

The role of multivitamins:
an investigation into the association with colorectal cancer survival

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A thesis
submitted in partial fulfillment of the
requirements for the degree of

Master of Public Health

University of Washington

2023

Committee:

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Program Authorized to Offer Degree

Epidemiology

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Abstract

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Background: Nutritional supplements are used by over half of United States adults, and many patients use supplements for their perceived anti-cancer benefit. Current evidence for the relationship between multivitamin use and colorectal cancer (CRC) survival is sparse. Some studies suggest that multivitamins may divert attention from healthful food-based diets or multivitamin use may be reflected in an effort to live a healthier lifestyle consequently impacting CRC survival. In this study, we examined the association of pre-diagnostic multivitamin use with CRC survival, while accounting for differences by fruit and vegetable consumption and smoking status. **Methods:** This study uses data from two large prospective patient cohorts; the Colon Cancer Family Registry (C-CFR) and the Advanced Colorectal Cancer of Serrated Subtype (ACCESS) study. A Cox Proportional Hazards regression was used to assess the relationship between pre-diagnostic multivitamin use and CRC-specific survival (reported as hazard ratios (HR) and 95% confidence intervals (CI)). We also examined effect modification by fruit and

vegetable consumption and smoking status. **Results:** The estimated HR of CRC death for individuals who use multivitamins is 1.05 (95% CI: 0.94-1.18, p=0.4) compared to individuals who do not use multivitamins, suggesting no statistically significant evidence of an association between pre-diagnostic multivitamin use and CRC-specific survival. Users of multivitamins were less likely to have a history of smoking and consumed higher levels of fruits and vegetables; however, there was no evidence of effect modification by these variables in the relationship of multivitamin use with CRC survival. **Conclusion:** We found no evidence of an association between pre-diagnostic multivitamin use and CRC survival, regardless of stratification by smoking status and fruit and vegetable consumption. Clinicians should discuss a variety of approaches for healthful activities individualized to the patient post CRC diagnosis in addition to multivitamin use advice.

Introduction

Nutritional supplements are used by more than half of adults in the United States (U.S.) over the age of twenty.¹ This growing use of supplements among U.S. adults contributes to a large proportion of nutrient intake and is known to be associated with health status.² Many patients diagnosed with cancer utilize supplements for their perceived anti-cancer benefit, despite guidelines from the American Cancer Society that advocate for obtaining nutrients from foods rather than through the use of supplements.³ However, the evidence regarding supplement use on cancer survival is largely controversial and warrants further investigation.⁴

Prior studies have examined the association between multivitamin use and colorectal cancer (CRC) incidence, finding that use of multivitamins is associated with lower risk of CRC, depending on duration of multivitamin use.⁵ Given that there were approximately 147,950 newly diagnosed CRC cases in 2020, and given that CRC is the second leading cause of cancer death in the US, it's also imperative to understand how multivitamin use can impact CRC survival.⁶ One previous study found that multivitamin use during and after adjuvant chemotherapy was not significantly associated with improved outcomes in patients with stage III colon cancer.⁷ Another study from 2001 found a slight reduction in CRC mortality among multivitamin users, and this association was strongest among moderate to heavy alcohol users.⁸ Other studies have researched the effects of diet on CRC survival, suggesting that diets higher in marine omega-3 fatty acids, Vitamin D, and fiber are associated with better CRC survival.⁹ Regarding the relationship between multivitamin use and diet, it is suggested that multivitamin use may divert attention from pursuing healthful food-based diets.³ Or, supplement usage may be one

component of a larger effort to live a healthier lifestyle; adopting better dietary patterns, exercising, maintaining a healthy body weight, and quitting or not starting smoking.²

In this study, we examined the relationship of pre-diagnostic multivitamin use with CRC survival, while accounting for differences in healthful diets via fruit and vegetable consumption and smoking status, using data from two large prospective patient cohorts. To the best of our knowledge, this is the first study of its kind.

Methods

Study Population

We utilized data from two population-based studies to assess the relationship between multivitamin use and CRC survival. Specifically, this analysis used data from the Colon Cancer Family Registry (C-CFR) and the Advanced Colorectal Cancer of Serrated Subtype (ACCESS) study. The C-CFR is an international collaborative effort between investigators in Australia, Canada, and the United States, with six contributing study centers.¹⁰ The ACCESS study recruited participants through the Puget Sound Surveillance, Epidemiology and End Results (SEER) cancer registry. The Puget Sound SEER collects information on all cancers from residents across 13 counties in western Washington State.

C-CFR recruitment protocols and eligibility criteria have been previously published.¹⁰ Briefly, the C-CFR study recruited women and men diagnosed with incident invasive CRC between January 1997 and June 2007. Inclusion in the present analysis was restricted to population-based cases, not selected on the basis of family history, recruited through one of four sites (University of Melbourne, Melbourne, Victoria, Australia; Cancer Care Ontario, Toronto, Ontario, Canada; Fred Hutchinson Cancer Center, Seattle, Washington, USA; Mayo Clinic, Rochester, Minnesota, USA). Study participants completed a standardized baseline questionnaire

regarding pre-diagnostic exposures via telephone interviews or mail at the time of enrollment. Interviews were administered an average of 11.4 months (median=9.4 months) after diagnosis. Survival information was available for 6,048 CRC cases.

Participants in the ACCESS study were diagnosed with new invasive CRC from April 1, 2016 to December 31, 2018 and were 20 - 74 years of age at the time of diagnosis.¹¹ Consenting participants were contacted by the Puget Sound SEER and completed a baseline questionnaire (adapted from the C-CFR study) either by phone, on paper, or online. The time from diagnosis to completing the questionnaire was on average 6.9 months (SD=3.6). The present analysis includes 438 CRC cases enrolled in the ACCESS Study.

Exposure and Covariates

The exposure of interest for this study was pre-diagnostic multivitamin use obtained from ACCESS and C-CFR baseline questionnaires. Participants were asked if they had ever taken multivitamin pills or tablets at least twice a week for more than a month. This variable was categorized as yes or no; anyone who answered unknown was classified as missing and excluded from the analysis (N=42). A variety of confounding variables were adjusted for due to their notable association with overall health, survival, and development or progression of CRC. The categories for each of the covariates of interest were: fruit/vegetable consumption (low = < 6 serving/week, medium = 6-28 servings/week, high = >28 servings/week), age (years), sex (male, female), smoking (yes, no), body mass index (BMI) (kg/m²), education (high school or less, some college, college graduate or higher), and CRC screening history (yes, no). The exposure of interest, and covariates, were asked in reference to an index date approximately 2 years prior to CRC diagnosis.

Outcome

The outcome of this study was CRC-specific survival. Using International Classification of Diseases, Oncology, Version 10 (ICD-10) codes, death was categorized as CRC-specific when the cause of death was classified as C18.0-C20.0 or C26.0. For the C-CFR study, vital status and date of death were ascertained via passive follow-up by routine linkage to cancer registries and national death indices. For some study sites, survival data was obtained through active follow up with cases or contact with relatives at, on average, five-year intervals after study recruitment. Regarding the ACCESS study, survival data was obtained via linkage of the Puget Sound SEER Registry with the National Death Index. Those with missing data for vital status were excluded from the analysis (N=1).

Statistical Analysis

Descriptive analyses were conducted to assess the frequency of multivitamin use within subgroups of our study population. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox Proportional Hazards regression where the time axis was defined as months since CRC diagnosis and the outcome of interest was CRC death. Participants did not contribute to the risk set until they had completed the baseline questionnaire. HRs were used to compare participants with pre-diagnostic multivitamin use to those with no pre-diagnostic multivitamin use with respect to CRC-specific survival. We stratified baseline hazards by study population and adjusted for the covariates listed above. Before including fruit and vegetable consumption as a confounder, we assessed for effect modification by fruit and vegetable consumption. Lastly, we stratified our model by fruit and vegetable consumption and smoking status. All analyses were conducted using RStudio (version 2022.02.0). Statistical significance was assessed with a Wald type test and a p-value <0.05 was considered statistically significant.

Results

Among our study population, 3,107 (48.2%) had used multivitamins regularly pre-diagnostically, whereas 3,339 had not regularly used multivitamins pre-diagnostically. Compared to participants who did use multivitamins, participants who did not use multivitamins were slightly more likely to have low fruit and vegetable consumption (9.7% vs. 6.4%), were more likely to be male (55.3% vs. 46.8%), more likely to have listed high school completion as their highest level of attained education (40.8% vs. 29.1%), and were more likely to be current smokers (13.4% vs. 9.3%). Multivitamin users and non-users were similar with respect to age at diagnosis, body mass index, and tumor site. There were no marked differences by site of CRC or stage at diagnosis (**Table 1**).

We fit a stratified Cox PH model that adjusted for education, fruit and vegetable consumption, age, sex, smoking status, BMI, history of CRC screening, and stratified on study population. The estimated hazard ratio of CRC death for individuals who used multivitamins was 1.05 (95% CI: 0.94-1.18, $p=0.4$) compared to individuals who did not use multivitamins, suggesting no association with pre-diagnostic multivitamin use overall (**Table 2**). We explored including an interaction term with fruit and vegetable consumption and the terms were not statistically significant. In stratified analyses, we found no statistically significant associations between multivitamin use and CRC death among participants who consumed low, medium, or high amounts of fruits and vegetables, or among participants of never, former, and current smoking categories (**Table 3**).

Discussion

Main Findings

In this large, population-based study, we observed no associations of pre-diagnostic multivitamin use with CRC-specific survival. Although regular users of multivitamins were less

likely to have a history of smoking and consumed higher levels of fruits and vegetables, there was no evidence of effect modification by these health attributes with regard to the relationship of multivitamin use with CRC survival.

Interpretation of Findings

Previous studies have found minimal or no associations between supplement use and cancer survival.^{7,8} One study found no association with multivitamin use during adjuvant chemotherapy and overall survival among patients with stage III colon cancer (HR = 0.94, 95% CI: 0.77 to 1.15).⁷ Another study found a weak association between folic-acid multivitamin use and improved colon cancer survival (RR = 0.92, 95%CI: 0.86 to 1.00).⁸ Although there is minimal evidence on the benefits of multivitamin use, many patients diagnosed with cancer are interested in supplement use.³ However, this may divert patient's attention from other healthful behaviors post-diagnosis, such as pursuing exercise and a holistic diet.³ The null findings from this study may suggest that, among patients who use multivitamins, there may be other factors that impact their CRC survival. Among those with low fruit and vegetable consumption, we observed no improvement in CRC survival indicating that pre-diagnostic multivitamin use to supplement a healthier diet has no significant effect on CRC survival. For some patients, multivitamin use may be beneficial to their diet, but they may still have poor health overall, regardless of their fruit and vegetable consumption. Clinicians should provide individualized advice and resources to patients that help them achieve a healthful lifestyle.

Strengths & Limitations

The results of this study should be interpreted in the context of study limitations. One limitation of this study was that we relied on self-reported multivitamin use, as well as self-reported data on other health behaviors, leading to potential misclassification. We knew from

prior research that people who use multivitamins are more likely to engage in healthful behaviors, which warranted control for prior screening history, smoking, BMI, and fruit and vegetable consumption variables.² However, residual confounding from unknown variables may be present. Participants who were diagnosed with CRC were not enrolled until a period of time past their diagnosis date. Consequently, those who survived sufficiently long to complete baseline questionnaires and successfully enroll into the study may have been different than with individuals diagnosed with CRC who experienced a very short survival time with regard to pre-diagnostic health behaviors (e.g., multivitamin use). Additionally, we were not able to capture meaningful detail regarding the timing or formulation of pre-diagnostic multivitamin use. Likewise, we only were able to capture pre-diagnostic data that was collected at one time point, limiting generalizability of conclusions we can make relative to multivitamin use after CRC diagnosis.

Some strengths of this study are that it is a well characterized, population-based study. Data from baseline questionnaires allowed us to control for a variety of confounders.

Conclusion

We found no evidence of an association between pre-diagnostic multivitamin use and CRC survival. Additionally, stratifying by smoking and fruit and vegetable consumption did not affect the relationship between multivitamin use and CRC survival. Clinicians should discuss a variety of approaches for healthful activities individualized to the patient post CRC diagnosis.

Tables

Table 1. Characteristics of the study population at baseline by multivitamin (MV) use status

	MV Use: No (n=3,107) N (column %)	MV Use: Yes (n=3,339) N (column %)	Total (N=6,446) N (column %)
Fruit and Vegetable Consumption*			
Low	280 (9.7%)	195 (6.4%)	475 (8.0%)
Medium	1,683 (58.4%)	1,833 (60.5%)	3,516 (59.4%)
High	921 (31.9%)	1,003 (33.1%)	1,924 (32.5%)
Missing	223	308	531
Highest Level of Education Completed			
High School	1,247 (40.8%)	957 (29.1%)	2,204 (34.7%)
Some College	1,080 (35.3%)	1,169 (35.5%)	2,249 (35.4%)
College	731 (23.9%)	1,163 (35.4%)	1,894 (29.8%)
Missing	49	50	102
Age at Diagnosis (years)			
Mean (SD)	55.3 (11.7)	55.2 (11.9)	55.3 (11.8)
Median [Min, Max]	55.0 [15.0, 85.0]	55.0 [21.0, 86.0]	55.0 [15.0, 86.0]
Missing	12	10	22
Sex			
Male	1,717 (55.3%)	1,563 (46.8%)	3,280 (50.9%)
Female	1,390 (44.7%)	1,776 (53.2%)	3,166 (49.1%)
Smoking Status			
Never	1,292 (41.8%)	1,505 (45.2%)	2,797 (43.5%)
Former	1,386 (44.8%)	1,516 (45.5%)	2,902 (45.2%)
Current	416 (13.4%)	308 (9.3%)	724 (11.3%)
Missing	13	10	23
BMI (kg/m²)			
Mean (SD)	27.6 (5.69)	27.6 (6.08)	27.6 (5.90)
Median [Min, Max]	27.0 [9.00, 61.0]	26.0 [9.00, 64.0]	27.0 [9.00, 64.0]
Missing	85	53	138
CRC Site			
Proximal	1,010 (33.5%)	1,201 (37.1%)	2,211 (35.4%)
Distal	1,012 (33.6%)	992 (30.6%)	2,004 (32.1%)
Rectal	990 (32.9%)	1,046 (32.3%)	2,036 (32.6%)
Missing	95	100	195
CRC Stage			

Localized	537 (18.1%)	736 (22.7%)	1,273 (20.5%)
Regional	2,140 (72.2%)	2,161 (66.8%)	4,301 (69.4%)
Distant	285 (9.6%)	340 (10.5%)	625 (10.1%)
Missing	145	102	247

MV: multivitamin, BMI: body mass index, CRC: colorectal cancer

*Fruit and vegetable consumption: low = < 6 serving/week, medium = 6-28 servings/week, high = >28 servings/week

Table 2. Multivariate survival analysis (Cox model)

Adjustment Variable	Survival: # CRC deaths / n	HR (95% CI)*	p-value
Multivitamin Use			
No	615/2,676	ref	ref
Yes	676/2,860	1.05 (0.94, 1.18)	0.38

*Adjusted for education, fruit/veg consumption, age, sex, smoking status, BMI, history of CRC screening, and stratified by study

Table 3. Stratified hazard ratios of CRC death for multivitamin users

	Survival: # CRC deaths / n	Multivitamin HR* (95% CI)	p-value
Fruit and Vegetable Consumption^a			
Low	83/381	1.15 (0.74, 1.81)	0.53
Medium	713/2,857	0.98 (0.84, 1.13)	0.76
High	400/1,649	1.18 (0.97, 1.45)	0.10
Smoking Status^b			
Never	473/2,164	1.01 (0.83, 1.20)	0.98
Former	566/2,202	1.07 (0.91, 1.27)	0.41
Current	157/521	1.15 (0.83, 1.58)	0.41

^aAdjusted for education, age, sex, smoking status, BMI, history of CRC screening, and stratified by study

^bAdjusted for education, age, sex, fruit/veg consumption, BMI, history of CRC screening, and stratified by study

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