Research Article

Cancer Epidemiology, Biomarkers & Prevention

The Impact of Body Mass Index and Physical Activity on Mortality among Patients with Colorectal Cancer in Queensland, Australia

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Abstract

Background: Few studies have investigated the impact of body mass index (BMI) and physical activity (PA) on mortality among colorectal cancer (CRC) patients and the results are inconsistent. We aimed to examine the impact of these lifestyle factors on all-cause and disease-specific mortality.

Methods: Population-based longitudinal study followed 1,825 patients diagnosed with stages I to III primary CRC during 2003 to 2004 in Queensland, Australia for 5 years. Sociodemographics and clinical characteristics were obtained via questionnaires and medical records.

Results: Participants with some level of PA following diagnosis had 25% to 28% lower risk of all-cause mortality within 5 years of diagnosis than sedentary participants [insufficiently active: HR = 0.72, 95% CI = 0.57–0.91; sufficiently active: HR = 0.75 (0.60–0.94)]; however, the differential for CRC-specific mortality was not significant. Increases in PA from five to 12 months postdiagnosis was associated with reduced CRC-specific mortality by 32% to 36% (increase $\leq$ 2 hour per week: HR = 0.68 (0.48–0.97); increase > 2 hour per week: HR = 0.64 (0.44–0.93) and 31% for all-cause mortality (increase >2 hour per week: HR = 0.69 (0.50–0.94). Compared with participants with healthy BMI, significant higher mortality risk was observed in underweight patients (all-cause: HR = 2.29 (1.47–3.59); CRC: HR = 1.74 (1.00–3.04), although lower risk in overweight (all-cause: HR = 0.75 (0.61–0.94); CRC: HR = 0.75 (0.59–0.97) and no difference in obese. Excessive weight loss was associated with increased mortality risk by three-fold but no difference in those who gained weight.

Conclusions: Protective effects of being physically active and increasing that activity underlines the importance of interventions to increase activity levels among people being diagnosed with CRC.

Impact: Increased mortality risks associated with being underweight or having weight loss over time is an important indicator for which clinicians, patients, and support personnel can monitor. *Cancer Epidemiol Biomarkers Prev; 20(7); 1410–20. ©2011 AACR.*

Introduction

Colorectal cancer (CRC) was the third most common cancer in men (663,000 cases or 10.0% of all cancers) and the second in women (570,000 cases or 9.4%) worldwide in 2008 (1) and is the 4th most common cause of cancer death (8% of all deaths; ref. 1). Along with other developed countries, Australia has one of the highest incidence rates of CRC in the world (1).

Previous studies have shown that lifestyle factors, including low levels of physical activity (PA) are associated with CRC incidence (2–4). There is convincing collective evidence that PA decreases the risk of colon cancer and higher body fat is a cause of CRC (5). Few studies have investigated the impact of dietary and lifestyle factors on CRC survival (6). A prospective observational study of 832 patients with stage III colon cancer (7) found patients who engaged in higher levels of PA after diagnosis had improved recurrence-free and overall survival. In 2 concurrent studies of males and females with stages I to III CRC, lower CRC-specific mortality and all-cause mortality were associated with increasing levels of postdiagnosis exercise (8, 9).

Studies reporting on the relationship between body mass index (BMI) and mortality outcomes for CRC patients are very limited; only 3 studies (10–12) have considered disease-specific and all-cause mortality for colon cancer patients, one of which (10) limited to those with stage III cancers found no association; another study

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limited to those with Duke B and C (equivalent to stage II/III), reported greater mortality in underweight and very obese patients (11), whereas the other (12) considered only women patients and found increased mortality risks among underweight and obese women. However, a study in CRC patients in Iran with a mean follow-up of 2 years reported an increased all-cause mortality risk for underweight patients but a reduced mortality for overweight patients (13).

Because of the limited number of published studies, the impact of postdiagnosis PA and BMI on survival outcomes for CRC patients is unclear. Using a large longitudinal population-based cohort of people diagnosed with CRC (stages I to III) in Queensland, Australia, our aim was to investigate the impact of PA and BMI on all-cause and CRC-specific mortality. In addition, the study aimed to examine the impact of changes in PA and weight (prediagnosis, 5 months postdiagnosis, and 12 months postdiagnosis) on all-cause and CRC-specific mortality.

Methods

Study population

Participants were part of a longitudinal study of CRC and quality of life, for which the details of the sampling procedure and methodology have been described in full previously (14). Briefly, 1,966 people diagnosed with primary CRC in Queensland, Australia between January 1, 2003 and December 31, 2004 were recruited into the study. Consenting patients completed a self-administered questionnaire and computer-assisted telephone interview at approximately 5 months postdiagnosis and then at 12 months postdiagnosis. Ethics approval was obtained from the University of Queensland. To increase the comparability of our study with previously published studies (7, 9), we also excluded those respondents who were diagnosed with stage 0 ($n = 22$, 1.1%) or IV ($n = 119$, 6.1%) CRC, leaving a final study cohort of 1,825 participants.

Measurements

Sociodemographics and clinical variables

Information collected during the 5-month telephone interview included: marital status, highest educational attainment, private health insurance, medical and surgical treatments received (Table 1) for their CRC, and details of any comorbid conditions present at diagnosis. Comorbidities were assessed by asking respondents to indicate whether their doctor had ever told them they had one of a list of conditions, including heart attack, angina, hypertension, hypercholesterol, other heart condition, stroke, diabetes, asthma, chronic bronchitis, emphysema, and others. The number of comorbidities noted by each respondent was then summed and categorized into "0", "1", "2," and "3 or more". Information about the site of the tumor, stage of disease, date of diagnosis, and age at diagnosis were collected from pathology reports and medical records.

PA levels

Participants were asked to report levels of PA in the 12 months before their cancer diagnosis ("prediagnosis", based on recall), at 5 months and 12 months postdiagnosis using questions based on "The Active Australia Survey", a standard validated instrument used to monitor PA participation in the Australian population (15–17). Questions included the amount of time spent in an average week over the 4 weeks preceding the interview in walking and in moderate and vigorous PA. The total PA time per week (in minutes) was the sum of the time spent walking, in moderate physical activities, and in vigorous physical activities. The time spent in vigorous activity was double weighted as it is considered more intense and has been shown to contribute greater health benefit (15). Total PA was then categorized into 3 groups: sedentary (0 minutes per week), insufficiently active (1–149 minutes per week), and sufficiently active for health benefit (at least 150 minutes per week) on the basis of Australian PA guidelines (15, 18). Although recollection of historical prediagnosis PA has been shown to have low levels of repeatability (19), categorizing PA of participants into these categories provides a higher level of test–retest reliability [moderate kappa coefficient = 0.62 (95% CI = 0.48–0.76; ref. 19].

BMI

Participants reported their height and weight prior to their cancer diagnosis (based on recall at the 5-month interview), at 5 months and 12 months postdiagnosis from which BMI was calculated (18, 20). BMI was categorized as: underweight (<18.5 kg/m^2), healthy weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese ($\geq$30.0 kg/m^2).

Smoking status

Using a series of questions about past and present smoking behavior, participants were grouped into lifelong nonsmokers, former smokers, and current smokers.

Measurement of mortality

Details about deaths because of CRC and other causes were obtained from death certificates through the Department of Births, Deaths, and Marriages. Information is checked against data from other sources including hospitals, nursing homes and coroners, and confirmed through matching of deceased patients with the National Death Index and Australian Bureau of statistics. Mortality information, including time between diagnosis and death, was available up to 31 December 2008, and included deaths registered outside Queensland.

Statistical analysis

χ^2 tests were used to test the significance of differences in the distribution of PA categories by baseline participant characteristics, medical factors, and other sociodemographic factors. Cox proportional hazards models were used to assess the HRs of all-cause death and

Table 1. Differences in the distribution of baseline demographic and disease characteristics of study participants by PA levels after diagnosis ($n = 1,825$)

	PA level (5 months postdiagnosis)			*P* value of χ^2 test
	Sedentary ($n = 748$, 41.0%)	**Insufficiently active ($n = 484$, 26.5%)**	**Sufficiently active ($n = 593$, 32.5%)**	
Sex				0.006
Male ($n = 1,089$)	38.7	26.1	35.2	
Female ($n = 736$)	44.4	27.2	28.4	
Age (y)				0.267
20–49 ($n = 151$)	39.1	31.8	29.1	
50–59 ($n = 350$)	43.1	25.4	31.4	
60–69 ($n = 610$)	38.5	25.4	36.1	
70+ ($n = 714$)	42.4	26.9	30.7	
BMI				0.023
Underweight ($n = 47$)	51.1	19.1	29.8	
Healthy ($n = 768$)	40.4	25.4	34.2	
Overweight ($n = 649$)	36.8	29.3	33.9	
Obese ($n = 315$)	48.9	24.8	26.3	
Missing	45.6	26.1	28.3	
Smoking status				<0.001
Never smoked ($n = 727$)	36.9	29.1	34.0	
Current smoked ($n = 150$)	60.0	22.0	18.0	
Former smoked ($n = 948$)	41.1	25.2	33.7	
Marital status				0.179
Never married ($n = 79$)	43.0	36.7	20.3	
Married/de facto ($n = 1,354$)	41.4	25.6	33.0	
Widowed ($n = 202$)	41.1	27.2	31.7	
Divorced/separated ($n = 190$)	36.9	28.4	34.7	
Education level				<0.001
<8 years ($n = 261$)	52.9	23.7	23.4	
8–11 years ($n = 725$)	46.5	24.7	28.8	
12 years/college ($n = 594$)	35.4	29.1	35.5	
University ($n = 245$)	25.7	28.6	45.7	
Private health insurance				0.007
Have ($n = 1,085$)	38.8	25.9	35.3	
Did not have ($n = 740$)	44.2	27.4	28.4	
Site				0.676
Colon ($n = 1,163$)	40.8	26.0	33.2	
Rectum ($n = 662$)	41.4	27.3	31.3	
Stage of disease				0.063
Stage I ($n = 448$)	38.4	25.7	35.9	
Stage II ($n = 590$)	43.7	23.6	32.7	
Stage III ($n = 562$)	42.3	28.5	29.2	
Unknown ($n = 225$)	35.6	31.1	33.3	
Treatment				0.001
Surgery only ($n = 1,020$)	39.7	24.8	35.5	
Surgery and adjuvant ($n = 747$)	42.8	27.4	29.7	
Missing ($n = 58$)	39.7	44.8	15.5	
Comorbidity				0.856
0 ($n = 709$)	41.3	27.2	31.5	
1 ($n = 678$)	41.4	25.4	33.2	
2 ($n = 310$)	38.7	26.5	34.8	
≥3 ($n = 128$)	42.2	28.9	28.9	

NOTE: Values given are in percentage.

CRC-specific death. Follow-up time was recorded until the date of death, or 31 December 2008, whichever came first. For the analysis of all-cause mortality, an event was defined as any death before the censor date. For the analysis of CRC-specific mortality, an event was defined as death from CRC, with all other deaths treated as censored cases. Crude and multivariate analyses for the individual risk factors were conducted. All analyses were done by using Stata (Version 11.1; StataCorp LP). All tests were 2-tailed and $P < 0.05$ were regarded as statistically significant. In the Cox regression models, significance tests for differences across variable categories were calculated by using the Wald χ^2 test.

Stratified analyses by potential effect modifiers were also conducted to examine the influence of PA (sedentary vs. insufficient and sufficient activity levels combined) and BMI (overweight and obese vs. the rest) across the strata of a range of other predictors of CRC mortality and all-cause mortality. The categories for these predictors were dichotomized for each presentation: age (<60 years vs. ≥60 years); sex, stage at diagnosis (I/II vs. III), smoking (current nonsmoker vs. current smoker); site (colon vs. rectum); treatment (surgery only vs. surgery and adjuvant therapy). For these stratified analyses, records with unknown or missing values for BMI, treatment and stage were excluded.

The impact of changes in PA and weight from T0 (prior to cancer diagnosis) to T1 (5 months postdiagnosis), and from T1 to T2 (12 months postdiagnosis) on all-cause and CRC-specific mortality were also examined. To compare our study results to previous literature, the change for PA were assessed by grouping patients into 3 groups: no change or decreased, increased by 2 hours per week or less, and increased by more than 2 hours per week. The changes for weight were assessed by grouping patients into 5 groups: more than 5 kg loss, 2 to 4.9 kg loss, 2 kg gain or loss, 2 to 4.9 kg gain, and more than 5 kg gain.

Results

Of 1,825 participants with stages I to III CRC (including those with unknown stage), 59.7% were male and the median age at diagnosis was 67 years (range: 21–82 years). Just under two-thirds (63.7%) were diagnosed with colon cancer; about half (55.9%) had surgery only with the remainder having surgery and adjuvant therapy. At 5 months postdiagnosis, more than half (52.8%) were overweight or obese, about 1 in 10 (8.2%) were current smokers, and 41.0% were sedentary.

Participants who were female, obese, or underweight, and current smokers had lower education levels, no private insurance, or had adjuvant treatment were significantly more likely to be sedentary at baseline (Table 1). There were no statistically significant differences in the reported PA levels according to age, marital status, tumor site, disease stage, or the number of comorbidities (Table 1).

At 31 December 2008, 462 (25.3%) participants were deceased. The median follow-up period for survivors was 4.9 years (range: 4.0–6.0 years). The majority of deaths (74.7%) were caused by CRC. Significantly more males ($n = 314$, 28.8% of males) than females ($n = 148$, 20.1%) died within the study period ($\chi^2 = 17.68$, $df = 1$, $P < 0.001$). There were also a greater proportion of deaths among patients who were sedentary ($n = 224$, 30.0%) compared with those who were insufficiently ($n = 111$, 22.9%) or sufficiently active ($n = 127$, 21.4%; $\chi^2 = 14.70$, $df = 2$, $P = 0.001$). Compared with those who were within normal BMI ($n = 217$, 28.3%), a greater proportion of deaths were observed among those who were underweight ($n = 24$, 51.1%), but fewer deaths among those overweight ($n = 140$, 21.6%) and obese ($n = 70$, 22.2%; $\chi^2 = 26.37$, $df = 3$, $P < 0.001$). When we excluded patients who died within 12 months of diagnoses from the analyses, the significant differences by PA in the proportion of patients who died (sedentary 26.5%, insufficiently active 20.6%, and sufficiently active 19.9%, $\chi^2 = 9.54$, $P = 0.008$) remained; similarly for BMI (underweight 47.7%, normal weight 24.9%, overweight 19.8%, and obese 20.2%, $\chi^2 = 21.79$, $P < 0.001$).

All-cause mortality

Cox regression models were used to assess the impact of PA, BMI, and other demographic, lifestyle, and clinical variables on all-cause mortality (Table 2). The bivariate analysis (not shown) showed that those who were more active (including insufficiently active and sufficiently active), female, younger, overweight or obese, never smoked, having earlier stage disease and having surgery only were associated with a significantly ($P < 0.05$) lower HR of all-cause mortality within 5 years of diagnosis. After adjustment, the above factors retained their significant ($P < 0.001$) association with a reduction in risk of overall mortality (Table 2), with the exception of smoking status which became nonsignificant. We found no evidence of significant interaction between sex and PA level or sex and BMI on all-cause mortality. A sensitivity analysis was conducted by excluding those who died within 12 months of diagnosis in the adjusted Cox model, and this approach did not alter the results significantly for PA [all-cause mortality: insufficiently active HR = 0.77 (0.60–0.99), sufficiently active HR = 0.80 (0.63–1.02)] and BMI [all-cause mortality: underweight HR = 2.25 (1.39–3.62), overweight HR = 0.78 (0.62–0.99)]. Additional sensitivity analyses produced similar results. When we only included patients with stage III cancer in the analysis ($n = 562$), there was no difference in all-cause mortality by PA ($P = 0.433$), but the increased mortality for underweight patients [HR = 2.19 (1.03–4.66)] and the reduced all-cause mortality risk for obese patients remained [HR = 0.63 (0.42–0.96)], although the differences in overweight group became insignificant [HR = 0.88 (0.66–1.19)]. Finally, we found similar results to that for the overall cohort, when we excluded those patients with unknown stage ($n = 225$); lower all-cause mortality risk was found in patients who were insufficiently active [HR = 0.70 (0.54–0.90)] and those who were

Table 2. Adjusted mortality HRs (CRC- and all-cause mortality) 5 years postdiagnosis by level of PA at 5 months postdiagnosis

			CRC mortality			All-cause mortality		
	No. of patients at risk ($n = 1,825$)	Time at risk (mo)	No. of deaths	HR (95% CI)	P^b	No. of deaths	HR (95% CI)	P^b
PA					0.585			0.007
Sedentary	748	37,000	151	1.00		224	1.00	
Insufficiently active	484	25,116	96	0.90 (0.69–1.17)		111	0.72 (0.57–0.91)	
Sufficiently active	593	31,386	98	0.88 (0.68–1.15)		127	0.75 (0.60–0.94)	
Sex					0.104			<0.001
Male	1,089	54,907	221	1.00		314	1.00	
Female	736	38,595	124	0.81 (0.64–1.04)		148	0.66 (0.53–0.82)	
Age (y)					0.212			<0.001
20–49	151	8,177	21	0.60 (0.37–0.97)		23	0.45 (0.29–0.70)	
50–59	350	18,460	71	0.88 (0.65–1.19)		75	0.61 (0.47–0.81)	
60–69	610	31,186	114	0.90 (0.70–1.16)		143	0.75 (0.60–0.93)	
70+	714	35,711	139	1.00		221	1.00	
BMI					0.006			<0.001
Underweight	47	1,970	15	1.74 (1.00–3.04)		24	2.29 (1.47–3.59)	
Healthy	768	3,8671	164	1.00		217	1.00	
Overweight	649	34,160	106	0.75 (0.59–0.97)		140	0.75 (0.61–0.94)	
Obese	315	16,355	50	0.70 (0.51–0.97)		77	0.78 (0.59–1.03	
Unknown	46	2,345	10	1.34 (0.70–2.58)		11	0.94 (0.51–1.74)	
Smoking status					0.429			0.251
Never smoked	727	37,458	141	1.00		171	1.00	
Current smoked	150	7,274	34	1.02 (0.68–1.53)		52	1.25 (0.89–1.75)	
Former smoked	948	48,770	170	0.87 (0.69–1.10)		239	0.95 (0.77–1.17)	
Marital status					0.374			0.435
Married/de facto	1,354	69,366	259	1.00		341	1.00	
Others[a]	471	24,136	86	1.03 (0.80–1.33)		121	1.09 (0.88–1.36)	
Education level					0.402			0.247
<8 years	261	13,231	52	1.00		81	1.00	
8–11 years	725	37,510	137	0.90 (0.65–1.26)		184	0.90 (0.68–1.18)	
12 years/college	594	30,170	117	0.87 (0.62–1.23)		147	0.82 (0.62–1.09)	
University	245	12,591	39	0.69 (0.45–1.07)		50	0.70 (0.49–1.01)	
Private health insurance					0.478			
Have	1,085	56,181	196	1.00		259	1.00	0.491
Did not have	740	37,322	149	1.08 (0.87–1.36)		203	1.07 (088–1.30)	
Site					0.842			0.976
Colon	1,163	59,506	207	1.00		286	1.00	
Rectum	662	33,996	138	1.02 (0.81–1.30)		176	1.00 (0.81–1.22)	
Stage of disease					<0.001			<0.001
Stage I	448	25,393	15	1.00		44	1.00	
Stage II	590	30,856	90	4.08 (2.35–7.11)		131	2.16 (1.53–3.07)	
Stage III	562	25,952	195	7.53 (4.27–13.26)		233	3.84 (2.65–5.55)	
Unknown	225	11,302	45	4.26 (2.33–7.80)		54	1.98 (1.30–3.02)	
Treatment					<0.001			<0.001
Surgery only	1,020	55,445	89	1.00		263	1.00	
Surgery and adjuvant	747	35,700	230	2.26 (1.67–3.05)		271	1.66 (1.29–2.12)	
Unknown	58	2,358	26	5.45 (2.27–9.07)		28	3.75 (2.36–5.96)	

(Continued on the following page)

Table 2. Adjusted mortality HRs (CRC- and all-cause mortality) 5 years postdiagnosis by level of PA at 5 months postdiagnosis (Cont'd)

			CRC mortality			All-cause mortality		
	No. of patients at risk (n = 1,825)	Time at risk (mo)	No. of deaths	HR (95% CI)	P^b	No. of deaths	HR (95% CI)	P^b
Number of comorbidities					0.733			0.982
0	709	36,560	125	1.00		170	1.00	
1	678	34,464	132	1.06 (0.82–1.35)		173	1.04 (0.84–1.29)	
2	310	15,845	66	1.09 (0.80–1.47)		86	1.05 (0.80–1.36)	
≥3	128	6,604	22	0.84 (0.52–1.32)		33	1.01 (0.69–1.48)	

NOTE: Cases with missing values (BMI, n = 46; treatment, n = 58) were recoded as unknown group and included in the analysis.
[a]Other marital status refers to "never married," "widowed," or "divorced/separated."
[b]P values were obtained from the Wald χ^2 test of parameters after estimation.

sufficiently active HR = 0.73 (0.58–0.93)] compared with those who were sedentary. For BMI, there was higher risk in underweight patients [HR = 2.30 (1.44–3.69)] compared with normal weight patients but lower risk in the overweight [HR = 0.73 (0.58–0.92)] and obese group [HR = 0.74 (0.55–1.00), P = 0.047].

The stratified analyses (Fig. 1A) shows that the reduced all-cause mortality risk for active (insufficiently and sufficiently active combined) participants compared with sedentary participants was evident across all the strata, although some strata-specific estimates were nonsignificant. Age, stage, and treatment type had a significant interaction effect with PA on all-cause mortality, with the protective effect of PA being most pronounced among those older (≥60 years), with less advanced disease (stage I/II) participants or surgery alone. Similar stratum-specific interactions with BMI were also observed (Fig. 1B). There was no evidence of interaction between BMI levels and separate strata-specific variables on all-cause mortality.

CRC-specific mortality

There was no association between PA and CRC-specific mortality, either in the unadjusted analyses (P = 0.109) or after adjustment (P = 0.585, Table 2). After adjustment, the risk of dying because of CRC within 5 years of diagnosis was significantly associated with BMI (P = 0.006), stage of disease at diagnosis (P < 0.001), and type of treatment (P < 0.001). Compared with participants in the healthy BMI range, those who were underweight were significantly more likely to die due to CRC within 5 years (HR = 1.74, 95% CI = 1.00–3.04), whereas participants who were overweight (HR = 0.75, 95% CI = 0.59–0.97) or obese (HR = 0.70, 95% CI = 0.51–0.97) were significantly less likely to die (Table 3). We found no evidence of significant interaction between sex and PA or sex and BMI on CRC-specific mortality. Additional sensitivity analyses produced similar results. When we reran the analysis by excluding those who died within 12 months after diagnosis (n = 60), the differences in CRC-specific mortality by BMI group became insignificant compared with the healthy BMI group [underweight HR = 1.75 (0.96–3.20)], overweight HR = 0.79 (0.61–1.04)], and obese HR = 0.72 (0.51–1.03)]. When the analysis was restricted to stage III patients (n = 562), the reduced CRC-specific mortality risk, compared with normal weight patients, remained significant for obese patients [HR = 0.58 (0.37–0.93)] but became nonsignificant for overweight patients [HR = 0.86 (0.62–1.19)] and nonsignificantly increased for underweight [HR = 2.15 (0.96–4.79)] patients. Finally, when we excluded patients with unknown stage (n = 225) from analysis, we found similar results to that for the main cohort with marginally higher CRC-mortality risk in the underweight group [HR = 1.80 (1.00–3.26), P = 0.051] and the significantly lower risk for both overweight [HR = 0.72 (0.55–0.94)] and obese participants [HR = 0.66 (0.47–0.94)] remaining.

The stratified analyses (Fig. 2A) show that the reduced CRC-specific mortality risk for active (insufficiently and sufficiently active combined) participants compared with sedentary participants was evident across most of the strata, although some strata-specific estimates (including those with inflated mortality risks) were nonsignificant. Similarly, the effects of BMI on CRC mortality were consistently evident across the strata (Fig. 2B), with the exception of current smokers, although this and some other strata-specific estimates were not statistically significant. There was no evidence of interaction between the PA levels or BMI levels and separate strata-specific variables on CRC-specific mortality.

The association of change of PA and weight on mortality

The change in PA level from prediagnosis to 5 months postdiagnosis did not have any impact on either all-cause or CRC-specific mortality (Table 3). However, at 12 months postdiagnosis, those who had increased their

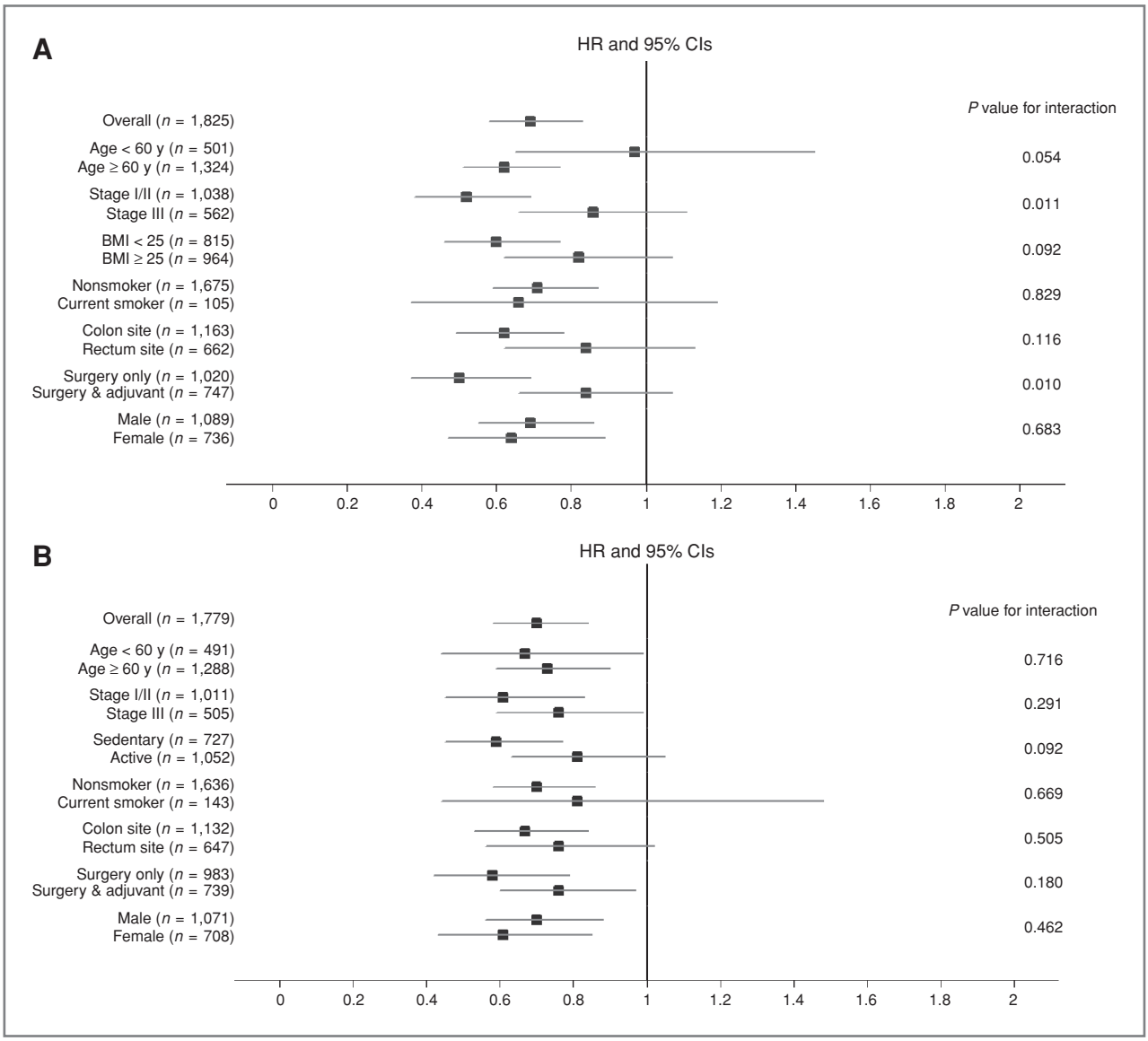

Figure 1. Stratified analysis of all-cause mortality. A, physical activity: active versus sedentary. B, body mass index: underweight/normal versus overweight/obese.

PA by more than 2 hours per week had significantly lower HRs for both all-cause and CRC-specific mortality even after adjustment for all potential confounders [HR = 0.69 (0.50–0.94); Table 3].

Weight loss of 5 kg or more at any period was significantly associated with higher HR for all-cause and CRC-specific mortality even after adjustment (Table 4). Similarly, a weight gain of 5 kg or more at 5 months postdiagnosis was significantly associated with a higher HR only for all-cause mortality [HR = 1.63 (1.02–2.61)].

Discussion

In this large population-based study of 1,825 adults diagnosed with stages I to III and unknown stage CRC in Queensland, Australia, people who had some level of PA following diagnosis were significantly less likely to die within 5 years of diagnosis than sedentary participants. Although there was a similar direction of effect of PA levels on CRC-specific mortality, the magnitude of this effect was not statistically significant. In contrast, the association between BMI and all-cause and CRC-specific mortality was consistent, with underweight participants having a higher mortality risk, and overweight and obese having lower mortality risks compared with participants in the healthy BMI range.

BMI

We found that self-reported BMI at 5 months postdiagnosis was a very strong predictor for both all-cause

Table 3. HRs of all-cause mortality and CRC-specific mortality by changes in PA

	HR of death (95% CI)			
	All-cause mortality		CRC mortality	
	Crude	Adjusted[a]	Crude	Adjusted[a]
Prediagnosis to 5 months postdiagnosis (n = 1,825)				
No change or decreased (n = 1,589)	1.00	1.00	1.00	1.00
Increased ≤2 h/wk (n = 138)	0.99 (0.70–1.40)	1.27 (0.88–1.83)	1.15 (0.79–1.67)	1.32 (0.89–1.98)
Increased >2 h/wk (n = 98)	0.76 (0.49–1.19)	1.06 (0.65–1.71)	0.78 (0.46–1.30)	1.03 (0.59–1.80)
Significance	0.494	0.449	0.467	0.389
5 months postdiagnosis to 12 months postdiagnosis (n = 1,554)[b]				
No change or decreased (n = 925)	1.00	1.00	1.00	1.00
Increased ≤2 h/wk (n = 358)	0.70 (0.53–0.92)	0.79 (0.59–1.04)	0.66 (0.47–0.93)	0.68 (0.48–0.97)
Increased >2 h/wk (n = 271)	0.70 (0.51–0.95)	0.69 (0.50–0.94)	0.73 (0.51–1.04)	0.64 (0.44–0.93)
Significance	0.007	0.030	0.026	0.015

[a]Adjusted for 5 months postdiagnosis PA level (sedentary, insufficient active, and sufficient active), age (<50, 50–59, 60–69, or ≥70 years), stage (stages I, II, III, or unknown), BMI (<18, 18–24.9, 25–29.9, ≥30, or unknown), smoking status (never smoked, current smoked, or former smoked), site (colon or rectum), treatment (surgery only, surgery and adjuvant, or unknown), sex and comorbidities (0, 1, 2, or ≥3).

[b]Patients who died within 12 months (including 12 months; n = 60) or had missing values for T2 PA (n = 271) were excluded (n = 271).

mortality and CRC-specific mortality in stages I to III CRC patients, with this association persisting after adjustment for a range of potential confounders. We are aware of no other directly comparable published studies. In an observational study of 1,053 stage III colon cancer patients in the United States undergoing chemotherapy (10), after adjustment for a range of clinical, demographic, and behavioral factors, there was no association between all-cause mortality risk and BMI. When we repeated our analysis including only stage III colon patients and using similar BMI cut-points to that of Meyerhardt and colleagues (10), the reduced risk for obese patients remained; however, the differences in other BMI groups became nonsignificant (results not shown). A longitudinal study of women diagnosed with colon cancer (12) found that all-cause mortality risk was significantly increased for women who were obese and for those who were underweight; however, substantial differences in study methodology, including having up to 20 years follow-up and BMI measurements collected up to 19 years prior to the cancer diagnosis may explain these differences. Consistent with our results, a recent study of 1,219 Iranian CRC patients (13), although with a reduced follow-up period (mean 2.2 years), reported significantly higher all-cause mortality among underweight colon and rectal cancer patients compared with those of normal weight, and lower all-cause mortality among overweight patients, but the difference was not significant among obese patients.

The higher mortality risks among overweight and obese CRC patients have been suggested to be mediated by a higher insulin resistance and higher concentrations of insulin and insulin-like growth factor I, which promote cell proliferation and inhibit apoptosis, or the process of programmed cell death (6). There is also emerging evidence that the ideal BMI range for older adults may be higher than for younger adults (21–23). A U.S. study of 5,899 nursing home residents reported significantly lower mortality rates for those with a BMI greater than 28 compared with those within the normal range (24), and a longitudinal study of 7,527 elderly people showed that mortality rates after 8 years of follow-up were significantly lower in the obese group (BMI >28.5 kg/m^2) compared with the thin group (<19.4 kg/m^2; ref. 25).

Participants who were underweight experienced significantly higher all-cause and CRC-specific mortality risks than healthy participants. It is possible that weight loss could reflect greater general morbidity and ill-health at diagnosis, although we did adjust for the number of comorbid conditions. We examined this hypothesis by excluding those patients who died within 12 months of diagnosis and found that the adjusted excess HR for all-cause mortality remained highly significant for the underweight group; however, the adjusted HR for CRC-specific mortality became nonsignificant.

This study found that weight loss of 5 kg or more at any period was associated with higher mortality risks for all-cause and CRC-specific death. One previous study (10) found no association between weight changes at 4 months and 14 months postsurgery and survival in 1,053 stage III CRC patients. When we repeated our analysis restricting to stage III participants only, the significant association between weight loss and risk of mortality remained.

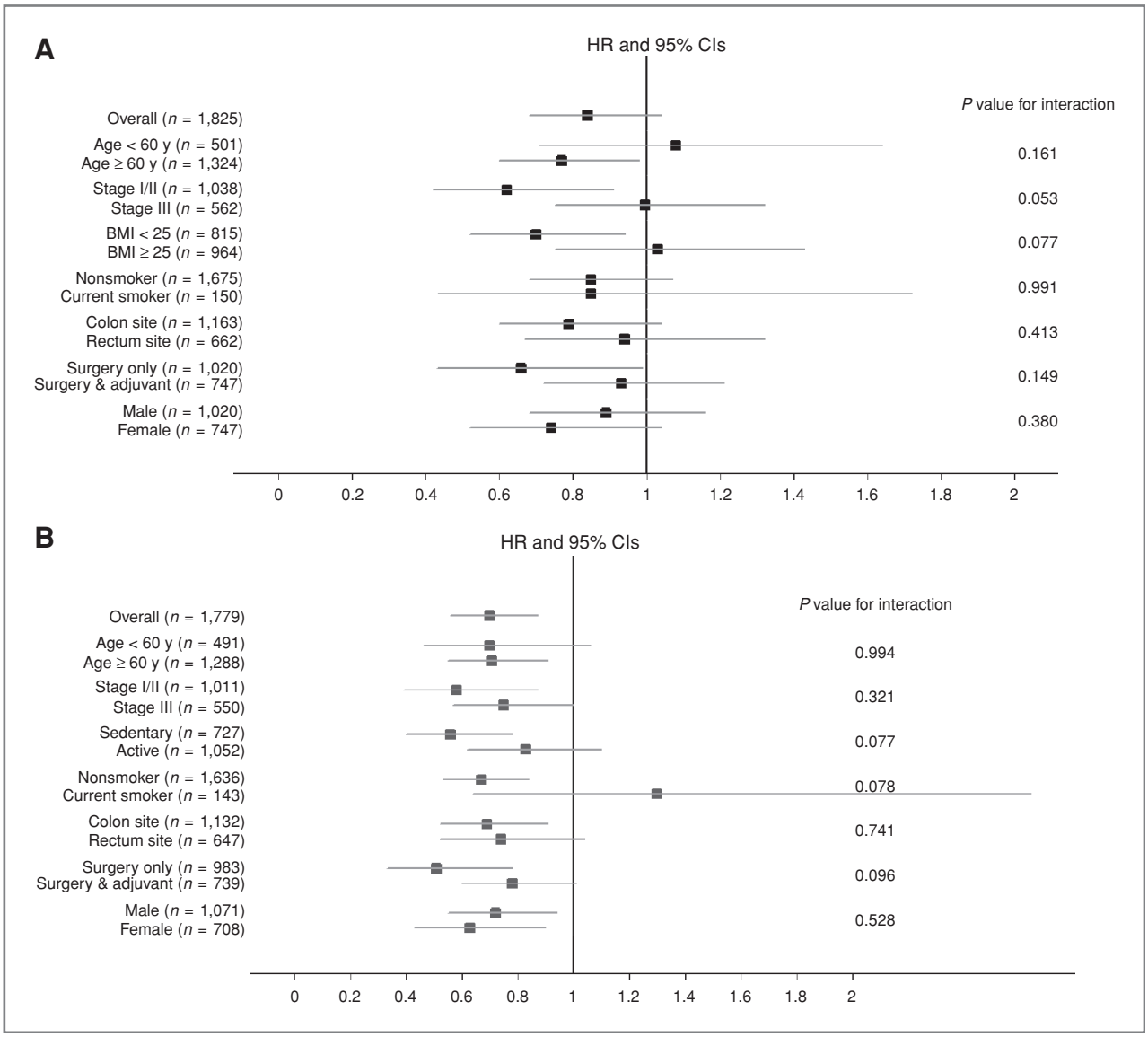

Figure 2. Stratified analysis of CRC-specific mortality. A, physical activity: active versus sedentary. B, body mass index: underweight/normal versus overweight/obese.

PA

Previous studies examining the relationship between being more physically active before diagnosis of CRC and survival found marginal (26) or no effects (8, 9). However, studies of postdiagnosis PA have shown that being more physically active after diagnosis reduces the risk of all-cause and disease-specific mortality in stages I to III CRC patients (7, 8) and reduced risk of cancer recurrence and overall mortality in stage III CRC patients (7). The results of our study support these findings. Although we did not find the protective effect of PA at 5 months postdiagnosis on CRC-specific mortality, our data show that people who had increased their activity by more than 2 hours per week by 12 months postdiagnosis had a significant lower adjusted HR for all-cause and CRC-specific mortality. Meyerhardt and colleagues (8) also found women who increased their activity from prediagnosis (median, 6 months before diagnosis) to 22 months after diagnosis (median) had a lower HR for all-cause mortality [HR = 0.51 (0.30–0.85)] and CRC mortality [HR = 0.48 (0.24–0.97)].

Advantages of this study include the large population-based cohort, with information on a range of clinical, demographic, and behavioral factors. Mortality information was ascertained through linking to a national death index which includes deaths registered in Queensland and other Australian states. The use of all-cause mortality, in addition to CRC-specific mortality, removes doubts about the accuracy of the cause of death coding. Limitations include the low response rate, with the initial

Table 4. HRs of all-cause mortality and CRC-specific mortality by changes in weight ($n = 1,825$)

	HR of death (95% CI)			
	All-cause mortality		CRC mortality	
	Crude	Adjusted[a]	Crude	Adjusted[a]
Prediagnosis to 5 months postdiagnosis ($n = 1,763$[b])				
>5 kg loss ($n = 658$)	1.85 (1.47–2.32)	1.63 (1.29–2.06)	1.95 (1.50–2.55)	1.64 (1.24–2.15)
2–4.9 kg loss ($n = 372$)	1.21 (0.91–1.59)	1.10 (0.83–1.46)	1.17 (0.84–1.63)	1.02 (0.73–1.42)
± 2 kg ($n = 585$)	1.00	1.00	1.00	1.00
2–4.9 kg gain ($n = 70$)	0.80 (0.43–1.49)	1.12 (0.60–2.09)	0.70 (0.33–1.52)	0.90 (0.41–1.96)
>5 kg gain ($n = 78$)	1.47 (0.93–2.33)	1.63 (1.02–2.61)	1.47 (0.86–2.51)	1.46 (0.84–2.53)
Significance	<0.001	<0.001	<0.001	0.001
5 months postdiagnosis to 12 months postdiagnosis ($n = 1,503$[c])				
>5 kg loss (68)	2.59 (1.72–3.89)	2.92 (1.89–4.49)	3.06 (1.92–4.89)	3.21 (1.95–5.31)
2–4.9 kg loss ($n = 103$)	1.41 (0.94–2.14)	1.68 (1.10–2.59)	1.51 (0.92–2.49)	1.59 (0.95–2.68)
± 2 kg ($n = 663$)	1.00	1.00	1.00	1.00
2–4.9 kg gain ($n = 251$)	0.96 (0.69–1.33)	0.95 (0.68–1.32)	1.09 (0.74–1.61)	1.02 (0.69–1.50)
>5 kg gain ($n = 418$)	1.12 (0.86–1.47)	0.91 (0.69–1.20)	1.20 (0.87–1.65)	0.89 (0.64–1.25)
Significance	<0.001	<0.001	<0.001	<0.001

[a]Adjusted for 5 months postdiagnosis weight, height, PA level (sedentary, insufficient active, and sufficient active), age (<50, 50–59, 60–69, or ≥70 years), stage (stages I, II, III, or unknown), smoking status (never smoked, current smoked, or former smoked), site (colon or rectum), treatment (surgery only, surgery and adjuvant, or unknown), sex and comorbidities (0, 1, 2, or ≥3).
[b]Subjects with missing values for prediagnosis weight, 5 months postdiagnosis weight or BMI were mutually excluded ($n = 62$).
[c]Subjects with missing values for 5-month postdiagnosis weight or BMI or 12 months postdiagnosis weight were mutually excluded ($n = 322$).

sample representing about 52% of the potentially eligible cohort of patients diagnosed with stages I to III CRC (including unknown stage) in Queensland. The follow-up period was relatively short when considering that this study did not measure the recurrence till death. Also, information about BMI and PA are based on self-report. Although high correlations between self-reported weight and height and the measurements in cancer treatment facilities have been reported (10), the difficulty of accurately assessing obesity and PA levels is well recognized (27).

The results from this study add important information to the limited existing knowledge about the role of PA and BMI on mortality for people diagnosed with CRC. The protective effects of being physically active and increasing that activity highlights the importance of interventions to increase activity levels among people being diagnosed with CRC. Similarly the increased mortality risks associated with being underweight or having weight loss over time highlights an important indicator for which clinicians, patients, and support personnel can monitor relatively easily.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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