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Association of physical activity and sitting time with incident colorectal cancer in postmenopausal women

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Abstract

Background—Findings from epidemiological studies have found physical activity (PA) is associated with lower colorectal cancer (CRC) risk. Recent studies have found an increased CRC risk with higher sitting time (ST); however, many studies did not include PA as a potential

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confounder. The objective of this project was to investigate the independent and joint associations of ST and PA with risk of incident colorectal cancer, specifically colon and rectal cancer.

Methods—Participants in the Women’s Health Initiative Observational Study (n = 74,870), 50–79 years of age self-reported ST and PA at baseline, year 3 and year 6. Incident CRC was the primary outcome; colon and rectal cancers were secondary outcomes which were centrally adjudicated.

Results—Over a 13-year follow-up, 1,145 incident cases of CRC were documented. A positive age-adjusted association was found between higher ST (≥ 10 versus <5 hrs/day) and CRC (p for trend=0.04) and colon cancer (p for trend=0.05); however, these associations were attenuated and no longer significant in multivariable-adjusted models. Compared to inactive women (1.7 MET-hrs/week), the multivariable risk of CRC in the high PA (> 20 MET-hrs/week) group was 0.81 (95% CI: 0.66 – 1.00; p for trend 0.04). Compared to inactive women with high ST (≥ 10 hrs/d), there was a trend for reduced multivariable CRC risks with higher PA regardless of ST level (interaction=0.64)

Conclusions—We observed an inverse association between leisure time PA and risk of CRC, particularly for rectal cancer. There was no association between ST and CRC in multivariable models.

Keywords

colorectal neoplasms; sedentary lifestyle; physical activity; postmenopause

Physical inactivity has been coined one of the largest public health problems of the 21st century (Blair, 2009). Additionally, sedentary behavior (SB) is an emerging independent risk factor for several chronic diseases (Katzmarzyk et al., 2009, Owen et al., 2010, Van der Ploeg et al., 2012) and is defined as the absence of whole-body movements, involving activities of very low energy expenditure (1.0–1.5 metabolic equivalent tasks) (Ainsworth et al., 2011). It has been estimated that life expectancy in the US population would increase 2 years if sitting time (ST) were reduced to < 3h/day (Katzmarzyk and Lee, 2012). The 2008 Physical Activity Guidelines for Americans were published by the federal government to define the amounts and types of leisure time physical activity associated with health benefits (Committee, 2008). The guidelines recommend 150 minutes of moderate intensity aerobic physical activity or 75 minutes of vigorous intensity aerobic physical activity. Previous research indicates that adults can meet the recommendations for leisure time PA, however if a majority of their day is spent sedentary, their metabolic health can still be jeopardized (Owen et al., 2010). Furthermore, time spent sitting has been found to be associated with increased mortality in men and women even after adjusting for PA; furthermore, PA did not diminish the effect of prolonged sitting (> 6 hrs/d) (Patel et al., 2010). In contrast to these previous findings, however, a recent meta-analysis reported that high levels of moderate intensity PA eliminated the increased risk of mortality attributable to high amounts of ST (Ekelund et al., 2016).

Colorectal cancer (CRC) is the third most common cancer among women in the United States (Siegel et al., 2012). Findings from epidemiological studies have consistently found increased PA levels to be associated with lower CRC risk (Samad et al., 2005). In a recent

analysis investigating the association of leisure time PA with risk of 26 cancer types in 1.44 million adults, a reduction in colon cancer (HR= 0.84, 95% CI, 0.77–0.91) and rectal cancer (HR=0.87, 95% CI, 0.80–0.95) with increased PA was observed (Moore et al., 2016). Colon and rectal cancer have different risk factors and etiology (Wei et al., 2004) which warrants investigating each separately. Evidence also suggests that SB is associated with risk of CRC. Cong and colleagues (Cong et al., 2014) conducted a meta-analysis on SB and risk of colon and rectal cancer that included twenty-three studies. Subgroup analyses indicated an increased risk of colon cancer with increased SB in women (RR=1.28, 95% CI, 1.19–1.41) and men (RR=1.30, 95% CI, 1.18–1.42). However, a majority of the studies included in the meta-analysis did not include PA as a potential confounder. This is a significant limitation as PA and ST are correlated (Chomistek et al., 2013) and postulated to confer health risks through related but separate mechanistic pathways (Hamilton et al., 2007). Therefore, the purpose of this project is to investigate the independent and joint associations of ST and PA with risk of incident colorectal cancer, as well as colon and rectal cancer separately, in the Women's Health Initiative Observational Study (WHI-OS).

Methods

Study Population

The goal of the WHI was to investigate major causes of morbidity and mortality in a nationally representative cohort of postmenopausal women. The WHI-OS enrolled 93,724 women aged 50 to 79 years at 40 clinical centers throughout the United States from 1994–1998. Baseline demographics, dietary and PA questionnaires, anthropometric measurements and fasting blood samples were collected on all eligible participants. Details of the reliability and measurement of baseline characteristics in the WHI have been previously published (Hays et al., 2003).

Of the original 93,676 women, we excluded 3572 women with implausible diet data at baseline, 10,997 with a history of cancer at baseline, 2299 who were unable to walk one block at baseline, 450 missing survival time follow-up data, 900 missing PA data, and 588 with missing ST data. Thus, 74,870 women were included in our analysis.

Exposure Assessment

Baseline characteristics were self-reported on questionnaires, including demographics, medical history, diet, PA and ST, smoking and other lifestyle factors. Participants completed follow-up assessments periodically after enrollment. The study protocol was approved by the institutional review board of each site and all women provided written informed consent.

Leisure time PA was self-reported at baseline and annually through year 8 on a detailed validated questionnaire. Information on frequency, duration and pace of walking outside of the home was collected as well as frequency and duration of participation in mild, moderate and strenuous PA. Examples of mild activity included slow dancing, bowling and golf. Examples of moderate activity were biking outdoors, using an exercise machine, calisthenics, easy swimming, popular or folk dancing. Examples of strenuous activity were aerobics, aerobic dancing, jogging, tennis and swimming laps. Each type of activity was

assigned a metabolic equivalent (MET) intensity score on the basis of absolute energy cost (Ainsworth et al., 2011) and PA-related energy expenditure (MET-hrs/wk) was calculated as the summed product of the frequency, duration and intensity of reported activities. A random sample of 536 participants had second measurements conducted on all PA variables approximately 10 weeks after baseline. Intraclass correlations for test-retest reliability were 0.77 for the total PA and 0.53 to 0.72 for the specific activity types (Langer et al., 2003).

Sedentary behavior in the present analysis was defined by self-reported usual daily sitting time (ST). ST was assessed by questionnaire at baseline and twice during follow-up (year 3 and year 6) with the following question: “During a usual day and night, about how many hours do you spend sitting? Be sure to include the time you spend sitting at work, sitting at the table eating, driving or riding in a car or bus, and sitting up watching TV or talking.” Eight categories were provided for the response, ranging from less than 4 hours to 16 or more hours.

Outcome Ascertainment

The primary outcome for this analysis was incident primary colorectal cancer further defined by incident colon and rectal cancer. Outcomes for OS participants were self-reported annually (Curb et al., 2003). Fatal cancer endpoints were confirmed through documentation on hospital or autopsy records. Once reported, medical records were gathered for independent physicians to adjudicate the event according to standardized criteria (Curb et al., 2003). All primary cancer cases, including colon and rectal, were sent to the Clinical Coordinating Center (CCC) for review and coding in accordance to Surveillance, Epidemiology, and End Results (National Cancer Institute) guidelines. Additionally, we examined colon and rectal cancer separately. Rectal cancer consisted of both rectum and rectosigmoid cancers.

Statistical Analysis

All analyses were performed using SAS statistical software (version 9.4, SAS Institute, Inc., Cary, North Carolina). Eligible participants contributed person-time from baseline to first CRC diagnosis, date of death, loss to follow-up or August 29, 2014, whichever occurred first. Baseline demographic characteristics for participants were examined across categories of baseline ST and PA. Linear models including the median of ST and PA categories were used to estimate a p-value for linear trend across categories for each baseline covariate.

We explored the independent associations of PA and ST on colorectal, colon, and rectal cancer. To reduce measurement error and represent long-term exposure (Hu et al., 2000), cumulative average exposure for PA and ST was calculated from questionnaires at baseline, year 3 and year 6 (Hu et al., 1999). Cumulative average of ST (hrs/day) was classified into 5 (hrs/d), 5.1 to 9.9 (hrs/d), and 10 (hrs/d), which approximates tertiles based on the distribution of the data. Cumulative average of PA was classified as: inactive (< 1.7 MET-hrs/wk), low (1.8–7.4 MET-hrs/wk), medium (7.5–20 MET-hrs/wk), and high activity (> 20 MET-hrs/wk) where 7.5 MET-hrs/wk is equivalent to accumulating 150 min/wk of moderate-intensity exercise as recommended in current PA guidelines (Haskell et al., 2007). Time-dependent Cox proportional hazards models were used to estimate hazard ratios (HR)

and 95% confidence intervals (CIs). The proportional hazard assumption was confirmed by the time-dependent covariate methods (i.e., detecting the significance of time-by-covariate interaction terms) in advance.

Three models were used to evaluate the independent association between change in PA and ST with incident colorectal, colon and rectal cancer. The first model was stratified by age only. The second model additionally included race, education, income, marital status, cigarette smoking, family history of CRC, history of CRC screening, alcohol consumption, hormone replacement therapy, total energy intake, fiber intake, vitamin D intake, red meat intake, aspirin use, multivitamin use, ST (for PA model), and PA (for ST model). The final model also adjusted for diabetes and body mass index (BMI). As BMI and diabetes may be intermediates on the causal pathway for the association of sitting time and PA with incident colorectal cancer, they were not included in the second model. Covariates that were reassessed during follow-up were updated over time with the most recent value.

To assess the joint association of ST and PA with risk of colorectal cancer, participants were cross-classified into 12 groups according to jointly defined levels of ST and PA. In order to maximize power, we only investigated the joint association for colorectal cancer risk. The interaction was assessed by the difference in -2 log likelihood between the model containing the cross-classified sitting time-PA variables and the main effects model.

Whether associations between ST and PA with risk of colorectal cancer varied by BMI (<25, 25 – <30, and ≥ 30 kg/m²), employment status (employed vs. unemployed), and age group (50–59, 60–69, and ≥ 70 years) was also investigated. Interactions were tested by the difference in -2 log likelihood between the model containing interactions with potential effect modifiers and the main effects model.

Results

During a median follow-up of 13.4 years, 1,145 incident cases of CRC were documented. Of the 1,145 CRC cases, 964 were colon cancer and 202 were rectal cancer. Compared to women who reported ≤ 5 hrs/d of ST, women who reported ≥ 10 hrs/d of ST at baseline were younger, less active, more likely to be current smokers, more likely to be college educated, and reported higher total caloric intake (Table 1). Additionally, women with more time spent sitting and less PA had a higher BMI (Table 1).

In age-adjusted analyses, a positive association was found between higher ST and CRC (HR: 1.22, 95% CI: 1.01–1.47 for ≥ 10 hrs/d; p for trend 0.04) and colon cancer (HR: 1.23, 95% CI: 1.00–1.50 for ≥ 10 hrs/d; p for trend 0.05), but not rectal cancer (p for trend=0.67) (Table 2). However, when models included PA and other covariates, the associations were no longer statistically significant for CRC (HR: 1.15, 95% CI: 0.95–1.40 for inactive ≥ 10 hrs/d; p for trend 0.16) or colon cancer (HR: 1.17, 95% CI: 0.95–1.45 for inactive ≥ 10 hrs/d; p for trend 0.14).

Higher levels of PA were associated with a decreased risk of CRC (p for trend<0.001), colon cancer (p for trend<0.01), and rectal cancer (p for trend<0.0001) (Table 2) in age-adjusted analyses. In multivariable-adjusted analyses, compared with inactive women as the reference

group (≤ 1.7 MET-hrs/week), the risk of CRC for low (1.8–7.4 MET-hrs/week), medium (7.5–20 MET-hrs/week), and high (> 20 MET-hrs/week) groups were 0.94 (95% CI: 0.78 – 1.14), 0.92 (95% CI: 0.77 – 1.10), and 0.81 (95% CI: 0.66 – 1.00), respectively (p for trend 0.04). For rectal cancer, compared with inactive women (≤ 1.7 MET-hrs/week), the risk for low (1.8–7.4 MET-hrs/week), medium (7.5–20 MET-hrs/week), and high (> 20 MET-hrs/week) groups were 0.95 (95% CI: 0.62 – 1.45), 0.87 (95% CI: 0.58 – 1.32), and 0.44 (95% CI: 0.26 – 0.74), respectively (p for trend < 0.001). There was not a significant association between PA and incident colon cancer in multivariable-adjusted analyses. Finally, the association between PA and CRC was attenuated and no longer statistically significant after adjustment for BMI and diabetes, while the association for rectal cancer was attenuated but remained statistically significant (p for trend 0.001).

Participants were then cross-classified based on ST and PA and CRC risk was examined according to jointly defined exposures (Table 3). The interaction of ST and PA was not statistically significant (P for interaction = 0.62). Although the estimates were not statistically significant, lower sitting time appeared beneficial in all groups regardless of PA levels. For women reporting the highest amount of PA (≥ 20 MET-hrs/week) and lowest amount of sitting (≤ 5 hrs/d), the HR for CRC was 0.75 (95% CI: 0.52–1.10).

There was no evidence of effect modification of the associations between ST or PA and CRC by age group (p for interaction = 0.97 and 0.55, respectively), BMI (p for interaction = 0.66 and 0.80, respectively) or employment status (p for interaction = 0.99 and 0.96, respectively) (Tables 4). Nonetheless, although the interaction was not significant, higher PA was associated with significantly lower CRC risk in employed women (HR: 0.68, 95% CI: 0.46–0.997 for high > 20 MET-hrs/week; p for trend 0.04) but not in unemployed women. Higher PA (> 20 MET-hrs/wk) was also associated with a significantly lower risk of CRC in normal weight women (HR: 0.72, 95% CI: 0.50–1.04; p for trend 0.02) but not for overweight or obese women.

Discussion

In this large prospective study of older postmenopausal women, we observed an inverse association between leisure time PA and incidence of CRC, in particular rectal cancer. Physical activity was also associated with lower risk of CRC in women who were employed, while there was no association in unemployed women. Although there was a significant positive association between ST and CRC risk in age-adjusted analyses, this association was attenuated and no longer statistically significant in the multivariable analyses. When examined as jointly classified exposures and compared to inactive women with the highest ST, there was a trend for reduced multivariable CRC risks with increasing PA regardless of ST level although the interaction was not statistically significant.

Previous studies on rectal cancer and PA have been consistent in finding a lack of association (Friedenreich and Orenstein, 2002, Lee, 2003, Samad et al., 2005, Robsahm et al., 2013). However, many of these studies had a small number of rectal cancer cases and few were conducted in older women. A recent study pooled 1.44 million adults and found beneficial associations for both colon and rectal cancer with high self-reported leisure time

PA (Moore et al., 2016). The current analysis, which assesses the independent and joint associations of PA and ST on colorectal, colon and rectal cancer incidence in a large cohort of postmenopausal women, is a significant contribution to the literature. Our finding of an inverse association between PA and risk of rectal cancer is consistent with results from Moore et al (Moore et al., 2016) who found a 13% decreased risk of rectal cancer in men and women. Because that study pooled data across several cohorts, the measurement of PA varied among studies and likely limited the approach to defining PA exposure groups for analysis. Our study showing the potential benefits of higher levels of energy expenditure in total leisure time PA with risk of rectal cancer used a reliable and validated questionnaire that surveyed usual PA types and intensities relevant to postmenopausal women lives.

A meta-analysis conducted by Cong et al. found a 30% increased risk of colon cancer associated with prolonged ST; however, many of the studies measured occupational behaviors, which may be different than non-occupational ST, particularly in older adults who may be retired (Moore et al., 2016) (Cong et al., 2014). Out of the 35 studies included in that analysis, only 9 adjusted for PA. Our age-adjusted results for total ST were very similar to these findings (HR: 1.34, 95% CI: 1.08–1.65); however, once we adjusted for multiple covariates, including PA, this association was attenuated and no longer significant. Our lack of significant findings regarding ST and colon cancer are similar to those published by Howard and colleagues (Howard et al., 2008) who found that the multivariable-adjusted RR for colon cancer associated with 9 hours/day of ST was 1.24 (95% CI: 0.90–1.70) compared to those sitting for < 3 hours/day in the NIH-AARP cohort of older women and men. In contrast, Keum et al. (Keum et al., 2015), found a 21% increased risk of CRC in women who sat while watching TV for 21 versus < 7 hours/week in the Nurses' Health Study. Perhaps our lack of significant findings for overall ST reflects a limitation in how ST was assessed in the WHI, which might have lower sensitivity to characterize sitting while watching television and may mask a true association with CRC as shown in previous work (Howard et al., 2008, Keum et al., 2015). Research has shown that other unhealthy behaviors occur while sitting watching television, such as increased caloric intake and unhealthy eating behaviors due to food advertising during television programming (Harris et al., 2009, Sisson et al., 2012), which could be contributing to CRC risk associated with ST time spent watching television.

Potential biological mechanisms by which PA reduces risk of colon cancer include improved energy balance, improved immune response, decreased levels of insulin and insulin-like growth factors (IGFs), and decreased gastrointestinal transit time (Rogers, 1992, Martínez et al., 1997, Sandhu et al., 2002). Moreover, emerging evidence suggests that PA may benefit the gut microbiome (Clarke et al., 2013) which has been shown to predict colorectal cancer in humans (Ahn et al., 2013). It is unclear if these mechanisms are similar for rectal cancer, as previous research indicated the risk factors for colorectal cancer could differ by subsite (Wei et al., 2004). Previous work has found a decrease in prostaglandin E₂ levels in rectal mucosa with increased leisure time PA (Martínez et al., 1999).

Strengths of our study include its prospective design, the large multiethnic cohort of postmenopausal women, data collected on a large number of relevant covariates, and detailed information on PA. Due to the timing of the questionnaires throughout the WHI-OS,

we were able to use updated exposure information and reduce random misclassification by using the cumulative average of our exposure variables. Additionally, we were also able to evaluate the joint association between overall ST and leisure time PA. Finally, our study included a substantial number of incident cancer cases that allowed for evaluation of overall CRC risk as well as colon and rectal cancer as separate endpoints.

Our study also has limitations including the fact that the analysis was limited to postmenopausal women and may not be generalizable to other populations including men and younger women. Both PA and ST were self-reported however the PA measurement has been validated in this cohort and measurement error is likely to be non-differential due to the prospective nature of the study (Meyer et al., 2009). Nonetheless, accelerometers could provide more accurate measurements of ST and PA. Also, we were unable to parse apart the different types of SB, such as television watching, occupational, and sitting during leisure time as the questionnaire only assessed overall ST. Finally, as with any observational study, the possibility of residual confounding by other lifestyle factors cannot be ruled out. However, because of the extensive adjustments performed in the present study, the observed associations are not likely explained in large extent by residual or unmeasured confounding.

In conclusion, lack of leisure time PA was associated with a significant increased risk of rectal cancer in postmenopausal women as well as a marginally significant increased risk of colorectal cancer overall. Our findings add to recent evidence supporting the beneficial effects of PA on rectal cancer. These current findings have important public health implications. Increasing PA among older women could potentially reduce risk of rectal cancer and enhance overall control of the cancer burden in an aging population.

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Table 1

Baseline Characteristics According to Categories of Sitting Time and Physical Activity, Women's Health Initiative-Observational Study

	Sitting Time (hrs/day)				Physical Activity (MET-hrs/week)				p value
	< 5 (n=25,758)	5-9.9 (n=30,729)	10 (n=18,383)	p Value	Inactive (1.7) (n=9,653)	Low (1.8-7.4) (n=19,080)	Medium (7.5-20) (n=28,398)	High (>20) (n=17,739)	
Age, yrs	64.0 (7.1)	64.0 (7.3)	61.2 (7.3)	<0.001	63.8 (7.6)	63.5 (7.5)	63.4 (7.3)	62.7 (7.1)	<0.001
Sitting time, h/day	3.7 (1.2)	7.4 (1.0)	11.9 (1.7)		7.9 (3.6)	7.5 (3.4)	7.2 (3.2)	6.6 (3.1)	<0.001
Physical activity, MET-h/wk	16.1 (16.1)	13.9 (13.8)	11.1 (12.1)	<0.001	0.6 (1.1)	5.0 (4.0)	13.5 (7.6)	31.8 (16.3)	<0.001
Race/Ethnicity, %				<0.001					
White	81	86	85		78	82	86	87	
African-American	9	6	8		12	9	6	5	
Hispanic/Latino	6	3	3		5	4	3	3	
Other	5	5	5		5	5	5	5	
Smoking status, %				<0.001					<0.001
Current	5	6	7		11	8	5	4	
Former	41	43	46		38	39	44	48	
Never	54	51	47		51	53	51	47	
Education level, %				<0.001					<0.001
High school or less	24	20	16		32	25	17	14	
Vocational training	12	10	9		12	11	9	7	
College	64	70	75		55	64	73	78	
Married, %	66	62	54	<0.001	59	59	63	65	<0.001
BMI, kg/m ²	26.5 (5.3)	27.0 (5.6)	27.9 (6.3)	<0.001	29.7 (6.8)	28.1 (5.9)	26.6 (5.2)	25.3 (4.7)	<0.001
Diabetes, %	5	5	5	0.26	8	6	4	3	<0.001
Aspirin Use, %	7	7	8	0.18	7	7	7	7	0.75
Family history of CRC, %	16	15	14	<0.001	15	15	15	15	0.62
History of CRC screening, %	53	54	52	<0.001	50	52	55	55	<0.001
Current HRT use, %	40	40	40	0.24	40	40	40	40	0.55
Total caloric intake (kcal/d)	1518 (598)	1577 (581)	1624 (609)	<0.001	1597 (676)	1576 (617)	1560 (567)	1557 (566)	<0.001
Alcohol intake (g/d)	5.3 (10.6)	5.8 (11.2)	5.8 (11.8)	<0.001	4.0 (10.8)	4.7 (10.4)	5.9 (10.9)	7.1 (12.1)	<0.001
Red meat intake (servings/d)	0.6 (0.5)	0.6 (0.5)	0.6 (0.5)	<0.001	0.8 (0.6)	0.7 (0.5)	0.6 (0.5)	0.5 (0.4)	<0.001
Calcium intake (mg/d)	816 (469)	844 (455)	845 (450)	<0.001	755 (447)	800 (448)	850 (452)	892 (478)	<0.001
Vitamin D intake (mg/d)	4.3 (3.2)	4.5 (3.1)	4.4 (3.0)	0.11	4.1 (3.1)	4.3 (3.1)	4.4 (3.0)	4.5 (3.2)	<0.001

Table 2

Hazard Ratios and 95% CIs for the Association Between Sitting Time, Total Physical Activity, and Risk of Colorectal, Rectal, and Colon Cancer

	Sitting Time (hrs/day)				Physical Activity (MET-hrs/week)				p trend	
	5	5.1–9.9	10	p trend	Inactive (1.7)	Low (1.8–7.4)	Medium (7.5–20)	High (>20)		
Colorectal										
Cases	365	516	264		249	430	282	184		
Person-yrs	336,659	410,944	252,054		171,432	350,331	212,285	265,607		
Age-adjusted	1.00	1.11 (0.97–1.28)	1.22 (1.01–1.47)	0.04	1.00	0.88 (0.73–1.06)	0.81 (0.68–0.96)	0.69 (0.57–0.84)	<0.001	
MV-adjusted	1.00	1.11 (0.97–1.28)	1.15 (0.95–1.40)	0.16	1.00	0.94 (0.78–1.14)	0.92 (0.77–1.10)	0.81 (0.66–1.00)	0.04	
MV + BMI & DM	1.00	1.10 (0.95–1.26)	1.12 (0.92–1.35)	0.29	1.00	0.96 (0.80–1.16)	0.96 (0.80–1.15)	0.87 (0.71–1.07)	0.15	
Rectal										
Cases	62	93	47		29	78	57	38		
Age-adjusted	1.00	1.13 (0.81–1.57)	1.11 (0.71–1.73)	0.67	1.00	0.90 (0.59–1.37)	0.80 (0.54–1.18)	0.39 (0.24–0.65)	<0.0001	
MV-adjusted	1.00	1.10 (0.79–1.53)	0.97 (0.61–1.53)	0.85	1.00	0.95 (0.62–1.45)	0.87 (0.58–1.32)	0.44 (0.26–0.74)	<0.001	
MV + BMI & DM	1.00	1.08 (0.78–1.51)	0.94 (0.59–1.48)	0.74	1.00	0.97 (0.64–1.49)	0.92 (0.61–1.39)	0.47 (0.28–0.80)	0.001	
Colon										
Cases	311	432	221		221	357	235	151		
Age-adjusted	1.00	1.11 (0.96–1.29)	1.23 (1.00–1.50)	0.05	1.00	0.89 (0.73–1.10)	0.81 (0.67–0.98)	0.75 (0.61–0.92)	<0.01	
MV-adjusted	1.00	1.12 (0.96–1.30)	1.17 (0.95–1.45)	0.14	1.00	0.96 (0.78–1.18)	0.92 (0.75–1.12)	0.89 (0.71–1.11)	0.31	
MV + BMI & DM	1.00	1.10 (0.95–1.28)	1.14 (0.92–1.40)	0.25	1.00	0.99 (0.80–1.21)	0.96 (0.79–1.18)	0.95 (0.76–1.19)	0.65	

MV model: Race, education, total caloric intake, fiber intake, calcium intake, vitamin D intake, red meat intake, alcohol, hormone replacement therapy, income, marital status, smoking, family history of CRC, CRC screening, aspirin, multivitamin use, physical activity (ST model), and sitting time (PA model)

Multivariable Adjusted HRs for Colorectal Cancer for the Joint Association between Total Physical Activity and Sitting Time

Table 3

		Physical Activity				
		Inactive (1.7)	Low (1.8–7.4)	Medium (7.5–20)	High (>20)	P for interaction
10		1.00	1.11 (0.75–1.65)	0.97 (0.65–1.43)	0.71 (0.41–1.22)	
Sitting Time	5.1–9.9	1.11 (0.78–1.58)	0.93 (0.66–1.30)	0.91 (0.66–1.27)	0.85 (0.60–1.20)	0.62
	5	0.76 (0.48–1.20)	0.85 (0.58–1.25)	0.89 (0.62–1.26)	0.75 (0.52–1.10)	

MV model: Race, education, total caloric intake, fiber intake, calcium intake, vitamin D intake, red meat intake, alcohol, hormone replacement therapy, income, marital status, smoking, family history of CRC, CRC screening, aspirin and multivitamin use

Table 4

Hazard Ratios and 95% CIs for the Association Between Sitting Time, Total Physical Activity, and Risk of Colorectal Cancer, Stratified by Age Group, BMI Group and Employment

	Sitting Time (hrs/day)			Physical Activity (MET-hrs/week)				p trend
	5	5.1-9.9	10	Inactive (1.7)	Low (1.8-7.4)	Medium (7.5-20)	High (>20)	
Colorectal								
Age Group ¹								
50-59	1.00	1.17 (0.82-1.65)	1.26 (0.84-1.87)	1.00	1.13 (0.75-1.69)	0.87 (0.58-1.32)	0.83 (0.52-1.33)	0.19
60-69	1.00	1.09 (0.89-1.33)	1.06 (0.80-1.41)	1.00	0.86 (0.65-1.14)	0.92 (0.71-1.19)	0.78 (0.58-1.06)	0.17
70+	1.00	1.14 (0.90-1.46)	1.21 (0.85-1.72)	1.00	0.99 (0.72-1.38)	0.98 (0.72-1.35)	0.90 (0.63-1.29)	0.49
BMI Group ²								
Normal	1.00	1.03 (0.82-1.28)	0.86 (0.61-1.21)	1.00	0.97 (0.61-1.39)	0.85 (0.61-1.20)	0.72 (0.50-1.04)	0.02
Overweight	1.00	1.22 (0.95-1.56)	1.34 (0.96-1.87)	1.00	0.86 (0.62-1.20)	0.96 (0.70-1.31)	0.93 (0.65-1.32)	0.09
Obese	1.00	1.12 (0.84-1.50)	1.22 (0.86-1.73)	1.00	1.08 (0.79-1.47)	1.07 (0.79-1.46)	1.00 (0.67-1.50)	0.67
Employment ³								
Employed	1.00	1.17 (0.87-1.56)	1.16 (0.93-1.62)	1.00	0.92 (0.66-1.28)	0.86 (0.62-1.19)	0.68 (0.46-0.99)	0.04
Unemployed	1.00	1.11 (0.95-1.31)	1.14 (0.89-1.45)	1.00	0.95 (0.75-1.20)	0.96 (0.77-1.20)	0.89 (0.69-1.14)	0.26

MV model: Race, education, total caloric intake, fiber intake, calcium intake, vitamin D intake, red meat intake, alcohol, hormone replacement therapy, income, marital status, family history of CRC, CRC screening, aspirin, multivitamin use, physical activity (ST model), and sitting time (PA model)

¹ Age Group: P for interaction: ST = 0.97 & PA = 0.55

² BMI Group: P for interaction: ST = 0.66 & PA = 0.80

³ Employment: P for interaction: ST = 0.99 & PA = 0.96