Prediagnostic physical activity and colorectal cancer survival: overall and stratified by tumor characteristics

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Abstract

Background—Physical activity is associated with a lower incidence of colorectal cancer (CRC); however, the relationship of physical activity with CRC survival is not yet clear. We evaluated the association between pre-diagnostic physical activity and CRC survival, overall and accounting for tumor-markers associated with CRC survival: *BRAF* and *KRAS* mutation status and microsatellite instability (MSI) status.

Methods—Participants were 20–74 year old CRC patients diagnosed between 1998 and 2007 from the population-based Seattle Colon Cancer Family Registry (S-CCFR). Self-reported physical activity in the years preceding CRC diagnosis was summarized as average metabolic equivalent-task hours per week (MET-h/week) (n=1309). Somatic *BRAF* and *KRAS* mutations and MSI status were evaluated on a subset of patients (n=1043). Cox regression was used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for overall and disease-specific survival after adjusting for relevant confounders. Stratified analyses were conducted across categories of *BRAF, KRAS* and MSI, as well as tumor stage and site.

Results—Higher pre-diagnostic recreational physical activity was associated with significantly more favorable overall survival (HR for highest vs. lowest category=0.70, 95% CI 0.52–0.96); associations were similar for CRC-specific survival. Results consistently indicated a favorable association with physical activity across strata defined by tumor characteristics.

Conclusion—Individuals who were physically active prior to CRC diagnosis experienced better survival than those who were inactive or minimally active.

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Impact—Our results support existing physical activity recommendations for CRC patients and suggest that the beneficial effect of activity is not specific to a particular molecular phenotype of CRC.

Keywords

physical activity; overall survival; colon-cancer specific survival; BRAF; KRAS; MSI

INTRODUCTION

Epidemiologic studies have established the benefits of physical activity throughout life in lowering the lifetime risk of developing (1–3) or dying (1, 2, 4–6) from several forms of cancer, including colorectal cancer (CRC) (7–9). Several studies have also suggested that overall survival after CRC diagnosis is more favorable in patients with high levels of pre- (10, 11) and post-diagnostic (10–16) physical activity. On the basis of such suggestive findings in CRC survivors, and in survivors of other cancers (17), guidelines for cancer survivors generally recommend 150 minutes of moderate-intensity or 75 minutes of vigorous exercise per week (6, 18).

Similar to general benefits of physical activity with respect to overall survival in CRC patients, there is consistent evidence to support a benefit of post-diagnostic physical activity with respect to CRC-specific survival (10–14). The association between pre-diagnostic physical activity and CRC-specific survival, however, is less conclusive: some studies indicate no association (13, 14) while others report a survival benefit with pre-diagnostic activity (10, 11, 16). Observed inconsistencies in the association between pre-diagnostic physical activity and CRC-specific survival could be partially attributed to differences in study population composition (e.g., age, smoking status) which, in turn, would translate to differences in the distribution of CRC attributes, such as tumor site and tumor-marker status. Thus, to better elucidate the relationship between pre-diagnostic physical activity and survival in CRC patients, with respect to both overall and CRC-specific survival, it is important to consider such potential sources of heterogeneity.

The presence of *BRAF* (19, 20) or *KRAS* (21, 22) somatic mutations in CRC has been associated with poorer survival, while the presence of MSI (23–25) has been consistently associated with better survival. Previous studies have also suggested some heterogeneity in the relationship of lifestyle factors with CRC risk and survival according to these tumor-markers (26–31). Thus, consideration of these tumor-markers may provide greater insight into the association between physical activity and CRC survival.

We evaluated the association between pre-diagnostic physical activity and CRC survival with consideration for potential sources of heterogeneity, including *BRAF*-mutation, *KRAS*-mutation, and MSI status.

MATERIALS AND METHODS

Study population

The Colon Cancer Family Registry (CCFR) is an international consortium of six study centers (32, 33). The present analysis utilized data on CRC patients in the Seattle CCFR (S-CCFR) site, all of whom were ascertained through the population-based Surveillance, Epidemiology and End Results (SEER) registry serving western Washington State. During the initial recruitment phase (1998–2002), eligible patients included adults aged 20–74 years diagnosed with CRC who resided in the King, Pierce and Snohomish counties at the time of diagnosis. Women aged 50–74 years who were diagnosed with CRC during the same time period and who resided in 10 additional Washington counties were also eligible. In a second recruitment phase (2002–2007), we enrolled individuals diagnosed with CRC between 18–49 years who resided within the 13-county Western Washington SEER area. Only English-speaking participants with publicly available phone numbers were eligible.

In total, 3525 individuals were identified and contacted for recruitment. Of these, 302 (9%) were already deceased, 401 (11%) refused participation, 92 (3%) could not be located, and 24 (1%) only partially completed their interview. Thus, 2706 CRC patients were available for the current analyses. This study was approved by the Institutional Review Board at the Fred Hutchinson Cancer Research Center.

Exposure and covariate assessment

Patients were enrolled and interviewed an average 8.5 (range 2.3–44.1) months after CRC diagnosis. In a structured telephone interview, they were asked to self-report detailed information on their recreational physical activity during defined age periods prior to diagnosis: ages 20–29, 30–49, and 50+ years. Questions covered different modes of activities (e.g., walking, jogging, running, bicycling, swimming, soccer, tennis, basketball, calisthenics), and the usual duration and frequency of each activity. Evaluation was limited to activities in which the patients were engaged for at least 30 minutes per week, for at least 3 continuous months. The parent questionnaire from which our questionnaire was derived has been previously validated and shown to provide a good measure of the underlying physical activity levels in other studies (34). Standard metabolic equivalent of task (MET) values were assigned to each activity (35, 36) and multiplied by the number of hours per week engaged in that activity to derive MET-hours per week (MET-h/week). Physical activity during the age period of a patient's CRC diagnosis (i.e., 20–29, 30–49, or 50+ years) was then summarized as average MET-h/week. Henceforth, we refer to these age period-specific physical activity levels as pre-diagnostic physical activity levels. For the present analysis, we categorized this variable as <3.5 (referent group), 3.5-<8.75, 8.75-<17.5, 17.5-<35, 35 MET-h/week, which is equivalent to the level of exertion from <1, 1-<2.5, 2.5-<5, 5–10, and >10 hours of brisk walking per week, respectively (35, 36). These cut-points, in addition to being easily interpretable, were based on uniform distribution of participants within each category. We also evaluated the effect of physical activity using a referent cut-point of 8.75 MET-h/week reflecting current recommendations of at least 2.5 hours of moderate activity or 75 minutes of vigorous activity per week among cancer survivors (8.75 MET-h/week) (6, 18, 37).

Patients also provided information on several other pre-diagnostic exposures, including smoking history (never, former, current), education, height, and weight. Information on tumor site (colon, rectum) was obtained from linkage to SEER. Tumor stage based on the 7th edition of American Joint Committee on Cancer (AJCC) staging system (38) was derived after combining information on TNM stage and SEER summary stage (39) (AJCC Stage 0-IV).

Exclusions and missing data

For the current analyses, we excluded patients missing data on pre-diagnostic physical activity (n=737, 27%). For greater comparability with previous studies that excluded patients with metastatic disease (10, 11, 13), and to account for the possibility of reverse causation such that those with advanced disease may have altered activity patterns prior to diagnosis, we excluded patients with stage IV disease at the time of diagnosis (n=370, 13.9%). Additionally, we excluded individuals with missing data on potential confounders (n=255) and those with somatic mutations in both *BRAF* and *KRAS* (n=6) (40). Finally, we excluded individuals in the topmost percentile of physical activity (MET-h/week>140, n=21) to eliminate outliers, leaving a total of n=1309 patients for primary analyses.

Outcomes ascertainment

Vital status and cause of death (classified according to ICD-10 conventions) were determined periodically through linkage to the Puget Sound SEER registry and the National Death Index; most recent linkage to vital status was completed in December 2012 (41). CRC-specific deaths included those with an underlying cause attributed to ICD-10 codes C18.0-C20.9 or C26.0 (41).

Tumor-marker status

Tumor-markers were evaluated from paraffin-embedded formalin-fixed tumor tissue samples. Forward and reverse sequencing was used to identify mutations in the coding sequence of *KRAS* exon 2 (codons 12/13) in a subset of patients (n=949) (42, 43). We also tested for the c.1799T>A (p.V600E) *BRAF*-mutation using a fluorescent allele-specific PCR assay (n=949) (44). MSI testing was performed as previously described (n=1040) (24). Most patients (60%) were tested using a 10-marker genetic panel (45, 46); tumors were classified as MSI-H if instability was observed in 30% or more of the markers and as microsatellite stable (MSS) otherwise. Additional patients were tested for MSI using immunohistochemistry (IHC) testing of four markers: MLH1, MSH2, MSH6, and PMS2 (47, 48); those with positive staining for all markers were grouped as MSS, whereas those negative for at least one marker were considered MSI-H. High concordance (97.7%) between IHC and PCR-based MSI methods has previously been demonstrated (49).

Statistical Analyses

We estimated the association between pre-diagnostic physical activity and survival after CRC diagnosis by calculating hazard ratios (HR) and 95% confidence intervals (CIs) using separate Cox models for overall and CRC-specific survival. Days since CRC diagnosis was used as the underlying time metric with left-censoring of patients until study enrollment.

Administrative censoring occurred at the last vital status assessment for patients alive until then. For CRC-specific survival, we censored individuals who died of causes other than CRC at the time of death. Confounders were determined *a priori* by identifying known correlates of both physical activity and survival; associations of these selected confounders with the exposure and outcome were also verified in the analytic dataset. Based on these considerations, we adjusted for age at diagnosis (continuous), sex, BMI (<25, 25–29, 30+), smoking history (never, former, current), education (less than high school, high school, some college, college graduate), and diagnosis year. In separate models, we further adjusted for tumor-marker status and stage. Tests for trend were based on the likelihood-ratio test associated with addition of the categorical physical activity variable in its continuous form (p-trend$_{overall}$). We also computed a separate trend test only among those who were physically active (p-trend$_{active}$). A two-sided p-value <0.05 was considered statistically significant. The validity of the proportional hazards assumption over time was tested using Schoenfeld's residuals (50).

In addition to the aforementioned models, we evaluated associations within strata defined by tumor-markers (*BRAF* and *KRAS* mutation status, MSI status), and by other tumor (site, stage) and patient characteristics (age, sex). All analyses were performed using STATA, release 13 (StataCorp, College Station, TX).

RESULTS

The distribution of baseline characteristics across categories of pre-diagnostic physical activity levels are presented in Table 1. There were no marked differences across physical activity categories for age at diagnosis, education, stage, tumor site or tumor-marker status. A difference across categories was noted for sex, such that males were more likely to be classified in the highest categories of pre-diagnostic physical activity. BMI appeared modestly elevated for those in the lowest pre-diagnostic physical activity. Patients were followed for a median of 6.1 years (range: 8 days-12.8 years). Of 1309 patients in the primary analytic dataset, 408 (31.2%) died, of whom 229 (56.1%) died from CRC. Compared with patients with complete data, those with missing data on physical activity were older, and were more likely to be female, ever smokers, and of a lower educational attainment (Supplementary table 1).

Table 2 presents results for overall and CRC-specific survival according to categories of pre-diagnostic physical activity. Increasing levels of pre-diagnostic physical activity, relative to <3.5 MET-h/week, was associated with a statistically significantly better overall survival in adjusted models [HR(95% CI) for 3.5-<8.75, 8.75-<17.5, 17.5-<35, 35 MET-h/week were 0.52 (0.38,0.71), 0.65 (0.49,0.86), 0.63 (0.47, 0.84) and 0.70 (0.52,0.96), respectively]. Adjustment for stage at diagnosis did not appreciably change these results. Results for CRC-specific survival were similar, such that patients with increasing physical activity levels >3.5 MET-h/week had statistically significantly better CRC-specific survival relative to the referent category (HR=0.61 (0.41,0.91) comparing the highest versus lowest activity level). In separate models, we also evaluated the impact of adjusting for *BRAF*, *KRAS*, and MSI status among those with available data on these markers. Results were similar to those in primary analyses, indicating statistically significantly better overall and CRC-specific

survival in physically active individuals (Supplementary Table 2). When stratified by *BRAF* mutation status, results did not appreciably differ by MSI status i.e. risk estimates were similar for *BRAF*-wildtype/MSS vs. *BRAF*-wildtype/MSI-H and for *BRAF*-mutated/MSS vs. *BRAF*-mutated/MSI-H), although numbers were limited (data not shown).

Figure 1 summarizes results for the association between pre-diagnostic physical activity and overall survival according to tumor characteristics (*BRAF*- and *KRAS*-mutation status, MSI status, stage, tumor site). In these stratified analyses, those with physical activity ≥ 8.75 MET-h/week had a better survival, regardless of tumor-marker strata or stage. However, these associations failed to reach statistical significance, likely due to the smaller subgroup sample sizes.. When evaluated by tumor sub-site in the colorectum, physical activity was inversely associated with overall survival among those with colon but not rectal cancers; however, interaction by tumor site was not statistically significant (p-interaction=0.27). There were no meaningful differences observed in overall survival after age or sex stratification (data not shown).

Figure 2 displays the results for stratified analyses in relation to CRC-specific survival. Patients engaged in ≥ 8.75 MET-h/week of pre-diagnostic physical activity had a better CRC-specific survival, regardless of tumor-marker strata, stage, or tumor site. The inverse association with physical activity was most pronounced among those with MSI-H tumors [HR=0.46 (0.17,1.25)] and weakest among those with *BRAF*-mutated CRC [HR=0.76 (0.30,1.95)]. Associations did not differ by age or sex for CRC-specific survival (data not shown).

DISCUSSION

In this cohort of patients with incident CRC, we observed that pre-diagnostic recreational physical activity was associated with favorable overall and CRC-specific survival. This association was unchanged after adjustment for tumor-marker status or stage. Analyses stratified by tumor characteristics consistently indicated more favorable survival in those with physical activity at or above the recommended threshold of ≥ 8.75 MET-h/week; the inverse association was the strongest among those with MSI-H CRC and weakest among those with *BRAF*-mutated CRC, although no statistically significant interaction was noted. To the best of our knowledge, this is the first study to explore the associations between physical activity and CRC survival by these tumor-markers.

Five studies, thus far, have assessed the relationship between pre-diagnostic physical activity and overall and CRC-specific survival (10, 11, 13, 14, 16), of which only three reported statistically significant findings (10, 11, 16). A recent meta-analysis summarized the results from these studies and reported a 26% better overall (95% CI, 11–38%) and a 38% better CRC-specific survival (95% CI, 9–38%) for higher versus low physical activity levels (51). In the largest study to-date, persons reporting greater than 8.75 MET-h/week had better overall survival [HR=0.72 (0.58,0.89)]; CRC-specific findings were also suggestive of favorable survival (11). However, none of these studies were able to evaluate differences in associations with physical activity by molecular subtypes of CRC.

CRC is a heterogeneous disease with several distinct molecular subtypes that are suggestive of different pathways of tumorigenesis and progression (52, 53). Thus, consideration of molecular markers that distinguish these pathways, such as *BRAF*, is important for better understanding the relationship between lifestyle factors and CRC risk and survival. We have previously identified differences in the relationship between smoking and CRC survival according to these markers (28, 29, 31). Additionally, in a previous paper from the S-CCFR, Coghill et al. found that the inverse association between use of non-steroidal anti-inflammatory drugs and survival after CRC diagnosis was restricted to proximal colon cancers, which are more commonly MSI-H and *BRAF*-mutated than distal CRC (54). Our results instead suggest that the beneficial effect of physical activity is not specific to a particular molecular phenotype of CRC. Although we observe that pre-diagnostic physical activity is broadly beneficial, it may not impact survival in certain case groups, particularly those with rectal cancers. We speculate that the differences in risk factors, natural history, and treatment between colon and rectal cancers, may explain the lack of benefit in overall survival associated with physical activity in rectal cancers in our data (Figure 1). Rectal cancers have been reported to have a greater diagnostic delay and are more likely to be symptomatic at the time of diagnosis (55); both factors may impact a person's pre-diagnostic physical activity and may explain our observed lack of benefit in rectal cancers.

Several biological mechanisms have been posited for an inverse association between physical activity prior to CRC diagnosis and survival. It is possible that the observed association reflects improved tolerance or decrease in systemic levels of inflammation and/or oxidative stress markers among physically active individuals, which have also been shown to affect CRC risk and survival (17). Physical activity may also increase plasma levels of insulin-like growth factors and C-peptides (17), which have been hypothesized to improve survival among CRC patients (56). Beyond an association with CRC-specific survival, physical activity has been shown to have an impact on risk of death from several other causes, particularly cardiovascular diseases (57, 58). Indeed, in sensitivity analyses we found physical activity to be associated with lower cardiovascular disease mortality in our data. However, as 56% deaths in our study population were CRC-related, we speculate that the overall survival estimates are probably more influenced by beneficial effects of physical activity on reducing CRC deaths than by associations with other causes of death. The breadth of that CRC survival benefit is further supported by the fact that the association we observe is mostly consistent across CRC case groups defined by tumor characteristics. We did not observe any pattern of increasingly favorable survival with increasing levels of physical activity among those who were physically active for either overall or CRC-specific analyses; rather, our results are most consistent with a threshold effect associated with being physically active prior to CRC diagnosis.

There are some limitations to this study. Selection bias in the form of survivor bias is possible if patients who died before they could be enrolled into the study were systematically different from those patients who survived long enough to be interviewed and enrolled into our study. The short lag-time from diagnosis to interview (average 8.5 months; range 2.3–44.1) may limit, but does not preclude, such bias. Additionally, we excluded patients with stage IV disease, as survivor bias is most likely to impact inference within this

group. Another important limitation of our study is the high proportion (27%) of missing data on physical activity. Patients with missing physical activity data were slightly different from patients included in the analysis with respect to age, sex, and education level and, thus, may have differed with respect to actual activity levels; such differences may have biased our results. As we were unable to evaluate the differences in survival taking into account the treatment received, we conducted a sensitivity analysis excluding individuals with zero physical activity to eliminate the possibility that such individuals may be different in terms of their care and therefore may have worse prognosis. However, the results did not differ from our reported estimates in Table 2. We also did not have information on disease recurrence, which may also influence survival. As most recurrences occur within 5 years post-diagnosis, we conducted sensitivity analyses restricting follow-up to 5 years after enrollment and the survival estimates were very similar to the ones we reported (data not shown). Lastly, the present analysis was limited to the evaluation of pre-diagnostic physical activity; post-diagnostic activity levels, and changes in physical activity following CRC diagnosis likely also have implications for CRC prognosis and merit further evaluation.

Our study also has several strengths. The population-based design of the S-CCFR cohort, the relatively large sample size, and the long duration of follow-up contribute to the generalizability of our study results. The availability of detailed information on tumor-marker status allowed us to evaluate the role of these molecular variants in the association between physical activity and survival.

In summary, our results, in conjunction with previous studies, suggest that physical activity in the years preceding CRC diagnosis may offer a survival benefit and provide additional support for existing public health recommendations regarding physical activity. Stratified analyses by tumor characteristics revealed a better survival for those with physical activity at or above the previously-recommended threshold irrespective of most measured patient and tumor characteristics. Further studies are needed to better understand the mechanisms through which physical activity may confer its survival benefit, so as to better inform physical activity recommendations for CRC survivors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Overall survival for patients with prediagnostic physical activity at or above recommended levels (8.75 MET-h/wk) relative to those with lower activity levels, stratified by tumor characteristics*†

*Risk estimates adjusted for age at diagnosis, sex, body mass index, smoking status, education and diagnosis year.

†Risk estimates based on 1282 CRC patients with local- or regional-stage disease and complete data on confounders.

Figure 2.
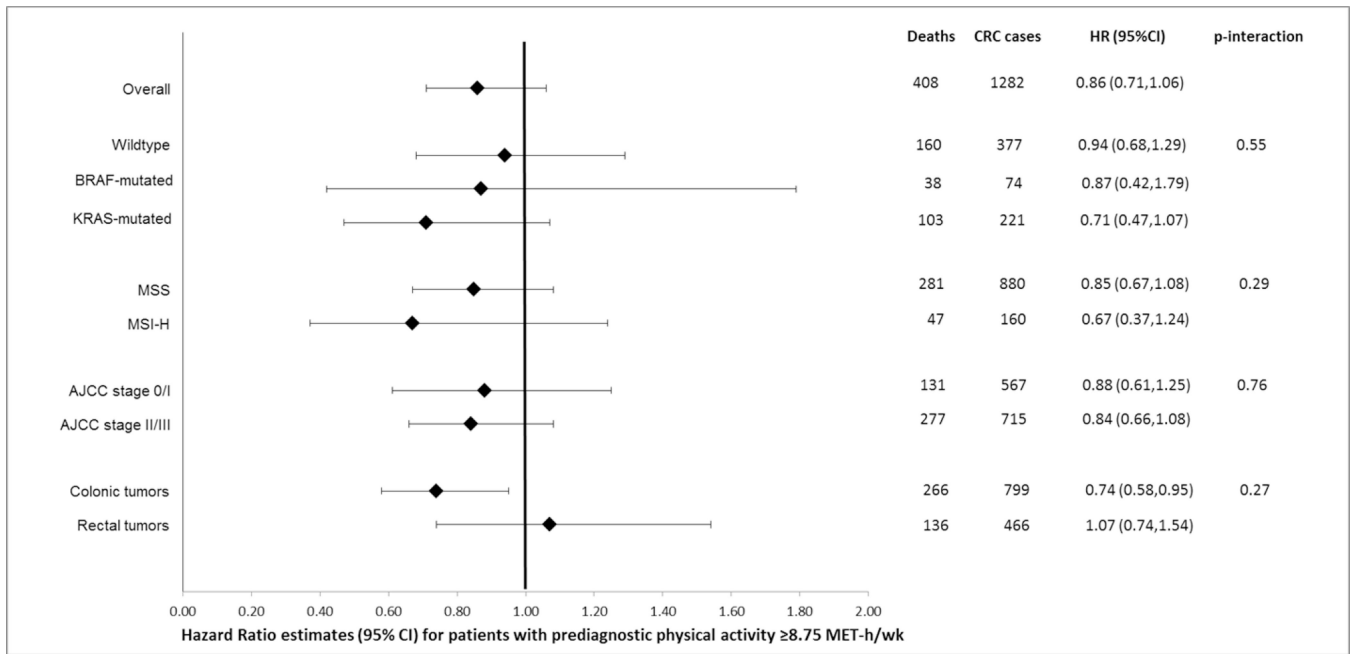CRC-specific survival for patients with prediagnostic physical activity at or above recommended levels (8.75 MET-h/wk) relative to those with lower activity levels, CRC stratified by tumor characteristics*†

*Risk estimates adjusted for age at diagnosis, sex, body mass index, smoking status, education and diagnosis year.

†Risk estimates based on 1282 CRC patients with local- or regional-stage disease and complete data on confounders.
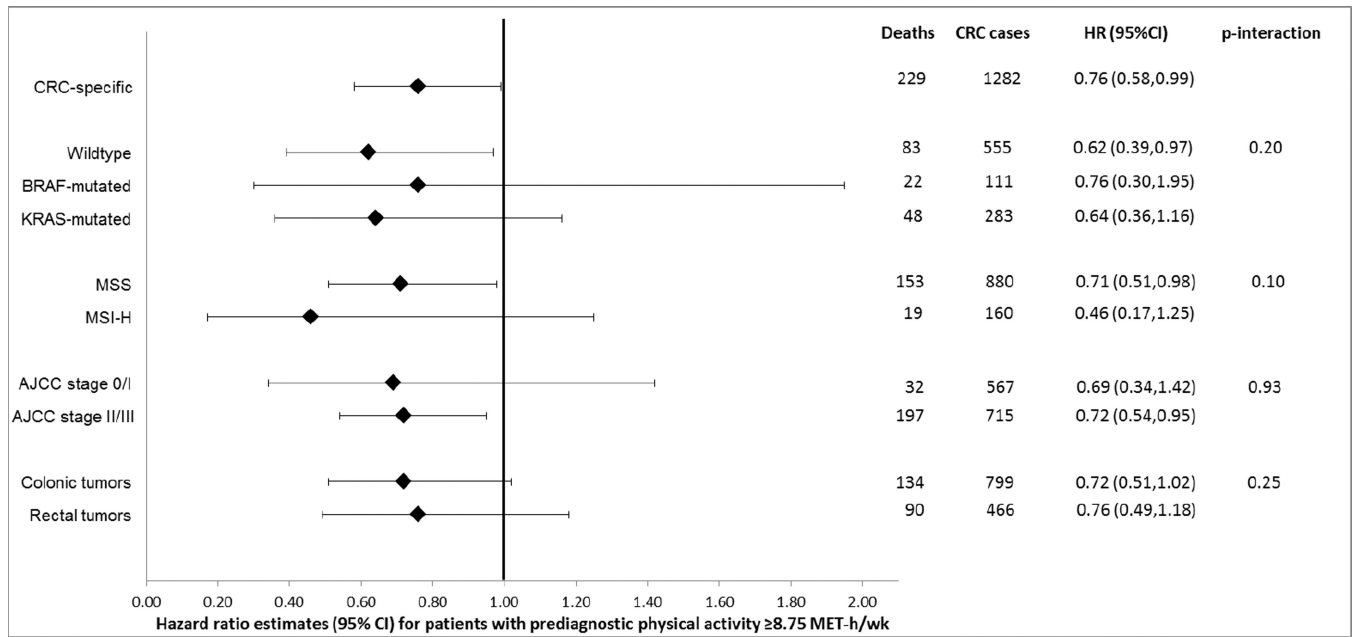

Table 1

Baseline characteristics of colorectal cancer patients across categories of prediagnostic physical activity in the Seattle Colon Cancer Family Registry among patients with local and regional stage disease (n = 1309)

Participant characteristics	Physical activity (MET-hours per week)*					
	0-<3.5 (n = 279)	3.5-<8.75 (n = 253)	8.75-<17.5 (n = 284)	17.5-<35 (n = 277)	35 (n = 216)	Total (n = 1309)
Age at diagnosis (years), Mean (SD)	56.9 (12)	55.8 (12)	56.2 (12)	55.2 (12)	53.8 (13)	55.7 (12)
Males, n(%)	136 (49)	121 (48)	154 (54)	160 (58)	139 (64)	710 (54)
BMI (kg/m2), Mean (SD)[1]	28.8 (7)	27.9 (6)	27.1 (5)	27.0 (5)	27.0 (6)	27.6 (6)
Smoking history[2], n(%)						
Never	113 (41)	130 (51)	128 (45)	118 (43)	77 (36)	566 (43)
Former	110 (39)	92 (37)	112 (39)	116 (42)	102 (47)	532 (41)
Current	56 (20)	31 (12)	44 (16)	43 (15)	37 (17)	211 (16)
Education level[3], n (%)						
<High school	22 (8)	14 (6)	6 (2)	12 (4)	20 (9)	74 (6)
High school	79 (28)	45 (18)	77 (27)	52 (19)	52 (24)	305 (23)
Some college/vocational school	92 (33)	98 (39)	81 (28)	98 (36)	73 (34)	442 (34)
College graduate	86 (31)	96 (38)	120 (42)	115 (41)	71 (33)	488 (37)
CRC stage at diagnosis (AJCC), n (%)						
0/I	120 (43)	116 (46)	119 (42)	128 (46)	93 (43)	576 (44)
II	49 (18)	51 (20)	65 (23)	51 (19)	44 (20)	260 (20)
III	110 (39)	86 (34)	100 (35)	98 (35)	79 (37)	473 (36)
Tumor site, n (%)						
Colon	187 (68)	155 (63)	168 (60)	177 (64)	133 (62)	820 (64)
Rectal	88 (32)	93 (37)	111 (40)	98 (36)	81 (38)	471 (36)
BRAF & KRAS mutation status[4], n (%)						
Wildtype	125 (60)	114 (62)	111 (55)	110 (55)	95 (60)	555 (58)
BRAF mutated	24 (12)	22 (12)	26 (13)	24 (12)	15 (9)	111 (12)
KRAS mutated	58 (28)	48 (26)	65 (32)	64 (32)	48 (31)	283 (30)
MSI status[5], n(%)						
MSS	199 (88)	172 (85)	186 (82)	180 (84)	143 (84)	880 (85)

Participant characteristics	Physical activity (MET-hours per week)*					
	0-<3.5 (n = 279)	3.5-<8.75 (n = 253)	8.75-<17.5 (n = 284)	17.5-<35 (n = 277)	35 (n = 216)	Total (n = 1309)
MSI-H	27 (12)	31 (15)	40 (18)	35 (16)	27 (16)	160 (15)

CRC Colorectal cancer, AJCC American Joint Committee on Cancer

*
MET hours per week translated into time equivalent spent walking per week: 3.5 = 1 hour; 8.75 = 2.5 hours; 17.5 = 5 hours; 35 = 10 hours; Topmost percentile of physical activity was excluded

[1] BMI assessment was missing in 8 individuals

[2] Smoking history assessed 2 years prior to colorectal cancer diagnosis; smoking data was missing for 3 individuals

[3] Education level was missing for 349 (15.6%) of individuals

[4] 858 (38.2%) individuals did not have *BRAF-KRAS* mutation status evaluated, n = 6 mutated on both *BRAF & KRAS* dropped

[5] 550 (24.4%) individuals did not undergo testing for MSI status

Table 2

Overall and colon cancer-specific survival by categories of prediagnostic physical activity levels among patients with local or regional disease (n = 1309)

Physical activity[a] (MET-hours /week)	Deaths/CRC	Unadjusted HR (95% CI)	Adjusted Model 1[1] HR (95% CI)	Adjusted Model 2[2] HR (95% CI)
Overall survival				
<3.5	117/279	REF	REF	REF
3.5-<8.75	62/253	0.48 (0.35,0.65)	0.52 (0.38,0.71)	0.53 (0.39,0.72)
8.75-<17.5	86/284	0.59 (0.45,0.78)	0.65 (0.49,0.86)	0.64 (0.48,0.85)
17.5-<35	77/277	0.55 (0.41,0.73)	0.63 (0.47,0.84)	0.64 (0.47,0.85)
35	66/216	0.62 (0.46,0.84)	0.70 (0.52,0.96)	0.70 (0.52,0.96)
$p\text{-trend}_{overall}$[3]		0.004	0.04	0.04
$p\text{-trend}_{active}$[3]		0.22	0.15	0.13
CRC-specific survival				
<3.5	69/279	REF	REF	REF
3.5-<8.75	38/253	0.52 (0.35,0.77)	0.56 (0.37,0.83)	0.58 (0.39,0.86)
8.75-<17.5	44/284	0.54 (0.37,0.78)	0.58 (0.39,0.84)	0.56 (0.38,0.83)
17.5-<35	42/277	0.54 (0.36,0.79)	0.58 (0.39,0.86)	0.60 (0.40,0.88)
35	36/216	0.61 (0.41,0.91)	0.62 (0.41,0.94)	0.63 (0.42,0.95)
$p\text{-trend}_{overall}$[3]		0.01	0.02	0.03
$p\text{-trend}_{active}$[3]		0.49	0.59	0.51

CRC Colorectal cancer; HR Hazard ratio; CI Confidence intervals

[a] MET hours per week translated into time equivalent spent walking per week: 3.5 = 1 hour; 8.75 = 2.5 hours; 17.5 = 5 hours; 35 = 10 hours; Topmost percentile of physical activity was excluded

[1] Adjusted for age at CRC diagnosis, sex, body mass index, smoking status, education and diagnosis year

[2] Adjusted for age at CRC diagnosis, sex, body mass index, smoking status, education, diagnosis year and stage at diagnosis

[3] Tests for trend were based on the likelihood-ratio test associated with addition of the categorical physical activity variable in its continuous form (p-trend_overall). We also computed a separate trend test only among those that were physically active (p-trend_active).