Physical Inactivity and Obesity in Relation to Tumor Site and Age Onset for CRC on the Rising Incidence of Early-onset Colon Cancer and Early-onset Rectal Cancer

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Abstract

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Background: Overall incidence of colorectal cancer (CRC) has declined in recent decades; however, the incidence of early-onset CRC, particularly early-onset rectal cancer, has been increasing steadily since the mid-1990s among younger adults. The factors underlying observed increases in early-onset rectal cancer remain unclear. This study assessed the association of physical activity and obesity with early-onset rectal cancer relative to early-onset colon and later-onset rectal cancers. This study aims to build on existing research and provide a greater understanding as to the distinct epidemiology of early-onset rectal cancer.

Methods: With a study population derived from the population-based Advanced Colorectal Cancer of Serrated Subtype (ACCESS) Study and the Seattle site of the Colon Cancer Family Registry (SCCFR), we utilized multivariate regression models to assess the association of physical activity levels and obesity with colorectal tumor site and age at onset via comparisons

across three case groups: early-onset rectal cancer vs. early-onset colon cancer and early-onset rectal cancer vs. later-onset rectal cancer.

Results: In this study of 1199 participants, including 362 patients with early-onset rectal cancer, 570 patients with early-onset colon cancer, no significant associations were found between physical activity levels and tumor site among those with early-onset CRC. Individuals with early-onset CRC and a BMI over 30kg/m^2 were significantly less likely to have tumors located in the rectum (OR = 0.6, p-value = 0.01). When comparing participants with early-onset rectal cancer to those with later-onset rectal cancer (N = 267), a suggestively inverse association was detected for physical activity levels; however, this pattern was not statistically significant. No other significant associations were observed between the three CRC cancer groups.

Conclusions: Findings from this study indicated that physical activity levels and obesity were unlikely to be contributing factors for the emerging trend of early-onset rectal cancer incidence, suggesting a need for future research on other potential risk factors associated with CRC tumor site and age at onset, specifically with early-onset rectal cancer.

INTRODUCTION

Colorectal cancer (CRC) is the third most commonly diagnosed cancer worldwide, and it is the second leading cause of cancer-related deaths globally.[1] In the United States, the median age at which CRC is diagnosed was 67 years in 2013-2017 and, currently, over 80% of CRC incidence occurs in the population aged > 50 years.[2,3] Although overall incidence of CRC has declined in recent decades, incidence of early-onset CRC has been increasing steadily since the mid-1990s. [4-6] The factors underlying these observed increases in early-onset CRC incidence, however, remain unclear.

Although colon and rectal cancers are commonly combined in studies of CRC etiology, their epidemiology can differ. In particular, observed patterns of increase in early-onset CRC incidence appear to be limited to an increase in early-onset rectal cancers. Between the early 1990s to 2013, rectal cancer incidence increased by 2.3% annually in adults aged 40-54 years.[6] In comparison, the corresponding annual increase in incidence rates for colon cancer over this time was 1.3% among adults age 40-49 and 0.5% per year among those aged 50-54.[6] While the increase of early-onset CRC incidence is largely attributed to increases in early-onset rectal cancer, limited literature has discussed the differential impact of risk factors in relation to CRC tumor sites among those with early-onset disease.

Prior literature has investigated physical inactivity and obesity as risk factors for CRC overall, and by tumor site.[2,7,8] These studies have suggested that body mass index (BMI) is more strongly associated with colon cancer compared to rectal cancer, while associations with physical inactivity appear to be predominantly linked with colon cancer.[2,8] However, the extent to which these distinctions apply to early-onset colon and rectal cancers remains uncertain. To address the current gap in knowledge as to the distinct epidemiology of early-onset rectal cancers, we assessed the association of physical activity and obesity with tumor site (among those with early-CRC) and with age at CRC onset (among those with rectal cancers). The

overarching goal of this study was to build on existing research and provide a greater understanding as to the distinct epidemiology of early-onset rectal cancer.

METHODS

Study Design and Setting

This study utilized data obtained from the population-based Advanced Colorectal Cancer of Serrated Subtype (ACCESS) Study[9] and the Seattle site of the Colon Cancer Family Registry (SCCFR).[10] Both studies were coordinated at the Fred Hutch Cancer Center and used parallel recruitment protocols and study materials. Participants were identified through the Cancer Surveillance System (CSS), a Surveillance, Epidemiology, and End Results (SEER) cancer registry serving western Washington State. For the SCCFR, eligible participants included persons diagnosed with incident CRC between 1998-2007 who, at the time of diagnosis, were aged 20-74 (1998-2002) or 18-49 (2002-2007) and resided in western Washington State.[10] For the ACCESS Study, eligible participants included persons diagnosed with incident CRC between April 1, 2016, and December 31, 2018, who were aged 20-74 and resided in western Washington State at the time of diagnosis.[9] Participants who enrolled in these studies completed a survey at the time of enrollment that covered a variety of topics, including family and personal medical history, demographic information, and lifestyle habits, such as aspects of diet, physical activity, and alcohol consumption.[9,10] Surveys were administered through either an online platform (ACCESS only), telephone interviews, or mailed questionnaires.

Study population

For the analysis, participants were included based on three case groups, delineated by age at diagnosis and tumor site: 1) early-onset rectal cancer cases (age <55 at diagnosis, tumor site classified as ICD-O-3 C19.9 or C20.9), 2) early-onset colon cancer cases (age <55 at diagnosis, tumor site classified as ICD-O-3 C18.0, C18.2-C18.9), and 3) later-onset rectal cancer cases (age >59 at diagnosis, tumor site classified as ICD-O-3 C19.9 or C20.9).[11] The

age cutoff for the early-onset case group was determined by the national trend showing that the incidence of CRC in individuals aged 50-54 has increased in a pattern similar to that observed among those under 50 years of age, particularly for early-onset rectal cancer.[12] Using this age cutoff allowed us to expand the sample size of our early-onset CRC case groups, enhancing the robustness of our study band better align the analysis with the national trends. Participants who did not belong to any of the three case groups (N = 1059) and those with missing responses on key variables under consideration (N = 381) were excluded from the present analysis.

Analysis

Key variables

The primary exposures for this study were physical activity level and obesity. Physical activity level data were obtained from the ACCESS and SCCFR surveys with questions that inquired as to regular participation in various physical activities. Specifically, participants were asked about frequency and duration of mild, moderate, and strenuous activities during their 20s, 30s, and 50s. To quantify physical activity, we calculated metabolic equivalents hours per week (MET hours) based on the Compendium of Physical Activities.[13] Mild activity was multiplied by a value of 2 MET hours/week for each hour of participation, while moderate and strenuous activities were multiplied by values of 4.5 and 8 MET hours/week, respectively.[13] Consistent with previous literature, we primarily categorized the calculated MET hours into the following categories to facilitate further analysis: <3.5, 3.5 - < 8.75, 8.75 - < 17.5, 17.5 - < 35, ≥35 MET-hours/week.[14] The latter two categories were merged to address low participant numbers in the highest tiers and ensure analytical robustness. For analysis, we used the aggregated MET-hours/week variable to represent the physical activity level during the age period closest to the age at diagnosis. This combined measure was chosen to reflect the relevant exposure period for the development of CRC.

For the assessment of obesity, participants were asked to report their typical weight two years prior to diagnosis and their current height. Based on these self-reported data, body mass

index (BMI) was calculated as a metric of body size.[15] BMI is calculated by dividing a person's weight by the square of their height in meters (BMI = kg/m^2). BMI data were stratified into four categorical groups: <18.5, 18.5-24.9, 25.0-29.9, and >30.0. Cutoffs were determined according to suggestion of the Centers for Disease Control and Prevention (CDC).[16] Participants with BMI values smaller than 10 were excluded (N = 2) to eliminate potential outliers. Moreover, the two lowest BMI categories were combined to ensure sufficient sample size for robust analysis. It is important to note that BMI, while widely used as a metric of body size, is an imperfect measure and carries inherent limitations as an indicator of body fat.[17]

Outcome

In this study, our primary outcome was CRC case group, which we defined as early-onset rectal cancer, early-onset colon cancer, or later-onset rectal cancer. Consistent with observed patterns in national cancer statistics, early-onset was defined as individuals diagnosed with CRC at an age younger than 55 years, while later-onset cases represented individuals diagnosed at an age older than 59 years.[5,6] The deliberate age gap in our definition of early- vs. later-onset was to draw a more distinct difference among various cases in the perspective of cancer etiology. Beyond the age distinction, rectal cancer is identified as the onset of carcinogenesis within the rectum, which is the last segment of the large intestine (tumor site classified as ICD-O-3 C19.9 or C20.9).[11] In contrast, colon cancer would refer to the development of tumors within the colon, which constitutes the first and longest segment of the large intestine (tumor site classified as ICD-O-3 C18.0, C18.2-C18.9).[11] This refined classification ensures a precise characterization of the anatomical sites and facilitates a nuanced analysis of the distinct epidemiological profiles across different CRC tumor sites.

Statistical Analysis

In the statistical analysis, descriptive statistics were conducted to provide a comparative overview of the key characteristics of our study population by three case groups. Results were collectively presented in Table 1.

We employed multivariate logistic regression models to estimate the independent associations of physical activity levels and BMI with tumor site among individuals with early-onset CRC. The logistic regression models were adjusted for covariates including biological sex, pre-diagnostic smoking status, and alcohol intake status. Odds ratio and 95% confidence intervals (CIs) were computed based on the coefficients derived from the logistic regression model. We repeated these analyses to examine the associations of physical activity and BMI with age at onset among those with rectal cancer. All statistical analyses were performed using R studio version 4.3.3 on MacOS. The results of the logistic regression analyses were presented in Table 2 and 3.

RESULTS

In this analysis, a total of 1199 participants were included, comprising 362 patients with early-onset rectal cancer, 570 patients with early-onset colon cancer, and 267 patients with later-onset rectal cancer. Individuals with early-onset rectal cancer were less likely than those with early-onset colon cancer and more likely than those with later-onset rectal cancer to the female (46% vs. 53% and 40%, respectively) (**Table 1**). The prevalence of pre-diagnostic smoking history was similar by tumor site among those with early-onset CRC, but was markedly higher among those with later-onset rectal cancer, although alcohol consumption patterns were similar across all included case groups. Patterns of weekly vegetable consumption were also similar across case groups, with some suggestion of lower fruit consumption among those with early-onset rectal cancers.

With respect to physical activity, we found that a higher proportion of participants with early-onset rectal cancer reported engaging in < 3.5 MET-hours/week of physical activities when compared to those with early-onset colon cancer and later-onset rectal cancer patients (62% vs. 59% and 53%, respectively, Table 1). Physical activity levels have shifted downward in younger population as compared to their older counterparts among our participants. This pattern did not

translate into statistically significant associations between physical activity levels and tumor site among those with early-onset CRC after adjusting for potential covariates in our logistic regression models. There was a suggestively inverse association with physical activity when comparing early- vs. later-onset rectal cancer case participants. However, these associations were constrained by the small sample sizes within each physical activity category and did not reach statistical significance (**Table 2**). These patterns of association persisted irrespective of the inclusion of an interaction term between physical activity level and obesity (**Table 3**).

Regarding BMI, a majority of early-onset rectal cancer case participants were categorized with a BMI <25 kg/m^2 (39%, Table 1), with a proportion that was slightly higher than among those in other case groups (34% and 38% among early-onset colon and later-onset rectal groups, respectively). Among individuals with early-onset CRC, those with a BMI greater than 30kg/m^2 were significantly less likely to have tumors located in the rectum (OR = 0.6, p-value = 0.01, Table 2). No other statistically significant associations were detected when comparing participants with early-onset rectal cancer to their counterparts with early-onset colon cancer or later-onset rectal cancer.

DISCUSSION

Overall, the results of this study highlighted several key patterns in the demographic and lifestyle characteristics of CRC participants across different tumor sites and age at onset. Participants with early-onset rectal cancer reported engaging less frequently in physical activity and were more likely to have lower BMI measures compared to participants with early-onset colon cancer and later-onset rectal cancer. Despite variations in physical activity levels and BMI, this study did not observe statistically significant associations linking these factors with tumor site and age at onset after multivariate adjustment, suggesting a need for further exploration of other potential risk factors specific to early-onset rectal cancer.

To date, several studies have inspected the associations of physical activity levels and BMI with CRC risk overall, or separately by age at onset or tumor site.[4,7,14] One study included the same population from SCCFR and found that the beneficial effect of physical activity is not specific to a particular CRC molecular phenotype or anatomic site.[14] While the above study did not specifically examine associations with risk of early-onset CRC by tumor site, our findings suggest that physical activity level is unlikely to contribute to patterns of rising incidence of early-onset rectal cancer. In contrast, one study that examined the association of sedentary lifestyle and the risk of early-onset CRC revealed that an inactive lifestyle was associated with increased risk of early-onset CRC, particularly early-onset rectal cancer.[18] While this association was discovered independently from physical activity level and obesity, it suggests that maintaining an active lifestyle remains beneficial and protective with regard to risk of early-onset CRC overall.[18] In contrast to previous findings, findings from our study specifically indicate that physical activity levels may not significantly influence the rising incidence of early-onset rectal cancer. This discrepancy highlights the need for further investigation into how early-onset rectal cancer may respond differently to lifestyle factors as compared to other CRC subtypes.

Our findings that pre-diagnostic obesity is likely less common among those with early-onset rectal cancers than among those in other case groups imply that obesity is unlikely to be a contributing factor to the rise in incidence of these tumors. Previous literature investigating the association of obesity with incidence of early-onset CRC has had mixed results. In one study that assessed various nongenetic determinants of early-onset CRC, researchers found that baseline BMI was not associated with the risk of early-onset CRC, with associations that were consistently null by tumor site (OR (95% CI) = 0.99 (0.93 – 1.06) vs. OR = 1.05 (0.99 – 1.10) for rectal cancer and colon cancer, respectively).[4] Another study examined the association between BMI at early adulthood and risk of early-onset CRC found a linear association and suggesting a slightly stronger association for early-onset rectal cancers.[19] These findings, in addition to our study, suggest that although obesity continues to be an important risk factor for CRC overall,

and perhaps for early-onset CRC, the role of obesity in the etiology of early-onset rectal cancer is unlikely to be strong enough to contribute to emerging patterns of early-onset rectal cancer incidence. One consideration is obesity observed at different stages of life. Due to the latent period of colorectal carcinogenesis, early-adulthood obesity may have greater impact to the risk of early-onset CRC as compared to obesity observed during later adulthood or baseline.[7] Another consideration would be obesity as an indirect risk factor to early-onset CRC and a surrogate to other established risk factors, such as a diet high in red meat consumption and sedentary lifestyle.[4,19] However, the underlying mechanisms remains unclear and merit future investigations.

We acknowledge that our study was subject to several limitations. Firstly, reliance on self-reported data collected through survey and interviews may introduce potential errors of recall and social desirability bias, which could eventually lead to measurement error and misclassification of exposures. However, we do not anticipate that this misclassification would be differential across the included case groups. Secondly, our classification of physical activity levels (MET hours/week) and obesity (BMI) are based on limited questionnaire items pertaining to a discrete pre-diagnostic period. It is important to acknowledge that these measures may not capture the complexities of real-world scenarios accurately. Thirdly, the generalizability of our study is constrained by the demographics of our study population. The ACCESS and SCCFR populations are skewed toward the experiences of the non-Hispanic White population, which may not fully represent the diversity found in the U.S. population. Hence, findings from our study may not be universally applicable to broader populations or populations with different demographic compositions. Lastly, the lack of cancer-free comparison group in the study design limits our ability to declare causal relationship or draw conclusions regarding CRC risk by age or tumor site, which highlights the need for future research that incorporates a cancer-free comparison groups to enhance study robustness.

Our study also has multiple strengths. One of the strengths of our study was the structured research design, which enabled direct comparisons among three distinct CRC case groups. As of our knowledge, no previous study has utilized the same comparison among the early-onset rectal vs. early-onset colon cancer and early-onset rectal cancer vs. later-onset rectal cancer groups, ensuring the uniqueness of our study and allowing us to contribute novel perspectives regarding the distinct epidemiology of early-onset rectal cancer. Another strength was the sufficient sample size to stratify case groups jointly by age at onset and tumor site. With participants obtained from two population-based surveys, the large sample size further enhanced the statistical power and reliability of our findings.

In conclusion, findings from our study indicated that physical activity levels and obesity were unlikely to be contributing factors for the emerging trend of early-onset rectal cancer incidence, suggesting a need for future research on other potential risk factors associate with CRC tumor site and age at onset, specifically with early-onset rectal cancer.

Table 1. Descriptive Statistics by Colorectal Cancer (CRC) Cancer Subtypes from Advanced Colorectal Cancer of Serrated Subtype (ACCESS) Study and Seattle Colon Cancer Family Registry (SCCFR) *(N = 1199)*

	Early-onset Rectal Cancer (N = 362)	Early-onset Colon Cancer (N = 570)	Later-onset Rectal Cancer (N = 267)
Sex (%)			
Female	167 (46)	300 (53)	106 (40)
Male	195 (54)	270 (47)	161 (60)
Age at diagnosis (years)			
Mean (SD*)	45.7 (6.39)	45.6 (7.21)	66.7 (4.33)
Median (IQR*)	47 (42, 51)	47 (42, 51)	67 (63, 70)
Range	21, 55	21, 55	60, 80
Pre-diagnostic smoking status (%)			
Ever	183 (51)	277 (49)	182 (68)
Never	178 (49)	293 (51)	85 (32)
Missing/unknown[1]	1	0	0
Alcohol intake (drinks/wk) (%)			
0	234 (89)	363 (91)	132 (90)
1-13	8 (3)	9 (2)	3 (2)
> 14	21 (8)	29 (7)	32 (8)
Missing/unknown	99	169	120
Weekly fruit intake (servings/wk) (%)			
< 1	12 (4)	26 (5)	12 (5)
1-3	93 (31)	135 (28)	45 (21)
4-9	130 (43)	178 (38)	87 (41)
≥ 10	68 (22)	136 (29)	70 (33)
Missing/unknown	59	95	53
Weekly vegetable intake (servings/wk) (%)			
< 1	3 (1)	4 (1)	0 (0)
1-3	38 (12)	71 (15)	23 (11)
4-9	168 (55)	237 (49)	117 (54)
≥ 10	97 (32)	168 (35)	75 (35)
Missing/unknown	56	90	52
Levels of physical activity (MET-hours/week*) (%)			
<3.5	159 (62)	240 (59)	81 (53)
3.5 - 8.74	50 (19)	88 (22)	32 (21)
8.75 - 17.4	29 (11)	54 (13)	22 (14)
≥17.5	20 (8)	26 (6)	17 (12)
Missing	104	162	115
Body Mass Index (BMI) at diagnosis (kg/m^2) (%)			
< 25	141 (39)	194 (34)	76 (28)
25 – 29.9	133 (37)	177 (31)	118 (45)
≥ 30	86 (24)	196 (35)	72 (27)
Missing/unknown	2	3	2

[1]Missing/unknown: percentage calculation for each value based on non-missing data.
*Abbreviation: SD: standard deviation, IQR: interquartile range, MET: metabolic equivalent of task

Table 2. Logistic Regression Analysis of Physical Activities Levels and BMI on Colorectal Cancer by Tumor Site and Onset Time (Excluding Interaction Term)

Variables	Early-onset Rectal Cancer vs. Early-onset Colon Cancer			Early-onset Rectal Cancer vs. later-onset Rectal Cancer		
	OR	95% CI	p-value	OR	95% CI	p-value
Physical activities (MET hours/wk)						
<3.5	1 (Ref)	--	--	1 (Ref)	--	--
3.5 - 8.74	1.0	0.6-1.5	0.88	0.8	0.4-1.6	0.54
8.75 - 17.4	0.7	0.4-1.3	0.26	0.6	0.3-1.4	0.23
≥17.5	1.7	0.3-3.7	0.20	0.5	0.2-1.1	0.08
BMI at diagnosis (kg/m^2)						
< 25	1 (Ref)	--	--	1 (Ref)	--	--
25.0-29.9	0.9	0.4-1.4	0.61	0.6	0.3-1.0	0.06
> 30.0	0.6	0.4-0.9	0.01*	0.9	0.4-1.7	0.69

Abbreviation: OR: Odds Ratio, CI: confidence interval
All models were adjusted for covariates including patients' biological sex, pre-diagnostic cigarette smoking status, and alcohol consumption status.

Table 3. Logistic Regression Analysis of Physical Activities Levels and BMI on Colorectal Cancer by Tumor Site and Onset Time (With Interaction Term)

Variables	Early-onset Rectal Cancer vs. Early-onset Colon Cancer			Early-onset Rectal Cancer vs. Later-onset Rectal Cancer		
	OR	95% CI	p-value	OR	95% CI	p-value
Physical activities (MET hours/wk)						
<3.5	1 (Ref)	--	--	1 (Ref)	--	--
3.5 - 8.74	1.1	0.6-2.2	0.70	1.1	0.4-3.2	0.86
8.75 - 17.4	0.5	0.2-1.3	0.13	0.3	0.1-1.2	0.09
≥17.5	3.5	0.9-14.6	0.08	1.3	0.2-7.7	0.75
BMI at diagnosis (kg/m^2)						
< 25	1 (Ref)	--	--	1 (Ref)	--	--
25.0-29.9	0.9	0.5-1.6	0.78	0.6	0.3-1.4	0.25
> 30.0	0.6	0.3-1.1	0.07	1.0	0.4-2.4	0.96

Abbreviation: OR: Odds Ratio, CI: confidence interval
All models were adjusted for covariates including patients' biological sex, pre-diagnostic cigarette smoking status, and alcohol consumption status.

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