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Association of Weight Change after Colorectal Cancer Diagnosis and Outcomes in the Kaiser Permanente Northern California Population

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Abstract

Background—Higher body mass index (BMI) is associated with incident colorectal cancer (CRC) but not consistently with CRC survival. Whether weight gain or loss is associated with CRC survival is largely unknown.

Methods—We identified 2,781 patients from Kaiser Permanente Northern California diagnosed with stages I-III CRC between 2006-2011 with weight and height measurements within 3 months of diagnosis and ~18 months post diagnosis. We evaluated associations between weight change and CRC-specific and overall mortality, adjusted for sociodemographics, disease severity, and treatment.

Results—Following completion of treatment and recovery from stage I-III CRC, loss of at least 10% of baseline weight was associated with significantly worse CRC-specific mortality (hazard ratio [HR] 3.20; 95% confidence interval [CI], 2.33-4.39; P trend <0.0001) and overall mortality (HR 3.27; 95% CI, 2.56-4.18; P trend <0.0001). For every 5% loss of baseline weight, there was a 41% increased risk of CRC-specific mortality (95% CI, 29%-56%). Weight gain was not significantly associated with CRC-specific mortality (P trend=0.54) or overall mortality (P trend=0.27). The associations were largely unchanged after restricting analyses to exclude patients who died within 6 months and 12 months of the second weight measurement. No significant interactions were demonstrated for weight loss or gain by gender, stage, primary tumor location, or baseline BMI.

Conclusions—Weight loss after diagnosis was associated with worse CRC-specific mortality and overall mortality. Reverse causation does not appear to explain our findings.

Impact—Understanding mechanistic underpinnings for the association of weight to worse mortality is important to improving patient outcomes.

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Conflicts of Interest: None

Keywords

Body mass index; weight change; survival; mortality; colorectal cancer

INTRODUCTION

Higher body mass index (BMI) has been associated with the risk of many cancer types.(1) In a systematic review of studies examining the association between BMI and the risk of colorectal cancer, with inclusion of over seven million subjects and over 93,000 cases, having a BMI of 23.0-24.9, 25.0-27.4, 27.5-29.9 and ≥ 30.0 kilogram (kg)/meter(m)^2 was associated with 14%, 19%, 24% and 41% increased risks of developing CRC (CRC), compared to BMI <23 kg/m^2. (2) The impact of excess adiposity on outcomes in CRC survivors has been less certain. Prospective observational cohort studies in colon and/or rectal cancer survivors have only shown a modest association with outcomes. (3-13) When detected, the association has primarily been restricted to those with BMI ≥ 35 mg/m^2 (class II and III obesity), with approximately 25% worse disease-free survival.(6, 7, 9, 13) Further, some studies have demonstrated a U-shaped curve with potential optimal BMI in the overweight range.(14) Studies have also varied in timing of ascertainment of exposure (prior to diagnosis, at diagnosis and after diagnosis/surgery).(15)

Once diagnosed with CRC, patients seek to know what actions can be taken to improve their outcomes, including changes to diet, level of exercise and weight. While many patients and providers assume that losing weight if overweight or obese would be beneficial and weight gain would be detrimental towards their cancer outcomes, few studies have examined weight change in CRC survivors.(16) In contrast, the breast cancer literature has several studies testing the association with change in weight and outcomes, with gain in weight associated with increased risk of recurrence and/or mortality in some (17-20) but not others (21-23) studies; furthermore, many of those studies have shown that large weight loss may also increase risk of recurrence and/or mortality.

Using electronic medical record (EMR) data collected as a part of standard clinical care, where weight and height were routinely measured at clinic visits, within Kaiser Permanente Northern California (KPNC), we sought to examine change in weight from diagnosis to approximately 18 months after diagnosis and the associations with CRC-specific and overall mortality. Given that KPNC is an integrated health care delivery system and patients receive all of their clinical care within the system, we derived the largest observational cohort to date of stage I – III CRC survivors with availability of multiple weight measurements as well as annotated demographics, tumor characteristics and treatment data.

MATERIALS and METHODS

Study Population

The study cohort was derived from the KPNC cancer registry with ascertainment of all patients diagnosed with Stage I-III invasive CRC between 2006 and 2011, ages 18-80 with weight and CT imaging around time of diagnosis (as part of a project called C-SCANS;

n=3409). This analysis of weight change after diagnosis was derived from the C-SCANS cohort, with the requirement of a baseline weight within 3 months of CRC diagnosis and prior to surgery and a follow-up weight approximately 18 months after diagnosis (range 15-21). Of the 3,409 patients in the C-SCANS cohort, 2,781 had weight measurements meeting these timing criteria. The study was approved by the KPNC institutional review board.

Data Collection

Percent Weight Change—Height and weight were measured and input to the EMR by medical assistants using standard procedures in the clinical practices of KPNC. BMI was computed in kilograms per meter squared. Change in weight was calculated by subtracting at diagnosis weight from weight after diagnosis and percentage change was calculated by dividing that weight difference by at diagnosis weight and multiplied by 100 (median time between 2 weight measures = 17.9 months [range 12.7 - 23.0 months]). We created categories of weight change by intervals of 5% (large loss ≥10%, moderate loss 5-9.9%, stable (−4.9 to +4.9%), modest gain 5-9.9%, large gain ≥10%).

Clinical variables and endpoints—We obtained information on prognostic factors, including disease stage, tumor characteristics, and receipt of chemotherapy or radiation from the KPNC Cancer Registry and the medical record. In addition, sociodemographics from the EMR were extracted and considered in multivariate models. Data on CRC-specific and overall mortality were obtained from the KPNC computerized mortality file, which is comprised of data from the California State Department of Vital Statistics, U.S. Social Security Administration, and KPNC utilization data sources. Deaths were considered “CRC-specific” if CRC was listed as a cause of death on the death certificate.

Statistical analysis

We used age-adjusted and multivariate-adjusted Cox proportional hazards regression models to examine associations between percent weight change and CRC-specific and overall mortality. Time was computed from the time of the follow-up weight measure to time of event or study end. To address possible reverse causality, we conducted sensitivity analyses, eliminating deaths occurring within 6 months and 12 months of the second weight measurement as well as considered “early” events (within 3 years of the second weight measurement) separately from later deaths.

In determining potential confounders in our regression model, we examined variables associated with CRC-specific mortality outcomes in previous epidemiologic studies and those suggested in preliminary analyses. Generally, inclusion of potential confounders in our final regression models were evaluated based on comparison of the regression coefficients both adjusted and unadjusted for the potential confounder under consideration, including the confounder if one or more of the regression coefficients changes by ≥10%. The proportional hazards assumption was met testing by Wald chi-square (P values: 0.67 for CRC-mortality and 0.73 for overall mortality). Restricted cubic splines were fitted to test the non-linear relationship of weight change and CRC survival.

We conducted analyses stratified by stage, BMI, site of primary tumor, gender, and age. Interactions were tested in a model with the main effect, the covariate of interest and a cross-product of the two. P-value reported is a Wald chi-square test. We also conducted tests of proportionality with variable by time interactions. Tests of statistical significance were two-sided. Significant results denote p-values ≤ 0.05 and were not adjusted for multiple comparisons.(24)

RESULTS

At KPNC, 2,781 patients diagnosed with stage I, II or III CRC between 2006 and 2011 were identified meeting cohort entry criteria. Of the 2,781 CRC patients, 549 died of any cause and 311 died of CRC, with median follow-up of 4.2 years (range 0.1-8.1 years), based on last update of death records through June 15, 2015.

Baseline characteristics

Baseline characteristics by percent weight change from diagnosis to follow-up are shown in Table 1. When compared to the overall cohort distribution of baseline characteristics, subjects that had large weight loss (≥10%) were more commonly female, stage III, had poorly differentiated tumors, had rectal primary tumors, and received chemotherapy and/or radiation. By contrast, those with large weight gain (≥10%) were more commonly stage II and III, had proximal colon cancer and received chemotherapy.

Percent Weight Change and Outcomes

In models adjusted for age, gender, and race, CRC-specific mortality was significantly associated with both large and modest weight loss ($P_{trend} < 0.0001$) and overall mortality was significantly associated with both large and modest weight loss ($P_{trend} < 0.0001$), while weight gain was not associated with any mortality outcomes (Table 2). After adjustment for other potential confounders (stage, grade of differentiation, site of primary tumor, receipt of chemotherapy or radiation therapy and baseline weight), weight loss remained significantly associated with CRC-specific mortality (HR 1.58; 95% CI 1.12-2.23 with moderate loss and HR 3.20; 95% CI 2.33-4.39 with large loss; $P_{trend} < 0.0001$). In categorical analysis, large and moderate weight losses were also significantly associated with overall mortality (HR 3.27; 95% CI 2.56-4.18 and HR 1.74; 95% CI 1.34-2.25, respectively; $P_{trend} < 0.0001$ in fully adjusted models). In contrast, weight gain was not associated with CRC-specific mortality ($P_{trend} = 0.54$) nor overall mortality ($P_{trend} = 0.27$). Figure 1 demonstrates unadjusted survival curves for these categories while Figure 2 provides adjusted spline curve representations of continuous weight change as function of hazard. For every 2% loss in weight, there was a 15% increase in CRC-specific mortality (95% CI, 11%-19%). Additionally, for every 5% loss in weight there was a 41% increase in CRC-specific mortality (95% CI, 29%-56%). Consideration of BMI change did not demonstrate any meaningfully different observations, when BMI loss was associated with worse CRC-specific and overall mortality while BMI gain was not associated with outcomes (data not shown).

In sensitivity analyses to address the potential for significant weight loss portending imminent death, we restricted analyses to patients alive at least 6 months after the second weight measurement (excluding 55 patients). Weight loss remained significantly associated with CRC-specific mortality (P_{trend} = <0.0001) and overall mortality (P_{trend} < 0.0001). Weight gain was not significantly associated with CRC-specific mortality (P_{trend} = 0.34) or overall mortality (P_{trend} = 0.12). Results were similar when we further excluded deaths that occurred within 12 months of the second weight measurement (excluding 117 patients). Weight loss predicted higher CRC-specific (P_{trend} =0.003) and overall mortality (P_{trend} < 0.0001), and weight gain was not associated with CRC-specific mortality (P_{trend} = 0.42), though was borderline-associated with overall mortality (P_{trend} = 0.08).

We considered mortality bias in our analyses. The associations we observed for large weight loss remained unchanged when limiting outcomes to within first three years after follow-up weight or only considered outcomes beyond three years after follow-up weight. For example, in analyses of CRC-specific mortality, large weight loss had an associated HR 3.71 (95% CI, 2.61-5.29) when restricting analyses to only events within first 3 years and a HR 2.39 (1.14-5.01) when restricting analyses to only events that occur beyond first 3 years. No significant associations were observed with weight gain in similar analyses by time of event.

Stratified analyses

In stratified analyses, there were no apparent differences by gender, site of primary tumor, stage of disease, smoking status, presence or absense of significant comorbidities, baseline BMI or receipt of chemotherapy (all P interactions > 0.05) for weight loss. There was a significant association for age for weight loss and overall mortality (P interaction =0.03) though the direction of the associations were similar for below and above median age. Two subgroup analyses for weight loss were of particular interest, by stage at diagnosis and baseline BMI (Table 3). Despite the number of events being low in stage I disease, there was consistency of point estimates for large weight loss for each stage of disease in both CRC-specific ($P_{interaction}$ = 0.95) and overall mortality ($P_{interaction}$ = 0.48). Similarly, regardless of baseline BMI, large weight loss was associated with worse CRC-specific mortality (P interaction = 0.96) and overall mortality ($P_{interaction}$ = 0.69).

Weight gain was not significantly associated with CRC-specific mortality or overall mortality in any specific subset of the cohort by demographics or tumor characteristics (data not shown).

DISCUSSION

In a population-based cohort housed within an integrated health care delivery system, patients with stage I-III CRC who lost ≥10% weight within 18 months after diagnosis experienced significantly increased risks of CRC-specific and overall mortality. This association was significant regardless of disease stage at diagnosis and whether patients were initially normal weight, overweight or obese. This association further persisted in sensitivity analyses considering reverse causation by restricting the examination to patients not having an event within 6 months and 12 months of the second weight measurement. In contrast, weight gain was not associated with CRC-specific mortality or overall mortality.

The KPNC cohort in this study is the largest to date to test association of weight change after CRC diagnosis with outcomes, allowing for more robust subgroup analyses. To our knowledge, only 3 other studies have reported on change in weight and mortality in CRC survivors. (7)(12)(25) Baade and colleagues ascertained weight and height prior to diagnosis, 5 months and 12 months after diagnosis in a population-based study of stage I-III CRC survivors in Queensland, Australia. (25) Weight loss was significantly associated with increased CRC-specific and overall mortality when considering change in weight prior to diagnosis and 5 months post-diagnosis, as well as change from 5 and 12 months post-diagnosis. Weight gain between pre-diagnosis and 5 months post-diagnosis was associated with increased risk of CRC-specific mortality (HR 1.63, 95% CI 1.02-2.61) but not overall mortality; however, neither CRC-specific nor overall mortality was significantly related to weight gain from 5-12 months post diagnosis. Similarly, Campbell et. al. reported significant associations between weight loss from pre-diagnosis to post-diagnosis and increased risk of CRC-specific and overall mortality but not weight gain in the Cancer Prevention Study-II Nutrition Cohort.(12) Meyerhardt and colleagues similarly found significant associations with worse disease-free and overall survival for weight loss (greater than 5 kg) but not weight gain between weights at time of initiation of chemotherapy to 15 months after completion of chemotherapy in stage III colon cancer patients participating in a National Cancer Institute-sponsored adjuvant chemotherapy trial.(7) Our study confirms these findings in a larger, population-based dataset including patients with stage I – III disease and evaluated by baseline (at diagnosis) BMI. The advantage of our study is use of a baseline clinic-measured weight within 3 months of diagnosis and prior to surgery, a measure truly reflective of the patient's adiposity at diagnosis (prior studies either utilized recall weight prior to diagnosis,(25) self-report weights years prior to diagnosis (12) or post surgery weight (7)).

While it is not known if weight loss after diagnosis is intended or unintentional, a key question is whether weight loss is a marker of disease progression or whether it influences the disease outcome. An assumption of prior reports is that the association of weight loss with increased CRC-specific and overall mortality is due to reverse causality. While this may in part be true, several observations in our data suggest additional potential explanations for our findings. First, the results remained largely unchanged even after excluding patients who died within 6 months and 12 months of the post diagnosis weight measurement. Second, the effects are apparent even among Stage 1 disease. Finally, weight loss in the first 18 months post-diagnosis is still associated with poor survival for deaths occurring later in the survival period (> 3 years post diagnosis). One potential explanation is that weight loss is frequently accompanied by loss of muscle mass and may lead to sarcopenia (ie. muscle depletion independent of adiposity). (26, 27) This may be especially pertinent to CRC survivors since at diagnosis approximately 35% of this population is already at risk for poor survival based on their low muscle level (unpublished data) and weight loss likely leads to further decreases in muscle mass. Adequate muscle mass, and possibly greater muscle mass than noncancer patients, has been shown to be a strong determinant of overall mortality in several studies of cancer patients. (28-39) Studies of CRC patients with advanced disease found that muscle wasting was associated with worse recurrence-free and/or overall survival(40) as well as poor response to chemotherapy.(41) Persons with low muscle mass experience elevated low-

grade systemic inflammation,(42) and altered mitochondrial function,(43, 44) both of which may influence cancer progression . Additionally because skeletal muscle is primarily responsible for insulin-mediated glucose uptake and disposal, progressive loss of muscle mass may promote insulin resistance(45-47) which in of itself has been related to poorer outcomes in cancer survivors.(48) It has also been demonstrated that tumor growth, inactivity post surgery and chemotherapy may all lead to proteolysis, further supporting the requirement for adequate muscle mass.(49, 50) Furthermore, loss of muscle mass typically results in a decrease in physical activity(42) and there are now a number of studies that physically active colorectal cancer survivors have improved outcomes,(51) hypothesized to be related improvements in hyperinsulinemia and/or insulin sensitivity, reduced inflammation or alteration in vitamin D levels and metabolism. Thus, several potential mechanistic pathways, all pointing to weight loss potentiating the risk of sarcopenia, may explain our findings. Nonetheless, the role of fat loss in this population is less clear particularly since there are different types of fat with potentially different roles on cancer survival in the context of weight loss.(52-55)

The lack of interaction between weight loss and baseline BMI suggests that even weight loss in obese patients may not necessarily have a positive effect. It is nonetheless important to consider that recent evidence in several chronic conditions including cancer, suggests that having a high BMI has no protective effect in the presence of sarcopenia, and that it is the latter condition rather than adipose tissue that associates with poor prognosis.(56) While we observed no interaction by BMI, the magnitude of risk was substantially less for the obese (who in general have more muscle mass) than the normal weight and overweight, also suggesting that considering muscle mass status before weight loss may be important . Therefore, the apparent “obesity paradox” may instead represent a “BMI paradox”(57) confounded by the lack of distinctive contributions of muscle versus adiposity tissue on survival outcomes. Future body composition studies are needed to clarify our findings. Additionally, while this dataset cannot determine etiology of weight loss, it demonstrates that weight loss in the first 18 months post-diagnosis is not infrequent (~20%) and it leads one to reconsider automatically advising weight loss in obese and overweight CRC patients in the immediate post-diagnosis period without understanding who will lose weight or the mechanisms underlying weight loss and mortality, and influences of muscle mass status. Further research should examine whether weight loss in the more distant post-diagnosis period may have beneficial effects.

The lack of association with weight gain and outcomes may have several possible explanations. One argument supporting the negative impact of weight gain in women with breast cancer is that weight gain leads to increases in circulating estrogens.(58) In CRC survivors, increased estrogen may be protective, as seen in an analysis of hormone replacement therapy in survivors.(59) Alternatively, while other factors related to energy balance have been implicated in outcomes of colorectal cancer survivors, including physical inactivity, high Western pattern diet and diets high in glycemic load and sugar sweetened beverages, (60) studies have not consistently demonstrated association between weight or BMI and outcomes in colorectal cancer survivors.(15, 61) Therefore, similarly one would not necessarily expect weight gain after diagnosis to negatively impact patient survival. Finally, gain in adipose tissue may have mixed effects on prognosis depending on

distribution of fat, as shown in a recent study in gastric cancer in which subcutaneous fat was associated with an improved survival while visceral fat was associated with a worse survival.(62)

There are strengths and limitations in this study that should be considered when interpreting the findings. KPNC represents a diverse integrated health care delivery system with use of clinical pathways to standardize patient care. KPNC represents approximately 30% of the California insured population and is highly representative except at the very lowest end of the socioeconomic spectrum.(63) Thus, compared to cohorts derived from clinical trials, this population should be more generalizable to the overall CRC population. Use of the EMR allows for prospective data collection, avoiding recall biases. However, the EMR lacks comprehensive data on patient factors that may be associated with the exposure of interest, including diet and physical activity as well as measures of fraility. While the current KPNC EMR does not allow for accurate determination of exact time of cancer recurrence, and weight loss could be related to undocumented recurrences, the vast majority of CRC survivors who develop recurrent disease die of the disease and, thus, CRC-specific mortality should be a reasonable surrogate of recurrence.

In conclusion, loss of weight approximately one year after diagnosis is associated with worse CRC-specific mortality and overall mortality whereas gain was not associated with outcomes in CRC survivors. While reverse causality may partially explain these findings, other potential explanations warrant further research as therapeutic interventions may be needed if sarcopenia or inadequate muscle mass is a mechanism underlying this association. Ongoing efforts in this cohort are measuring muscle mass from computer tomography scans to examine associations of baseline body composition and change in body composition on outcomes.

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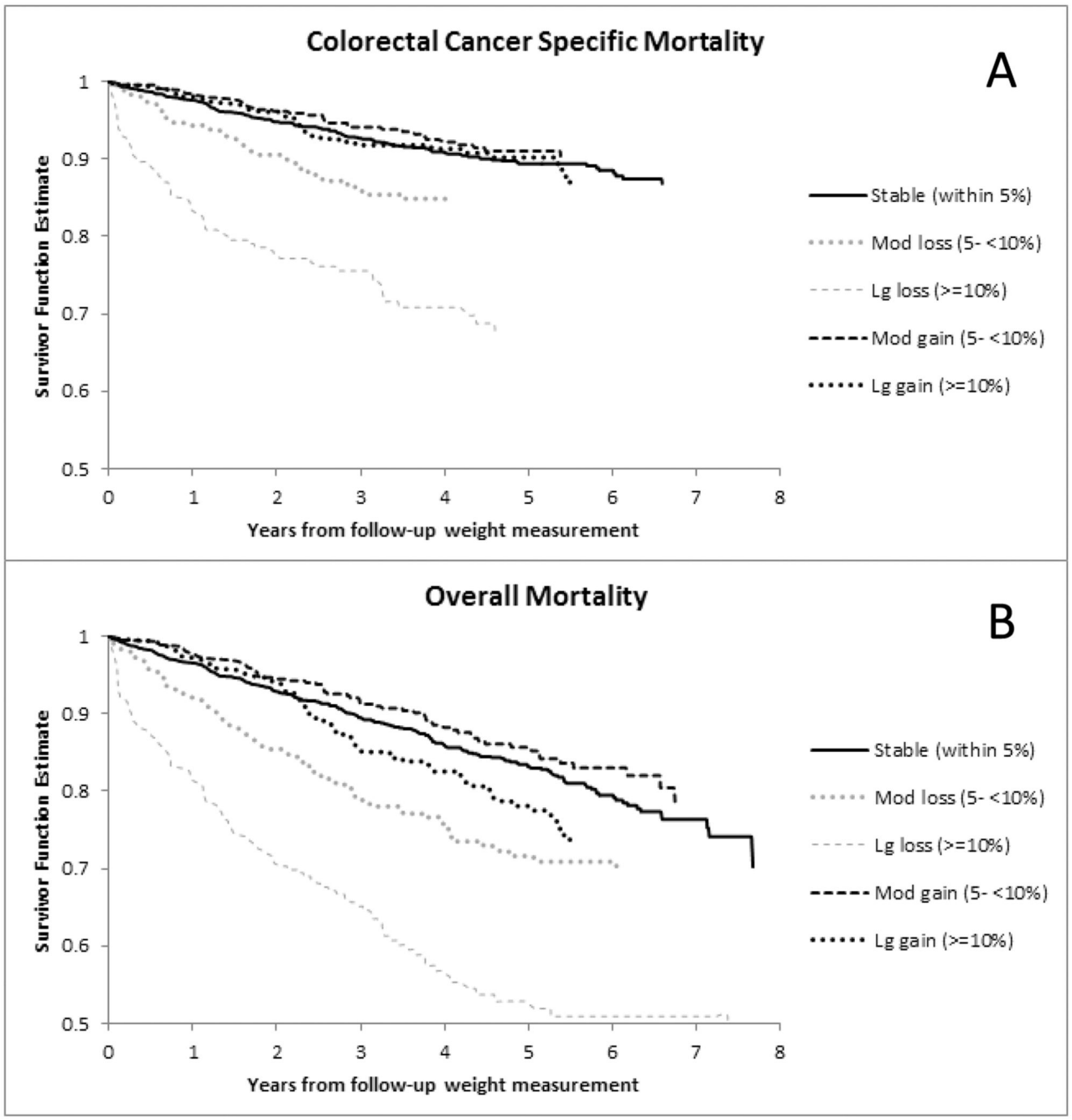

Figure 1.

Kaplan Meier curves for Colorectal Cancer Specific Death (A) and Overall Mortality (B) by Categories of Percentage Weight Change Within 3 months Diagnosis (prior to surgery) and 15-21 months After Diagnosis

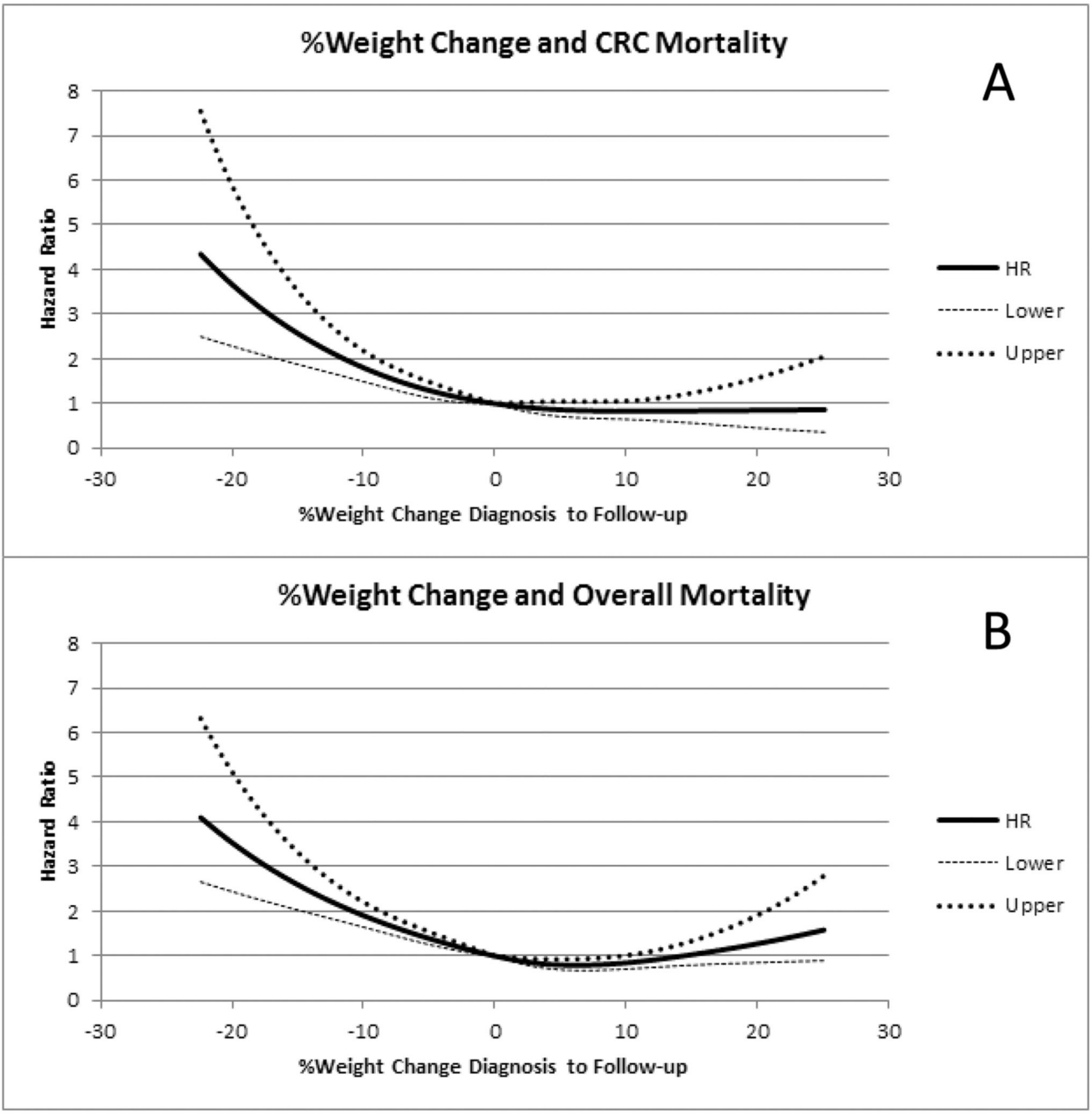

Figure 2.

Adjusted Spline curves for Colorectal Cancer Specific Death (A) and Overall Mortality (B) as Continuous Percentage Weight Change Within 3 months Diagnosis (prior to surgery) and 15-21 months after diagnosis

Table 1

Selected characteristics according to categories of percentage weight change in the Kaiser Permanente Northern California population of colorectal cancer patients diagnosed from 2006-2011 (N=2,781)

	% Weight Change (range 15-21 months post diagnosis)					
	Large Loss (≥10%)	**Modest Loss (5-9.9%)**	**Stable (−4.9-4.9%)**	**Modest Gain (5-9.9%)**	**Large Gain (≥10%)**	**Overall**
N	239	309	1460	453	320	2781
Median change(kg)	−14.0	−6.8	0.0	7.0	14.2	1.0
Median Age at Diagnosis (Years)						
	63	64	62	62	62	63
Sex (%)						
Female	62.8	55.0	47.3	51.2	49.4	50.4
Race/Ethnicity (%)						
White	71.8	65.7	65.1	65.1	61.3	65.3
Black	7.6	5.5	8.0	5.3	7.5	7.2
Hispanic	10.1	11.0	10.2	12.6	14.7	11.2
Asian	10.1	16.5	16.3	16.8	15.6	15.8
Other	0.4	1.3	0.5	0.2	0.9	0.6
BMI at Baseline (%), kg/m^2						
<25	22.2	29.5	30.5	35.1	47.2	32.4
25-<30	31.8	38.8	36.2	39.5	32.5	36.2
30-<35	22.2	19.7	21.0	17.7	15.3	19.7
>=35	23.8	12.0	12.3	7.7	5.0	11.7
BMI at Follow-up (%), kg/m^2						
<25	53.1	45.0	29.8	23.6	17.8	31.1
25-<30	26.4	31.7	36.5	38.2	32.2	34.9
30-<35	11.7	16.5	21.5	22.5	31.9	21.5
>=35	8.8	6.8	12.2	15.7	18.1	12.5
Tumor Stage (%)						
I	20.1	28.2	32.9	27.4	17.8	28.7
II	28.5	31.4	29.9	37.1	39.1	32.1
III	51.5	40.5	37.2	35.5	43.1	39.2
Grade of differentiation (%)						
Well	7.1	3.6	6.8	8.4	7.2	6.8
Moderate	66.9	80.9	78.4	73.7	76.3	76.7
Poor	20.1	11.7	10.5	12.1	12.2	11.9
Undifferentiated	5.9	3.9	4.4	5.7	4.4	4.7
Missing	7.1	3.6	6.8	8.4	7.2	6.8
Site of Primary Cancer (%)						
Proximal	43.1	43.4	42.1	49.9	51.6	44.7

	% Weight Change (range 15-21 months post diagnosis)					
	Large Loss (≥10%)	**Modest Loss (5-9.9%)**	**Stable (−4.9-4.9%)**	**Modest Gain (5-9.9%)**	**Large Gain (≥10%)**	**Overall**
Distal	17.6	21.4	28.4	26.5	25.9	26.1
Rectal	39.3	35.3	29.5	23.6	22.5	29.2
Treatment (%)						
Chemotherapy	61.7	49.7	44.7	44.8	52.5	47.6
Radiation	29.0	22.7	14.9	13.2	13.4	16.5

Table 2

Weight Change and Survival: Diagnosis to Follow-up

	% Weight Change [Hazard Ratio (95% Confidence Interval)]						
	Large Loss (≥10%)	**Modest Loss (5-9.9%)**	**Stable (−4.9-4.9%)**	**Modest Gain (5-9.9%)**	**Large Gain (≥10%)**	**P Loss**	**P Gain**
Colorectal Cancer Specific-Mortality							
# Events / At risk	65/239	43/309	136/1460	35/453	32/320		
Minimally Adjusted *	3.82 (2.83-5.15)	1.66 (1.18-2.35)	Referent	0.83 (0.57-1.20)	1.09 (0.74-1.60)	<0.0001	0.26
Fully Adjusted **	3.20 (2.33-4.39)	1.58 (1.12-2.23)	Referent	0.84 (0.58-1.22)	0.93 (0.63-1.37)	<0.0001	0.54
Overall Mortality							
# Events / At risk	104/239	79/309	235/1460	63/453	68/320		
Minimally Adjusted *	3.59 (2.84-4.53)	1.76 (1.36-2.27)	Referent	0.85 (0.64-1.12)	1.33 (1.01-1.74)	<0.0001	0.11
Fully Adjusted **	3.27 (2.56-4.18)	1.74 (1.34-2.25)	Referent	0.86 (0.65-1.14)	1.20 (0.91-1.58)	<0.0001	0.27

* Adjusted for age at diagnosis (continuous), gender, and race

** Adjusted for age and weight at diagnosis (continuous), gender (female versus male), race/ethnicity (Black, Hispanic or Asian versus non-Hispanic white), stage (II or III versus I), grade (moderate or poorly/undifferentiated versus well differentiated), chemotherapy (not received versus received), radiation therapy (not received versus received), and cancer site (colon versus rectal).

Table 3

Multivariate Adjusted Weight Loss and Survival by Stage and Baseline BMI: Diagnosis to Follow-up

	# Events	Large Loss (≥10%)	Modest Loss (5-9.9%)	Stable (−4.9-4.9%)	P Loss	P interaction
Colorectal Cancer Specific-Mortality						
Stage I (N=797)	24	6.76 (1.93-23.6)	1.63 (0.44-6.02)	Referent	0.03	
Stage II (N=894)	72	2.42 (1.19-4.93)	1.48 (0.72-3.07)	Referent	0.01	
Stage III (N=1090)	215	3.44 (2.37-5.00)	1.59 (1.05-2.41)	Referent	<0.0001	0.95
BMI 18.5-24.9 kg/m^2 (N=835)	93	3.22 (1.67-6.23)	1.46 (0.77-2.78)	Referent	0.01	
BMI 25-29.9 kg/m^2 (N=1014)	106	3.72 (2.17-6.39)	1.66 (0.91-3.00)	Referent	<0.0001	
BMI ≥30 kg/m^2 (N=889)	103	2.68 (1.62-4.43)	1.30 (0.68-2.51)	Referent	<0.0001	0.96
Chemotherapy (N=1315)	219	3.02 (2.10-4.35)	1.28 (0.83-1.97)	Referent	<0.0001	
No Chemotherapy (N=1447)	88	4.07 (2.14-7.74)	2.44 (1.35-4.43)	Referent	0.0001	0.19
Age <63 (N=1392)	154	3.76 (2.39-5.92)	1.41 (0.82-2.42)	Referent	<0.0001	
Age >=63 (N=1389)	157	2.94 (1.89-4.58)	1.74 (1.10-2.74)	Referent	<0.0001	0.63
Men (N=1380)	154	3.54 (2.19-5.73)	1.33 (0.78-2.26)	Referent	<0.0001	0.45
Women (N=1401)	157	2.96 (1.93-4.52)	1.81 (1.14-2.87)	Referent	<0.0001	
Colon (N=1969)	208	3.67 (2.48-5.45)	1.33 (0.84-2.11)	Referent	<0.0001	0.21
Rectal (N=812)	103	2.98 (1.75-5.06)	2.17 (1.26-3.76)	Referent	<0.0001	
Smoking-Never (N=1307)	129	2.31 (1.33-4.00)	1.55 (0.94-2.58)	Referent	0.003	0.55
Smoking-Former (N=1149)	138	3.87 (2.45-6.13)	1.84 (1.10-3.07)	Referent	<0.0001	
Smoking-Current (N=322)	44	5.21 (2.08-13.02)	0.72 (0.16-3.31)	Referent	0.003	
No significant comorbidities (N=1941)	196	2.94 (1.97-4.38)	1.47 (0.94-2.28)	Referent	<0.0001	0.89
Significant comorbidities at diagnosis (N=840)	115	3.76 (2.23-6.34)	1.80 (1.02-3.17)	Referent	<0.0001	
Overall Mortality						
Stage I (N=797)	87	6.01 (3.16-11.4)	2.34 (1.23-4.46)	Referent	<0.0001	
Stage II (N=894)	168	2.17 (1.34-3.51)	1.36 (0.83-2.23)	Referent	0.0001	
Stage III (N=1090)	294	3.50 (2.52-4.85)	1.80 (1.27-2.55)	Referent	<0.0001	0.48
BMI 18.5-24.9 kg/m^2 (N=835)	164	4.20 (2.58-6.85)	1.50 (0.91-2.48)	Referent	<0.0001	
BMI 25-29.9 kg/m^2 (N=1014)	193	3.17 (2.07-4.84)	2.22 (1.47-3.35)	Referent	<0.0001	

	# Events	Large Loss (≥10%)	Modest Loss (5-9.9%)	Stable (−4.9-4.9%)	P Loss	P interaction
BMI ≥30 kg/m^2 (N=889)	176	2.83 (1.91-4.20)	1.31 (0.80-2.15)	Referent	<0.0001	0.69
Chemotherapy (N=1315)	296	3.05 (2.22-4.17)	1.36 (0.94-1.96)	Referent	<0.0001	
No Chemotherapy (N=1447)	247	3.72 (2.51-5.52)	2.27 (1.57-3.27)	Referent	<0.0001	0.09
Age <63 (N=1392)	212	4.14 (2.83-6.04)	1.21 (0.74-1.98)	Referent	<0.0001	
Age >=63 (N=1389)	337	2.98 (2.16-4.16)	2.12 (1.56-2.88)	Referent	<0.0001	0.03
Men (N=1380)	285	3.40 (2.35-4.91)	1.84 (1.27-2.65)	Referent	<0.0001	0.85
Women (N=1401)	264	2.98 (2.13-4.16)	1.54 (1.07-2.21)	Referent	<0.0001	
Colon (N=1969)	389	3.76 (2.79-5.07)	1.58 (1.14-2.19)	Referent	<0.0001	0.12
Rectal (N=812)	160	2.64 (1.71-4.08)	2.12 (1.37-3.28)	Referent	<0.0001	
Smoking-Never (N=1307)	199	2.23 (1.39-3.59)	1.55 (1.03-2.34)	Referent	0.0001	0.41
Smoking-Former (N=1149)	264	3.80 (2.69-5.38)	2.07 (1.44-2.98)	Referent	<0.0001	
Smoking-Current (N=322)	85	6.12 (3.16-11.83)	1.30 (0.51-3.29)	Referent	<0.0001	
No significant comorbidities (N=1941)	298	2.68 (1.90-3.78)	1.42 (0.98-2.05)	Referent	<0.0001	0.43
Significant comorbidities at diagnosis (N=840)	251	3.90 (2.73-5.57)	2.04 (1.41-2.94)	Referent	<0.0001	

Adjusted for age and weight at diagnosis (continuous), gender (female versus male), race/ethnicity (Black, Hispanic or Asian versus non-Hispanic white), stage (II or III versus I), grade (moderate or poorly/ undifferentiated versus well differentiated), chemotherapy (not received versus received), radiation therapy (not received versus received), and cancer site (colon versus rectal).