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Inverse associations of dietary fiber and menopausal hormone therapy with colorectal cancer risk in the Multiethnic Cohort Study

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Abstract

In the Multiethnic Cohort Study, we previously reported that dietary fiber intake was inversely associated with colorectal cancer risk in men only. In women, the inverse relationship was weaker and appeared to be confounded by menopausal hormone therapy (MHT). We re-examined this observation with a greatly increased power. Using Cox proportional hazards models, we analyzed data from 187,674 participants with 4,692 cases identified during a mean follow-up period of 16 years. In multivariable-adjusted models, dietary fiber intake was inversely associated with colorectal cancer risk in both sexes: HR = 0.73, 95% CI: 0.61–0.89 for highest vs. lowest quintile, p_{trend} = 0.0020 in men and HR = 0.76, 95% CI: 0.62–0.91, p_{trend} = 0.0067 in women. Postmenopausal women who ever used MHT had a 19% lower risk of colorectal cancer (95% CI: 0.74–0.89) compared to MHT never users. In a joint analysis of dietary fiber and MHT, dietary fiber intake was associated with a lower colorectal cancer risk in MHT never users (HR = 0.75, 95% CI: 0.59–0.95, p_{trend} =0.045), but did not appear to further decrease the colorectal cancer risk of MHT ever users (p_{trend} = 0.11). Our results support the overall protective roles of dietary fiber and MHT against colorectal cancer and suggest that dietary fiber may not lower risk further among women who ever used MHT. If confirmed, these results would suggest that MHT and dietary fiber may share overlapping mechanisms in protecting against colorectal cancer.

Keywords

colorectal cancer; dietary fiber; menopausal hormone therapy; multiethnic population

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[4]Deceased

Introduction

Dietary fiber intake has often been linked to a lower risk of colorectal cancer in population-based studies[1,2], confirming the hypothesis first proposed by Burkitt in 1971.[3] The 2007 World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) expert report concluded that the evidence of a protective effect of dietary fiber on colorectal cancer was “probable”.[4] In 2011, the Continuous Update Project (CUP) of the WCRF/AICR re-examined the association of dietary fiber with colorectal cancer.[5] Based on 15 cohort studies, a meta-analysis showed a 10% decreased risk for each increase of 10g/day of dietary fiber, and this effect was apparent in men and women. Consequently, the CUP expert panel upgraded the evidence on the role of dietary fiber in colorectal cancer etiology from “probable” to “convincing”. Randomized trials found that a high dietary fiber diet did not affect the recurrence of colorectal adenoma, precursors of most colorectal cancer,[6–9] but none of the trials was eligible for inclusion in the CUP systematic literature review.

In a previous analyses of the Multiethnic Cohort (MEC) after an average 7.3 years of follow-up with 2,110 colorectal cancer cases, which was included in the CUP, we found a 38% lowered risk (95% Confidence Interval (CI) for Hazard Ratio (HR): 0.48–0.79) in the highest intake quintile among men, but a 12% reduction (95% CI for HR: 0.67–1.14) among women (compared to 25%, 95% CI: 0.61–0.92, before adjustment for other lifestyle factors).[10] In our analysis, menopausal hormone therapy (MHT) use, which was common at the time the cohort was assembled (being reported by 45% of the MEC female participants), appeared to be a strong confounder of the association in women. MHT use has been associated with a decrease in colorectal cancer risk in several studies[11–15] including a randomized trial of estrogen plus progestin in postmenopausal women.[16] Therefore, in the present study, we took advantage of a longer follow-up period (average 16 years), updated information on MHT use form follow-up questionnaires and a two-fold greater number of incident cases (n = 4,692) to further examine the sex-specific association of dietary fiber with colorectal cancer and its interaction with MHT use based on baseline and follow-up information.

Material and Methods

Study population

The Multiethnic Cohort (MEC) was established in Hawaii and California (mostly in Los Angeles County) to investigate the association of lifestyle and genetic factors with cancer and other chronic diseases.[17] It was designed to include adults aged 45–75 years from five targeted ethnic/racial groups: African American, Native Hawaiian, Japanese American, Latino, and white. More than 215,000 adults entered the cohort by completing a 26-page self-administered mailed questionnaire between 1993 and 1996. The primary sampling source was the drivers’ license files in both states. The institutional review boards at the University of Hawaii and the University of Southern California approved the study protocol.

For the current analyses, we excluded participants who were not in one of the five targeted ethnic groups (n = 13,987), had a previous colorectal cancer diagnosis reported on the baseline questionnaire (n = 2,251) or identified from the tumor registries (n = 300), reported

implausible dietary intakes based on energy and macronutrients (n = 8,137)[18], or had missing information on MHT use among women (n = 3,275). Therefore, the analyses included 187,674 participants. In multivariate-adjusted models, we further excluded participants with missing information on history of intestinal polyps, smoking, body mass index (BMI), physical activity, non-steroidal anti-inflammatory drug use, and multivitamin use (n = 19,859), resulting in 167,815 participants remaining.

Assessment of dietary fiber intake and MHT use

Dietary intake at baseline was assessed by a quantitative food frequency questionnaire (QFFQ) containing questions on more than 180 items.[17] The QFFQ was developed from a 3-day food records kept by 60 men and women in each ethnic group. A calibration study was conducted and showed satisfactory correlations between the QFFQ and three repeated 24-hour recalls for all ethnic-sex groups.[19] Correlation coefficients for dietary fiber densities (grams of dietary fiber per 1,000 kcal per day) ranged from 0.68 to 0.79. Daily nutrient intakes from the QFFQ were calculated using the food composition table developed and maintained at the University of Hawaii Cancer Center for use in the MEC.

The baseline questionnaire included questions about the use of MHT. Women were asked to indicate whether they ever took estrogen or progesterone for menopause or other reasons. Information on MHT use was also collected in the first (1999–2002) and second (2003–2007) follow-up questionnaires. In the current study, we defined MHT ever users as women who were currently taking estrogen, with or without progesterone, or used to take it but then stopped, using responses to the baseline and follow-up questionnaires.

Identification of colorectal cancer cases

Incident cases of colorectal cancer were identified by linkage to the Surveillance, Epidemiology, and End Results (SEER) Program cancer registries covering Hawaii and California. Deaths were identified by linkage to death-certificate files in both states and the National Death Index. Case and death ascertainment was complete through December 31, 2012. Cases in this study were limited to participants diagnosed with invasive adenocarcinoma of the large bowel (n = 4,692) and were categorized according to anatomical subsites using International Classification of Disease (ICD)-O2 codes: C18.0–C18.5 for right colon, C18.6–C18.7 for left colon, and C19.9 and C20.9 for rectum. During an average follow-up period of 16 years, 3,599 colon and 1,058 rectal cancer cases were identified, while 35 cases had synchronous tumors at both sites.

Statistical analysis

Dietary fiber intake values, expressed as energy densities (g/1,000 kcal/day), were divided into quintiles based on the distributions of intakes among all participants. We estimated hazard ratios and 95% confidence intervals from Cox proportional hazards models using age as the time metric. Base models were adjusted for age at cohort entry and ethnicity as covariates. Multivariate models were further adjusted for a number of additional covariates added to the log-linear model component: family history of colorectal cancer (yes/no), history of colorectal polyp (yes/no), BMI (<25, 25–<30, ≥30 kg/m^2), pack-years of cigarette smoking (continuous), multivitamin use (yes/no), non-steroidal anti-inflammatory drug use

(yes/no), physical activity (hours spent in vigorous work or sports per day), menopausal status and MHT use (premenopausal; postmenopausal: never; past; current use) as a time-dependent variable for women only, and total energy (log transformed kcal/day). In addition, adjustment was also done for the following dietary variables: alcohol consumption (g/day), red meat (g/1,000 kcal/day), calcium (mg/day from food and supplements), folate (μg/day from food and supplements), and vitamin D (IU/day from food and supplements). These covariates were selected because they have been shown consistently in the literature to be associated with colorectal cancer risk or were identified as confounders in our study. MHT use was modeled as a time-dependent variable using information from the baseline questionnaire (1993–1996), as well as from the first (1999–2002) and second (2003–2007) follow-up questionnaires, using a counting process where multiple records were created per person, corresponding to different surveys. Women who did not report their menopausal status but were older than 55 years at cohort entry were assumed to be postmenopausal (n = 5,814). For premenopausal women (n = 16,035) including those aged 55 years or younger with missing menopausal status at cohort entry, records were split at age 55, assigning the first part to premenopausal and the latter part to postmenopausal. HRs were estimated for MHT past, current, and ever use, estrogen-alone and estrogen plus progesterone use, and ≤2, 3–9, and ≥10 year use, compared to never use among postmenopausal women. Type and duration of MHT use were updated as time-dependent variables based on follow-up information. In multivariate models for MHT use, dietary fiber (g/1,000 kcal/day) was included as a covariate. Trend tests were conducted by inclusion of a continuous variable in the model assigned the sex- and ethnic-specific median values within the appropriate quintile. We ran the models for colorectal, right colon, left colon, and rectal cancer, separately.

We investigated whether the association of dietary fiber intake with colorectal cancer risk varied by sex, ethnicity, and MHT use among women. In joint analyses of dietary fiber and MHT use among women, dietary fiber intakes were divided into quintiles based on the distribution among women. Test for interaction were based on the Wald statistics for cross-product terms using trend variables. All analyses were repeated using dietary fibers values calibrated to the average from 24-hour recalls to correct for measurement error.[19] All analyses were conducted using SAS statistical software, version 9.4 (SAS Institute, Inc., Cary, North Carolina).

Results

Table 1 presents the distributions and means for the study covariates by quintiles of dietary fiber intake. Men and women with high intake of dietary fiber were older, less likely to smoke, more likely to take multivitamins, to be more physically active, and to have a lower BMI than those with low intake of dietary fiber. They also consumed less alcohol and red meat and more calcium, folate, and vitamin D. Women in the high intake groups were more likely to use MHT. Similar relationships were found both in MHT ever users and never users among women (Supplementary Table 1).

The HRs for colorectal cancer by quintiles of dietary fiber intake are shown in Table 2. Higher intake of dietary fiber was associated with a lower risk of colorectal cancer in both

men (HR = 0.61, 95% CI: 0.53–0.70 for highest vs. lowest quintile, $p_{trend} < 0.0001$) and women (HR = 0.73, 95% CI: 0.63–0.85, $p_{trend} < 0.0001$) with adjustment for age and ethnicity. These base models were rerun among participants without missing covariate and the risk estimates did not change (data not shown). Multivariate adjustment for age, ethnicity, total energy intake, multivitamin use, and the non-dietary variables only slightly weakened the association (data now shown). Further adjustment for dietary variables and MHT use in women still resulted in significant inverse associations for both sexes (HR = 0.73, 95% CI: 0.61–0.89, $p_{trend} = 0.0020$ in men; HR = 0.76, 95% CI: 0.62–0.91, $p_{trend} = 0.0067$ in women). Although the difference in HRs between men and women for the dietary fiber-colorectal cancer association was smaller than in the previous MEC report where sex-specific quintiles were used,[10] the inverse association was still weaker in women than in men ($p_{interaction} = 0.039$). In addition, all four higher quintiles of dietary fiber showed a significant decrease in risk compared to the lowest quintile in men, while only the HR for the highest quintile was statistically significant in women. In the anatomical subsite analyses (Table 2), the association of dietary fiber with cancer of the right colon appears to be less strong compared to that of the left colon and rectum in men. The same pattern was observed in women.

Table 3 shows the associations between MHT use and colorectal cancer risk among women. MHT past and current users had a lower risk of colorectal cancer compared to MHT never users (HR = 0.87, 95% CI: 0.78–0.97 and HR = 0.75, 95% CI: 0.66–0.84, respectively) with multivariate adjustment. The inverse association was seen for both estrogen alone use (HR = 0.85, 95% CI: 0.76–0.94) and estrogen plus progesterone use (HR = 0.76, 95% CI: 0.68–0.86). MHT use of three years or longer was associated with a lower risk of colorectal cancer. Decreased risk with MHT use was found for all three subsites with a stronger association for the rectum (HR = 0.67, 95% CI: 0.54–0.83 for ever vs. never users) and left colon (HR = 0.78, 95% CI: 0.65–0.94) than for the right colon (HR = 0.89, 95% CI: 0.78–1.01).

In analyses of the joint effect of dietary fiber and MHT use on colorectal cancer risk among women (Table 4), a dose-dependent inverse association with dietary fiber was apparent among never users of MHT (HR = 0.75, 95% CI: 0.59–0.95 for highest vs. lowest quintile, $p_{trend} = 0.045$). Overall, MHT ever users had a 19% lower risk of colorectal cancer (95% CI: 0.74–0.89) compared to MHT never users as shown in Table 3. At each level of dietary fiber intake, ever users of MHT appeared to have a lower colorectal cancer risk than never users, whereas there was no further decrease in risk of colorectal cancer with higher intake of dietary fiber among MHT ever users ($p_{trend} = 0.11$). A similar pattern was found for left colon cancer. When analyzing the data for MHT past (n = 14,655) and current users (n = 38,138) separately, estrogen-alone (n = 25,502) and estrogen plus progesterone users (n = 27,291) separately, and by duration of MHT use (<3 years, n = 18,828; ≥3 years, n = 33,089), there was no indication that the dietary fiber-colorectal cancer relationship differed between subgroups ($p_{interaction} > 0.6$) (data not shown).

In ethnic-specific analyses (Table 5), no heterogeneity of effect on colorectal cancer risk was suggested for dietary fiber across ethnicities either in men ($p_{interaction} = 0.26$) or women ($p_{interaction} = 0.36$). Among postmenopausal women, a decreased risk with current MHT use

was found in Japanese Americans and whites, but not in the other ethnic groups ($p_{interaction}$ = 0.049).

The analyses using calibrated dietary fiber intake produced similar results to those using uncalibrated values (data not shown). We also assessed the risk of colorectal cancer according to food sources of dietary fiber (fruits, vegetables, grains, and legumes) (Supplementary Table 2). The inverse association with colorectal cancer was only found for dietary fiber from vegetables in men (HR = 0.81, 95% CI: 0.66–0.98, p_{trend} = 0.047), although the HRs for the highest quintiles were below 1.0 for most of the other food sources of dietary fiber in both men and women.

Discussion

In this analysis in the MEC, we observed an inverse association between dietary fiber and colorectal cancer in both sexes. Among postmenopausal women, ever users of MHT had a lower risk of colorectal cancer compared to MHT ever users, and dietary fiber did not appear to further reduce their risk. In both sexes, the inverse association was stronger for the left colon and rectum than for the right colon, which is consistent with the CUP meta-analysis[5]. We also found no evidence for differences in the fiber-colorectal cancer association among the five racial/ethnic groups of the MEC in both men and women. The current findings support the conclusion on dietary fiber and colorectal cancer from the Continuous Update Project of the WCRF/AICR, along with that of other more recent prospective studies[20,21], including the updated analysis confirming the previous findings from the European Prospective Investigation into Cancer and Nutrition.[22]

Besides the MEC, two cohort studies in Scandinavia[20] and Japan[23] reported a stronger inverse association in men than in women. It is unclear why the association was weaker in women in these studies. Colorectal cancer is more common in men than in women in the United States.[24] Indeed, in our analysis in the MEC, men had a 43% higher risk compared to women with adjustment for age and ethnicity. MHT use, estrogen alone or with progestin, has been proposed to explain the sex-differential in incidence and the gender discrepancy in the dietary fiber-colorectal cancer association.[10,20,25] Since in the current study we observed a similar risk reduction with dietary fiber in MHT never users as in men, MHT use may have also accounted for the weaker fiber-colorectal cancer association among women overall when found in past studies.

It is also notable that while a higher intake of dietary fiber was related to a lower colorectal cancer risk in MHT never users, there appeared to be no further decrease in risk with higher dietary fiber intake among MHT ever users. These women had a lower risk compared to MHT never users regardless of dietary fiber consumption level. In other words, the protective effect of MHT appears to trump that of dietary fiber. Whether this observation reflects overlapping mechanisms is an interesting possibility that remains to be explored.

Data regarding the role of sex hormones in colorectal cancer are conflicting.[26–28] A protective effect of postmenopausal hormone use against colorectal cancer has been supported by a substantial number of studies[11–15,29] including meta-analyses.[30,31] The

Women's Health Initiative (WHI) Clinical Trial found that randomization to estrogen plus progestin therapy lowered colorectal cancer risk.[16] However, in the WHI Clinical Trial, randomization to estrogen-alone therapy had no effect on lowering colorectal cancer risk, and tumors in the estrogen plus progestin group were more advanced compared with the placebo group.[16,32] Recently, the WHI Clinical Trial reported an inverse association between endogenous estrogen levels and colorectal cancer risk among women who were not assigned to the estrogen-alone or estrogen plus progestin intervention groups,[33] while increased risk with endogenous estrogen levels has been reported in the WHI Observational Study.[34] Other studies found a positive[35] or no association[36] between endogenous estrogen and colorectal cancer risk in postmenopausal women. Dietary fiber has been suggested to reduce colorectal cancer risk through multiple mechanisms, including dilution or absorption of fecal carcinogens, reduction of bowel transit time, alterations in bile acid metabolism, increase of the production of short-chain fatty acids, and promotion of a favorable colonic microflora.[37,38] Dietary fiber has also been hypothesized to lower endogenous estrogen levels.[39,40] However, as far as we know, no biological link has been demonstrated for dietary fiber and exogenous hormones.

Our study has some limitations that need to be considered when interpreting the results. Measurement error is inevitable in dietary assessment. To investigate the effect of measurement error on our findings, we repeated our main analysis using calibrated fiber intake data and found the results to be similar to those presented in this report. Another limitation of our analysis is that diet was only assessed at baseline, although dietary intake may change over time. Since we repeated our dietary measurement about 10 years after baseline on a subset of participants in the MEC, we will be able to assess the effects of change in dietary fiber consumption on colorectal cancer incidence as more follow-up accrues. Strengths of our study include the prospective design, the large representative sample of participants with different ethnic/racial backgrounds, and the ability to control for a wide range of potential confounders in the analyses. The follow-up period was sufficiently long to accumulate large numbers of cases for the subgroup analyses.

In conclusion, this updated analysis of the MEC after 16 years of follow-up showed an inverse association between dietary fiber and colorectal in both women and men, not just in men as suggested in our previous report. It revealed that dietary fiber did not lower risk further among women who ever used MHT and that the association with fiber did not differ across the five ethnic/racial groups in the MEC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

MEC	Multiethnic Cohort

MHT menopausal hormone therapy

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Novelty and Impact

In a large multiethnic cohort with a mean follow-up of 16 years, we found an inverse association of dietary fiber with colorectal cancer both in men and women. Postmenopausal women who had ever used menopausal hormone therapy (MHT) were at lower risk of colorectal cancer. Dietary fiber intake was associated with a lower colorectal cancer risk in MHT never users, but did not appear to further decrease the colorectal cancer risk of MHT ever users. No difference in these associations was suggested across the five ethnic/racial groups included. These findings update an earlier report from the MEC that found an inverse association for fiber only in men.

Table 1

Baseline characteristics of men and women according to quintiles of dietary fiber intake

	Quintiles of dietary fiber intake (g/1,000 kcal)[1]				
	<8.1	**8.1–<10.2**	**10.2–<12.4**	**12.4–<15.3**	**≥15.3**
Men	n = 23,104	n = 19,100	n = 16,750	n = 14,618	n = 12,333
Age, mean (SD)	57.6 (8.8)	59.9 (8.9)	61.1 (8.7)	61.7 (8.5)	62.3 (8.3)
Race/ethnicity, n (%)					
African American	2882 (12.5)	2860 (15.0)	2365 (14.1)	2041 (14.0)	1806 (14.6)
Native Hawaiian	2788 (12.1)	1357 (7.1)	804 (4.8)	607 (4.2)	417 (3.4)
Japanese American	9781 (42.3)	6037 (31.6)	4343 (25.9)	3193 (21.8)	2031 (16.5)
Latino	2270 (9.8)	3875 (20.3)	4747 (28.3)	5088 (34.8)	4933 (40.0)
White	5383 (23.3)	4971 (26.0)	4491 (26.8)	3689 (25.2)	3146 (25.5)
Family history of colorectal cancer, n (%)	1805 (7.8)	1454 (7.6)	1149 (6.9)	974 (6.7)	799 (6.5)
History of colorectal polyp, n (%)	1573 (6.8)	1370 (7.2)	1151 (6.9)	992 (6.8)	779 (6.3)
Multivitamin user, n (%)	8968 (39.4)	8627 (46.0)	8284 (50.4)	7617 (53.2)	6660 (55.3)
Non-steroidal anti-inflammatory drug user, n (%)	10556 (46.4)	9657 (51.5)	8762 (53.3)	7642 (53.7)	6338 (52.9)
Ever smokers, n (%)	17671 (77.1)	13413 (70.9)	11246 (67.9)	9484 (65.8)	7665 (63.2)
Pack-years of cigarette smoking, mean (SD)[2]	25.1 (17.3)	21.0 (16.5)	19.0 (16.0)	17.2 (15.4)	16.1 (14.9)
Body mass index, kg/m^2, mean (SD)	26.8 (4.5)	26.8 (4.3)	26.7 (4.1)	26.6 (4.0)	26.3 (4.0)
Vigorous physical activity, h/day, mean (SD)	0.59 (1.08)	0.56 (1.00)	0.56 (0.97)	0.59 (0.99)	0.62 (1.04)
Dietary intake					
Alcohol intake, g/day, mean (SD)	26.9 (50.9)	14.2 (26.6)	10.6 (20.6)	8.2 (15.9)	5.4 (12.2)
Total energy, kcal/day, mean (SD)	2450 (1077)	2409 (1093)	2381 (1131)	2347 (1125)	2238 (1098)
Red meat, g/1,000 kcal/day, mean (SD)	23.4 (13.3)	22.6 (12.6)	21.1 (13.2)	18.4 (12.9)	13.8 (12.1)
Calcium, mg/day, mean (SD)[3]	779 (468)	942 (530)	1024 (577)	1089 (601)	1118 (615)
Folate, μg/day, mean (SD)[3]	374 (262)	489 (307)	573 (341)	664 (385)	794 (451)
Vitamin D, IU/day' mean (SD)[3]	270 (304)	325 (334)	355 (345)	382 (364)	399 (383)
Dietary fiber, g/1,000 kcal/day, mean (SD)	6.4 (1.2)	9.2 (0.6)	11.3 (0.6)	13.7 (0.8)	18.4 (2.9)
Women	n = 13,919	n = 18,351	n = 20,864	n = 23,171	n = 25,464
Age, years, mean (SD)	55.9 (8.6)	58.0 (8.8)	59.6 (8.7)	60.9 (8.6)	61.7 (8.4)

	Quintiles of dietary fiber intake (g/1,000 kcal)[1]				
	<8.1	**8.1–<10.2**	**10.2–<12.4**	**12.4–<15.3**	**≥15.3**
Race/ethnicity, n (%)					
African American	2584 (18.6)	3579 (19.5)	4095 (19.6)	4551 (19.6)	5149 (20.2)
Native Hawaiian	2073 (14.9)	1659 (9.0)	1405 (6.7)	1332 (5.7)	1097 (4.3)
Japanese American	4820 (34.6)	5794 (31.6)	6030 (28.9)	5930 (25.6)	5292 (20.8)
Latino	1289 (9.3)	2729 (14.9)	4125 (19.8)	5635 (24.3)	7626 (29.9)
White	3153 (22.7)	4590 (25.0)	5209 (25.0)	5723 (24.7)	6300 (24.7)
Family history of colorectal cancer, n (%)	1151 (8.3)	1542 (8.4)	1871 (9.0)	2044 (8.8)	2161 (8.5)
History of colorectal polyp, n (%)	523 (3.8)	758 (4.1)	957 (4.6)	1078 (4.7)	1125 (4.4)
Multivitamin user, n (%)	5857 (42.8)	9007 (50.0)	10979 (53.8)	12898 (56.9)	14901 (60.1)
Non-steroidal anti-inflammatory drug user, n (%)	7124 (52.2)	9665 (53.7)	11041 (54.0)	12331 (54.5)	13160 (53.2)
Postmenopause, n (%)	10190 (73.2)	14698 (80.1)	17648 (84.6)	20277 (87.5)	22921 (90.0)
Menopausal hormone therapy ever user among postmenopausal women, n (%)	5333 (52.3)	7932 (54.0)	9736 (55.2)	11238 (55.4)	12484 (54.5)
Ever smokers, n (%)	7703 (55.9)	8751 (48.2)	9034 (44.0)	9480 (41.7)	9519 (38.2)
Pack-years of cigarette smoking, mean (SD)[2]	20.0 (15.8)	16.8 (14.9)	15.1 (14.1)	13.8 (13.6)	12.6 (12.9)
Body mass index, kg/m^2, mean (SD)	27.0 (6.4)	26.8 (6.1)	26.6 (5.8)	26.4 (5.6)	26.1 (5.3)
Vigorous physical activity, h/day, mean (SD)	0.19 (0.56)	0.19 (0.53)	0.20 (0.53)	0.21 (0.52)	0.25 (0.58)
Dietary intake					
Alcohol intake, g/day, mean (SD)	10.1 (30.4)	5.2 (14.6)	4.0 (10.8)	3.0 (8.3)	2.0 (6.4)
Total energy, kcal/day, mean (SD)	1985 (961)	1967 (953)	1961 (940)	1950 (943)	1892 (926)
Red meat, g/1,000 kcal/day, mean (SD)	22.4 (13.9)	21.3 (12.5)	19.1 (12.0)	16.3 (11.2)	11.7 (10.3)
Calcium, mg/day, mean (SD)[3]	808 (568)	961 (638)	1051 (668)	1139 (716)	1209 (769)
Folate, µg/day, mean (SD)[3]	322 (245)	418 (279)	495 (309)	574 (346)	706 (411)
Vitamin D, IU/day' mean (SD)[3]	256 (297)	303 (319)	336 (336)	364 (355)	394 (382)
Dietary fiber, g/1,000 kcal/day, mean (SD)	6.7 (1.2)	9.2 (0.6)	11.3 (0.6)	13.7 (0.8)	18.6 (3.0)

[1]Based on the distribution for all participants of dietary fiber intake quantified as g/1,000 kcal/day.

[2]Based on ever smokers only.

[3]From food plus supplements.

Table 2

Association between dietary fiber intake and colorectal cancer risk in the Multiethnic Cohort Study, 1993–2012

Dietary fiber (g/1,000 kcal)	Men (n = 85,905)				Women (n = 101,769)				$p_{interaction}$[4]
	Cases	HR (95% CI)[1]	Cases[2]	HR (95% CI)[3]	Cases	HR (95% CI)[1]	Cases[2]	HR (95% CI)[3]	
Colorectum									
<8.1	755	1.00 (ref)	703	1.00 (ref)	302	1.00 (ref)	273	1.00 (ref)	0.039
8.1–<10.2	551	0.79 (0.71–0.89)	501	0.86 (0.76–0.97)	387	0.86 (0.74–1.00)	341	0.88 (0.75–1.04)	
10.2–<12.4	463	0.73 (0.65–0.82)	420	0.83 (0.72–0.95)	455	0.82 (0.71–0.95)	406	0.88 (0.75–1.04)	
12.4–<15.3	404	0.71 (0.62–0.80)	354	0.82 (0.70–0.96)	525	0.80 (0.69–0.93)	462	0.87 (0.73–1.03)	
≥15.3	303	0.61 (0.53–0.70)	260	0.73 (0.61–0.89)	547	0.73 (0.63–0.85)	455	0.76 (0.62–0.91)	
p_{trend}		<0.0001		0.0020		<0.0001		0.0067	
Right colon									
<8.1	269	1.00 (ref)	249	1.00 (ref)	137	1.00 (ref)	126	1.00 (ref)	0.92
8.1–<10.2	230	0.88 (0.74–1.05)	205	0.91 (0.75–1.11)	208	0.99 (0.80–1.23)	178	0.96 (0.76–1.21)	
10.2–<12.4	201	0.82 (0.68–0.99)	184	0.92 (0.74–1.14)	239	0.91 (0.73–1.12)	211	0.93 (0.74–1.18)	
12.4–<15.3	180	0.81 (0.67–0.98)	158	0.92 (0.72–1.17)	273	0.86 (0.70–1.07)	240	0.89 (0.70–1.13)	
≥15.3	165	0.84 (0.69–1.03)	140	0.97 (0.74–1.29)	316	0.87 (0.70–1.06)	259	0.84 (0.64–1.09)	
p_{trend}		0.075		0.91		0.085		0.16	
Left colon									
<8.1	239	1.00 (ref)	224	1.00 (ref)	94	1.00 (ref)	83	1.00 (ref)	0.13
8.1–<10.2	164	0.77 (0.63–0.94)	153	0.88 (0.71–1.10)	103	0.77 (0.58–1.02)	92	0.82 (0.61–1.12)	
10.2–<12.4	138	0.71 (0.58–0.89)	121	0.82 (0.64–1.06)	121	0.76 (0.58–1.00)	108	0.84 (0.62–1.14)	
12.4–<15.3	115	0.67 (0.53–0.84)	103	0.84 (0.63–1.12)	144	0.79 (0.60–1.03)	124	0.85 (0.62–1.16)	
≥15.3	66	0.45 (0.34–0.60)	54	0.55 (0.37–0.80)	124	0.61 (0.46–0.81)	105	0.65 (0.45–0.94)	
p_{trend}		<0.0001		0.0052		0.0022		0.040	
Rectum									
<8.1	233	1.00 (ref)	217	1.00 (ref)	65	1.00 (ref)	58	1.00 (ref)	0.047
8.1–<10.2	142	0.70 (0.57–0.87)	131	0.78 (0.62–0.98)	65	0.68 (0.48–0.96)	61	0.77 (0.53–1.11)	
10.2–<12.4	109	0.60 (0.48–0.76)	101	0.69 (0.53–0.91)	84	0.72 (0.52–1.00)	78	0.84 (0.59–1.21)	
12.4–<15.3	102	0.63 (0.50–0.81)	87	0.70 (0.51–0.94)	98	0.72 (0.52–0.99)	88	0.83 (0.57–1.21)	
≥15.3	64	0.47 (0.35–0.62)	58	0.56 (0.38–0.82)	96	0.62 (0.45–0.86)	81	0.67 (0.44–1.04)	

Dietary fiber (g/1,000 kcal)	Men (n = 85,905)				Women (n = 101,769)				$p_{interaction}$[4]
	Cases	HR (95% CI)[1]	Cases[2]	HR (95% CI)[3]	Cases	HR (95% CI)[1]	Cases[2]	HR (95% CI)[3]	
p_{trend}		<0.0001		0.0024		0.027		0.14	

[1]Adjusted for age at cohort entry and ethnicity.

[2]Excluding participants with missing information on covariates.

[3]Further adjusted for family history of colorectal cancer, history of colorectal polyp, BMI, pack-years of cigarette smoking, multivitamin use, non-steroidal anti-inflammatory drug use, vigorous physical activity, menopausal status and MHT use as a time-dependent variable for women only, alcohol consumption, total energy, red meat, calcium, folate, and vitamin D.

[4]Test of interaction between the dietary fiber trend variable and sex based on the multivariate-adjusted models.

Table 3

Association between menopausal hormone therapy (MHT) use and colorectal cancer risk among postmenopausal women in the Multiethnic Cohort Study, 1993–2012

MHT use[1]	Cases	HR (95% CI)[2]	Cases[3]	HR (95% CI)[4]
Colorectum				
Never use	1,052	1.00 (ref)	903	1.00 (ref)
Past use	605	0.85 (0.77–0.94)	531	0.87 (0.78–0.97)
Current use	470	0.72 (0.64–0.80)	421	0.75 (0.66–0.84)
Ever use	1,075	0.79 (0.72–0.86)	952	0.81 (0.74–0.89)
E-alone ever use	625	0.83 (0.75–0.92)	547	0.85 (0.76–0.94)
E+P ever use	450	0.73 (0.66–0.82)	405	0.76 (0.68–0.86)
Past E-alone use	384	0.90 (0.80–1.01)	333	0.91 (0.80–1.03)
Past E+P use	221	0.78 (0.68–0.91)	198	0.81 (0.69–0.95)
Current E-alone use	241	0.74 (0.64–0.85)	214	0.77 (0.66–0.89)
Current E+P use	229	0.69 (0.60–0.80)	207	0.72 (0.62–0.84)
≤2 years	375	0.92 (0.82–1.03)	328	0.93 (0.82–1.05)
3–9 years	263	0.73 (0.63–0.83)	241	0.77 (0.66–0.89)
≥10 years	354	0.72 (0.64–0.82)	315	0.74 (0.65–0.85)
Right colon				
Never use	528	1.00 (ref)	453	1.00 (ref)
Past use	341	0.93 (0.81–1.07)	291	0.91 (0.78–1.06)
Current use	265	0.86 (0.74–0.99)	234	0.87 (0.74–1.02)
Ever use	606	0.90 (0.80–1.01)	525	0.89 (0.78–1.01)
Left colon				
Never use	288	1.00 (ref)	243	1.00 (ref)
Past use	145	0.78 (0.64–0.95)	131	0.87 (0.70–1.08)
Current use	120	0.63 (0.50–0.78)	108	0.69 (0.55–0.88)
Ever use	265	0.70 (0.59–0.83)	239	0.78 (0.65–0.94)
Rectum				
Never use	210	1.00 (ref)	184	1.00 (ref)
Past use	103	0.75 (0.59–0.95)	94	0.77 (0.60–0.99)
Current use	78	0.55 (0.43–0.72)	72	0.57 (0.43–0.75)
Ever use	181	0.65 (0.53–0.80)	166	0.67 (0.54–0.83)

E: estrogen; P: progesterone

[1] All MHT variables are updated as time-dependent variables based on follow-up information.

[2] Adjusted for age at cohort entry and ethnicity.

[3] Excluding participants with missing information on covariates.

[4] Further adjusted for family history of colorectal cancer, history of colorectal polyp, BMI, pack-years of cigarette smoking, multivitamin use, non-steroidal anti-inflammatory drug use, vigorous physical activity, alcohol consumption, total energy, red meat, calcium, folate, vitamin D, and dietary fiber.

Table 4

Association between dietary fiber intake and colorectal cancer risk by menopausal hormone therapy (MHT) use among postmenopausal women in the Multiethnic Cohort Study, 1993–2012[1]

Dietary fiber (g/1,000kcal)	MHT never users (n = 36,917)		MHT ever users (n = 52,793)		$p_{interaction}$[3]
	Cases	HR (95% CI)[2]	Cases	HR (95% CI)[2]	
Colorectum					
<8.9	185	1.00 (ref)	163	0.77 (0.62–0.95)	0.50
8.9–<11.0	190	0.98 (0.80–1.21)	199	0.79 (0.64–0.96)	
11.0–<13.2	166	0.82 (0.66–1.01)	187	0.68 (0.55–0.84)	
13.2–<16.1	195	0.93 (0.75–1.15)	217	0.75 (0.61–0.93)	
≥16.1	167	0.75 (0.59–0.95)	186	0.64 (0.50–0.81)	
p_{trend}		0.045		0.11	
Right colon					
<8.9	84	1.00 (ref)	87	0.91 (0.68–1.24)	0.97
8.9–<11.0	98	1.08 (0.80–1.45)	110	0.93 (0.70–1.24)	
11.0–<13.2	79	0.81 (0.59–1.11)	103	0.78 (0.58–1.05)	
13.2–<16.1	101	0.99 (0.73–1.35)	116	0.82 (0.60–1.10)	
≥16.1	91	0.82 (0.58–1.15)	109	0.75 (0.54–1.04)	
p_{trend}		0.54		0.080	
Left colon					
<8.9	54	1.00 (ref)	42	0.69 (0.46–1.04)	0.54
8.9–<11.0	53	0.97 (0.66–1.42)	54	0.77 (0.52–1.13)	
11.0–<13.2	46	0.81 (0.54–1.22)	45	0.60 (0.40–0.91)	
13.2–<16.1	51	0.88 (0.58–1.32)	58	0.75 (0.50–1.12)	
≥16.1	39	0.63 (0.39–1.01)	40	0.51 (0.32–0.82)	
p_{trend}		0.034		0.47	
Rectum					
<8.9	40	1.00 (ref)	30	0.62 (0.39–1.00)	0.44
8.9–<11.0	36	0.90 (0.57–1.42)	31	0.57 (0.35–0.92)	
11.0–<13.2	38	0.92 (0.58–1.47)	33	0.57 (0.36–0.93)	

Dietary fiber (g/1,000kcal)	MHT never users (n = 36,917)		MHT ever users (n = 52,793)		$p_{interaction}$[3]
	Cases	HR (95% CI)[2]	Cases	HR (95% CI)[2]	
13.2–<16.1	37	0.89 (0.55–1.44)	38	0.64 (0.40–1.04)	
≥16.1	33	0.76 (0.44–1.30)	34	0.58 (0.34–0.99)	
p_{trend}		0.30		0.93	

[1] Excluding participants with missing information on covariates.

[2] Adjusted for age at cohort entry, ethnicity, family history of colorectal cancer, history of colorectal polyp, BMI, pack-years of cigarette smoking, multivitamin use, non-steroidal anti-inflammatory drug use, vigorous physical activity, alcohol consumption, total energy, red meat, calcium, folate, and vitamin D.

[3] Test of interaction between MHT use and the dietary fiber trend variable.

Table 5

Association between dietary fiber intake, menopausal hormone therapy (MHT) use, and colorectal cancer risk by race/ethnicity in the Multiethnic Cohort Study, 1993–2012[1]

	African American		Native Hawaiian		Japanese American		Latino		White		$p_{interaction}$[4]
	Cases	HR (95% CI)[2]	Cases	HR (95% CI)[2]	Cases	HR (95% CI)[2]	Cases	HR (95% CI)[2]	Cases	HR (95% CI)[2]	
Dietary fiber (g/1,000 kcal)											
Men											
<8.1	71	1.00 (ref)	72	1.00 (ref)	355	1.00 (ref)	74	1.00 (ref)	131	1.00 (ref)	0.26
8.1–<10.2	77	1.00 (0.72–1.40)	32	0.89 (0.57–1.40)	188	0.86 (0.71–1.04)	104	0.80 (0.58–1.09)	100	0.88 (0.67–1.16)	
10.2–<12.4	67	0.94 (0.65–1.35)	24	1.04 (0.61–1.79)	148	0.94 (0.75–1.17)	92	0.57 (0.41–0.79)	89	0.91 (0.67–1.24)	
12.4–<15.3	46	0.74 (0.48–1.12)	15	0.95 (0.48–1.88)	106	0.94 (0.72–1.22)	104	0.58 (0.41–0.82)	83	1.07 (0.76–1.49)	
≥15.3	52	0.86 (0.54–1.36)	4	0.36 (0.12–1.14)	58	0.83 (0.58–1.18)	94	0.51 (0.34–0.76)	52	0.85 (0.56–1.29)	
p_{trend}		0.31		0.24		0.42		0.0012		0.75	
Women											
<8.1	70	1.00 (ref)	43	1.00 (ref)	93	1.00 (ref)	15	1.00 (ref)	52	1.00 (ref)	0.36
8.1–<10.2	71	0.68 (0.48–0.95)	22	0.64 (0.38–1.10)	128	1.01 (0.77–1.33)	46	1.32 (0.73–2.37)	74	0.96 (0.67–1.39)	
10.2–<12.4	84	0.65 (0.46–0.90)	21	0.72 (0.40–1.30)	147	1.04 (0.79–1.37)	64	1.21 (0.68–2.15)	90	0.97 (0.67–1.40)	
12.4–<15.3	107	0.71 (0.51–0.99)	15	0.49 (0.24–0.98)	152	1.01 (0.75–1.36)	95	1.22 (0.69–2.15)	93	0.88 (0.60–1.29)	
≥15.3	128	0.68 (0.47–0.98)	20	0.92 (0.43–1.95)	123	0.86 (0.61–1.23)	85	0.74 (0.40–1.35)	99	0.79 (0.52–1.21)	
p_{trend}		0.24		0.61		0.37		0.0086		0.20	
MHT use[3]											
Never	232	1.00 (ref)	57	1.00 (ref)	299	1.00 (ref)	151	1.00 (ref)	164	1.00 (ref)	0.049
Past	135	1.04 (0.84–1.29)	29	0.93 (0.59–1.47)	145	0.68 (0.56–0.84)	84	0.97 (0.74–1.27)	138	0.85 (0.68–1.08)	
Current	70	0.87 (0.66–1.14)	19	0.74 (0.43–1.25)	176	0.75 (0.62–0.90)	60	0.83 (0.61–1.12)	96	0.60 (0.46–0.78)	

[1] Excluding participants with missing information on covariates.

[2] Adjusted for age at cohort entry, family history of colorectal cancer, history of colorectal polyp, BMI, pack-years of cigarette smoking, multivitamin use, non-steroidal anti-inflammatory drug use, vigorous physical activity, menopausal status and MHT use as a time-dependent variable for women only, alcohol consumption, total energy, red meat, calcium, folate, and vitamin D.

[3] Among postmenopausal women.

[4] Test of interaction between race/ethnicity and the dietary fiber trend variable.