Healthier Prediagnosis Lifestyle and Long-term Survival in Colorectal Cancer: Evidence from the Singapore Chinese Health Study

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ABSTRACT

Background: Evidence from Western populations suggests that healthier prediagnosis lifestyles are associated with improved relative survival after colorectal cancer. We quantified the survival differences by composite prediagnosis lifestyle.

Methods: Incident colorectal cancer cases (n = 2,124) were identified from the Singapore Chinese Health Study via registry linkage. Deaths (all-cause and colorectal cancer–specific) through December 2022 were ascertained. Prediagnosis lifestyle (diet, physical activity, smoking, body mass index, and sleep) was assessed at enrollment (1993–1998) and combined into a composite score. Cox models estimated hazard ratios (HR); restricted mean survival time (RMST) quantified absolute differences at 10 years after diagnosis. Models were adjusted for stage, age at diagnosis, sex, education, alcohol, and the interval from enrollment to diagnosis.

Results: During a median of 4.8 years (interquartile range 1.2–11.8 years) of follow-up, 1,557 all-cause deaths occurred, including 1,103 colorectal cancer–specific deaths. Patients with high versus low prediagnosis lifestyle scores had lower hazards of all-cause mortality [$HR_{adjusted}$ 0.74; 95% confidence interval (CI), 0.65–0.92]. The adjusted 10-year RMST difference (high minus low) for all-cause mortality was 0.85 years (95% CI, 0.34–1.35). In patients aged ≤70 years (n = 922), the associations were similar, with a 10-year RMST difference of 1.15 years (0.35–1.95). Stage dominated outcomes, with a 10-year RMST difference (late minus early) of −3.33 years (−3.72 to −2.93).

Conclusions: Although stage at diagnosis remains the principal driver of survival for patients with colorectal cancer, healthier prediagnosis lifestyles are associated with modest improvements in long-term survival.

Impact: Longitudinally collected behaviors at multiple time points will complement our findings, providing stronger evidence on the health behaviors that support better survivorship.

Introduction

Colorectal cancer is among the most commonly diagnosed cancers and a major cause of cancer mortality worldwide (1). Population-based and opportunistic screening has shifted diagnosis toward earlier stages, contributing to improved survival and a growing population of colorectal cancer survivors (2). Survival rates differ markedly by stage at diagnosis, with substantially higher 5-year survival rates for early-stage disease than for late-stage disease (3). Nonetheless, outcomes vary; some patients with late-stage colorectal cancer achieve long-term survival, whereas some patients with early-stage disease die soon after diagnosis. Beyond age at diagnosis, established prognostic factors include tumor biology, treatment modality and timeliness, and socioeconomic context (4–8). We hypothesized that a healthier prediagnosis lifestyle, higher dietary quality, and greater physical activity may contribute to improved postdiagnosis survival, complementing the benefits of early detection and optimal treatment (3).

Lifestyle factors, such as poor diet quality, low physical activity, smoking, and high adiposity, are associated with increased colorectal cancer risk (6, 9–13). Higher diet quality (e.g., anti-inflammatory diet, lower Healthy Eating Index, or lower Mediterranean Diet Score) is associated with an 8% to 56% lower colorectal cancer risk when comparing the least with the most adherent groups (13). These behaviors influence metabolic, inflammatory, and microbiome pathways implicated in colorectal cancer (14–16). Healthy lifestyle behaviors are also positively associated with survival among patients with colorectal cancer—this has been reported for both pre- and postdiagnosis lifestyle—although the evidence is more consistent for the latter (17–22).

Composite lifestyle scores have been examined in relation to colorectal cancer survival because patients rarely exhibit uniformly healthy or unhealthy profiles with respect to individual behaviors. Across multiple cohorts, higher lifestyle scores (pre- or post-diagnosis) are associated with lower all-cause mortality, with typical relative reductions of approximately 37% when comparing the highest with the lowest categories (23). A prediagnosis lifestyle that is more consistent with the American Cancer Society (ACS) recommendations has similarly been linked to reduced all-cause mortality (16). Although hazard ratios (HR) are informative, restricted mean survival time (RMST) complements them by quantifying absolute differences in survival time between lifestyle groups.

Evidence from predominantly Western populations suggests that a healthier prediagnosis composite lifestyle is associated with improved overall survival after colorectal cancer, yet absolute survival gains have rarely been reported (24). Earlier analyses among participants of the Singapore Chinese Health Study (SCHS) reported

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that adherence to multiple healthy lifestyle factors was associated with substantial gains in life expectancy at age 50 years (8.1 years for women and 6.6 years for men; ref. 25). Although the effects of individual components on cancer mortality varied, the composite lifestyle score showed a consistent, monotonic inverse association with cancer death (24). Extending this to colorectal cancer survivors, in this study, we quantified survival differences between patients with healthier versus less healthy prediagnosis lifestyles using RMST at 5 and 10 years after diagnosis, and we examined individual prediagnosis lifestyle components as potential drivers of these differences.

Materials and Methods

Study population

This study identified colorectal cancer cases from the SCHS, which is described elsewhere (26, 27). In brief, SCHS recruited Chinese individuals living in public housing estates between April 1993 and December 1998 (26, 27). Participants aged between 45 and 74 years were enrolled. Colorectal cancer cases diagnosed on or before December 31, 2015 were identified by matching them to the National Disease Registry Office. Among noncancer individuals at enrollment, incident colorectal cancer cases (n = 2,144) were identified from their International Classification of Diseases, 10th Revision, codes C18 to C20. Twenty patients who were diagnosed at the time of death were excluded. Tumor stage was mostly available for cases diagnosed after the year 2003. The SCHS is continuously reviewed and approved by the Institutional Review Board of the National University of Singapore. All the participants provided written informed consent at recruitment. The study was conducted following the Declaration of Helsinki.

Outcome of interest: Mortality

Death status, including the cause and date of death, up to December 31, 2022, was obtained from the Registry of Births and Deaths. The follow-up time was calculated as the time between the date of cancer diagnosis and death or December 31, 2022, whichever was earlier.

Demographic and risk factors from questionnaire

All the participants completed a structured questionnaire at enrollment, from which we obtained demographic and lifestyle information, including age at interview, sex (male, female), education (none, primary, secondary, postsecondary), the number of comorbidities, and alcohol consumption (nondrinker, drinker). Diet was assessed using a food frequency questionnaire (27). The quantile of the Alternative Healthy Eating Index (AHEI) without the alcohol component was used to quantify diet quality, with 0 being the least and 3 being the healthiest. A composite prediagnosis lifestyle score was derived using the body mass index (BMI; <20, 20.0–22.9, and 23 kg/m^2), smoking status (never, ex-smoker, and current), average sleep (hours/day), and weekly physical activity (yes and no). This lifestyle score takes values from 0 (least healthy) to 7 (healthiest), and the coding is detailed in Supplementary Table S1.

Statistical analysis

The differences in demographic and risk factors by mortality status (all-cause mortality within 20 years after diagnosis) were assessed using the χ^2 test for categorical variables and the Kruskal–Wallis test for continuous variables. The associations of demographic and risk factors with the prediagnosis lifestyle score were similarly tested.

To study the impact of precolorectal cancer diagnosis lifestyle on mortality (all-cause and colorectal cancer–specific), we classified participants with prediagnosis lifestyle scores of 0 to 2 as "low," 3 to 4 as "medium," and 5 to 7 as "high" in relation to adherence to healthy lifestyle recommendations. Cause-specific HRs from Cox proportional hazard models were used to study the association between prediagnosis lifestyle scores and mortality. The RMST models were used to estimate the absolute years gained from having a healthier lifestyle ("medium" and "high") when compared with the individuals in the "low" category. Although both RMST and HR have straightforward clinical interpretations, RMST does not require the proportional hazard assumption (28). Hence, RMST ratios are presented to provide an alternative comparison to the HR. We adjusted for confounders, stage at diagnosis (early, late, and unknown), age at diagnosis (continuous), sex, education, alcohol consumption, and the interval between cohort enrollment and diagnosis. We used the survival and survRM2 packages in R for this analysis (28, 29).

To understand the contributions of the individual components of the prediagnosis lifestyle score, we repeated the analysis for each component of the lifestyle score: sleep (<5 or ≥9 hours vs. 6–8 hours), AHEI without alcohol score (0 vs. 1–3), physical activity (no vs. yes), and smoking status (ex- or current smoker vs. never). For each component, we adjusted for all other components of the prediagnosis lifestyle score.

The SCHS is an established cohort in which lifestyle factors were measured only at baseline; additionally, colorectal cancer stage at diagnosis (a major determinant of survival) had a high proportion of missing values. Hence, we conducted a series of sensitivity analyses. First, to assess the potential exposure misclassification arising from behavioral changes over time, we performed a stratified, covariate-adjusted analysis by quartiles of the interval between cohort enrollment and colorectal cancer diagnosis. For comparability with the published literature, we used Cox proportional hazard models. Notably, stratification by quartile reduced the sample size to 25% per stratum. Hence, we interpreted these results primarily in terms of the direction of association and the magnitude of effect estimates.

In addition, we conducted a subgroup analysis of individuals who were diagnosed at age ≤70 years. In Singapore, the life expectancy at birth for females is 86.3 years (30); hence, restricting the analysis to those diagnosed at age ≤70 years increases the likelihood of adequate follow-up to evaluate long-term outcomes, including survival up to 15 years after diagnosis. The age restriction considers that elderly patients aged 70 years and above are likely to be more heterogeneous in relation to comorbidities and overall health status.

Missing data were generally absent apart from the stage at diagnosis. Sensitivity analyses were conducted using multiple imputations to address the missing stage information. Using the *mice* package in R, we employed logistic regression with 60 imputations and 20 iterations. Predictors included age at interview, sex, education, lifestyle score and its components, log-transformed survival time, and death status. The Rubin pooling rules were used to pool the results.

We conducted a sensitivity analysis to estimate the adjusted RMST differences for lifestyle categories (medium minus low and high minus low) within stage strata (early and late) using multiple imputations, given the substantial missingness in stage at diagnosis.

The analysis was done using R version 4.4.3.

Results

A total of 2,124 patients with incident colorectal cancer were included in our study (**Table 1**). Fifty-two percent of the participants were male. The median age at diagnosis was 72 years [interquartile range (IQR) 66–77]; 28% were diagnosed with early-stage colorectal cancer, 35% with late-stage colorectal cancer, and 37% with unreported stage. With a median follow-up time of 4.8 years (IQR 1.2–11.8) after diagnosis, we observed 1,557 (73% of 2,124) deaths from any cause. Of these, 1,103 (70%) were colorectal

Table 1. Characteristics of study population, by death status at the end of study follow-up.

		Status at the end of study		
Characteristic	**All** ***n*** **= 2,124**	**Alive** ***n*** **= 567**	**All-cause death** ***n*** **= 1,557**	***P***
Median age at interview (IQR), years	60 (53–66)	53 (49–58)	62 (56–67)	<0.001
Median age at diagnosis (IQR), years	72 (66–77)	68 (63–73)	73 (67–79)	<0.001
Median age at last follow-up (IQR), years	79 (73–85)	82 (76–87)	78 (71–84)	<0.001
Median last follow-up time from diagnosis (IQR), years	4.78 (1.17–11.78)	13.46 (9.74–17.85)	2.36 (0.67–6.71)	<0.001
Median time from lifestyle measurement to colorectal cancer diagnosis (IQR), years	12.24 (6.93–16.68)	14.79 (10.26–18.22)	11.26 (6.38–15.90)	<0.001
Stage				
Early	586 (28)	278 (49)	308 (20)	<0.001
Late	748 (35)	164 (29)	584 (38)	
Unknown	790 (37)	125 (22)	665 (43)	
Sex				
Male	1,108 (52)	251 (44)	857 (55)	<0.001
Female	1,016 (48)	316 (56)	700 (45)	
Education				
None	627 (30)	121 (21)	506 (32)	<0.001
Primary	1,006 (47)	264 (47)	742 (48)	
Secondary	411 (19)	143 (25)	268 (17)	
Postsecondary	80 (4)	39 (7)	41 (3)	
Prediagnosis lifestyle score				
1	165 (8)	27 (5)	138 (9)	<0.001
2	301 (14)	57 (10)	244 (16)	
3	433 (20)	118 (21)	315 (20)	
4	562 (26)	149 (26)	413 (27)	
5	404 (19)	125 (22)	279 (18)	
6	259 (12)	91 (16)	168 (11)	
Comorbidities				
0	1,439 (68)	439 (77)	1,000 (64)	<0.001
1	536 (25)	106 (19)	430 (28)	
2+	149 (7)	22 (4)	127 (8)	
Median BMI (IQR), kg/m^2	23.1 (21.3–24.8)	23.1 (21.4–25)	23.1 (21.2–24.7)	0.388
BMI, kg/m^2				
<20	310 (15)	75 (13)	235 (15)	0.560
20–22.9	708 (33)	192 (34)	516 (33)	
≥23	1,106 (52)	300 (53)	806 (52)	
Smoking				
Never	1,338 (63)	408 (72)	930 (60)	<0.001
Ex-smoker	311 (15)	73 (13)	238 (15)	
Current smoker	475 (22)	86 (15)	389 (25)	
Median sleep (IQR), hours/day	7 (6–8)	7 (6–8)	7 (6–8)	0.862
Sleep, hours/day				
5	214 (10)	52 (9)	162 (10)	0.078
6–8	1,758 (83)	485 (86)	1,273 (82)	
9–10	152 (7)	30 (5)	122 (8)	
Any weekly physical activity				
No	1,427 (67)	370 (65)	1,057 (68)	0.276
Yes	697 (33)	197 (35)	500 (32)	
AHEI without alcohol				
0	566 (27)	127 (22)	439 (28)	0.040
1	511 (24)	136 (24)	375 (24)	
2	532 (25)	157 (28)	375 (24)	
3	515 (24)	147 (26)	368 (24)	
Alcohol consumption				
Nondrinker	1,662 (78)	433 (76)	1,229 (79)	0.227
Drinker	462 (22)	134 (24)	328 (21)	

NOTE: *P* value from χ^2 test for categorical variables and Kruskal–Wallis test for continuous variables.

cancer–specific. The median overall survival was 4.8 years [95% confidence interval (CI) 4.3–5.6]. Patient characteristics according to all-cause and colorectal cancer–specific death status are shown in **Table 1** and Supplementary Table S2, respectively.

In our study population, there were no patients reporting having "less healthy" prediagnostic lifestyle behaviors for all domains (i.e., score = 0) or the "healthier" prediagnostic lifestyle behaviors for all domains (i.e., score = 7; Supplementary Table S3). At the highest observed score (i.e., score = 6), 32% reported not engaging in weekly physical activity, 1% did not report 6 to 8 hours of sleep, 25% had a BMI of ≥23 kg/m^2, and 8% had a BMI of <20 kg/m^2. Female sex and higher education attainment were associated with a healthier lifestyle before diagnosis and a lower risk of all-cause death (Supplementary Table S3; **Table 1**). Prediagnostic lifestyle was not associated with the presence or absence of self-reported comorbidities at the time of the interview (χ^2 test P value = 0.467), stage at diagnosis (χ^2 test P value = 0.481), or age at diagnosis (Kruskal–Wallis test P value = 0.099; Supplementary Table S3).

The median survival was 3.6 years (95% CI, 3–4.5) for patients with low, 4.1 years (3.9–5.8) for medium, and 7.1 years (5.5–9.1) for high prediagnosis lifestyle scores. **Fig. 1A** and **B** show the Kaplan–Meier curves for the first 10 years after diagnosis, stratified by prediagnosis lifestyle score and stage at diagnosis. Among patients diagnosed at a late stage, the median survival was 2.2 years (95% CI, 1.7–2.9 years) for patients with low, 2.6 years (2.3–3.3) for medium, and 3.0 years (2.1–4.0) for high scores. Among patients diagnosed at an early stage, fewer than 50% died within 10 years of diagnosis, precluding estimation of median survival.

Incremental decreases in mortality with higher prediagnosis lifestyle scores

Compared with patients with low prediagnosis lifestyle scores (0–2; reference), those with high scores (5–7) had lower hazards of death. Violation of the proportional hazards was not observed over the 10 years postdiagnosis follow-up (**Table 2**; **Fig. 1**). With follow-up truncated at 10 years after diagnosis, the adjusted HR was 0.77 (95% CI, 0.65–0.92) for all-cause death and 0.75 (95% CI, 0.63–0.90) for colorectal cancer–specific death, adjusting for age at diagnosis, sex, stage, highest educational attainment, alcohol consumption, and the interval between cohort enrollment and diagnosis (**Table 2**). Patients with medium scores (3–4) showed intermediate associations; when compared with patients with low scores, the adjusted HRs for all-cause death and colorectal cancer–specific death were 0.83 (95% CI, 0.73–0.96) and 0.85 (95% CI, 0.73–1.00, P = 0.044), respectively (**Table 2**). Stratification by quantiles of the interval between cohort enrollment and diagnosis in years (0.0507, 6.93), (6.93, 12.2), (12.2, 16.7), and (16.7, 23.4) showed HRs comparable in direction of association and effect size to the main analysis (Supplementary Table S4).

Five- and ten-year RMST estimates by prediagnosis lifestyle score are shown in Supplementary Table S5. At 5 years, the adjusted RMST differences between patients with high and low scores were not statistically significant (range 0.11–0.21 years; all $P > 0.05$; Supplementary Table S6). At 10 years, the adjusted RMST differences were statistically significant. Patients with high scores lived, on average, 0.85 years longer (95% CI, 0.34–1.35) for all-cause death and 0.71 years longer (95% CI, 0.18–1.25) for colorectal cancer–specific death than those with low scores. Patients with medium scores experienced smaller gains over 10 years than those with low scores (Supplementary Table S6). The corresponding RMST ratios are presented in Supplementary Table S7.

Diet and physical activity before diagnosis improved RMST

Having a healthier diet and engaging in weekly physical activity before diagnosis were associated with improved survival (**Fig. 2**). The model included individual lifestyle components, stage, age at

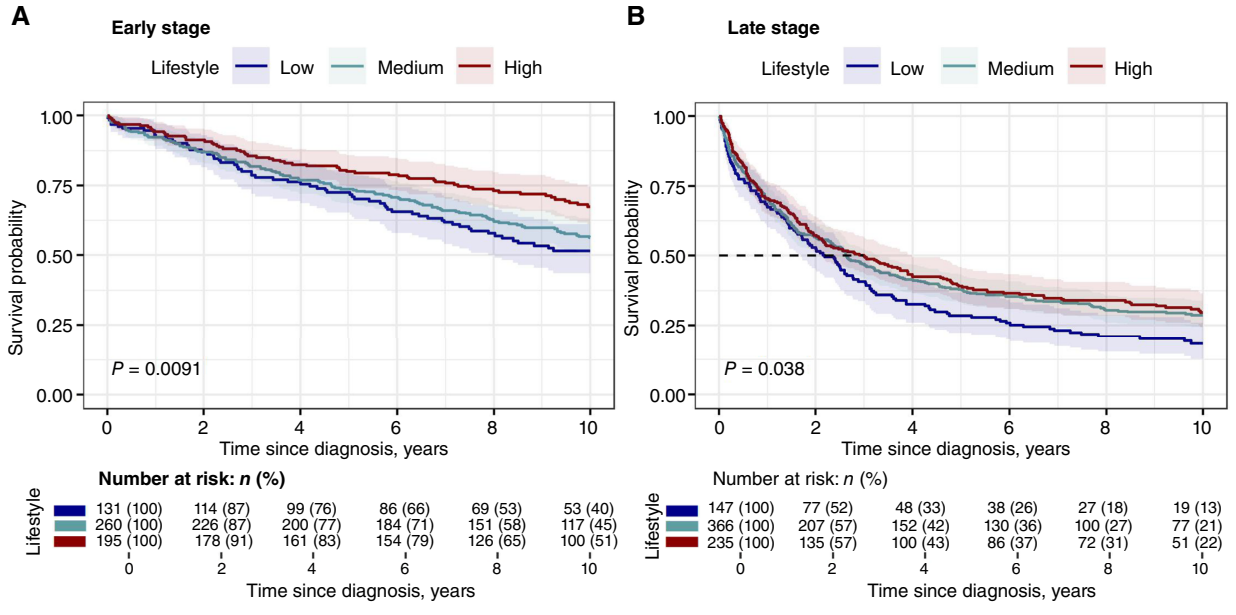


Figure 1.

Kaplan–Meier curves for all-cause mortality by prediagnosis lifestyle score at enrollment in (**A**) early-stage and (**B**) late-stage colorectal cancer. Prediagnosis lifestyle scores were categorized into low (0–2), medium (3, 4), and high (5–7). The dashed line marks the median survival time.

Table 2. Cox proportional hazard models for (A) all-cause death and (B) colorectal cancer–specific death, in the full dataset ($N = 2{,}124$).

		Unadjusted			Adjusted		
Time	**Lifestyle score**	**HR (95% CI)**	***P* value**	**Global proportion hazard test**	**HR (95% CI)**	***P* value**	**Global proportion hazard test**
(A) All-cause death							
5 years				0.685			0.272
	Low	1 (Reference)			1 (Reference)		
	Medium	0.87 (0.75–1.01)	0.076		0.86 (0.74–1)	0.052	
	High	0.74 (0.63–0.87)	<0.001		0.77 (0.65–0.92)	0.004	
10 years				0.308			0.066
	Low	1 (Reference)			1 (Reference)		
	Medium	0.84 (0.73–0.96)	0.010		0.83 (0.73–0.96)	0.011	
	High	0.70 (0.60–0.81)	<0.001		0.74 (0.63–0.87)	<0.001	
(B) Colorectal cancer–specific death							
5 years				0.098			0.009
	Low	1 (Reference)			1 (Reference)		
	Medium	0.90 (0.76–1.06)	0.199		0.87 (0.74–1.03)	0.115	
	High	0.74 (0.62–0.89)	0.001		0.76 (0.63–0.93)	0.006	
10 years				0.080			0.103
	Low	1 (Reference)			1 (Reference)		
	Medium	0.87 (0.75–1.01)	0.073		0.85 (0.73–1)	0.044	
	High	0.73 (0.61–0.86)	<0.001		0.75 (0.63–0.90)	0.002	

NOTE: The adjusted model includes age at diagnosis, sex, education, alcohol, time interval between enrollment and diagnosis, and stage at diagnosis. Stage was modeled using the strata function in coxph(). Prediagnosis lifestyle scores were categorized into low (0–2), medium (3, 4), and high (5–7).

diagnosis, education, and alcohol consumption. In the 5 years after diagnosis, individuals with a healthier diet (AHEI without alcohol 1–3) had, on average, 0.20 years longer colorectal cancer–specific survival (95% CI, 0.02–0.38), and those engaging in weekly physical activity had 0.19 years longer colorectal cancer–specific survival (95% CI, 0.02–0.37; **Fig. 2**; Supplementary Table S8). Similar associations were observed for all-cause death. In relation to the first 5 years, gains in all-cause and colorectal cancer–specific survival approximately doubled in the 10-year follow-up period (Supplementary Table S8). Sleep was not significantly associated with either colorectal cancer–specific or all-cause death after adjustment (**Fig. 2**; Supplementary Table S8). However, smoking was associated with lower survival within 10 years after diagnosis.

Survival benefits were greater in younger patients (≤70 years)

Among patients diagnosed at age ≤70 years ($n = 922$), the associations between prediagnosis lifestyle and survival were similar to those observed in the overall cohort ($n = 2{,}124$). The RMST for prediagnosis lifestyle score comparisons was larger than that for the overall cohort (Supplementary Table S9). At 5 years after diagnosis, the adjusted RMST differences (high minus low and medium minus low) for all-cause death were 0.41 years (95% CI, 0.05–0.77) and 0.35 years (95% CI, 0.03–0.67), respectively (**Table 3**). At 10 years, the corresponding differences were 1.15 years (95% CI, 0.35–1.95) and 0.92 years (95% CI, 0.22–1.62; **Table 3**). The increment in adjusted RMST differences at 5 and 10 years after diagnosis in this younger subgroup was small when compared with that observed in

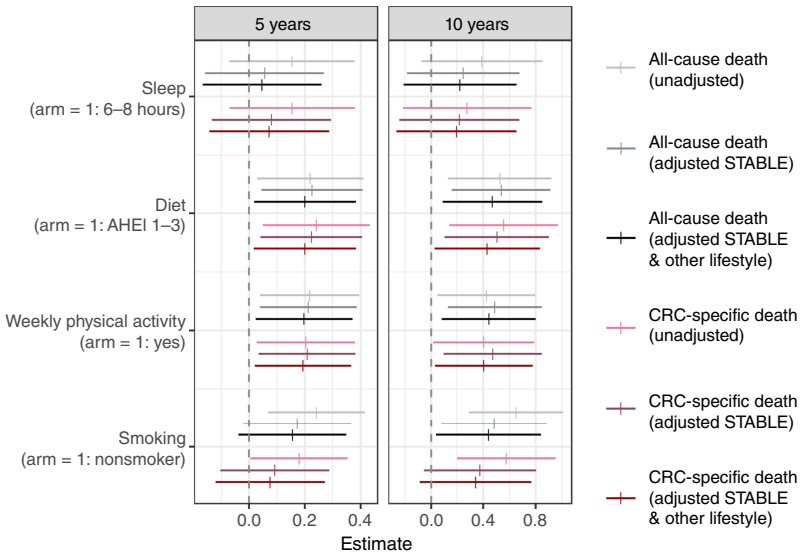


Figure 2.
Comparison of mortality outcomes [all-cause and colorectal cancer–specific (CRC) death] for individuals with less healthy lifestyle components (arm = 0) with those with healthier lifestyle components (arm = 1), using RMST difference (arm = 1 – arm = 0). Variables used to derive lifestyle include sleep, AHEI score without alcohol for diet (AHEI), physical activity, and smoking status at the time of enrollment. Estimates are presented for (i) unadjusted estimates; (ii) adjusted for stage at diagnosis (S), time interval between enrollment and diagnosis (T), age at diagnosis (A), alcohol (B), education level (L), and sex (E); and (iii) adjusted for lifestyle components (binary classification) other than the one under study.

Table 3. Five-, ten-, and fifteen-year all-cause and colorectal cancer–specific RMST difference comparing individuals with (A) medium prediagnosis lifestyle score and (B) high prediagnosis lifestyle score to individuals with a healthier lifestyle, in patients diagnosed at age 70 years and below ($n = 922$).

		Prediagnosis lifestyle, no. of deaths			RMST difference (medium – low)				RMST difference (high – low)			
					Unadjusted		Adjusted[a]		Unadjusted		Adjusted[a]	
Status	Time (Tau)	Low $n = 202$	Medium $n = 423$	High $n = 297$	Estimate (95% CI)	*P*	Estimate (95% CI)	*P*	Estimate (95% CI)	*P*	Estimate (95% CI)	*P*
All-cause death	5	105	172	113	0.40 (0.08–0.72)	0.015	0.35 (0.03–0.67)	0.03	0.49 (0.15–0.83)	0.005	0.41 (0.05–0.77)	0.026
	10	121	208	130	0.96 (0.26–1.65)	0.007	0.92 (0.22–1.62)	0.01	1.25 (0.51–1.99)	<0.001	1.15 (0.35–1.95)	0.005
	15	137	232	145	1.59 (0.54–2.63)	0.003	1.71 (0.62–2.79)	0.002	2.18 (1.06–3.31)	<0.001	2.05 (0.82–3.27)	0.001
Colorectal cancer–specific death	5	92	159	101	0.27 (−0.05 to 0.59)	0.093	0.23 (−0.09 to 0.54)	0.163	0.41 (0.07–0.74)	0.017	0.33 (−0.03 to 0.69)	0.07
	10	103	183	114	0.76 (0.06–1.47)	0.034	0.71 (−0.01 to 1.42)	0.052	1.12 (0.37–1.86)	0.003	0.96 (0.15–1.77)	0.02
	15	109	194	119	1.31 (0.21–2.41)	0.02	1.40 (0.25–2.55)	0.017	1.92 (0.76–3.09)	0.001	1.59 (0.30–2.87)	0.016

Abbreviations: *P*, *P* value; SE, standard error.
[a]Adjusted for stage, age at diagnosis, sex, education, alcohol, and time interval between enrollment and diagnosis.

the overall cohort; that is, patients with medium scores were more similar to those with high scores. Extending the follow-up to 15 years in younger patients doubled the adjusted RMST difference for both high-minus-low [2.05 (95% CI, 0.82–3.27)] and medium-minus-low [1.71 (95% CI, 0.62–2.79)] scores. For colorectal cancer–specific death, although the pattern was similar albeit smaller than that of all-cause death, the RMST differences did not reach statistical significance at 5 years (both medium minus low and high minus low) and 10 years (medium minus low; **Table 3**). At 15 years after diagnosis, the adjusted RMST difference was observed for both the high-minus-low [1.59 (95% CI, 0.30–2.87)] and medium-minus-low [1.40 (95% CI, 0.25–2.55)] scores (**Table 3**). The corresponding RMST ratios are presented in Supplementary Table S10.

The prediagnosis lifestyle component analysis in the subset of patients diagnosed at age ≤70 years found evidence of improved all-cause and colorectal cancer–specific survival in individuals with a healthier prediagnosis diet (Supplementary Figs. S1 and S2; Supplementary Table S11). Although the RMST differences for physical activity were similar to those of the overall cohort at 5 and 10 years after diagnosis, they did not reach statistical significance (**Fig. 3**; Supplementary Table S11). Unlike physical activity, the RMST difference for smoking status in younger patients was smaller than that in the overall cohort (Supplementary Table S11). Similar to that in the overall cohort sleep was not associated with survival (**Fig. 3**; Supplementary Table S11).

Consistent results were observed using imputed values of stage: sensitivity analysis

Given the potential for nonrandom missingness in the stage at diagnosis, missing values were modeled as a separate category to preserve the study population and reduce bias associated with complete-case analysis. The results from the multiply imputed datasets will be reported in the subsequent parts of the Results section. The mean proportion of early-stage colorectal cancer was 43%, closely matching the 44% observed in the original (non-imputed) stage distribution. The pooled adjusted HRs from Cox models were similar to those obtained when including "stage missing" as a separate indicator category (Supplementary Table S12). For RMST, the pooled adjusted differences from the imputed datasets had CIs that included the main analysis point estimates and were generally smaller than those in the main analysis for both all-cause and colorectal cancer–specific deaths in the overall cohort ($n = 2{,}124$; Supplementary Table S13). A similar pattern (smaller adjusted RMST differences in the imputed analyses) was observed for younger patients (≤70 years) when comparing medium and low lifestyle scores. In contrast, for younger patients comparing high versus low lifestyle scores, the imputed analyses produced larger adjusted RMST differences than did the main analysis (Supplementary Table S13).

Larger survival differences observed between early and late stages

Survival differences were more pronounced by stage at diagnosis (early vs. late) than by prediagnosis lifestyle (lifestyle score: low, medium, and high; Supplementary Fig. S1–S4). The unadjusted RMST difference (early minus late) for stage was −1.53 years (95% CI, −1.72 to −1.35 years) at 5 years and −3.33 years (95% CI, −3.72 to −2.93 years) at 10 years for all-cause mortality (Supplementary Table S14). Larger differences were observed for colorectal cancer–specific death: −1.65 years (95% CI, −1.82 to −1.47 years) and −3.89 years (95% CI, −4.28 to −3.50 years) at 5 and 10 years, respectively. Adjusting for lifestyle, age at diagnosis, sex, highest education attainment, alcohol consumption, and time interval between enrollment and diagnosis saw slight decreases in the RMST difference (Supplementary Table S14). In addition, restricting the study to younger patients tended to decrease the difference in RMST (Supplementary Table S14). The pooled adjusted RMST differences were larger than those calculated with "stage missing" as a separate indicator category (Supplementary Table S15).

Lifestyle RMST differences potentially vary by stage at diagnosis

Among early-stage patients, we did not observe adjusted RMST differences between lifestyle levels at 5 years after diagnosis (all *P* values >0.05; Supplementary Table S16). The adjusted RMST differences were observed at 10 years, with differences of high minus low [all-cause: 1.07 (95% CI, 0.79–1.35) and colorectal cancer–specific: 0.76 (0.40–1.12)] more than double those of medium minus low [all-cause: 0.40 (95% CI, 0.18–0.62) and colorectal cancer–specific: 0.18 (95% CI, −0.10 to 0.47; Supplementary Table S16)]. Among late-stage patients, the adjusted RMST differences were similar for medium minus low and high minus low at both 5 and 10 years. The adjusted RMST differences for high minus low were

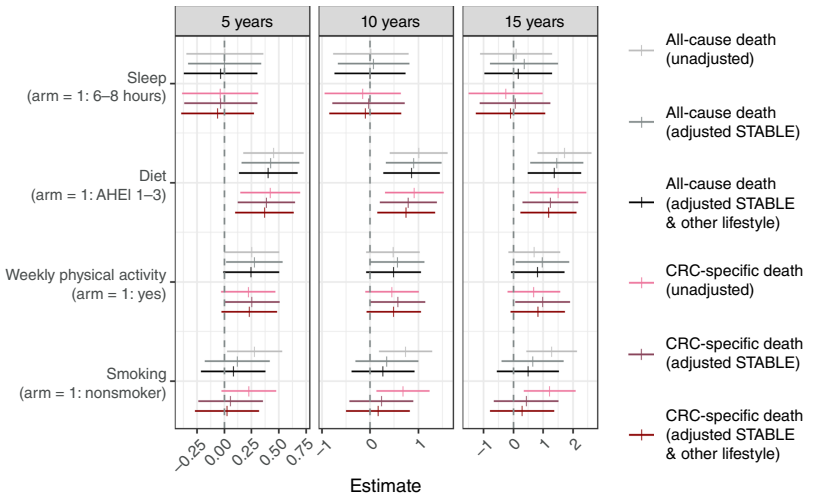


Figure 3.
Long-term follow-up, comparing mortality outcomes [all-cause and colorectal cancer (CRC)–specific death] for individuals with less healthy lifestyle components (arm = 0) with those with healthier lifestyle components (arm = 1), using RMST difference (arm = 1 – arm = 0), in patients diagnosed at age 70 years and below. Variables used to derive lifestyle include sleep, AHEI score without alcohol for diet (a), physical activity, and smoking status at the time of enrollment. Estimates are presented for (i) unadjusted estimates; (ii) adjusted for stage at diagnosis (S), time interval between enrollment and diagnosis (T), age at diagnosis (A), alcohol (B), education level (L), and sex (E); and (iii) adjusted for lifestyle components (binary classification) other than the one under study.

0.25 (95% CI, 0.10–0.40) for all-cause mortality at 5 years and 0.80 (95% CI, 0.68–0.91) at 10 years (Supplementary Table S16).

Discussion

Although stage at diagnosis was the most prominent determinant of survival in this cohort, in both early- and late-stage patients, healthier prediagnosis lifestyles were associated with improved survival after colorectal cancer diagnosis. Compared with patients with the least healthy scores, those with the healthiest scores showed lower hazards of all-cause [$HR_{adjusted_10year}$ 0.75 (95% CI, 0.64–0.88)] and colorectal cancer–specific [$HR_{adjusted_10year}$ 0.76 (95% CI, 0.63–0.91)] mortality and a larger absolute gain in survival time. At 10 years after diagnosis, patients with the healthiest scores lived, on average, 0.85 years longer than patients with the least healthy scores. Among patients diagnosed at age ≤70 years, the gain approached 1 year. Patients with medium lifestyle scores had intermediate outcomes, consistent with a dose–response pattern. Among the components of the prediagnosis lifestyle score, having a higher quality diet was consistently associated with improved survival.

The stage at diagnosis is an established determinant of colorectal cancer prognosis (3). In our cohort, the adjusted difference in survival years between early- and late-stage disease was approximately six times larger than the difference between high and low prediagnosis lifestyle scores. The stage at diagnosis is influenced by colorectal cancer screening (31–33). Colonoscopy can reduce colorectal cancer incidence and shift diagnosis toward earlier stages by removing precancerous lesions (32, 34); however, it also advances the time of diagnosis. Individuals with one or more adenomas ≥10 mm have an increased risk compared with those without adenomas (35). In addition, the relationship between lifestyle and screening uptake is not singular. Individuals with healthier lifestyles may correlate with greater participation ("healthy user" bias; ref. 36). However, some individuals with healthier behaviors may feel healthy and defer screening (37). In the absence of screening information, our analyses implicitly assume comparable prognosis for screen- and symptom-detected cancers of the same stage. We acknowledge that unmeasured screening behavior may introduce lead time and length time biases (38), which we were unable to quantify.

A healthier prediagnosis lifestyle has been shown to improve overall survival in Western colorectal cancer survivor populations (24). In SCHS, we observed an adjusted HR of 0.77 (95% CI, 0.64–0.94) comparing high versus low lifestyle scores, similar to that reported by Romaguera and colleagues (HR 0.79; 95% CI, 0.65–0.98; ref. 39) in the European cohort. Both studies had similarly long intervals between the measured lifestyle components and colorectal cancer diagnosis. Meta-analytical evidence from cohort studies indicated that when lifestyle components were assessed closer to diagnosis or by recall at diagnosis, lifestyle had a stronger effect on mortality (24). Across the six studies (excluding Romaguera and colleagues; refs. 23, 39, 40–43) reporting only on colorectal cancer tumors, HRs ranged from 0.51 to 0.75, and the pooled HR was 0.61 (95% CI, 0.53–0.69, $I^2 = 0\%$) using a random effects meta-analysis model. Variation in score construction, domains included, and extremity of category contrasts likely contributed to between-study differences in effect sizes.

Few studies have examined the composite lifestyle scores in relation to colorectal cancer–specific death. Although they reported a consistent direction of a less healthy lifestyle increasing the risk of death, the effect sizes varied. Romaguera and colleagues (39), using the EPIC cohort that our study design closely resembles, reported a stronger association for colorectal cancer–specific death (HR 0.70; 95% CI, 0.56–0.89) than for all-cause death, using prediagnosis lifestyle assessed years before diagnosis. In SCHS, we did not observe materially different associations for colorectal cancer–specific versus all-cause death. Several factors may contribute to these differences across cohorts, including age at diagnosis, overall burden of death, cause-of-death composition, and tumor site distribution. SCHS had a higher proportion of deaths (73%) than EPIC (approximately 34%), and the share of deaths attributed to colorectal cancer was slightly lower in SCHS (70%) than in EPIC (78%), which may have influenced cause-specific analyses through competing risks. The differences in the mix of colon and rectal cancers could influence the association between lifestyle and colorectal cancer–specific death. Pelser and colleagues (23) reported that a composite lifestyle score was associated with lower colorectal cancer–specific death in rectal cancer but not in patients with colon cancer in the US population. Furthermore, a study by Song and colleagues (40) reported a nonsignificant association between lifestyle score and colorectal cancer–specific death but a larger and significant association with all-cause death.

Consistent with prior studies using cause-specific Cox proportional hazard models, we observed significant contrasts between the

healthiest and the least healthy lifestyle groups. The HR is a relative measure of the instantaneous hazard of death and cannot be directly translated into an RMST difference, which quantifies absolute differences in average survival time up to a prespecified horizon. When summarizing the average survival up to prespecified horizons (5, 10, and 15 years) with RMST, the absolute difference between individuals with healthier and less healthy prediagnosis lifestyles was comparatively small. This is plausible given the heterogeneous lifestyle patterns in SCHS and our predominantly binary categorization of lifestyle components, which reduces contrast compared with multicategory or continuous indices.

Composite lifestyle scores are generally robust to reasonable variations in component selection and measurement, although effect sizes can differ modestly depending on how scores are operationalized (24). Most studies have anchored composite scores to recommendations from the Cancer Research Fund (WCRF)/ American Institute for Cancer Research (AICR) or ACS survivorship guidelines. Diet quality within these composites has typically been derived from food frequency questionnaires using established indices such as the Mediterranean Diet Score, measurement of intakes of dietary fiber and alcohol, average daily nutrient intake, ACS Nutrition and Physical Activity Diet subscore, and the Healthy Eating Index 2005 (23, 25, 40–43). In our study, we incorporated the AHEI-2010 without alcohol to quantify diet quality. We observed that healthier diet groups were consistently associated with longer RMST, aligning with prior work that showed higher AHEI-2010 scores associated with lower mortality in both the general population and colorectal cancer survivors (19). Given that cardiovascular disease is a leading cause of mortality in Singapore and screening for hypertension and hyperlipidemia is widespread, lifestyle recommendations are often communicated in a cardiometabolic framework for the general population. Notably, dietary guidance for cardiometabolic health largely aligns with cancer prevention recommendations and supports unified lifestyle messaging.

Engaging in physical activity and not smoking are potential modifiable behaviors linked to improved survival among people with colorectal cancer (44, 45), and similar results were observed in the present cohort. Self-reported weekly physical activity was associated with improved survival. Physical activity in the form of exercise may influence early colorectal carcinogenesis through the modulation of the insulin-like growth factor pathway, with higher IGFBP-3 levels among physically active patients associated with lower colorectal cancer–specific mortality. It may also interact with immune function and tumor molecular features, including β-catenin signaling (44). Not smoking was associated with improved survival in unadjusted analyses. Although it remained directionally protective after adjusting for potential confounders, the estimates were attenuated and did not reach statistical significance. This attenuation is likely to reflect confounding and correlated lifestyle patterns. Current smokers were disproportionately concentrated in lower composite lifestyle scores, with 58% in low lifestyle scores and only 2% scoring 5. None had a score of 6. After accounting for other lifestyle factors, the independent association between smoking status and survival was smaller.

Our analysis draws on incident colorectal cancer cases from a large, population-based Asian cohort, improving generalizability beyond Western colorectal cancer survivor populations. Lifestyle factors were measured prior to diagnosis, minimizing recall bias and the influence of preclinical disease on behavior (reverse causation). To quantify prognosis, we employed a model-free metric, the RMST, yielding absolute, time-bounded differences in average survival between healthier and less healthy prediagnosis lifestyle groups and avoiding assumptions of proportional hazards (28).

The limitations of our study include the single measurement of prediagnosis lifestyle many years before the colorectal cancer diagnosis. Lifestyle patterns may have changed in the interim, leading to exposure misclassifications. Postdiagnosis lifestyle factors and treatment were unavailable; prior studies suggested that healthier postdiagnosis behaviors, particularly diet quality and physical activity, can have moderate effects on survival, which we could not account for. Residual confounding is possible owing to the lack of adjustment for treatment details, tumor molecular subtypes, granular stage at diagnosis (stages I–IV), and comorbidities. In addition, screening detection status was unavailable, and stage at diagnosis was missing for a substantial proportion of patients; these limitations may introduce selection and information bias and could result in residual confounding if detection mode or stage (or their missingness) is associated with both lifestyle and outcomes. More broadly, our observed associations may reflect a combination of cancer-related biological pathways (e.g., inflammation and immune function), noncancer pathways (e.g., cardiometabolic disease and frailty/sarcopenia), and care pathways; our data do not allow these mechanisms to be separated or quantified. Finally, competing risks may differentially affect the outcomes. All-cause death often shows clearer associations with lifestyle, in part because it captures cardiovascular and metabolic deaths that are influenced by these behaviors, whereas colorectal cancer–specific death may be less sensitive to lifestyle variation. Notably, the cohort's age at diagnosis was relatively old (median, 72 years), and we observed larger survival differences among patients diagnosed at age ≤70 years. Therefore, the absolute survival differences reported here may not generalize directly to populations with a different age distribution at diagnosis, particularly given potential effect heterogeneity by age and differences in baseline risk.

In this cohort, a healthier prediagnosis lifestyle was associated with modest improvements in long-term survival after colorectal cancer. Although we cannot disentangle or quantify the relative contributions of cancer-related biological, noncancer, and care-related pathways (e.g., screening, treatment adherence) underlying these associations, our results suggest that the stage at diagnosis remains the dominant determinant of outcomes, underscoring the importance of early detection. After adjustment for stage and other covariates, a healthier prediagnosis lifestyle was associated with lower mortality, with the diet quality component (AHEI-2010 without alcohol) showing the most consistent associations. Absolute survival gains estimated by RMST were small overall but larger among patients diagnosed at age ≤70 years. These observational findings suggest that maintaining healthy behaviors before diagnosis, especially diet, may complement early detection and optimal treatment to support better survivorship.

Data Availability

The data used in this analysis may be available from the corresponding author upon reasonable request.

Authors' Disclosures

No disclosures were reported.

Authors' Contributions

P.J. Ho: Conceptualization, formal analysis, visualization, methodology, writing–original draft, writing–review and editing. **A. Jin:** Formal analysis, writing–review and editing. **J.-M. Yuan:** Resources, data curation, writing–review and editing. **W.-P. Koh:** Conceptualization, resources, data curation, funding acquisition, writing–review and editing. **A. Seow:** Conceptualization, supervision, funding acquisition, writing–review and editing.

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Note

Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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