December 31, 2005 were censored at that point. The proportional hazard assumptions were tested

Table 1. Characteristics of women diagnosed with colon cancer according to body mass index and waist to hip ratio tertiles

Variable	BMI (kg/m^2)					WHR tertiles			
	<18.5 (*n* = 14)	18.5-24.9 (*n* = 370)	25-29.9 (*n* = 417)	≥30 (*n* = 295)	*P*	<0.81 (*n* = 376)	0.81-0.88 (*n* = 356)	>0.88 (*n* = 358)	*P*
Mean age at colon cancer diagnosis (y)	71.5	73.6	72.9	73.0	0.41	73.0	73.4	73.0	0.72
Education beyond high school* (%)	57.1	39.4	37.9	27.2	0.002	39.5	39.3	28.4	0.002
Regular physical activity* (%)	37.5	45.4	41.2	31.0	0.0006	50.5	37.1	34.2	<0.0001
Multivitamin use* (%)	25.0	37.4	26.9	24.6	0.001	33.1	29.1	23.5	0.02
Alcohol drinker, yes* (%)	42.9	48.4	43.7	30.2	<0.0001	50.8	39.3	34.6	<0.0001
Smoking ever* (%)	64.3	40.1	31.5	28.2	0.0006	35.9	32.9	33.1	0.36
Hormone replacement therapy, ever† (%)	35.7	44.2	39.1	33.9	0.06	41.5	42.5	33.5	0.03
History of diabetes† (%)	7.1	7.0	10.8	26.8	<0.0001	7.2	11.5	22.9	<0.0001
History of hypertension† (%)	28.6	35.1	48.4	63.4	<0.0001	34.8	48.9	59.8	<0.0001
History of heart disease† (%)	21.4	17.8	17.5	24.1	0.13	14.3	22.2	21.2	0.01
Stage at diagnosis									
In situ	0	3.9	3.2	5.2	0.19‡	3.8	2.3	5.4	0.15
Local	28.6	41.3	36.3	32.4		40.0	38.5	32.3	
Regional	35.7	41.6	43.9	43.6		41.6	43.7	44.0	
Distant	35.7	13.2	16.7	18.8		14.8	15.5	18.3	
Surgery, yes§ (%)	100	95.1	94.7	92.2	0.36‡	96.8	93.5	92.5	0.03
Chemotherapy, yes§ (%)	0	17.3	18.9	21.0	0.18‡	14.9	19.7	21.8	0.05
Radiation, yes§ (%)	0	1.4	2.9	1.6	0.50‡	2.1	2.8	1.1	0.27

*Variables at baseline (in 1986).
†Variables up to colon cancer diagnosis.
‡Monte-Carlo estimate for the Fisher's exact test was used to calculate *P* values.
§Initial course of therapy.

by including interaction terms between anthropometric characteristics and follow-up time, and were found not to be violated.

Separate analyses and tests for trend were done for each anthropometric measure. Multivariate-adjusted HRs for all-cause and colon cancer mortality and 95% CI were computed after adjustment for confounders. Covariates from Table 1 were included in the model if they were associated with mortality or the anthropometric characteristic being tested and if they altered parameter estimates for the association between the anthropometric measure and mortality by >10%. Using these criteria, the final model for colon cancer mortality and all-cause mortality included age at diagnosis, education level, smoking (smoking status and pack-years), and tumor stage at colon cancer diagnosis. In addition, HRs were adjusted for history of heart disease and diabetes that were modeled as time-dependent variables. Other variables that were tested, but not included into the final model, were alcohol consumption, multivitamin use, HRT use, hypertension, physical activity, and tumor grade. Further, we tested whether stage, history of diabetes, or HRT use modified associations between anthropometric characteristics and all-cause death. No effect modifications were detected (all *P* values were >0.1). Additionally, separate analyses for proximal and distal types of colon cancers were conducted.

All anthropometric characteristics included in the main analysis were self-measured at baseline in 1986 (weight, height, and waist and hip circumferences) or calculated from baseline characteristics (BMI, WHR). Because weight could have changed over time, we repeated analyses with weight and BMI at the follow-up closest to the colon cancer diagnosis. Because the associations did not substantively change, final analyses included anthropometric characteristics measured at baseline.

Finally, to exclude the potential effect of preclinical cancer on anthropometric characteristics, we repeated all analyses after excluding women diagnosed with colon cancer within two years after the baseline ($n = 95$). As the associations were practically unchanged after this exclusion, all women with colon cancer were included in the main analysis.

Results

There were 1,096 women who developed colon cancer during follow-up of up to 20 years. The cases were 56 to 89 years at diagnosis (mean was 73 years). At diagnosis, 39.8% had *in situ* or localized disease, 42.0% had regional spread, 16.0% had distant spread, and 2.2% had an unspecified stage of disease. Of these 1,096 cases, 493 died during follow-up (median survival time was about 10 years). Among all women who died, 289 had colon cancer as the underlying cause of death.

Among our analytical cohort, 38.1% of the women were overweight, 26.9% were obese, and about 1.3% women were underweight prior to diagnosis (using standard BMI cut points). Compared with the whole IWHS cohort (36.9% overweight, 23.5% obese, and 1% underweight women), the proportion of overweight/obese women was slightly higher among those who developed colon cancer, 65.0% versus 60.4%.

Pearson correlations between anthropometric characteristics were calculated among women with colon cancer. Weight characteristics were interrelated: waist circumference with BMI or weight (Pearson coefficient $r = 0.83$), waist circumference with WHR ($r = 0.63$), whereas the correlations of WHR with BMI ($r = 0.41$) and of WHR with weight ($r = 0.37$) were much smaller.

The distribution of patients' characteristics across four BMI categories (underweight, normal, overweight, and obese) and WHR tertiles is shown in Table 1. The distribution of age and stage of diagnosis did not significantly differ across BMI or WHR categories. However, there were more women diagnosed with distant-stage colon cancer among those with the lowest and highest versus normal BMI and among those in the 3rd versus the 1st WHR tertile. As WHR and BMI increased, the percentage of women with histories of diabetes, hypertension, or heart disease before their cancer diagnosis also increased, as did the percentage of women who had chemotherapy as the initial treatment for their cancer, whereas the percentage of those who underwent surgery decreased.

Figure 1A to D presents Kaplan-Meier survival plots across WHR tertiles and BMI categories. Both all-cause

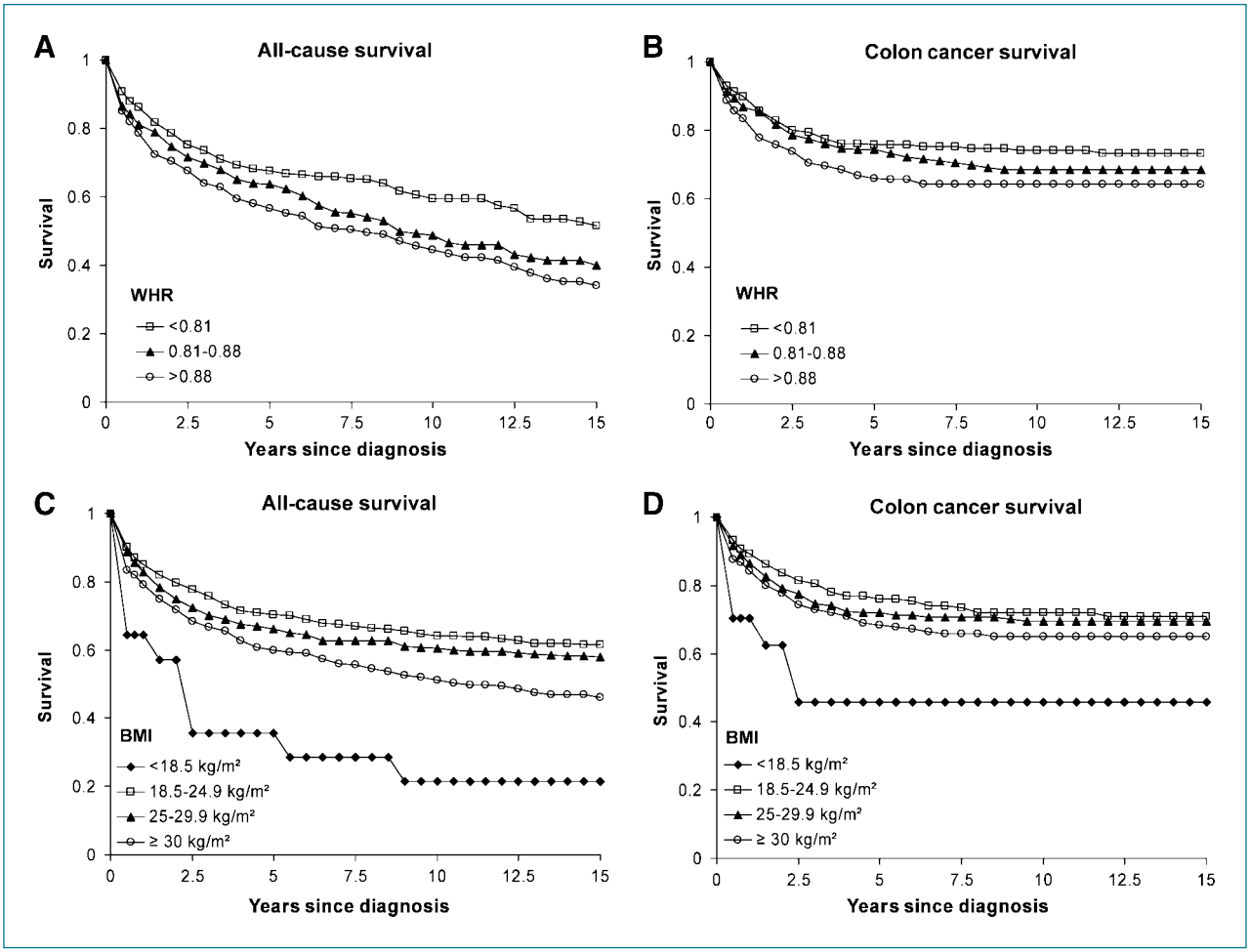

Figure 1. Kaplan-Meier estimates of survival functions among colon cancer patients, IWHS, 1986-2005. A, all-cause survival across WHR tertiles. B, colon cancer survival across WHR tertiles. C, all-cause survival across BMI categories. D, colon cancer survival across BMI categories.

Table 2. Multivariate-adjusted hazard ratios of all-cause death among colon cancer patients across anthropometric measures

Baseline anthropometric measure	All-cause HR (95% CI)				
	No. of all deaths	Adjusted for age at diagnosis	Multivariate-adjusted (1)*	Multivariate-adjusted (2)†	Multivariate-adjusted (3)‡
Weight (pounds)					
≤139	157	1 (reference)	1 (reference)	1 (reference)	1 (reference)
140-165	157	1.03 (0.83-1.28)	1.13 (0.90-1.42)	1.12 (0.89-1.42)	1.13 (0.89-1.42)
≥166	179	1.29 (1.04-1.60)	1.39 (1.10-1.76)	1.37 (1.08-1.73)	1.34 (1.07-1.69)
P trend		0.02	0.005	0.009	0.01
BMI (kg/m^2)					
<18.5	11	3.01 (1.63-5.57)	1.89 (1.01-3.53)	1.90 (1.01-3.57)	2.01 (1.07-3.80)
18.5-24.9	145	1 (reference)	1 (reference)	1 (reference)	1 (reference)
25-29.9	178	1.11 (0.89-1.38)	1.12 (0.89-1.41)	1.11 (0.88-1.40)	1.11 (0.88-1.39)
≥30	159	1.52 (1.22-1.91)	1.45 (1.14-1.85)	1.42 (1.11-1.82)	1.46 (1.15-1.86)
WHR tertiles					
<0.81	142	1 (reference)	1 (reference)	1 (reference)	1 (reference)
0.81-0.88	160	1.31 (1.05-1.64)	1.21 (0.96-1.53)	1.20 (0.95-1.52)	1.24 (0.98-1.57)
>0.88	187	1.51 (1.22-1.88)	1.36 (1.08-1.72)	1.34 (1.08-1.69)	1.34 (1.06-1.69)
P trend		0.0002	0.008	0.02	0.01
Waist tertiles					
≤32.4	143	1 (reference)	1 (reference)	1 (reference)	1 (reference)
32.5-37.4	150	1.07 (0.85-1.34)	1.11 (0.87-1.41)	1.11 (0.87-1.41)	1.10 (0.87-1.40)
≥37.5	197	1.60 (1.29-1.99)	1.45 (1.15-1.82)	1.40 (1.13-1.81)	1.41 (1.12-1.77)
P trend	0	<0.0001	0.001	0.003	0.003

*(1) Adjusted for age at diagnosis, stage, education, and smoking (smoking status and number of pack-years).
†(2) Analysis (1) adjusted for history of heart disease and diabetes as time-dependent covariates.
‡(3) Analysis (1) adjusted for first course treatment surgery, chemotherapy, and radiation.

(Fig. 1A) and colon cancer (Fig. 1B) mortality differed across WHR tertiles; the highest risk of death was observed for the highest tertile (*P* values for log-rank test were 0.02 for colon cancer and 0.0003 for all-cause mortality). All-cause (Fig. 1C) and colon cancer (Fig. 1D) mortality also differed across BMI categories: underweight and obese patients had the highest risk of death (*P* values for log-rank test were 0.02 for both colon cancer and all-cause mortality). Of note, the shapes of the curves were different between all-cause and colon cancer mortality. All-cause (Fig. 1A and C) mortality had a sharp drop in survival early but still declined, if at a decreasing rate after that, whereas for colon cancer death (Fig. 1B and D) there was a sharp decrease in survival early but essentially a flat line after that (i.e., practically no additional colon cancer mortality after five years after diagnosis).

In a multivariate-adjusted model, after controlling for age at diagnosis, education, smoking status, pack-years of smoking, and stage of colon cancer at diagnosis (Table 2), all-cause mortality was associated positively with weight, WHR, and waist: HRs were increased by 36% to 45% for the highest versus lowest tertiles. The risk of all-cause death across BMI categories had a U-shaped pattern. Compared with those with a BMI of 18.5 to 24.9 kg/m^2, HR was 1.45 (95% CI, 1.14-1.85) for obese women (BMI ≥30 kg/m^2) and 1.89 (95%CI, 1.01-3.53) among the few underweight women (BMI <18.5 kg/m^2). After further adjustment for diabetes and heart disease as time-dependent variables, these associations did not substantively change. Nor were the associations markedly changed after adjustment for the first course of treatment, whether surgery, radiation, or chemotherapy (Table 2). Stratification by stage yielded similar patterns for all stages.

Hereafter, we will present analyses for mortality attributed to colon cancer. We observed positive trends for colon cancer–specific mortality with weight, WHR, and waist circumference, and a U-shape for BMI in multivariate-adjusted models similar to the trends for all-cause mortality (Table 3). These associations were not altered after further adjustment for diabetes and heart disease. However, contrary to all-cause mortality, the statistically significant associations for colon cancer mortality were observed only for waist (HR, 1.34; 95% CI, 1.01-1.80; *P* trend = 0.05) and WHR (HR, 1.37; 95% CI, 1.02-1.85; *P* trend = 0.04) for the highest versus lowest tertile. The HRs were slightly attenuated after adjustment

Table 3. Multivariate-adjusted hazard ratios of colon cancer death among colon cancer patients across anthropometric measures

Baseline anthropometric measure	Death from colon cancer HR (95% CI)				
	No. of colon cancer deaths	Adjusted for age at diagnosis	Multivariate-adjusted (1)*	Multivariate-adjusted (2)†	Multivariate-adjusted (3)‡
Weight (pounds)					
≤139	94	1 (reference)	1 (reference)	1 (reference)	1 (reference)
140-165	100	1.11 (0.84-1.48)	1.29 (0.96-1.75)	1.29 (0.96-1.75)	1.30 (0.96-1.76)
≥166	95	1.13 (0.85-1.51)	1.31 (0.96-1.79)	1.33 (0.57-1.81)	1.25 (0.92-1.70)
P trend		0.39	0.09	0.08	0.16
BMI (kg/m^2)					
<18.5	7	2.87 (1.33-6.19)	1.84 (0.84-4.03)	1.90 (0.86-4.16)	2.13 (0.96-4.73)
18.5-24.9	87	1 (reference)	1 (reference)	1 (reference)	1 (reference)
25-29.9	109	1.15 (0.86-1.52)	1.18 (0.87-1.54)	1.18 (0.88-1.59)	1.18 (0.87-1.58)
≥30	86	1.35 (1.00-1.82)	1.32 (0.95-1.82)	1.34 (0.96-1.86)	1.30 (0.95-1.80)
WHR tertiles					
<0.81	86	1 (reference)	1 (reference)	1 (reference)	1 (reference)
0.81-0.88	89	1.17 (0.87-1.57)	1.11 (0.80-1.50)	1.10 (0.81-1.50)	1.11 (0.82-1.51)
>0.88	112	1.48 (1.12-1.96)	1.37 (1.02-1.85)	1.40 (1.03-1.89)	1.31 (0.97-1.77)
P trend		0.006	0.04	0.03	0.09
Waist tertiles					
≤32.4	89	1 (reference)	1 (reference)	1 (reference)	1 (reference)
32.5-37.4	85	0.99 (0.73-1.33)	1.05 (0.77-1.43)	1.05 (0.78-1.44)	1.05 (0.77-1.43)
≥37.5	113	1.46 (1.11-1.93)	1.34 (1.01-1.80)	1.38 (1.02-1.86)	1.28 (0.95-1.71)
P trend		0.008	0.05	0.04	0.11

*(1) Adjusted for age at diagnosis, stage, education, and smoking (smoking status and number of pack-years).
†(2) Analysis (1) adjusted for history of heart disease and diabetes as time-dependent covariates.
‡(3) Analysis (1) adjusted for first course treatment surgery, chemotherapy, and radiation.

for first course of treatment (Table 3). The positive associations between anthropometric characteristics and colon cancer death held for both proximal and distal colon cancers; for example, for the highest versus lowest WHR tertiles, HRs were 1.52 (95% CI, 1.04-2.21) for proximal and 1.38 (95% CI, 0.81-2.56) for distal colon cancer.

We did not observe formal interactions between any of the anthropometric characteristics and stage (P = 0.11-0.39). However, we could have limited power for the analysis of interaction. To further examine a potential modifying effect of stage, we repeated the analyses after stratifying by stage. There were no associations between any of the anthropometric characteristics and colon cancer mortality among women with *in situ*/local stage at diagnosis (Table 4). There were positive trends of WHR and waist with colon cancer mortality among women with regional stage; the association was stronger with WHR than with waist, and was statistically significant for WHR. No associations were observed for BMI or weight in the regional stage. There were positive trends between all anthropometric measures and colon cancer mortality for women with distant stage at diagnosis: the associations were statistically significant for BMI and weight.

In addition, when participants were stratified into two groups by time between baseline and cancer diagnosis (at the median of about 11 years), similar patterns of associations between anthropometric characteristics and all-cause and colon cancer mortality were observed in each group. For instance, for the highest versus lowest WHR tertile, HRs of colon cancer were 1.28 (95% CI, 0.87-1.89) for time <11 years between baseline and colon cancer diagnosis, and 1.27 (95% CI, 0.76-2.10) for time >11 years.

Discussion

This study showed that greater weight, waist, and WHR before diagnosis (at baseline) were risk factors for all-cause mortality for women diagnosed with colon cancer. These associations were independent of age at diagnosis, education, smoking, and stage. The HR of all-cause mortality was also increased among those in the obese BMI category and among those few women in the underweight BMI category compared with women of normal weight. This pattern is similar to the relationship between BMI and all-cause mortality among all IWHS women (7, 20).

There were also statistically significant positive associations of colon cancer mortality with waist circumference and WHR. Women in the highest tertiles of waist and WHR had a 30% to 40% greater colon cancer mortality (similar to all-cause mortality) compared with the lowest tertiles. However, BMI and weight were not significantly associated with colon cancer mortality. Thus, WHR, which reflects abdominal obesity, and waist circumference, which characterizes both abdominal and general obesity, better predict colon cancer death than do the more general markers of obesity, that is, weight and BMI. Of note, the positive relations between anthropometric characteristics and colon cancer death were similar for proximal and distal cancers. Our study was among the first to examine the effects of abdominal adiposity, measured by waist and WHR, on colon cancer mortality.

The magnitude of the associations between anthropometric characteristics and all-cause mortality held for each stage at diagnosis. In contrast, for colon cancer mortality there were no associations with any of the anthropometric measures among women diagnosed with *in situ*/local stage of colon cancer. This could be explained by the fact that colon cancer patients at this stage mostly survive their colon cancer and die from other causes such as cardiovascular disease, which is also associated with obesity. This can diminish the association between colon cancer death and obesity.

Most studies investigating the influence of obesity on survival of colon cancer patients used BMI at diagnosis. Three of them that included participants enrolled in clinical trials of adjuvant chemotherapies showed inconsistent results. Meyerhardt et al. (2003) reported that obese women (BMI $\geq$30 kg/m^2) with colon cancer in stages II and III had a significantly increased risk of overall mortality (by 34%) compared with normal-weight women (BMI 21-24.9 kg/m^2; ref. 13). Similarly, Dignam et al. (2006) examined colon cancer patients with stages II and III and observed an increase in overall mortality (by 28%) and colon cancer death (by 36%) for very obese (BMI $\geq$35 kg/m^2) patients as well as an increase for underweight patients (49% for overall, and 23% for colon cancer mortality) compared with those with normal weight (10). Contrary to these results, a recent study by Meyerhardt et al. (2008), which included patients with stage III colon cancer, detected no statistically significant associations between BMI and cancer recurrence or death (14). Although it is difficult to compare our findings with the results of these studies because of different study designs (these studies included colon cancer patients with stages II and III participating in clinical trials of chemotherapy and used

Table 4. Multivariate-adjusted hazard ratios of colon cancer death among colon cancer patients across anthropometric measures according to stage

Baseline anthropometric measure	Colon cancer death HR* (95% CI)		
	Local and *in situ* (*n* = 437; colon cancer deaths = 31)	Regional (*n*= 460; colon cancer deaths = 109)	Distant (*n* = 175; colon cancer deaths = 141)
Weight (pounds)			
≤139	1 (reference)	1 (reference)	1 (reference)
140-165	0.65 (0.27-1.58)	1.40 (0.87-2.25)	1.43 (0.90-2.25)
≥166	0.95 (0.40-2.23)	0.99 (0.60-1.63)	1.83 (1.14-2.92)
P trend	0.90	0.96	0.01
BMI (kg/m^2)†			
18.5-24.9	1 (reference)	1 (reference)	1 (reference)
25-29.9	0.61 (0.26-1.45)	1.04 (0.65-1.65)	1.57 (0.99-2.50)
≥30	0.93 (0.38-2.30)	0.99 (0.60-1.64)	1.87 (1.13-3.09)
P trend	0.87	0.98	0.02
WHR tertiles			
<0.81	1 (reference)	1 (reference)	1 (reference)
0.81-0.88	0.60 (0.24-1.50)	1.38 (0.82-2.31)	1.09 (0.70-1.70)
>0.88	0.65 (0.28-1.54)	1.83 (1.11-3.00)	1.36 (0.88-2.11)
P trend	0.33	0.02	0.32
Waist tertiles			
≤32.4	1 (reference)	1 (reference)	1 (reference)
32.5-37.4	0.78 (0.33-1.86)	0.81 (0.49-1.36)	1.34 (0.85-2.12)
≥37.5	0.98 (0.42-2.32)	1.37 (0.86-2.19)	1.47 (0.95-2.27)
P trend	0.97	0.19	0.09

*Adjusted for age at diagnosis, education, and smoking (smoking status and number of pack-years).
†Underweight women were not included in this analysis because of small numbers.

BMI measured after cancer diagnosis), our findings for overall and colon cancer mortality are consistent with the findings of Meyerhardt et al. (2003) and Dignam et al. (2006; refs. 10, 13).

Another study from Wisconsin included 633 postmenopausal women with colorectal cancer (cases from a case-control study) who were followed prospectively (11). All-cause mortality was 50% higher for overweight and underweight women compared with normal-weight women. The HR of death from colon cancer was 2.1 (95% CI, 1.1-3.8) for those with BMI >30 kg/m^2, and HR was 2.3 (95% CI, 1.0-5.4) for patients with BMI <20 kg/m^2 compared with colon cancer patients with normal BMI. These results agree with our data in direction, but the HR of mortality from colon cancer for the highest BMI was stronger than that in our study (2.3 versus 1.4, respectively). This could be potentially explained by differences in study design and study populations.

None of the above-mentioned studies explored the association of abdominal obesity with survival of cancer patients, although abdominal obesity measured by waist circumference or WHR may be better predictors of colon cancer incidence and death (3, 7, 21). To our knowledge, the only study that investigated the association of precancer abdominal and general obesity with survival of colorectal cancer patients was an Australian prospective cohort study of 526 patients with anthropometrics measured at baseline (12). Similar to our study, that study found higher waist circumference and increased percent body fat to be associated with increased overall and disease-specific death. HRs for mortality from colorectal cancer were 1.33 (95% CI, 1.04-1.71) per 10-kg increase in body fat and 1.20 (95% CI, 1.05-1.37) per 10-cm increase in waist circumference. In parallel to our study, the Australian cohort study did not observe significant association of colorectal cancer–specific mortality with BMI.

The possible mechanisms of the relation between mortality of colon cancer patients and anthropometric characteristics are not clear. Comorbidities and advanced stage at diagnosis may partially explain these associations: in the IWHS, women with the highest BMI or in the third WHR tertile tended to have more comorbidities and were somewhat more likely to be diagnosed with later stage disease compared with women with normal BMI or low WHR, respectively (Table 1). However, the observed positive relations persisted after adjustment for stage and measured comorbidities. We speculate that some other factors may explain these associations. Obese patients often start therapy later than normal-weight patients or receive different treatments (14, 22). For instance, in the IWHS, women with colon cancer were less likely to undergo surgery for colon cancer if they had higher baseline WHR: in a model adjusted for stage and age at diagnosis, the odds ratio of surgery was 0.75 for the 2nd and 0.45 for the 3rd WHR tertile versus the lowest tertile (P trend = 0.08). This explanation agrees with the slight attenuation of associations between colon cancer death and waist and WHR after adjusting for first course treatment, which is usually surgery for most colon cancer patients. In addition, the absorption of hydrophilic and hydrophobic medications is altered in obese patients, often resulting in incorrect dosages of medication for these patients (23-26). Overweight women could have different pathophysiology of colon cancer, making it more aggressive, its treatment less effective, or leading to unusual complications after treatment.

Furthermore, because we observed a potentially adverse effect of WHR and waist not only on all-cause but also on colon cancer mortality, abdominal obesity may have a direct biological effect (12, 13). The exact mechanism of this effect is unknown, but abnormal glucose tolerance, high levels of insulin, insulin-like growth factor I, and leptin, and increased oxidative stress, typical for patients with abdominal obesity, are known to promote colon cancer progression and increased mortality of colon cancer patients (27-31).

Of note, increased all-cause and colon cancer mortality for underweight colon cancer patients, which is in agreement with several other studies (10, 11), may be explained by the same factors that account for higher mortality of underweight people in general: worse recovery after respiratory and infectious diseases, and worse tolerance of treatment (32, 33). Low numbers of underweight women with colon cancer did not allow us to examine this group in more detail.

The main strength of our study is that we were able to measure general and abdominal obesity using several anthropometric characteristics before cancer diagnosis and examine their role in both all-cause and colon cancer mortality. However, our study has important limitations. For some patients, the anthropometric characteristics had been measured a long time before cancer diagnosis and could have changed over time. However, in the sensitivity analysis that included the measures of weight and BMI closest to diagnosis, associations did not markedly change. Additionally, when participants were stratified into two groups by time between baseline and cancer diagnosis based on the median of about 11 years, the trends between anthropometric characteristics and mortality were observed in each group. Another limitation is that anthropometric measures were self- or friend-measured, and although this is a limitation, studies including those conducted in the IWHS cohort showed these characteristics to be valid and reliable (19, 34). The main weakness of our study is that we lack information about the molecular profile of tumors, about cancer recurrence, and about confounders after cancer diagnosis. We had data only about first course of treatment rather than full treatment or medications, the list of measured covariates after cancer diagnosis was not comprehensive, and the data on comorbidities such as diabetes or heart disease were collected only by self-report. Further, we had only limited statistical power to evaluate associations in subgroups of study participants, particularly among subgroups of women defined by tumor stage. Finally, our findings

were observed for white postmenopausal women and may not generalize to other subgroups of the population.

Our results give further evidence that obesity is not only a risk factor for colon cancer incidence, but it may also increase mortality of postmenopausal women after colon cancer diagnosis.

Our findings suggest that abdominal obesity is more predictive of mortality from colon cancer than is general obesity. Prediagnostic obesity may be a modifiable risk factor for death in patients diagnosed with colon cancer, providing another reason for postmenopausal women to keep their weight and WHR within normal limits.

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