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; however, the relationship of physical activity with colorectal cancer survival is not yet clear. We evaluated the association between prediagnostic physical activity and colorectal cancer survival, overall and accounting for tumor markers associated with colorectal cancer survival: BRAF and KRAS mutation status and microsatellite instability (MSI) status.

Methods: Participants were 20- to 74-year-old colorectal cancer 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 colorectal cancer diagnosis was summarized as average metabolic equivalent task hours per week (MET-h/wk; n = 1,309). Somatic BRAF and KRAS mutations and MSI status were evaluated on a subset of patients (n = 1043). Cox regression was used to estimate HRs 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 prediagnostic 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 colorectal cancer-specific survival. Results consistently indicated a favorable association with physical activity across strata defined by tumor characteristics.

Conclusion: Individuals who were physically active before colorectal cancer diagnosis experienced better survival than those who were inactive or minimally active.

Impact: Our results support existing physical activity recommendations for colorectal cancer patients and suggest that the beneficial effect of activity is not specific to a particular molecular phenotype of colorectal cancer. Cancer Epidemiol Biomarkers Prev; 24(7): 1130–7. ©2015 AACR.

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 (7–9). Several studies have also suggested that overall survival (OS) after colorectal cancer diagnosis is more favorable in patients with high levels of pre- (10, 11) and postdiagnostic (10–16) physical activity.

On the basis of such suggestive findings in colorectal cancer 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 OS in colorectal cancer patients, there is consistent evidence to support a benefit of postdiagnostic physical activity with respect to colorectal cancer-specific survival (10–14). The association between prediagnostic physical activity and colorectal cancer-specific survival, however, is less conclusive: Some studies indicate no association (13, 14) whereas others report a survival benefit with prediagnostic activity (10, 11, 16). Observed inconsistencies in the association between prediagnostic physical activity and colorectal cancer-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 colorectal cancer attributes, such as tumor site and tumor-marker status. Thus, to better elucidate the relationship between prediagnostic physical activity and survival in colorectal cancer patients, with respect to both overall and colorectal cancer-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 colorectal cancer has been associated with poorer survival, whereas the presence of microsatellite instability (MSI;
levels as prediagnostic physical activity levels. For the present –30
KRAS mutation, and MSI status.

soccer, tennis, basketball, calisthenics), and the usual duration
Western Washington State. During the initial recruitment phase
Surveillance, Epidemiology and End Results (SEER) registry serving
site, all of whom were ascertained through the population-based
research phase (1998–2002), eligible patients included adults ages 20 to 74 years
diagnosed with colorectal cancer who resided in the King, Pierce,
and Snohomish counties at the time of diagnosis. Women ages 50
74 years who were diagnosed with colorectal cancer 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 colorectal cancer
between 18 and 49 years who resided within the 13-county
Western Washington SEER area. Only English-speaking partici-
pants with publicly available phone numbers were eligible.

In total, 3,525 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, 2,706
colorectal cancer 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 colorectal cancer diagnosis. In a struc-
tured telephone interview, they were asked to self-report
detailed information on their recreational physical activity
during defined age periods before 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 mea-
sure 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/wk). Physical activity during the age period of
a patient’s colorectal cancer diagnosis (i.e., 20–29, 30–49, or
50+ years) was then summarized as average MET-h/wk. Hence-
forth, we refer to these age period-specific physical activity
levels as prediagnostic 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/wk, 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 cutoff points, in addition to being easily
interpretable, were based on uniform distribution of partici-
pants within each category. We also evaluated the effect of
physical activity using a referent cutoff point of ≥8.75 MET-h/
wk 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/wk; refs. 6, 18, 37).

Patients also provided information on several other prediag-
nostic exposures, including smoking history (never, former, and
current), education, height, and weight. Information on tumor
site (colon, rectum) was obtained from linkage to SEER. Tumor
stage based on the seventh edition of American Joint Committee
on Cancer (AJCC) staging system (38) was derived after combin-
ing information on TNM stage and SEER summary stage (AJCC
stage 0–IV; ref. 39).

Exclusions and missing data
For the current analyses, we excluded patients missing data on
prediagnostic physical activity (n = 737, 27%). For greater com-
parability with previous studies that excluded patients with met-
astatic disease (10, 11, 13), and to account for the possibility of
reverse causation such that those with advanced disease may have
altered activity patterns before diagnosis, we excluded patients
with stage IV disease at the time of diagnosis (n = 370, 13.9%). In
addition, we excluded individuals with missing data on potential
confounders (n = 255) and those with somatic mutations in both
BRAF and KRAS (n = 6; ref. 40). Finally, we excluded individuals
in the topmost percentile of physical activity (MET-h/wk ≥ 140, n
= 21) to eliminate outliers, leaving a total of 1,309 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). Colorectal cancer–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 forma-
lin-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 = 943; refs. 42,
43). We also tested for the c.1799T>A (p.V600E) BRAF mutation
using a fluorescent allele-specific PCR assay (n = 949; ref. 44). MSI
testing was performed as previously described (n = 1,040; ref. 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 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 prediagnostic physical activity and survival after colorectal cancer diagnosis by calculating HRs and 95% confidence intervals (CI) using separate Cox models for overall and colorectal cancer–specific survival. Days since colorectal cancer 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 colorectal cancer–specific survival, we censored individuals who died of causes other than colorectal cancer 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. On the basis of these considerations, we adjusted for age at diagnosis (continuous), sex, body mass index (BMI; < 25, 25–29.9, ≥30), smoking history (never, former, and current), education (less than high school, high school, some college, and 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 of < 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, and MSI status), and by other tumor (site and stage) and patient characteristics (age and sex). All analyses were performed using STATA, release 13 (StataCorp.).

Results

The distribution of baseline characteristics across categories of prediagnostic 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 prediagnostic physical activity. BMI appeared modestly elevated for those in the lowest prediagnostic physical activity. Patients were followed for a median of 6.1 years (range, 8 days–12.8 years). Of 1,309 patients in the primary analytic dataset, 408 (31.2%) died, of whom 229 (56.1%) died from colorectal cancer. 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 S1).

Table 1. Baseline characteristics of colorectal cancer (CRC) patients across categories of prediagnostic physical activity in the Seattle Colon Cancer Family Registry among patients with local- and regional-stage disease (n = 1,309)

<table>
<thead>
<tr>
<th>Participant characteristics</th>
<th>0 ≤ 3.5 (n = 279)</th>
<th>3.5 ≤ 8.75 (n = 253)</th>
<th>8.75 ≤ 17.5 (n = 284)</th>
<th>17.5 ≤ 35 (n = 277)</th>
<th>≥35 (n = 216)</th>
<th>Total (n = 1,309)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis (y), mean (SD)</td>
<td>56.9 (12)</td>
<td>55.8 (12)</td>
<td>56.2 (12)</td>
<td>55.2 (12)</td>
<td>53.8 (13)</td>
<td>55.7 (12)</td>
</tr>
<tr>
<td>BMI (kg/m²), mean (SD)</td>
<td>28.8 (7)</td>
<td>27.9 (6)</td>
<td>27.1 (5)</td>
<td>27.0 (5)</td>
<td>27.0 (6)</td>
<td>27.6 (6)</td>
</tr>
<tr>
<td>Smoking history, n (%)</td>
<td>136 (49)</td>
<td>121 (48)</td>
<td>154 (54)</td>
<td>160 (58)</td>
<td>139 (64)</td>
<td>710 (54)</td>
</tr>
<tr>
<td>Education level, n (%)</td>
<td>28.8 (7)</td>
<td>27.9 (6)</td>
<td>27.1 (5)</td>
<td>27.0 (5)</td>
<td>27.0 (6)</td>
<td>27.6 (6)</td>
</tr>
<tr>
<td>Colon cancer stage at diagnosis (AJCC), n (%)</td>
<td>Never 113 (41)</td>
<td>130 (51)</td>
<td>128 (45)</td>
<td>118 (43)</td>
<td>77 (36)</td>
<td>566 (43)</td>
</tr>
<tr>
<td>High school 79 (28)</td>
<td>45 (18)</td>
<td>77 (27)</td>
<td>52 (19)</td>
<td>52 (24)</td>
<td>305 (23)</td>
<td></td>
</tr>
<tr>
<td>College graduate 86 (31)</td>
<td>96 (37)</td>
<td>112 (39)</td>
<td>116 (42)</td>
<td>102 (47)</td>
<td>532 (41)</td>
<td></td>
</tr>
<tr>
<td>CRC stage at diagnosis (AJCC), n (%)</td>
<td>0/I 120 (43)</td>
<td>116 (46)</td>
<td>119 (42)</td>
<td>128 (46)</td>
<td>93 (43)</td>
<td>574 (44)</td>
</tr>
<tr>
<td>II 49 (18)</td>
<td>51 (20)</td>
<td>65 (23)</td>
<td>51 (19)</td>
<td>44 (20)</td>
<td>260 (20)</td>
<td></td>
</tr>
<tr>
<td>III 110 (39)</td>
<td>86 (34)</td>
<td>100 (35)</td>
<td>98 (35)</td>
<td>79 (37)</td>
<td>473 (36)</td>
<td></td>
</tr>
<tr>
<td>Tumor site, n (%)</td>
<td>Colon 187 (68)</td>
<td>155 (63)</td>
<td>168 (60)</td>
<td>177 (64)</td>
<td>133 (62)</td>
<td>820 (64)</td>
</tr>
<tr>
<td>Rectal 88 (32)</td>
<td>93 (37)</td>
<td>111 (40)</td>
<td>98 (36)</td>
<td>81 (38)</td>
<td>471 (36)</td>
<td></td>
</tr>
<tr>
<td>BRAF and KRAS mutation status*, n (%)</td>
<td>Wild-type 125 (60)</td>
<td>114 (62)</td>
<td>111 (55)</td>
<td>110 (55)</td>
<td>95 (60)</td>
<td>555 (58)</td>
</tr>
<tr>
<td>BRAF mutated 24 (12)</td>
<td>22 (12)</td>
<td>26 (13)</td>
<td>24 (12)</td>
<td>15 (9)</td>
<td>111 (12)</td>
<td></td>
</tr>
<tr>
<td>KRAS mutated 58 (28)</td>
<td>48 (26)</td>
<td>65 (32)</td>
<td>64 (32)</td>
<td>48 (31)</td>
<td>283 (30)</td>
<td></td>
</tr>
<tr>
<td>MSI status†, n (%)</td>
<td>MSS 199 (88)</td>
<td>172 (85)</td>
<td>186 (82)</td>
<td>180 (84)</td>
<td>143 (84)</td>
<td>880 (85)</td>
</tr>
<tr>
<td>MSI-H 27 (12)</td>
<td>31 (15)</td>
<td>40 (18)</td>
<td>35 (16)</td>
<td>27 (16)</td>
<td>160 (15)</td>
<td></td>
</tr>
</tbody>
</table>

*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.

†BMI assessment was missing in 8 individuals.

‡Smoking history assessed 2 years before colorectal cancer diagnosis; smoking data were missing for 3 individuals.

§Education level was missing for 249 (15.6%) individuals.

¶858 (38.2%) individuals did not have BRAF–KRAS mutation status evaluated, n = 6 mutated on both BRAF and KRAS dropped.

©550 (24.4%) individuals did not undergo testing for MSI status.
Table 2 presents results for overall and colorectal cancer–specific survival according to categories of prediagnostic physical activity. Increasing levels of prediagnostic physical activity, relative to <3.5 MET-h/wk, was associated with a statistically significantly better OS in adjusted models [HR (95% CI) for 3.5–8.75, 8.75–17.5, 17.5 ≤ 35, ≥35 MET-h/wk 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 colorectal cancer–specific survival were similar, with patients having increased physical activity levels ≥3.5 MET-h/wk had statistically significantly better colorectal cancer–specific survival relative to the referent category (HR, 0.61; 95% CI, 0.41–0.91; comparing the highest vs. 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 colorectal cancer–specific survival in physically active individuals (Supplementary Table S2). When stratified by BRAF mutation status, results did not appreciably differ by MSI status, that is, risk estimates were similar for BRAF–wild-type/MSI-S versus BRAF–wild-type/MSI-H and for BRAF–mutated/MSI-S versus BRAF–mutated/MSI-H, although numbers were limited (data not shown).

Figure 1 summarizes for the association between prediagnostic physical activity and OS 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/wk 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 OS among those with colon but not rectal cancers; however, interaction by tumor site was not statistically significant (Pinteraction = 0.27). There were no meaningful differences observed in OS after age or sex stratification (data not shown).

**Discussion**

In this cohort of patients with incident colorectal cancer, we observed that prediagnostic recreational physical activity was associated with favorable overall and colorectal cancer–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/wk; the inverse association was the strongest among those with MSI-H colorectal cancer and weakest among those with BRAF–mutated colorectal cancer, 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 colorectal cancer survival by these tumor markers.

Five studies, thus far, have assessed the relationship between prediagnostic physical activity and overall and colorectal cancer–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 colorectal cancer–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/wk had better OS (HR, 0.72; 95% CI, 0.58–0.89); colorectal cancer–specific findings were also

Table 2. Overall and colon cancer (CRC)–specific survival by categories of prediagnostic physical activity levels among patients with local or regional disease (n = 1,309).

<table>
<thead>
<tr>
<th>Physical activitya (MET-h/wk)</th>
<th>Deaths/CRC</th>
<th>Unadjusted HR (95% CI)</th>
<th>Adjusted model 1b HR (95% CI)</th>
<th>Adjusted model 2c HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3.5</td>
<td>117/279</td>
<td>REF</td>
<td>REF</td>
<td>REF</td>
</tr>
<tr>
<td>3.5 ≤ 8.75</td>
<td>62/253</td>
<td>0.48 (0.35–0.65)</td>
<td>0.52 (0.38–0.71)</td>
<td>0.53 (0.39–0.72)</td>
</tr>
<tr>
<td>8.75 ≤ 17.5</td>
<td>86/284</td>
<td>0.59 (0.45–0.78)</td>
<td>0.65 (0.49–0.86)</td>
<td>0.64 (0.48–0.85)</td>
</tr>
<tr>
<td>17.5 ≤ 35</td>
<td>77/277</td>
<td>0.55 (0.40–0.73)</td>
<td>0.61 (0.47–0.84)</td>
<td>0.64 (0.47–0.85)</td>
</tr>
<tr>
<td>≥35</td>
<td>66/216</td>
<td>0.62 (0.46–0.84)</td>
<td>0.70 (0.52–0.96)</td>
<td>0.70 (0.52–0.96)</td>
</tr>
<tr>
<td>P trend overalld</td>
<td>0.004</td>
<td>0.04</td>
<td>0.04</td>
<td>0.13</td>
</tr>
<tr>
<td>ρ trend active</td>
<td>0.22</td>
<td>0.15</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td>CRC-specific survival</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3.5</td>
<td>69/279</td>
<td>REF</td>
<td>REF</td>
<td>REF</td>
</tr>
<tr>
<td>3.5 ≤ 8.75</td>
<td>38/253</td>
<td>0.52 (0.35–0.77)</td>
<td>0.56 (0.37–0.83)</td>
<td>0.58 (0.39–0.86)</td>
</tr>
<tr>
<td>8.75 ≤ 17.5</td>
<td>44/284</td>
<td>0.54 (0.37–0.78)</td>
<td>0.58 (0.39–0.84)</td>
<td>0.56 (0.38–0.83)</td>
</tr>
<tr>
<td>17.5 ≤ 35</td>
<td>42/277</td>
<td>0.54 (0.36–0.79)</td>
<td>0.58 (0.39–0.86)</td>
<td>0.60 (0.40–0.89)</td>
</tr>
<tr>
<td>≥35</td>
<td>36/216</td>
<td>0.61 (0.41–0.91)</td>
<td>0.62 (0.41–0.94)</td>
<td>0.63 (0.42–0.95)</td>
</tr>
<tr>
<td>P trend overalld</td>
<td>0.01</td>
<td>0.02</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>ρ trend active</td>
<td>0.49</td>
<td>0.59</td>
<td>0.51</td>
<td></td>
</tr>
</tbody>
</table>

aMET 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.

bAdjusted for age at CRC diagnosis, sex, BMI, smoking status, education, and diagnosis year.

cAdjusted for age at CRC diagnosis, sex, BMI, smoking status, education, and diagnosis year.

dTests 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).
suggestive of favorable survival (11). However, none of these studies were able to evaluate differences in associations with physical activity by molecular subtypes of colorectal cancer.

Colorectal cancer 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 colorectal cancer risk and survival. We have previously identified differences in the relationship between smoking and colorectal cancer survival according to these markers (28, 29, 31). In addition, in a previous article from the S-CCFR, Coghill and colleagues (54) found that the inverse association between use of nonsteroidal anti-inflammatory drugs and survival after colorectal cancer diagnosis was restricted to proximal colon cancers, which are more commonly MSI-H and BRAF-mutated than distal colorectal cancer. Our results instead suggest that the beneficial effect of physical activity is not specific to a particular molecular subtype of colorectal cancer. Although we observe that prediagnostic physical activity is broadly beneficial, it may not affect 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 OS associated with physical activity in rectal cancers in our data (Fig. 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 affect a person’s prediagnostic physical activity and may explain our observed lack of benefit in rectal cancers.

Several biologic mechanisms have been posited for an inverse association between physical activity before colorectal cancer 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 colorectal cancer 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 colorectal cancer patients (56). Beyond an association with colorectal cancer-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 colorectal cancer related, we speculate that the OS estimates are probably more influenced by beneficial effects of physical activity on reducing colorectal cancer deaths than by associations with other causes of death. The breadth of that colorectal cancer survival benefit is further supported by the fact that the association we observe is mostly consistent across colorectal cancer 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 colorectal cancer–specific analyses; rather, our results are most consistent with a threshold effect associated with being physically active before colorectal cancer 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. In addition, we excluded patients

![Figure 1](image-url).

Figure 1.

OS 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.

<table>
<thead>
<tr>
<th>Tumor Characteristics</th>
<th>Deaths</th>
<th>CRC cases</th>
<th>HR (95% CI)</th>
<th>P-interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>408</td>
<td>1282</td>
<td>0.86 (0.71–1.06)</td>
<td>0.55</td>
</tr>
<tr>
<td>Wildtype</td>
<td>160</td>
<td>377</td>
<td>0.94 (0.68–1.29)</td>
<td>0.55</td>
</tr>
<tr>
<td>BRAF-mutated</td>
<td>38</td>
<td>74</td>
<td>0.87 (0.42–1.79)</td>
<td>0.72</td>
</tr>
<tr>
<td>KRAS-mutated</td>
<td>103</td>
<td>221</td>
<td>0.71 (0.47–1.07)</td>
<td>0.55</td>
</tr>
<tr>
<td>MSS</td>
<td>281</td>
<td>880</td>
<td>0.85 (0.67–1.08)</td>
<td>0.29</td>
</tr>
<tr>
<td>MSI-H</td>
<td>47</td>
<td>160</td>
<td>0.67 (0.37–1.24)</td>
<td>0.29</td>
</tr>
<tr>
<td>AJCC stage 0/I</td>
<td>131</td>
<td>567</td>
<td>0.88 (0.61–1.25)</td>
<td>0.76</td>
</tr>
<tr>
<td>AJCC stage I/II</td>
<td>277</td>
<td>715</td>
<td>0.84 (0.66–1.08)</td>
<td>0.12</td>
</tr>
<tr>
<td>Colonic tumors</td>
<td>266</td>
<td>799</td>
<td>0.74 (0.58–0.95)</td>
<td>0.27</td>
</tr>
<tr>
<td>Rectal tumors</td>
<td>136</td>
<td>466</td>
<td>1.07 (0.74–1.54)</td>
<td>0.55</td>
</tr>
</tbody>
</table>
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 after 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). Finally, the present analysis was limited to the evaluation of prediagnostic physical activity; postdiagnostic activity levels and changes in physical activity following colorectal cancer diagnosis likely also have implications for colorectal cancer 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 colorectal cancer 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 colorectal cancer survivors.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Disclaimer
The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the article.

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References


