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Long-term weight loss after colorectal cancer diagnosis is associated with lower survival: the Colon Cancer Family Registry

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Precis:
Weight loss 5-years after CRC diagnosis was significantly associated with decreased subsequent long-term survival. These results suggest the importance of avoiding weight loss in CRC survivors.

Keywords: Colorectal neoplasms, body mass index, weight loss, mortality, survivors, epidemiology, follow-up studies

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Abstract

Background: Body weight is associated with colorectal cancer (CRC) risk and survival, but the impact of long-term post-diagnostic weight change is unclear. We investigated whether weight change over the 5 years following CRC diagnosis is associated with survival.

Methods: CRC cases diagnosed from 1997-2008 were identified through four population-based cancer registry sites. Participants enrolled within two years of diagnosis and reported their height and weight two years prior. Follow-up questionnaires were administered ~5 years after diagnosis. Associations of change in weight (kg) or body mass index (BMI) with overall and CRC-specific survival were estimated using Cox regression adjusted for age, sex, stage, baseline BMI, NSAID use, smoking, time between diagnosis and enrollment, and study site.

Results: At the five-year post-diagnostic survey, 2,049 participants reported higher (53%, median +5kg), unchanged (12%), or lower (35%, median -4kg) weight. Over a median 5.1 years (range 0.3-9.9) of subsequent follow-up, 344 participants died (91 from CRC). Long-term weight loss (per 5kg) was associated with poorer overall (Hazard Ratio [HR]: 1.13, 95% Confidence Interval [CI]: 1.07–1.21) and CRC-specific survival (HR: 1.25, 95% CI: 1.13–1.39). Significantly lower survival was similarly observed for relative weight loss (>5% vs. ≤5% change), BMI reduction (per 1 unit), or BMI category change (overweight to normal vs. remaining overweight).

Conclusions: Weight loss 5-years after CRC diagnosis was significantly associated with decreased long-term survival, suggesting the importance of avoiding weight loss in CRC survivors. Future research should attempt to evaluate this association accounting for whether this weight change was intentional, or represents a marker of declining health.

Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the fourth leading cause of cancer death worldwide [1]. Improvements in CRC screening and treatment have contributed to a growing population of CRC survivors [2]. As such, efforts to identify modifiable behaviors and risk factors associated with CRC survival are of increasing clinical [3, 4] and public health [5, 6] importance.

Body mass index (BMI) has been associated with both the risk of developing CRC [7-11] and survival after CRC diagnosis [12-16]. Most prior studies have relied upon measurements of BMI taken at a single time point either before, at, or after CRC diagnosis [14], the timing of which may be important for prognosis [12]. As weight loss is a common side-effect of CRC, longitudinal studies of weight change over time may provide a more complete picture of how body weight is associated with cancer survival.

Growing evidence suggests that weight gain is associated with increased CRC risk [17, 18]. Fewer studies have evaluated adult weight change as it relates to CRC survival [12, 13, 19-22], but have suggested that post-diagnostic weight loss may be associated with lower survival. These studies have differed in the duration of the time interval over which weight change is measured and in the relation of timing of weight measurements to time of diagnosis, and have focused on weight change in the 6-24 month period immediately following diagnosis. To our knowledge, no study has investigated long-term post-diagnostic weight change as it relates to CRC survival.

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We investigated whether long-term weight change, rather than absolute weight/BMI, in the five-year period following CRC diagnosis is associated with long-term survival.

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Methods

Study participants

The Colon Cancer Family Registry (CCFR) is an international consortium focused on CRC research [23, 24]. This study included data from four population-based CCFR study sites: Cancer Care Ontario/Lunenfeld-Tanenbaum Research Institute (Toronto, Ontario, Canada), Fred Hutchinson Cancer Research Center (Seattle, Washington, USA), Mayo Clinic (Rochester, Minnesota, USA), and University of Melbourne (Melbourne, Victoria, Australia).

Details of the CCFR have been previously described [13, 24-28], and are available online [23]. Briefly, incident CRC cases diagnosed from 1997-2008 were identified through population-based cancer registries. Enrolled participants completed questionnaires at baseline and at five-year intervals. Local study approval was provided by the institutional review boards at each study center, and all participants provided written informed consent.

Only participants who completed both the baseline and the 5-year post-diagnosis follow-up questionnaire were included in this analysis. Of these 3,001 cases, we excluded those: whose baseline survey was completed >2 years after diagnosis (n=283), whose follow-up survey was completed >6 years after enrollment (n=245), those with <3 months of follow-up time after the follow-up survey (n=410), and participants with missing information on weight (n=212), height (n=16), smoking status (n=8) or NSAID use (n=48). Thus, data on 2,049 participants remained for analyses.

Data collection

Participants completed a structured telephone interview or self-administered questionnaire at a median 9 months (range 0-24 months) after diagnosis (Figure 1) in which they self-reported demographic, epidemiologic, and dietary characteristics two years prior. These responses thus correspond to participant characteristics at a median of 15.0 months (range 1-24 months) before diagnosis. Participants were actively followed via periodic contact, and completed follow-up questionnaires a median 4.9 years (range 3.5-6.0 years) after enrollment (i.e., median 5.9 years after CRC diagnosis).

Cancer stage at diagnosis was derived from information on TNM stage and SEER summary stage into American Joint Committee on Cancer (AJCC) stages I-IV [29]. Follow-up for vital status and cause of death was completed through periodic linkage to population-based registries, contact with relatives, and the collection of death certificates. Vital status information was available through June 2014. ICD-10 codes retrieved from death records were used to classify whether deaths were due to CRC (C18.0, C18.2-C20.9, or C26.0) or any other cause [30].

Data definitions and statistical analyses

Participants self-reported height and weight at baseline (weight 2 years prior) and 5-year follow-up (current weight) [24]. Change in weight was calculated by subtracting weight at the 5-year follow-up

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from baseline weight. Relative weight change was calculated as weight change divided by weight at baseline, multiplied by 100. Body mass index (BMI) was categorized according to WHO criteria [31] as underweight (<18.5 kg/m^2), normal weight (18.5–24.9), overweight (25.0–29.9), or obese (≥30.0). Smoking history and non-steroidal anti-inflammatory drug (NSAID) use were defined as never/ever regular users.

Delayed-entry Cox regression models were used to estimate the Hazard Ratio (HR) and 95% Confidence Interval (95% CI) for the association between weight change and overall or CRC-specific survival. Survival time was calculated starting at the date of the 5-year follow-up survey and ending at either death or date of last follow-up. Models adjusted for the following potential confounders [32]: age at diagnosis, sex, smoking history, NSAIDs use, stage at diagnosis, days between diagnosis and baseline survey, and baseline BMI category. In order to more fully capture potential associations with survival, associations with weight change were assessed for several continuous and categorical parameterizations: linear weight change (per 5kg); linear BMI change (per 1kg/m^2); categorical weight change (gained >2kg, or lost >2kg, versus ≤2kg difference); and categorical relative weight change (gained >5%, or lost >5%, versus ≤5% difference). Additional analyses examined categorical BMI change (moved into a higher BMI category, or lower BMI category, versus no change). Proportional hazards assumptions were verified by testing for a non-zero slope of the scaled Schoenfeld residuals on ranked failure times [33]. All *P*-values are two-sided, with $P<0.05$ denoting statistical significance. Analyses were performed using Stata version 14 [34].

Results

Among the 2,049 individuals included in the analytic dataset, 344 died (91 from CRC) over a median 5.1 years of follow-up (range 0.3-9.9 years) after the 5-year follow-up survey. Participant characteristics are presented in *Table 1*, both overall and by category of relative weight change (>5% loss, ≤5% change, or >5% gain). At follow-up, 1,090 participants (53%) had gained weight (median +5kg), 244 (12%) reported the same weight, and 715 (35%) had lost weight (median -4kg). The majority of participants (72%) were in the same BMI category at both time points (*Table 2*).

Weight loss was consistently associated with lower survival (*Table 3*). Modeled continuously, weight loss (per 5kg) after CRC diagnosis was significantly associated with lower overall (HR=1.13, 95% CI: 1.07–1.21) and CRC-specific survival (HR=1.25, 95% CI: 1.13–1.39), as was a decrease in BMI (per 1kg/m^2; overall HR=1.07, 95% CI: 1.03–1.11, CRC-specific HR=1.13, 95% CI: 1.06–1.20). Modeled categorically, relative weight loss of >5% (vs. ≤5%) was significantly associated with decreased overall (HR=2.58, 95% CI: 1.97–3.38) and CRC-specific survival (HR=4.31, 95% CI: 2.63–7.06), as was absolute weight loss of >2kg (vs. ≤2kg; overall HR=2.03, 95% CI: 1.52–2.70, CRC-specific HR=4.22, 95% CI: 2.38–7.49). Weight gain was not associated with survival.

Moving from overweight to normal BMI over the post-diagnosis period (vs. overweight at both time points) was significantly associated with lower overall (HR=3.67, 95% CI: 2.41–5.60) and CRC-specific survival (HR=6.68, 95% CI: 3.06–14.55) (*Table 4*). Moving from obese to overweight was also associated with lower overall survival (HR=1.69, 95% CI: 1.00-2.85).

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Several post-hoc exploratory analyses were performed to further explore these associations. Sensitivity analyses excluding those with stage IV CRC, missing stage information, or both, did not substantially alter the results in *Table 3 or Table 4* (*Supplementary Table 1*).In sensitivity analyses of continuous weight change stratified by BMI category at baseline, weight loss remained statistically significant among those overweight and obese at baseline for overall survival, and among those overweight at baseline for CRC-specific survival (*Supplementary Table 2*). In sensitivity analyses of categorical weight change stratified by BMI category at baseline, the associations of loss of either >5% or >2kg body weight with survival remained statistically significant among those of normal or overweight, but not obese, BMI at baseline.

Additional exploratory analyses evaluated participant sex or cancer stage at diagnosis as potential effect modifiers of the association between weight change and survival. Likelihood ratio tests of nested models containing interaction terms with weight change were not statistically significant for stage at diagnosis, but suggested a potential difference by sex for CRC-specific survival (*Supplementary Table 3)*. In sex-stratified analyses, associations between weight loss and survival had larger effect sizes and remained statistically significant in males, but had reduced effect sizes and were not statistically significant in females.

Discussion

Weight loss in the ~5-year period after CRC diagnosis was significantly associated with lower overall and CRC-specific survival. This association was consistently observed whether weight loss was modeled continuously or categorically, or in relative or absolute terms. These findings support the importance of weight loss as a potential indicator of declining health in cancer survivors, even years after diagnosis.

Emerging evidence suggest a J-shaped association between body weight and CRC survival, where overweight survivors may have the lowest risk of mortality [16, 35, 36]. This relationship may vary by cancer stage, with higher BMI associated with lower survival for early-stage CRC but higher survival for later-stage CRC [15]. Meta-analyses of clinical trials suggest that underweight and obese (but not overweight) BMI may be detrimental for stage II-III CRC [37], and that lower BMI (<28kg/m^2) may be detrimental for stage IV CRC [38]. The timing of weight assessment in relation to diagnosis appears important when considering prognosis, with pre-diagnostic BMI perhaps more informative for prognosis than post-diagnostic BMI [12]. Most previous research, however, has utilized static BMI measurements to evaluate the association of body weight with survival. As weight often changes over time, there is a recognized need investigating the impact of weight change in cancer survivors [3, 39, 40].

Weight loss related to CRC symptoms and treatment is common, and may negatively impact subsequent survival. Previous studies have demonstrated that weight control is important to CRC survivorship, observing lower survival with pre-diagnostic weight gain [13], pre- to post-diagnosis weight loss [12, 21], and short-term post-diagnostic weight loss [20, 22]. While an early study reported no association with short-term post-diagnostic weight change [19], a recent meta-analysis suggests that weight maintenance after diagnosis may be advantageous for cancer survivors who are overweight after diagnosis [35]. Of note, these previous studies have generally evaluated shorter time intervals for weight change after diagnosis (1-2 years), and have had near-term periods of follow-up (up to 5 years). Ours is the first study to evaluate the association of long-term (4-6 years) weight change after CRC diagnosis with subsequent long-term (>5 years) survival.

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Consistent with studies of short-term weight changes, we observe that weight loss is associated with lower survival, and that weight maintenance may be beneficial even if a patient is initially overweight. Notably, these findings are in conflict with current survivorship guidelines, which recommend that patients obtain and maintain a normal weight [36, 41]. This conflict is particularly striking as our findings relate to long-term weight change 4-6 years after diagnosis, when a cancer survivor is likely moving past the period of active cancer treatment. While CRC-related issues and symptoms are most prominent during the first three years post-diagnosis, long-term effects can persist [42]. More research is needed to identify whether additional factors, such as long-term effects or metabolic dysfunction, may contribute to the observed lower survival after weight loss.

Associations of post-diagnostic weight loss with lower survival has been reported in several other cancer types [43], including breast [44, 45], endometrial [46], lung [47], prostate [48], and esophageal cancer [49]. Involuntary weight and muscle loss leading to cachexia and sarcopenia, respectively, are common in cancer patients and are indicators of poor prognosis [3, 20, 50]. Together, these results suggest the importance of avoiding weight loss after diagnosis, and may point towards weight maintenance as a prudent goal for survivors of some cancers [44]. Potential biological rationale for better survival with higher weight in cancer survivors includes extra nutritional reserves, greater muscle mass, a lower likelihood of dose-limiting toxicity, or potentially less aggressive tumors [3, 51, 52].

BMI is a crude measure of adiposity, and does not capture differences in body composition (muscle vs. fat) or fat distribution (subcutaneous vs. visceral) [53]. These differences also vary by sex, with females generally carrying proportionately more body fat and males having more central adiposity [54], which may be contributing to the differential associations of weight loss and survival observed in the sex-stratified exploratory analyses. Body habitus is also likely influenced by many factors that change over time, both lifestyle (caloric intake, diet, physical activity, etc.) and medical (access to medical care, treatments, co-morbidities, adverse events, and late effects). As such, it is difficult to determine the proportional contribution of weight change on long-term survival. We are unable to determine whether the weight loss reported in our study was intentional (e.g., through diet and/or exercise) or unintentional (e.g., cachexia or sarcopenia). Given that unintentional weight loss likely relates to treatment effects or disease progression/recurrence, and could be a general marker of declining health, this limitation should be considered before encouraging clinical implementation of our findings.

We were unable to evaluate how diet and exercise may have contributed to energy balance and weight change. Exercise may be particularly important in cancer survivors, as weight loss independent of exercise may promote sarcopenia or loss of lean mass [36, 55] and increased physical activity after CRC diagnosis is associated with improved survival [56, 57]. Guidelines for weight management in adults recommend a three-pronged approach of dietary energy restriction, regular physical activity, and behavioral modification [58]. Additional investigation is needed to identify how these factors influence weight change in CRC survivors, and to determine how sarcopenia or cachexia may be involved in the observed association with survival.

This study has several limitations. Our results are based on long-term changes in weight among participants who survived ≥5 years after their diagnosis. This inherent survival bias meant that our sample comprised proportionately more participants who were younger, had an early-stage cancer at diagnosis, and likely had fewer comorbidities, potentially limiting the generalizability of these findings.

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Another limitation is that body weight was self-reported at each time point, perhaps resulting in measurement error with regard to weight change. However, questionnaire-based body weight recall tends to be fairly accurate [59]. Participants are also likely to have internal consistency in their reporting, such that change in weight may be less prone to such bias than individual weight measurements. Finally, participants may have undergone large fluctuations in weight during the post-diagnosis period that would not have been captured by our surveys. Although we included established and suspected factors that might confound the relationship under study, there may nonetheless be other unmeasured confounding factors influencing these findings, such as participants' area of residence or access to treatment [60]. Future studies with longer and more frequent follow-up of participants who develop CRC are needed to evaluate how the pace, trajectory, or pattern of weight change may affect the association of body weight with CRC survival.

Our study has several strengths that improve confidence in our results. These include a large sample size, long follow-up time, well-characterized outcomes, and detailed information on both the primary exposure and potential confounders. Another major strength is the population-based design, which allows for an estimate of the association between weight change and CRC survival that is more likely to be generalizable. These findings are also consistent with findings from shorter-term studies, and warrant replication and exploration in larger and more frequently-characterized study populations. Exploratory analyses suggesting that these associations may be particularly relevant for males and those who are overweight at diagnosis also warrant future investigation.

Conclusion

These findings suggest the importance of avoiding weight loss among long-term CRC survivors, even among those who are overweight or obese. This conflicts with current recommendations to achieve and maintain a normal weight. Patients and physicians should be aware of the potential decreased survival among those with weight loss after CRC, even many years after diagnosis. Additional research is warranted to evaluate the additional contribution of diet, physical activity, and body composition for CRC survival within the context of weight change following diagnosis.

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Figure Legend:

Figure 1 - Study timeline, representing relative timing of diagnosis, baseline survey, follow-up survey, and subsequent follow-up for survival outcomes.

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Table 1 – Study population characteristics.

Categories	Total		Lost weight (> 5%)		Maintained weight (≤ 5% change)		Gained weight (> 5%)	
Participants, Total and by site, n (%)	2,049		386	19	985	48	678	33
Cancer Care Ontario	499	24%	99	20	232	46	168	34
Fred Hutchinson Cancer Research Center	962	47%	188	20	425	47	322	33
Mayo Clinic	246	13%	42	17	135	55	69	28
University of Melbourne	347	17%	57	17	166	49	119	35
Deaths, n (%)	344	17%	117	30	139	14	88	13
CRC deaths, n (%)	91	4%	40	10	31	3	20	3
Years between diagnosis and baseline survey, mean (SD)	0.8	0.4	0.9	0.4	0.9	0.4	0.8	0.4
Years between baseline and follow-up surveys, mean (SD)	5.0	0.5	5.0	0.5	5.0	0.5	5.0	0.5
Years of follow-up from diagnosis, mean (SD)	10.4	2.1	10.0	2.2	10.6	2.0	10.4	2.1
Years of follow-up from 5-year survey, mean (SD)	4.6	1.9	4.2	2.0	4.7	1.8	4.6	1.9
Age at diagnosis (years), mean (SD)	54.8	11.1	57.2	11.2	55.6	10.9	52.2	10.9
Sex (Female), n (%)	1,028	50%	193	50	451	46	384	57
Baseline weight (kg), mean (SD)	80.1	18.6	87.1	20.8	79.5	17.2	76.9	18.3
Follow-up weight (kg), mean (SD)	81.7	19.5	76.4	18.5	79.6	17.2	87.6	21.6
Weight change (kg), mean (SD)	1.6	9.7	-10.7	7.6	0.2	2.2	10.7	8.6
Height (cm), mean (SD)	170.1	10.0	170.3	10.2	171.2	9.8	169.7	10.0
Baseline BMI (kg/m2), mean (SD)	27.4	5.4	29.9	6.1	27.0	4.9	26.5	5.2
Follow-up BMI (kg/m2), mean (SD)	28.0	5.8	26.2	5.3	27.1	4.9	30.3	6.4
BMI change (kg/m2), mean (SD)	0.6	3.4	-3.7	2.6	0.1	0.8	3.8	3.1
Cancer stage at diagnosis, n (%)								
I	571	28%	98	25	308	31	165	24
II	565	28%	118	31	256	26	191	28
III	415	20%	67	17	204	21	144	21
IV	130	6%	26	7	68	7	36	5
Missing	368	18%	77	20	149	15	142	21
Smoking history, n (%)								
Never	928	45%	164	42	460	47	304	45
Ever	1,121	55%	222	58	525	53	374	55
NSAID use, n (%)								
Never	1,187	58%	224	58	559	57	404	60
Ever	862	42%	162	42	426	43	274	40

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Table 2 - Participant BMI category over time.

		BMI (follow-up) *				
		Underweight	Normal	Overweight	Obese	Total
BMI (baseline)	Underweight	9	16	1	3	29
	Normal	15	514	169	15	713
	Overweight	3	110	531	147	791
	Obese	1	9	84	422	516
	Total	28	649	785	587	2,049

* Shading refers to cases that moved to a higher (red) or lower (green) BMI category from baseline to follow-up.

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Table 3 - Association of long-term changes in weight or BMI with overall and CRC-specific survival, modeled continuously or categorically.

	Overall mortality				CRC-specific mortality			
	n(deaths)	HR*†	95% CI	p-value	n(deaths)	HR*	95% CI	p-value
Per 5kg loss	2049(344)	1.13	1.07–1.21	**<0.001**	2049(91)	1.25	1.13–1.39	**<0.001**
Per 1kg/m^2 loss	2049(344)	1.07	1.03–1.11	**<0.001**	2049(91)	1.13	1.06–1.20	**<0.001**
Gain >5%	678(88)	1.01	0.76–1.35	0.95	678(20)	0.9	0.51–1.60	0.73
Same (+/-5%)	985(139)	Ref.			985(31)	Ref.		
Loss >5%	386(117)	2.58	1.97–3.38	**<0.001**	386(40)	4.31	2.63–7.06	**<0.001**
Gain >2kg	821(114)	1.11	0.83–1.48	0.50	821(27)	1.22	0.67–2.24	0.52
Same (+/-2kg)	711(92)	Ref.			711(18)	Ref.		
Loss >2kg	517(138)	2.03	1.52–2.70	**<0.001**	517(46)	4.22	2.38–7.49	**<0.001**

*Adjusted for age at diagnosis, sex, smoking history, NSAID use, stage at diagnosis, time from diagnosis to baseline survey, baseline BMI category, and study.

†Stratified by age at diagnosis (proportional hazards violation).

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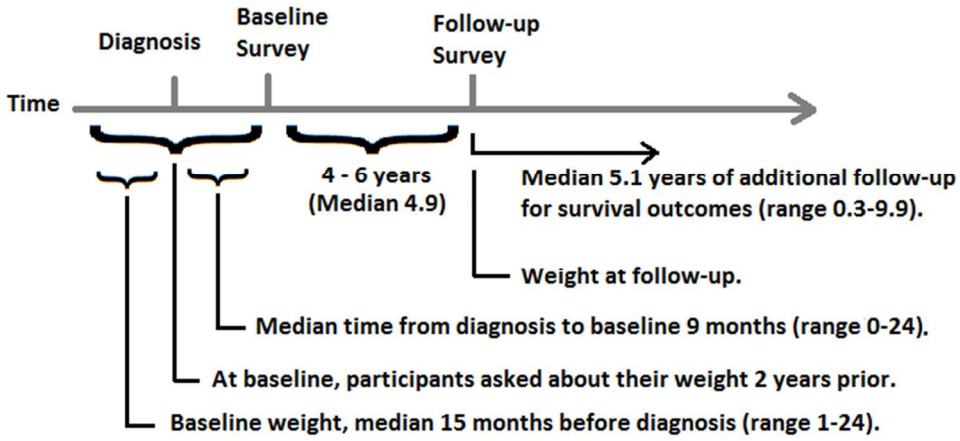
Table 4 - Association of long-term BMI category change with long-term overall and CRC-specific survival.

	Overall mortality				CRC-specific mortality			
	n(deaths)	HR*	95% CI	p-value	n(deaths)	HR*	95% CI	p-value
Normal to Obese	15(4)	†			15(1)	†		
Normal to Overweight	169(15)	0.84	0.47–1.53	0.58	169(6)	0.84	0.31–2.26	0.73
Maintained Normal	514(75)	Ref.			514(19)	Ref.		
Normal to Underweight	15(5)	2.23	0.87–5.71	0.09	15(2)	†		
Overweight to Obese	147(16)	0.88	0.50–1.55	0.65	147(2)	†		
Maintained Overweight	531(76)	Ref.			531(17)	Ref.		
Overweight to Normal	110(41)	3.67	2.41–5.60	**< 0.001**	110(15)	6.68	3.06–14.55	**<0.001**
Overweight to Underweight	3(0)	†			3(0)	†		
Maintained Obese	422(75)	Ref.			422(18)	Ref.		
Obese to Overweight	84(22)	1.69	1.00–2.85	**0.049**	84(6)	1.86	0.67–5.18	0.24
Obese to Normal	9(3)	†			9(2)	†		
Obese to Underweight	1(0)	†			1(0)	†		

*Adjusted for age at diagnosis, sex, smoking history, NSAID use, stage at diagnosis, time from diagnosis to baseline survey, baseline BMI, and study.

†Estimate not reported due to <5 events.

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Study timeline, representing relative timing of diagnosis, baseline survey, follow-up survey, and subsequent follow-up for survival outcomes

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Supplementary Table 1 - Sensitivity analysis excluding those with stage IV and/or missing stage information

Table 3a - Association of long-term changes in weight or BMI with overall and CRC-survival, modeled continuously or categorically.

		Overall mortality				CRC-specific mortality			
		n (deaths)	HR * †	95% CI	p-value	n (deaths)	HR *	95% CI	p-value
Per 5 kg loss	Total	2049 (344)	1.13	1.07 - 1.21	**< 0.001**	2049 (91)	1.25	1.13 - 1.39	**< 0.001**
	Exclude missing stage	1681 (303)	1.13	1.06 - 1.21	**< 0.001**	1681 (82)	1.25	1.12 - 1.40	**< 0.001**
	Exclude stage IV	1919 (315)	1.12	1.05 - 1.19	**0.001**	1919 (75)	1.22	1.08 - 1.37	**0.001**
	Exclude missing and stage IV	1551 (274)	1.11	1.03 - 1.19	**0.004**	1551 (66)	1.21	1.07 - 1.38	**0.003**
Per 1 BMI unit loss	Total	2049 (344)	1.07	1.03 - 1.11	**< 0.001**	2049 (91)	1.13	1.06 - 1.20	**< 0.001**
	Exclude missing stage	1681 (303)	1.07	1.03 - 1.11	**0.001**	1681 (82)	1.13	1.06 - 1.20	**< 0.001**
	Exclude stage IV	1919 (315)	1.07	1.03 - 1.11	**0.001**	1919 (75)	1.12	1.04 - 1.20	**0.003**
	Exclude missing and stage IV	1551 (274)	1.06	1.02 - 1.11	**0.003**	1551 (66)	1.11	1.03 - 1.20	**0.006**
Gain > 5%	Total	678 (88)	1.01	0.76 - 1.35	0.95	678 (20)	0.90	0.51 - 1.60	0.73
	Exclude missing stage	536 (76)	0.98	0.72 - 1.33	0.89	536 (18)	0.89	0.48 - 1.63	0.71
	Exclude stage IV	642 (84)	1.04	0.77 - 1.40	0.81	642 (18)	0.95	0.52 - 1.75	0.87
	Exclude missing and stage IV	500 (72)	1.00	0.73 - 1.38	1.00	500 (16)	0.97	0.50 - 1.85	0.91
Same (+/- 5%)	Total	985 (139)	Ref.	.	.	985 (31)	Ref.	.	.
	Exclude missing stage	836 (126)	Ref.	.	.	836 (28)	Ref.	.	.
	Exclude stage IV	917 (128)	Ref.	.	.	917 (26)	Ref.	.	.
	Exclude missing and stage IV	768 (115)	Ref.	.	.	768 (23)	Ref.	.	.
Loss > 5%	Total	386 (117)	2.58	1.97 - 3.38	**< 0.001**	386 (40)	4.31	2.63 - 7.06	**< 0.001**
	Exclude missing stage	309 (101)	2.66	1.99 - 3.54	**< 0.001**	309 (36)	4.66	2.77 - 7.85	**< 0.001**
	Exclude stage IV	360 (103)	2.42	1.82 - 3.21	**< 0.001**	360 (31)	3.69	2.13 - 6.38	**< 0.001**
	Exclude missing and stage IV	283 (87)	2.46	1.81 - 3.34	**< 0.001**	283 (27)	4.01	2.23 - 7.20	**< 0.001**
Gain > 2 kg	Total	821 (114)	1.11	0.83 - 1.48	0.50	821 (27)	1.22	0.67 - 2.24	0.52
	Exclude missing stage	652 (99)	1.13	0.83 - 1.54	0.45	652 (23)	1.12	0.59 - 2.11	0.73
	Exclude stage IV	774 (108)	1.11	0.82 - 1.50	0.51	774 (24)	1.22	0.64 - 2.32	0.54
	Exclude missing and stage IV	605 (93)	1.12	0.81 - 1.54	0.51	605 (20)	1.13	0.57 - 2.23	0.72
Same (+/- 2 kg)	Total	711 (92)	Ref.	.	.	711 (18)	Ref.	.	.
	Exclude missing stage	608 (84)	Ref.	.	.	608 (17)	Ref.	.	.
	Exclude stage IV	917 (128)	Ref.	.	.	665 (16)	Ref.	.	.
	Exclude missing and stage IV	562 (78)	Ref.	.	.	562 (15)	Ref.	.	.
Loss > 2 kg	Total	517 (138)	2.03	1.52 - 2.70	**< 0.001**	517 (46)	4.22	2.38 - 7.49	**< 0.001**
	Exclude missing stage	421 (120)	2.20	1.62 - 2.99	**< 0.001**	421 (42)	4.46	2.46 - 8.09	**< 0.001**
	Exclude stage IV	360 (103)	1.85	1.37 - 2.50	**< 0.001**	480 (35)	3.38	1.82 - 6.27	**< 0.001**
	Exclude missing and stage IV	384 (103)	1.98	0.47 - 0.82	**< 0.001**	384 (31)	3.54	1.85 - 6.77	**< 0.001**

Table 4a - Association of moving to another BMI category over the post-diagnosis period with long-term overall and CRC-specific survival.

		Overall mortality				CRC-specific mortality			
		n (deaths)	HR*	95% CI	p-value	n (deaths)	HR *	95% CI	p-value
Normal to Obese	Total	15 (4)	†	.	**.**	15 (1)	†	.	.
	Exclude missing stage	11 (4)	†	.	**.**	11 (1)	†	.	.
	Exclude stage IV	13 (2)	†	.	**.**	13 (0)	†	.	.
	Exclude missing and stage IV	9 (2)	†	.	**.**	9 (0)	†	.	.
Normal to Overweight	Total	169 (15)	0.84	0.47 - 1.53	0.58	169 (6)	0.84	0.31 - 2.26	0.73
	Exclude missing stage	130 (10)	0.72	0.36 - 1.46	0.37	130 (5)	0.87	0.30 - 2.56	0.80
	Exclude stage IV	157 (15)	0.88	0.48 - 1.61	0.69	157 (6)	0.82	0.30 - 2.27	0.71
	Exclude missing and stage IV	118 (10)	0.78	0.38 - 1.59	0.49	118 (5)	0.88	0.29 - 2.67	0.83
Maintained Normal BMI	Total	514 (75)	Ref.	.	.	514 (19)	Ref.	.	.
	Exclude missing stage	420 (64)	Ref.	.	.	420 (16)	Ref.	.	.
	Exclude stage IV	478 (66)	Ref.	.	.	478 (16)	Ref.	.	.
	Exclude missing and stage IV	384 (55)	Ref.	.	.	384 (13)	Ref.	.	.
Normal to Underweight	Total	15 (5)	2.23	0.87 - 5.71	0.09	15 (2)	†	.	**.**
	Exclude missing stage	14 (5)	1.99	0.77 - 5.12	0.15	14 (2)	†	.	**.**
	Exclude stage IV	11 (4)	2.78	0.95 - 8.14	0.06	11 (1)	†	.	**.**
	Exclude missing and stage IV	10 (4)	2.40	0.81 - 7.09	0.11	10 (1)	†	.	**.**
Overweight to Obese	Total	147 (16)	0.88	0.50 - 1.55	0.65	147 (2)	†	.	.
	Exclude missing stage	122 (14)	0.80	0.44 - 1.46	0.47	122 (2)	†	.	.
	Exclude stage IV	143 (16)	0.93	0.52 - 1.64	0.79	143 (2)	†	.	.
	Exclude missing and stage IV	118 (14)	0.84	0.46 - 1.54	0.56	118 (2)	†	.	.
Maintained Overweight BMI	Total	531 (76)	Ref.	.	.	531 (17)	Ref.	.	.
	Exclude missing stage	449 (71)	Ref.	.	.	449 (17)	Ref.	.	.
	Exclude stage IV	500 (73)	Ref.	.	.	500 (14)	Ref.	.	.
	Exclude missing and stage IV	418 (68)	Ref.	.	.	418 (14)	Ref.	.	.
Overweight to Normal	Total	110 (41)	3.67	2.41 - 5.60	**< 0.001**	110 (15)	6.68	3.06 - 14.55	**< 0.001**
	Exclude missing stage	85 (37)	4.03	2.59 - 6.28	**< 0.001**	85 (14)	6.41	2.90 - 14.20	**< 0.001**
	Exclude stage IV	102 (35)	3.13	2.00 - 4.89	**< 0.001**	102 (12)	7.32	3.03 - 17.66	**< 0.001**
	Exclude missing and stage IV	77 (31)	3.44	2.14 - 5.51	**< 0.001**	77 (11)	7.06	2.86 - 17.45	**< 0.001**
Overweight to Underweight	Total	3 (0)	†	.	**.**	3 (0)	†	.	**.**
	Exclude missing stage	0 (0)	†	.	**.**	0 (0)	†	.	**.**
	Exclude stage IV	0 (0)	†	.	**.**	0 (0)	†	.	**.**
	Exclude missing and stage IV	0 (0)	†	.	**.**	0 (0)	†	.	**.**
Maintained Obese BMI	Total	422 (75)	Ref.	.	.	422 (18)	Ref.	.	.
	Exclude missing stage	350 (67)	Ref.	.	.	350 (15)	Ref.	.	.
	Exclude stage IV	398 (69)	Ref.	.	.	398 (15)	Ref.	.	.
	Exclude missing and stage IV	326 (61)	Ref.	.	.	326 (12)	Ref.	.	.
Obese to Overweight	Total	84 (22)	1.69	1.00 - 2.85	**0.049**	84 (6)	1.86	0.67 - 5.18	0.24
	Exclude missing stage	71 (19)	1.68	0.96 - 2.95	0.07	71 (6)	2.93	0.99 - 8.67	0.052
	Exclude stage IV	78 (21)	1.66	0.97 - 2.95	0.06	78 (5)	1.95	0.64 - 5.94	0.24
	Exclude missing and stage IV	65 (18)	1.66	0.92 - 2.97	0.09	65 (5)	3.30	1.01 - 1.78	**0.048**
Obese to Normal	Total	9 (3)	†	.	.	9 (2)	†	.	**.**
	Exclude missing stage	5 (1)	†	.	.	5 (1)	†	.	**.**
	Exclude stage IV	9 (3)	†	.	.	9 (2)	†	.	**.**
	Exclude missing and stage IV	5 (1)	†	.	.	5 (1)	†	.	**.**
Obese to Underweight	Total	1 (0)	†	.	.	1 (0)	†	.	.
	Exclude missing stage	0 (0)	†	.	.	0 (0)	†	.	.
	Exclude stage IV	0 (0)	†	.	.	0 (0)	†	.	.
	Exclude missing and stage IV	0 (0)	†	.	.	0 (0)	†	.	.

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Supplementary Table 2 - Sensitivity analysis stratifying by BMI category at baseline.

Table 3b - Association of long-term changes in weight or BMI with overall and CRC-survival, modeled continuously or categorically, stratified by BMI at baseline.

		Overall mortality				CRC-specific mortality			
		n (deaths)	HR * †	95% CI	p-value	n (deaths)	HR *	95% CI	p-value
Per 5 kg loss	Total	2049 (344)	1.13	1.07 - 1.21	**< 0.001**	2049 (91)	1.25	1.13 - 1.39	**< 0.001**
	Normal	713 (99)	1.00	0.84 - 1.19	0.98	713 (28)	1.23	0.87 - 1.73	0.24
	Overweight	791 (133)	1.31	1.16 - 1.49	**< 0.001**	791 (34)	1.56	1.29 - 1.87	**< 0.001**
	Obese	513 (100)	1.11	1.01 - 1.21	**0.02**	516 (26)	1.15	1.00 - 1.33	0.053
Per 1 BMI unit loss	Total	2049 (344)	1.07	1.03 - 1.11	**< 0.001**	2049 (91)	1.13	1.06 - 1.20	**< 0.001**
	Normal	719 (99)	0.99	0.90 - 1.08	0.74	713 (28)	1.08	0.90 - 1.31	0.41
	Overweight	791 (133)	1.18	1.09 - 1.26	**< 0.001**	791 (34)	1.30	1.17 - 1.45	**< 0.001**
	Obese	516 (100)	1.06	1.01 - 1.12	**0.02**	516 (26)	1.08	0.99 - 1.18	0.07
Gain > 5%	Total	678 (88)	1.01	0.76 - 1.35	0.95	678 (20)	0.90	0.51 - 1.60	0.73
	Normal	274 (26)	0.97	0.57 - 1.67	0.92	274 (8)	0.97	0.37 - 2.53	0.95
	Overweight	242 (32)	1.57	0.95 - 2.62	0.08	242 (5)	0.71	0.24 - 2.10	0.53
	Obese	144 (21)	0.77	0.41 - 1.42	0.40	144 (4)	0.61	0.18 - 2.01	0.41
Same (+/- 5%)	Total	985 (139)	Ref.	.	.	985 (31)	Ref.	.	.
	Normal	362 (48)	Ref.	.	.	362 (11)	Ref.	.	.
	Overweight	405 (48)	Ref.	.	.	281 (6)	Ref.	.	.
	Obese	209 (40)	Ref.	.	.	209 (9)	Ref.	.	.
Loss > 5%	Total	386 (117)	2.58	1.97 - 3.38	**< 0.001**	386 (40)	4.31	2.63 - 7.06	**< 0.001**
	Normal	77 (25)	2.78	1.53 - 5.06	**0.001**	77 (9)	5.13	2.03 - 12.93	**0.001**
	Overweight	144 (53)	4.85	3.06 - 7.68	**<0.001**	144 (18)	6.98	3.16 - 15.45	**< 0.001**
	Obese	163 (39)	1.44	0.88 - 2.36	0.14	163 (13)	1.92	0.81 - 4.57	0.14
Gain > 2 kg	Total	821 (114)	1.11	0.83 - 1.48	0.50	821 (27)	1.22	0.67 - 2.24	0.52
	Normal	303 (29)	0.97	0.57 - 1.66	0.91	303 (9)	0.94	0.36 - 2.49	0.90
	Overweight	307 (41)	1.40	0.83 - 2.35	0.21	307 (7)	0.86	0.28 - 2.62	0.79
	Obese	193 (35)	1.08	0.58 - 2.02	0.80	193 (8)	1.61	0.43 - 6.12	0.48
Same (+/- 2 kg)	Total	711 (92)	Ref.	.	.	711 (18)	Ref.	.	.
	Normal	312 (40)	Ref.	.	.	312 (9)	Ref.	.	.
	Overweight	281 (29)	Ref.	.	.	281 (6)	Ref.	.	.
	Obese	109 (20)	Ref.	.	.	109 (3)	Ref.	.	.
Loss > 2 kg	Total	517 (138)	2.03	1.52 - 2.70	**< 0.001**	517 (46)	4.22	2.38 - 7.49	**< 0.001**
	Normal	98 (30)	2.18	1.22 - 3.92	**0.01**	98 (10)	4.10	1.60 - 10.48	**0.003**
	Overweight	203 (63)	3.32	2.04 - 5.38	**< 0.001**	203 (21)	5.82	2.29 - 14.81	**< 0.001**
	Obese	214 (45)	1.27	0.70 - 2.31	0.44	214 (15)	2.58	0.74 - 9.01	0.14

* Adjusted for age at diagnosis, sex, smoking history, NSAID use, stage at diagnosis, time from diagnosis to baseline survey, and study.

† Models stratified by age at diagnosis due to proportional hazards violation.

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Supplementary Table 3 - Sensitivity analysis of interaction with sex and stage.

Table 3c - Association of long-term changes in weight or BMI with overall and CRC-survival, modeled continuously or categorically.

		Overall mortality							CRC-specific mortality					
		n (deaths)	HR * †	95% CI	p-value	Sex p-LRT	Stage p-LRT		n (deaths)	HR *	95% CI	p-value	Sex p-LRT	Stage p-LRT
Per 5 kg loss	Total	2049 (344)	1.13	1.07 - 1.21	**< 0.001**	0.23	0.14	Total	2049 (91)	1.25	1.13 - 1.39	**< 0.001**	**0.001**	0.35
	Male	1021 (204)	1.17	1.07 - 1.27	**< 0.001**			Male	1021 (53)	1.49	1.31 - 1.71	**<0.001**		
	Female	1028 (140)	1.06	0.98 - 1.16	0.15			Female	1028 (38)	0.99	0.86 - 1.13	0.85		
Per 1 BMI unit loss	Total	2049 (344)	1.07	1.03 - 1.11	**< 0.001**	0.09	0.15	Total	2049 (91)	1.13	1.06 - 1.20	**< 0.001**	**0.002**	0.28
	Male	1021 (204)	1.10	1.04 - 1.16	**< 0.001**			Male	1021 (53)	1.29	1.18 - 1.40	**< 0.001**		
	Female	1028 (140)	1.03	0.99 - 1.08	0.18			Female	1028 (38)	0.99	0.92 - 1.06	0.80		
Gain > 5%	Total	678 (88)	1.01	0.76 - 1.35	0.95	0.12	0.40	Total	678 (20)	0.90	0.51 - 1.60	0.73	**0.02**	0.48
	Male	294 (49)	1.28	0.86 - 1.89	0.22			Male	294 (10)	1.07	0.47 - 2.42	0.87		
	Female	384 (39)	0.75	0.47 - 1.19	0.22			Female	384 (10)	0.69	0.30 - 1.56	0.37		
Same (+/- 5%)	Total	985 (139)	Ref.	.	.			Total	985 (31)	Ref.	.	.		
	Male	534 (84)	Ref.	.	.			Male	534 (15)	Ref.	.	.		
	Female	451 (55)	Ref.	.	.			Female	451 (16)	Ref.	.	.		
Loss > 5%	Total	386 (117)	2.58	1.97 - 3.38	**< 0.001**			Total	386 (40)	4.31	2.63 - 7.06	**< 0.001**		
	Male	193 (71)	3.16	2.19 - 4.56	**< 0.001**			Male	193 (28)	7.78	3.97 - 15.25	**< 0.001**		
	Female	193 (46)	1.85	1.19 - 2.89	**0.01**			Female	193 (12)	1.76	0.78 - 3.98	0.17		
Gain > 2 kg	Total	821 (114)	1.11	0.83 - 1.48	0.50	0.73	0.33	Total	821 (27)	1.22	0.67 - 2.24	0.52	0.11	0.60
	Male	383 (65)	1.30	0.87 - 1.94	0.21			Male	383 (13)	1.24	0.51 - 3.04	0.64		
	Female	438 (49)	1.00	0.63 - 1.61	0.99			Female	438 (14)	0.99	0.43 - 2.29	0.99		
Same (+/- 2 kg)	Total	711 (92)	Ref.	.	.			Total	711 (18)	Ref.	.	.		
	Male	358 (52)	Ref.	.	.			Male	358 (8)	Ref.	.	.		
	Female	353 (40)	Ref.	.	.			Female	353 (10)	Ref.	.	.		
Loss > 2 kg	Total	517 (138)	2.03	1.52 - 2.70	**< 0.001**			Total	517 (46)	4.22	2.38 - 7.49	**< 0.001**		
	Male	280 (87)	2.25	1.54 - 3.30	**< 0.001**			Male	280 (32)	6.68	3.00 - 14.90	**< 0.001**		
	Female	237 (51)	1.91	1.18 - 3.10	**0.01**			Female	237 (14)	1.90	0.77 - 4.69	0.16		

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