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The Association Between Prebiotic Fiber Supplement Use and Colorectal Cancer Risk and Mortality in the Women's Health Initiative

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Abstract

Background: Fiber-based prebiotic supplements are marketed for maintaining bowel health and promoting beneficial gut bacteria. However, the association between prebiotic supplement use and colorectal cancer (CRC) risk and mortality is unknown.

Methods: The association between prebiotic use and CRC risk and mortality was evaluated in postmenopausal women in the Women's Health Initiative study. Self-reported prebiotic use was documented at study enrollment. Adjudicated CRC cases and mortality were captured using medical and death records. Cox proportional hazards models were used to estimate the hazard ratio related to prebiotic use and CRC risk and mortality.

Results: In total, 3,032 CRC cases were diagnosed during an average 15.4 years of follow-up. Overall, 3.7% of women used a prebiotic with psyllium the majority fiber type. Use of any prebiotic supplement was not associated with CRC risk or mortality. The type of prebiotic supplement (none vs. insoluble or soluble) was not associated with CRC risk; however, use of insoluble fiber prebiotics compared to none was associated with higher CRC-mortality (HR: 2.79; 95%CI: 1.32-5.90; p=0.007). Likelihood ratio tests indicated no significant interactions between prebiotic use and other CRC risk factors including metabolic syndrome.

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Conclusion: Prebiotic fiber supplement use was not associated with CRC risk. Insoluble but not soluble prebiotic fiber use was associated with higher CRC-mortality. These findings do not support the promotion of prebiotic fiber supplements to reduce CRC risk or CRC-mortality.

Impact: Further investigation is warranted for findings regarding insoluble prebiotic fiber and higher CRC-mortality in post-menopausal women.

Keywords

Colorectal cancer; prebiotic; chemoprevention; dietary supplements; fiber

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer among women in the United States (US), accounting for approximately 8% of new female cancer cases annually (1). Fiber is often promoted as a dietary CRC prevention strategy, with daily intakes of ≥25 grams (2) recommended as part of a healthy diet (3). Prebiotics are defined as carbohydrates that are resistant to digestion and are instead fermented by gut microbiota in the colon; these can be both soluble and insoluble fibers in foods or supplements (4). Soluble prebiotic fibers form viscous gels when dissolved in water, whereas insoluble prebiotic fibers do not dissolve in or gel in water (5). Such isolated prebiotic fibers may have a protective effect in colorectal carcinogenesis as indicated in some studies (6–8). Prebiotics are widely available as over-the-counter dietary supplements, also labeled as fiber-containing bulk laxatives, and commonly are used to regulate bowel movements and alter digestive symptoms.

Fiber maintains a critical physiological role in digestion where it promotes healthy bowel functioning including reduced transit time and bulking of stool (9). Other potential protective mechanisms of fiber include fermentation of fiber in the colon by microbiota producing butyrate, a substrate which inhibits carcinogenesis and promotes normal homeostasis of the colonic epithelium (10,11). Metabolic syndrome (MetS), a clinical condition characterized by higher waist circumference, dyslipidemia, insulin resistance and hypertension, is related to CRC risk (12). MetS, independent of body mass index (BMI), is associated with an increased risk of CRC in women (13). Fiber may mitigate risk related to MetS through regulating systemic glucose and insulin responses (14). Calcium supplementation remains a common recommendation for the prevention of CRC (2,15) and may interact with supplemental fiber and impact the effect on recurrent adenomas in high risk individuals (16). Additionally, calcium supplementation, while not associated with CRC risk in the Women's Health Initiative (WHI) (17) has been previously inversely associated with CRC risk in observational studies and recent meta-analyses (18). Thus, both of these exposures warrant investigation as effect modifiers of any potential relationship between prebiotic supplements and CRC.

Epidemiological observational evidence generally supports the potential role for dietary fiber in CRC risk reduction (19,20). In a pooled analysis of two clinical trials, high dietary fiber intake in men, but not women, was associated with a lower odds of adenoma recurrence, a precursor for CRC (21). Recent analyses within WHI indicated a modest trend toward lower CRC risk with increasing intake of total dietary fiber, as well as soluble and

insoluble dietary fiber (22). Additionally, higher dietary fiber intake has been associated with higher CRC survival (23). Yet, this evidence has largely overlooked the role of supplemental prebiotic fiber. Nonetheless, increasing evidence is linking individual prebiotics to the regulation of inflammation and gut microbiota (24), as well as metabolic biomarkers, suggesting potential to favorably modulate CRC risk and potentially CRC outcomes (25).

Although efficacy studies remain limited in humans, approximately 2.0-3.3% of the US adult population report use of fiber-based prebiotic supplements (26). The majority of older adults who take fiber supplements report using the supplement to promote good colon health with many taking such supplements daily for five years or more (27). To date, few epidemiological studies have investigated use of prebiotic supplements and CRC risk (28,29), suggesting the need to more robustly evaluate the role these supplements in cancer outcomes. Despite prevalence data indicating frequent prebiotic use in women, current prebiotic marketing shifts and provider recommendations for selected use of prebiotic supplements (30), there is a distinct gap in the literature related to gender specific CRC risk and CRC-specific mortality and prebiotic use. Our objective was to examine the associations between prebiotic supplement use and CRC risk as well as CRC-specific mortality in the Women's Health Initiative cohort. We hypothesized that supplemental prebiotics would be associated with lower risk of CRC and CRC-specific mortality in post-menopausal women. We further hypothesized that this protective association would be attenuated in the presence of MetS.

MATERIALS AND METHODS

Study Sample

The WHI is a multi-center longitudinal study of post-menopausal women in the United States. Recruitment and enrollment methods have been published previously (31,32). In brief, 161,808 women were enrolled from 40 clinic sites throughout the U.S. between 1993-1998 and were followed for events including cancer and mortality. There are two major components of the WHI: an observational cohort study (OS, n= 93,676) and three clinical trials (CT, n= 68,132) including randomized trials of hormone therapy, a low-fat diet and calcium plus vitamin D supplementation. Women in OS and CT components completed comprehensive baseline examinations and were followed over time and were included in this analysis. Women with a history of CRC at enrollment or who developed CRC within the first year of follow-up (n= 923) or who were missing follow-up data (n= 690) were excluded from the analysis, leaving 160,195 women in the analytical cohort.

Exposure Assessment

Prebiotic use was captured at baseline on the current medications and dietary supplement forms. During the in-person clinic visit, the following questions were asked on the study questionnaires regarding use of prebiotic fiber supplements: 1) "Do you take bulk laxatives or fiber-containing medications?" and 2) "Do you use any medications to help you with digestion?". Women were able to write-in "other" on either form. Prebiotic use was categorized as 'user' if they reported use of any medication, digestive aid or other dietary

supplement containing fiber, determined by generic product name (e.g. psyllium, methylcellulose, polycarbophil, pectin, etc.). Based on the primary generic ingredient, the prebiotic supplement fiber type was categorized as soluble or insoluble as established in published literature. Absence of any reported use at baseline was categorized as 'non-user'.

Outcome Assessment

WHI participants were followed for outcomes through March 2018. Information on new CRC diagnoses was collected by self-report annually and adjudicated through medical chart review and centralized review by trained WHI physician adjudicators. Stage data for CRC diagnoses were matched to the SEER [Surveillance, Epidemiology, and End Results Program] database when available. Mortality and cause of death were determined by medical record and death certificate review (33). The primary outcomes for these analyses were CRC diagnosis and CRC-specific mortality. Time to CRC diagnosis was calculated from the date of study enrollment until recorded date of CRC diagnosis. Time to CRC-mortality was calculated as the time of study enrollment until the date of recorded death due to CRC. If a woman did not experience either a CRC or mortality outcome, her follow-up time was censored as last documented follow-up day.

Covariates

Other reported medications, including pharmaceutical-based laxatives, non-steroidal anti-inflammatory drugs, and aspirin, were coded separately. Dietary intake, including total dietary fiber was estimated through the administration of the previously validated WHI food frequency questionnaire for use as a covariate in the model (34). Neighborhood socioeconomic status (NSES; range: 0-100) was calculated as a summary measure of several dimensions of wealth and income using previously described methods (35). Additional information regarding demographics, physical activity, other medication use, medical history and use of supplemental calcium and/or vitamin D were completed through self-report questionnaires at baseline.

Statistical Analysis

Descriptive statistics of participants' baseline characteristics by current prebiotic users and non-users were obtained: comparisons of the baseline characteristics between the two groups were conducted using Chi-squared test for categorical variables and t-tests for continuous variables. Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI) for the association of prebiotic use and CRC risk and separately, CRC-mortality, with and without adjusting for potential confounders. The exposure for each model was overall prebiotic use (user vs. non-user) and categorical prebiotic supplement fiber type (insoluble vs. soluble). Analyses were performed for CRC risk, and separate CRC-mortality, within each prebiotic use category.

Likelihood ratio tests were utilized to compare models with and without interaction terms between prebiotic use and other factors associated with CRC in prior published work (36) including: baseline calcium supplementation, meeting dietary fiber recommendations, history of a colonoscopy, and age to determine potential effect modification. Concurrent use of calcium supplements was evaluated as binary (use and non-use). Meeting

recommendations for dietary fiber intake was categorized into fiber intake <25g (below recommendations) and ≥25g (at or above recommendations).

All models were adjusted for demographic and lifestyle characteristics including: study assignment (OS or CT and randomization arm), age, BMI, ethnicity and race, smoking status, alcohol intake, dietary fiber intake, total calcium and vitamin D intake, physical activity, NSES, aspirin use, family history of colorectal cancer, and history of: colonoscopy, hemoccult test, and adenoma removal. Other risk factors including red and processed meat intake, use of non-steroidal anti-inflammatory medication and other laxatives as well as CRC stage at diagnosis did not change crude HR estimates >10% and therefore were not included in final adjusted models. The proportional hazards assumption was tested by evaluating the residuals versus time in all models with Schoenfeld residuals and no violations were observed in any model. All statistical analyses were conducted using STATA 15.1 (StataCorp LLC, College Station, TX, USA). All tests were two sided and a p-value <0.05 was considered statistically significant.

Sensitivity Analysis

Earlier work from the WHI suggested that metabolic disruption was associated with the development of CRC (37). To evaluate the association of prebiotic supplementation in presence of MetS on CRC risk, a sensitivity analysis was completed using adjusted Cox proportional hazard models in a subsample of participants. The presence of MetS was calculated for the sample using available laboratory values collected on 6% of the sample (n= 5,370) at baseline. Clinical MetS was defined using the Third Report of the National Cholesterol Education Program's Adult Treatment Panel (ATP III) (38). Presence of MetS was determined if any individual met any three or more of the following: 1) waist circumference >88.0cm; 2) serum triglycerides ≥150mg/dL; 3) blood pressure ≥130/85mmHg; 4) HDL cholesterol <50mg/dL; and 5) serum glucose ≥100mg/dL.

RESULTS

A total of 3,032 CRC cases were diagnosed during an average 15.4 years of follow-up. Overall, 35,746 women died during follow up, of which, 841 were due to CRC. Overall, prebiotic users (n= 5,944, 3.7%) were predominately non-Hispanic whites, non-smokers, with a normal BMI. The majority of prebiotic supplement used was soluble fiber (85.4% for CRC cases and 88.2% for non-cases). The majority (87.8%) of prebiotic users did not meet recommendations to consume ≥ 25g/day of dietary fiber and the majority of prebiotic users had a history of a colonoscopy (72.4%). In comparison, 89.7% of non-users did not meet dietary fiber recommendations and 45.7% previously had a colonoscopy (Table 1).

Stage data obtained via the SEER database was available for 87.5% (n= 2,653) of CRC cases (Table S1). The majority of women (53.1%; n= 1,408) were diagnosed with stage III-IV CRC with the remaining women diagnosed at stage I-II CRC (44.9%, n= 1,192). Of the CRC cases which used any prebiotic (n= 107), over half of the women who used soluble fiber prebiotic supplements were diagnosed with stage I-II CRC (51%, n= 48) whereas the majority of women who used insoluble fiber prebiotic supplements were diagnosed with stage III-IV CRC (57%, n= 8). Among all women, psyllium was the most common prebiotic

fiber reported (74% of users), followed by polycarbophil (13%) and methylcellulose (9%) (Table 2).

Unadjusted models indicated no statistically significant association between prebiotic supplement use and CRC risk. Estimates were similar in the adjusted models (HR: 1.13; 95%CI: 0.93-1.39) (Table 3). Prebiotic supplement fiber type (none vs. insoluble or soluble) was not associated with CRC risk. There were no statistically significant interactions between prebiotic use and other CRC risk factors including calcium supplementation (p= 0.14), meeting dietary fiber recommendations (p= 0.13), previous history of a colonoscopy (p= 0.28) or age (p= 0.16).

There was no overall association between the use of any prebiotic supplements and CRC mortality in unadjusted and adjusted models (Table 3). In unadjusted models of prebiotic supplement fiber type, insoluble fiber had a significant positive association with CRC-mortality compared to soluble fiber (HR: 2.56; 95%CI:1.22-5.40, p= 0.013). After adjustment, this relationship remained (HR: 2.79; 95%CI: 1.32-5.90; p= 0.0007). Likelihood ratio tests indicated no statistically significant interactions present between CRC-mortality and prebiotic use and calcium supplementation (p= 0.86), meeting dietary fiber recommendations (p= 0.17), previous history of a colonoscopy (p= 0.39), or age (p= 0.81).

There was no association between prebiotic supplement use and CRC risk in the subsample of individuals with laboratory data available to evaluate the presence or absence of clinical MetS (Table 4). In women with MetS and available covariate data (n= 796), there was a non-significant higher risk for CRC in prebiotic users (HR: 2.98; 95%CI: 0.73-12.15). Likelihood ratio tests indicated no interaction between CRC risk and prebiotic use and MetS (p= 0.08).

DISCUSSION

Overall, when assessing both soluble and insoluble prebiotic use, there was no association with CRC risk in post-menopausal women within the WHI. Dietary fiber intake, calcium supplementation, previous history of a colonoscopy, age nor MetS did not significantly modulate the associations observed between prebiotic use and increased CRC risk or mortality. Importantly, use of insoluble fiber prebiotics compared to soluble fiber prebiotics was strongly associated with CRC-specific mortality.

Low prevalence of prebiotic use in the WHI cohort may have influenced observed associations, but reported use was comparable to nationwide prevalence (26). At baseline, prebiotics were reported primarily as a ‘fiber-containing bulk laxatives’ within the WHI. This reflects product marketing trends of the era. Recent rebranding and marketing currently characterize these products as prebiotics. While previous estimates have indicated that prebiotic use has remained stable over the past decade (26), recent analyses indicate that the use of prebiotics increased four-fold from 2007-2012 (39). Indications for prebiotic use include the management of digestive symptoms as well as increasing overall dietary fiber intake. Further, gastrointestinal (GI) symptom burden may influence use. The most commonly reported prebiotic supplements (psyllium, polycarbophil, and methylcellulose),

have previously demonstrated prebiotic activity, evidenced by modulation of the gut microbiota and production of butyrate (40–42). The estimated average daily dose of supplemental fiber from available psyllium labeling instructions in this sample was 5 grams (43), increasing daily total fiber intake to 22 grams in psyllium users. This level of total fiber intake is just below current fiber recommendations (44).

Given these estimates of average exposure in WHI women, we would have expected, contrary to what we found, that supplementation was sufficient to demonstrate a biological effect associated with healthy gut microbiota and potentially a lower CRC risk and CRC-mortality. However, our data do not provide specifics on regularity of use or indication. The findings presented here could be due to reverse causality wherein women who used prebiotics were already at increased risk for CRC because of GI symptoms that may have indicated the need for a colonoscopy. In fact, women who reported using prebiotics in our sample were more likely to previously have had a colonoscopy or an adenoma; therefore, it is possible that women were taking such prebiotic supplements to manage GI symptoms. These same women also may be predisposed to CRC and subsequently, prone to poorer CRC outcomes.

The finding related to insoluble fiber prebiotics and CRC-specific mortality is interesting and begs further investigation. The broader literature-based evidence related specifically to insoluble fiber and CRC remains inconsistent and is limited for supplemental insoluble prebiotics. Previous evaluation in the Nutrition Examination Survey (NHANES) III showed a protective effect for CRC mortality comparing high *dietary* insoluble fiber intake to low intake (45), which is contrary to our findings regarding supplemental insoluble fiber prebiotics. One large wheat bran fiber (an insoluble fiber) supplement trial in older (> 50 years) adults with a previous history of colonic polyps did not show any protective effect from insoluble fiber against recurrent colorectal adenomas (46). Mechanistically, *in vitro* findings suggest that insoluble fiber supplements may downregulate CRC promoting genes and upregulate CRC inhibiting genes (47), while other studies indicated that some insoluble fibers may stimulate colonic cell proliferation and carcinogenesis when combined with carcinogen exposure (48). Further, intake of insoluble fiber may impact CRC outcomes through drastically changing the primary site of microbiota fermentation in the colon which may shift butyrate concentrations and colonic microbiota composition (49,50).

Contrary to our hypothesis, use of a prebiotic supplement did not show any statistically significant association with CRC risk in women with or without MetS. Similarly, calcium supplementation and dietary fiber intake, previous history of a colonoscopy, and age were not effect modifiers in relation to prebiotic use and CRC risk or mortality.

Strengths and Limitations

This study is among the first to provide evidence of supplemental prebiotics and CRC risk and mortality. The WHI cohort provided rich data on lifestyle, medication use, medical history and dietary intake to adjust for confounding of known CRC risk factors. Effect modification of MetS on prebiotic supplement use and CRC-risk was able to be evaluated with available biomarker data for clinical MetS.

We were not able to further investigate duration of exposure and indication for use due to the limited number of total prebiotic users who were recruited in the mid-1990s. However, dietary supplement use is commonly a habitual regimen where users take their chosen products daily for many years (51). Therefore, using available self-report data from a single time point is a common approach in evaluating association between dietary supplements and CRC risk (18). The significant finding of insoluble fiber prebiotic supplement use with CRC mortality is limited in its generalizability as our data were based on nine CRC deaths among insoluble prebiotic users. Further, we were limited in our analyses regarding the role of MetS on prebiotic supplement use and CRC-mortality due to six CRC-specific deaths in the MetS subsample of which one reported insoluble prebiotic use. Additionally, the available data was limited with consideration to CRC site and subtype and therefore, we were not able to evaluate this marker of clinical importance in the presented analyses. Women diagnosed with stage III-IV CRC more commonly used insoluble prebiotic fiber supplements, however, CRC stage did not change the magnitude of any estimates in any model. Thus, the estimates seen in our analysis may be the result of residual confounding that could not be accounted for with available data. While this association is statistically significant, this may not necessarily be clinically significant.

Common primary treatment for symptoms related to colonic diverticulitis, chronic idiopathic constipation and irritable bowel syndrome is fiber therapy, either through dietary modifications or prebiotic supplements (52–54). These conditions demonstrate similar symptoms and underlying etiology and are potential precursors to CRC (55). Practitioners may decide to recommend prebiotic supplements to patients due to the potential digestive benefits and to mediate bowel symptoms (30). Caution about prescribing insoluble fiber prebiotics for CRC prevention specifically should be exercised given our current findings which will require replication. Our findings do not support use of prebiotic supplements to reduce risk of CRC or CRC-specific mortality among post-menopausal women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

CRC	colorectal cancer
WHI	Women’s Health Initiative
MetS	metabolic syndrome

BMI	body mass index
NSES	Neighborhood socioeconomic status
SEER	Surveillance, Epidemiology, and End Results Program

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Table 1.

Baseline characteristics and colorectal cancer risk factors for Women's Health Initiative (1993-1998) participants stratified by use of any fiber supplement (n= 160,195).

	Fiber Supplementation		
Characteristic[a]	**Non-User (n= 154,251)**	**User (n= 5,944)**	***P*-value**[b]
Age, years	63.2 (7.2)	65.1 (7.1)	<0.00001
Neighborhood Socioeconomic Status[c]	75.6 (8.7)	76.6 (7.6)	<0.00001
Ethnicity[d]			<0.0001
White, Non-Hispanic	127,026 (82.4)	5,422 (91.2)	
Black or African American	14,142 (9.2)	250 (4.2)	
Other/Unknown	12,688 (8.2)	260 (4.4)	
Body Mass Index Category			<0.0001
Normal Weight (<24.9 kg/m^2)	53,564 (34.7)	2,334 (39.3)	
Overweight (25.0 - 29.9 kg/m^2)	53,127 (34.4)	2,054 (34.6)	
Obesity (≥30.0 kg/m^2)	46,195 (29.9)	1,517 (25.5)	
Lifestyle Factors			
Physical Activity (METhrs/wk)	12.4 (13.7)	13.6 (13.9)	<0.00001
Alcohol Intake (g/day)	3.7 (1.6)	3.7 (1.7)	0.05
Smoking (pack years)			0.70
Never Smoked	77,741 (50.4)	2,967 (49.9)	
<5 years	21,538 (14.0)	844 (14.2)	
5 - 20 years	21,364 (13.9)	840 (14.1)	
≥ 20 years	28,051 (18.2)	1,111 (18.7)	
Meeting Fiber Recommendations, ≥25g/day	15,849 (10.3)	723 (12.1)	<0.0001
Dietary Intake			
Total Energy (kJ/day)	1,625.9 (718.9)	1616.0 (649.9)	0.30
Dietary Fiber (g/day)	15.9 (7.2)	16.7 (7.0)	<0.00001
Dietary Soluble Fiber (g/day)	4.3 (1.9)	4.5 (1.9)	<0.00001
Dietary Insoluble Fiber (g/day)	11.5 (5.3)	12.2 (5.2)	<0.00001
Vegetables (servings/day)	2.2 (1.3)	2.3 (1.3)	<0.00001
Fruits (servings/day)	1.9 (1.2)	2.0 (1.2)	<0.00001
Red Meat (servings/day)	0.7 (0.6)	0.7 (0.5)	<0.00001
Processed Meat (servings/day)	0.2 (0.2)	0.2 (0.2)	0.03
Dietary Calcium (mg/day)	814.6 (468.2)	848.5 (461.2)	<0.00001
Total Calcium[e] (mg/day)	1165.2 (742.8)	1325.0 (750.7)	<0.00001
Dietary Vitamin D (mcg/day)	4.3 (3.1)	4.5 (3.1)	<0.00001
Total Vitamin D[e] (mcg/day)	9.2 (7.0)	11.0 (7.2)	<0.00001
Concurrent Medication and Supplement Use			
Saline or Stimulant Laxative	2,281 (1.5)	358 (6.0)	<0.0001
Aspirin	32,577 (21.1)	1,939 (32.6)	<0.0001

Characteristic[a]	Fiber Supplementation		
	Non-User (*n*= 154,251)	User (*n*= 5,944)	*P*-value[b]
Non-Steroidal Anti-Inflammatory (NSAIDs)	29,088 (18.9)	1,577 (26.5)	<0.0001
Multivitamin Supplement	59,521 (38.6)	3,030 (51.0)	<0.0001
Calcium Supplement	34,136 (22.1)	1,734 (29.2)	<0.0001
Vitamin D Supplement	5,990 (3.9)	344 (5.8)	<0.0001
Medical History			
Family History of CRC	23,231 (15.1)	1,021 (17.2)	<0.0001
Colonoscopy	73,213 (45.7)	4,304 (72.4)	<0.0001
Adenoma Removal[f]	12,263 (7.6)	954 (16.0)	<0.0001
Hemoccult Blood Test	107,966 (67.4)	4,932 (83.0)	<0.0001
Presence of Metabolic Syndrome[g]	1,094 (21.0)	28 (17.9)	0.36

[a] Continous variables reported as mean (standard deviation), categorical variables reported as frequency and (percent). Not all values may add up to 100% due to rounding or missing data; all missing data <10% unless otherwise specified.

[b] p-value for continuous variables determined by t-test; p-value for categorical variables determined by Chi-squared test

[c] Neighborhood Socioeconomic Status is a summary score that is a standardized sum of 6 established z-scores related to census data (35) with higher scores indicating better socioeconomic status. Percent missing data: 10% (n= 16,030).

[d] Other ethnicity contains Hispanic/Latino, American Indian/Alaskan Native, Asian/Pacific Islander and unknown.

[e] Sum of intake from diet and supplement sources.

[f] Only individuals with a previous history of colonoscopy were queried about adenoma removal.

[g] Biospecimens were only collected on a subset of population (n=5,370). Presence of Metabolic Syndrome criteria: 3 or more of the following conditions: waist circumference >88.9 cm; serum triglycerides ≥150 mg/dL, blood pressure ≥130/85 mmHg; HDL cholesterol <50 mg/dL; serum glucose ≥100 mg/dL.

Table 2.

Prebiotic supplement generic product name and fiber type for users of prebiotic supplements among participants of the Women's Health Initiative, 1993-1998 (n= 5,944).

	n	% of prebiotic supplement users[a]	Fiber Type
Psyllium	4,383	73.74	Soluble
Polycarbophil	798	13.43	Soluble
Methylcellulose	551	9.27	Insoluble
Wheat Bran	128	2.15	Insoluble
Pectin	37	0.62	Soluble
Resistant Starch	25	0.42	Soluble
Soy Fiber	14	0.24	Insoluble
Guar Gum	5	0.08	Soluble
Beta-Glucan	3	0.05	Soluble

[a]All values may not add up to 100% due to rounding

Table 3.

Association between prebiotic fiber supplement use and CRC risk and CRC-specific mortality within the Women's Health Initiative, 1993-2018.

		CRC Risk		CRC-Specific Mortality	
	n	**Crude[a] HR (95% CI)**	**Adjusted[b] HR (95% CI)**	**Crude[a] HR (95% CI)**	**Adjusted[b] HR (95% CI)**
Prebiotic Supplement Use					
None	112,638	1.0	1.0	1.0	1.0
Any	4,654	1.13 (0.93-1.39)	1.12 (0.91-1.38)	1.21 (0.83-1.76)	1.21 (0.83-1.77)
Prebiotic Supplement Fiber Type					
None	112,638	1.0	1.0	1.0	1.0
Soluble	4,119	1.10 (0.88-1.36)	1.08 (0.87-1.34)	1.04 (0.68-1.22)	1.03 (0.67-1.58)
Insoluble	535	1.42 (0.84-2.40)	1.48 (0.87-2.51)	2.56 (1.22-5.40)[c]	2.79 (1.32-5.90)[d]

[a]Only subjects with non-missing values for all variables considered as confounders in adjusted analysis are included in model.

[b]All models adjusted for age, race/ethnicity, neighborhood socioeconomic status, body mass index, total dietary fiber intake, total calcium intake, total vitamin D intake, total alcohol intake, smoking pack years, physical activity (METhrs/week), aspirin use, family history of colorectal cancer, and history of: colonoscopy, hemoccult test, and adenoma removal, as well as study component (OS or CT and randomization assignment).

[c]p= 0.013

[d]p= 0.007

Table 4.

Cox proportional hazard ratios of association of prebiotic fiber supplement use and CRC risk with presence of metabolic syndrome (MetS) within the Women's Health Initiative, 1993-2018.

	Metabolic Syndrome			No Metabolic Syndrome		
Prebiotic Supplement Use	n	Crude[a] HR (95%CI)	Adjusted[b] HR (95% CI)	n	Crude HR[a] (95%CI)	Adjusted[b] HR (95% CI)
None	777	1.0	1.0	2881	1.0	1.0
Any Use	19	2.24 (0.57-8.74)	2.98 (0.73-12.15)	99	1.80 (0.56-5.77)	1.98 (0.60-6.55)
p-value		0.25	0.13		0.33	0.26

[a]Only subjects with non-missing values for all variables considered as confounders in adjusted analysis are included in model

[b]All models adjusted for age, race/ethnicity, neighborhood socioeconomic status, body mass index, total dietary fiber intake, total calcium intake, total vitamin D intake, total alcohol intake, smoking pack years, physical activity (METhrs/week), aspirin use, family history of colorectal cancer, and history of: colonoscopy, hemoccult test, and adenoma removal, as well as study component (OS or CT and randomization assignment).