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Fiber intake and survival after colorectal cancer diagnosis

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Abstract

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Data Access, Responsibility, and Analysis

Drs Song and Chan have full access to all of the data in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis.

No other conflict of interest exists.

Importance—Although high dietary fiber intake has been associated with lower risk of colorectal cancer (CRC), it remains unknown whether fiber benefits CRC survivors.

Objective—To assess the association of post-diagnostic fiber intake with mortality.

Design—Prospective cohort study

Setting—Health professionals in the United States

Participants—1,575 patients with stage I to III CRC in the Nurses' Health Study and Health Professionals Follow-up Study.

Exposure—Consumption of total fiber and different sources of fiber and whole grains assessed by a validated food frequency questionnaire between 6 months and 4 years after CRC diagnosis

Main outcomes and measures—Hazard ratios (HRs) and 95% confidence intervals (CIs) of CRC-specific and overall mortality after adjusting for other potential predictors for cancer survival.

Results—Over a median of 8 years of follow-up, we documented 773 deaths, including 174 from CRC. High intake of total fiber after diagnosis was associated with lower mortality. The multivariable HR per each 5-g increment in intake per day was 0.78 (95% CI, 0.65-0.93, P=0.006) for CRC-specific mortality and 0.86 (95% CI, 0.79-0.93, P<0.001) for all-cause mortality. Patients who increased their fiber intake after diagnosis from levels before diagnosis had a lower mortality and each 5-g/day increase in intake was associated with 18% lower CRC-specific mortality (95% CI, 7-28%, P=0.002) and 14% lower all-cause mortality (95% CI, 8-19%, P<0.001). According to source of fiber, cereal fiber was associated with lower CRC-specific mortality (HR per 5-g/day increment, 0.67, 95% CI, 0.50-0.90, P=0.007) and all-cause mortality (HR, 0.78, 95% CI, 0.68-0.90, P<0.001); vegetable fiber was associated with lower all-cause mortality (HR, 0.83, 95% CI, 0.72-0.96, P=0.009) but not CRC-specific mortality (HR, 0.82, 95% CI, 0.60-1.13, P=0.12); no association was found for fruit fiber. Whole grain intake was associated with lower CRC-specific mortality (HR per 20-g/day increment, 0.72, 95% CI, 0.59-0.88, P=0.002), and this beneficial association was attenuated after adjusting for fiber intake (HR, 0.77, 95% CI, 0.62-0.96, P=0.02).

Conclusions and relevance—Higher fiber intake after the diagnosis of non-metastatic CRC is associated with lower CRC-specific and overall mortality. Increasing fiber consumption after diagnosis may confer additional benefits to patients with CRC.

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer and third leading cause of cancer death in the United States.[1] Given advances in early detection and treatment, the number of CRC survivors is estimated to exceed 1.4 million in 2016 and expected to grow dramatically over the coming decades.[2] Many cancer survivors are highly motivated to seek self-care strategies, particularly dietary counseling, to facilitate their treatment and recovery.[3] However, due to lack of data on post-diagnostic diet and CRC survival, most dietary recommendations for CRC survivors are primarily based on incidence studies.[4,5] Therefore, identifying prognostic dietary factors is urgently needed to improve CRC survivorship.

Fiber has been associated with lower risk of CRC in many but not all studies.[6] The most recent expert report concludes that evidence that consumption of foods containing dietary fiber protects against CRC is convincing.[7] Fiber helps minimize exposure to intestinal carcinogens by diluting fecal content and decreasing transit time,[10] and also has systemic benefits on insulin sensitivity and metabolic regulation,[8] which have been linked to CRC prognosis.[9] Moreover, fiber can be fermented by the gut bacteria into short-chain fatty acids (SCFAs), such as butyrate, acetate, and propionate, that possess a diversity of tumor-suppressive effects.[11,12] Preclinical studies have indicated the potential of butyrate and its analogs as chemotherapeutic agents in several tumor models,[13,14] including CRC.[15]

Despite these data, to our knowledge no study has yet examined the association between fiber intake and survival of CRC patients. Therefore, we used data from two large prospective cohorts, the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS), to test the hypothesis that high consumption of fiber and its major food sources after CRC diagnosis might be associated with lower mortality.

METHODS

Study population

The NHS enrolled 121 700 US registered female nurses who were aged 30-55 years in 1976. The HPFS enrolled 51 529 US male health professionals who were aged 40-75 years in 1986. Details about the two cohorts have been described elsewhere.[16,17] Briefly, participants were mailed a questionnaire inquiring about their medical history and lifestyle factors at baseline, and every two years thereafter. Dietary data were collected and updated every four years using the food frequency questionnaires (FFQs). In the present analysis, we used 1980 for the NHS and 1986 for the HPFS as baseline, when we first collected detailed data on fiber intake. The follow-up rates have been 95.4% in the NHS and 95.9% in the HPFS for each of the questionnaires through 2010. This study was approved by the Institutional Review Board at the Brigham and Women's Hospital and the Harvard T.H. Chan School of Public Health.

Ascertainment of CRC cases

On each biennial follow-up questionnaire, participants were asked whether they had had a diagnosis of CRC during the previous 2 years. For participants who reported CRC diagnosis, we asked for their permission to acquire medical records and pathologic reports. Study physicians, blinded to exposure data, reviewed all medical records to confirm CRC diagnosis and to record the disease stage, histologic findings, and tumor location.[18] In this analysis, we included a total of 1,575 participants who were diagnosed with stage I to III CRC throughout follow-up and completed the FFQ after diagnosis (N=963 in the NHS and 612 in the HPFS) (see the flow chart in eFigure 1).

Ascertainment of deaths

Deaths were identified through review of the National Death Index, and family members or the postal system in response to the follow-up questionnaires. The cause of death was

assigned by study physicians based on all available data including medical records. More than 96% of deaths have been identified using these methods.[19]

Assessment of fiber intake

Dietary intake data were collected repeatedly by FFQs in which participants were asked how often, on average, they consumed each food of a standard portion size during the previous year. We calculated the daily intake for each nutrient by multiplying the reported frequency of consumption of each item by its nutrient content and then summing across from all foods. Fiber intake was calculated using the Association Official Analytical Chemists method (accepted by the U.S. Food and Drug Administration and the Food and Agriculture Organization of the WHO for nutrition labeling purposes). We adjusted fiber intake for total caloric intake using the nutrient residual method.[20] FFQs have shown good reproducibility and validity for assessing fiber intake (Supplementary Methods).[21]

Fiber intake from major food sources, including cereals, vegetables, and fruits, was considered separately. We also assessed whole grain consumption from all grain-containing foods (rice, bread, pasta, and breakfast cereals) according to the dry weight of whole grain ingredients in each food, as previously described.[22].

For post-diagnostic intake, the first FFQ collected at least 6 months but no more than 4 years after diagnosis (median, 2.2 years) was used to avoid assessment during the period of active treatment.[23] In a sensitivity analysis, we also examined the cumulative average intake of fiber throughout the entire post-diagnostic period (Supplementary Methods). Pre-diagnostic intake was based on the last FFQ reported before CRC diagnosis.

Statistical analysis

We calculated person-time of follow-up from the return date of the FFQ that was used for post-diagnostic assessment to death, or the end of the study period (June 1, 2012 for the NHS, January 31, 2012 for the HPFS), whichever came first. In the main analysis, death from CRC was the primary end point, and deaths from other causes were censored. In secondary analyses, death from any cause was the end point.

We used cause-specific Cox proportional hazards regression models with time since diagnosis as the time scale, accounting for left truncation due to differences between patients in the timing of post-diagnostic assessment.[26] We calculated hazard ratios (HRs) and 95% confidence intervals (CIs) of death, adjusted for pre-diagnostic fiber intake and other potential predictors for cancer survival (see Supplementary Methods). Test for trend was performed using the median for each quartile of fiber intake as a continuous variable. We tested proportional hazards assumption by including the interaction term between fiber intake and time into the model, and did not find statistical evidence for violation of this assumption.

To reduce residual confounding, we further adjusted for a propensity score that reflected associations of fiber consumption with potential confounding covariates.[27] To minimize any bias resulting from the availability of post-diagnostic questionnaire data, we applied the inverse probability weighting method to all survival analyses.[28] We examined the dose-

response relationship between fiber intake and mortality using the restricted cubic spline analysis.[29] More details about these analyses are provided in the Supplementary Methods.

We also calculated the change in fiber intake by subtracting the pre-diagnostic intake from the post-diagnostic intake, and examined the association with mortality. Moreover, we assessed consumption of whole grain and different sources of fiber. Finally, we conducted the stratified analysis by clinicopathological and lifestyle factors. *P* value for interaction was calculated using the likelihood ratio test. We used SAS 9.4 for all analyses (SAS Institute, Cary, NC). All statistical tests were two-sided and $P<0.05$ was considered statistically significant.

RESULTS

Basic characteristics of participants

Among 1,575 eligible patients diagnosed with stage I to III CRC, we documented 773 deaths, of which 174 were classified as CRC-specific deaths over a median of 8 years of follow-up. Other major causes of death included cardiovascular diseases (n=168) and cancers other than CRC (n=121). The overall 5-year survival rates were 83% (95% CI, 79-86%) for stage I cancer, 82% (95% CI, 78-86%) for stage II cancer, and 72% (95% CI, 67-76%) for stage III cancer. These rates appeared to be comparable to national estimates.[30]

Participants with higher fiber intake tended to have a healthier lifestyle (eTable 1). Anatomic subsite and grade of differentiation did not differ across quartiles of fiber intake, whereas patients with the highest fiber intake were more likely to have stage I cancer than others. To stringently control for any confounding effect by stage, we performed stage-stratified Cox regression for all the association analyses.

Total fiber intake after diagnosis and survival

As shown in Table 1, fiber intake was inversely associated with CRC-specific mortality after adjusting for other potential determinants for cancer prognosis. The multivariable HR per each 5-g increase in intake per day was 0.78 (95% CI, 0.65-0.93, $P=0.006$) for CRC-specific mortality and 0.86 (95% CI, 0.79-0.93, $P<0.001$) for all-cause mortality. Similar findings were obtained when cumulative average fiber consumption after diagnosis was used for the analysis (eTable 2).

The spline analysis showed a linear relationship between fiber intake after diagnosis and CRC-specific mortality. For all-cause mortality, a statistically significant nonlinear relationship was observed ($P=0.007$); the benefit associated with increasing fiber intake achieved its maximum at about 24 g/day and no further reduction in mortality was found beyond this level of intake (Figure 1).

To minimize bias associated with occult recurrences or other undiagnosed major illnesses that could influence dietary intake, we excluded the first year of follow-up in a sensitivity analysis. The results remained essentially unchanged, with the multivariable HR per 5-g/day increment for CRC-specific mortality of 0.80 (95% CI, 0.66-0.97, *P* for trend=0.02) and the HR for all-cause mortality of 0.85 (95% CI, 0.78-0.93, *P* for trend=0.002). Similar results

were also obtained in the propensity score analysis, with the corresponding HRs of 0.80 (95% CI, 0.67-0.96, *P* for trend=0.02) and 0.86 (95% CI, 0.79-0.93, *P* for trend<0.001), respectively, indicating the robustness of our findings to confounding.

No statistically significant interaction was detected between fiber intake and tumor subsite or stage (*P* for interaction>0.05) (eTable 3). In a subset of patients with chemotherapy data (n=375), fiber intake was similar among those who received chemotherapy (median=19.5 g/day) versus those who did not (median=19.1 g/day) (*P* for Wilcoxon test =0.13).

Change in total fiber intake after diagnosis and survival

Pre- and post-diagnostic intake of fiber was modestly correlated (Spearman correlation coefficient r=0.58). We assessed whether changing fiber intake after diagnosis was associated with mortality. As shown in Table 1, patients who increased their fiber intake after diagnosis from levels before diagnosis had a lower mortality and each 5-g/day increase in fiber intake was associated with 18% lower CRC-specific mortality (95% CI, 7-28%, *P*=0.002) and 14% lower all-cause mortality (95% CI, 8-19%, *P*<0.001).

Fiber intake of different food sources and survival

Next, we examined associations by major dietary sources of fiber, including those from cereals, vegetables and fruits. Fiber intakes from these sources were weakly correlated (Spearman correlation coefficient r<0.25, eTable 4). As shown in Table 2, fiber from cereals showed an inverse association with lower mortality after mutual adjustment for fruit and vegetable fiber. The HR associated with 5-g/day increment in cereal fiber was 0.67 (95% CI, 0.50-0.90, *P* for trend=0.007) for CRC-specific mortality and 0.78 (95% CI, 0.68-0.90, *P* for trend<0.001) for all-cause mortality. In contrast, no association was found for fruit fiber. Vegetable fiber was associated with lower all-cause mortality (HR per 5-g/day increment, 0.83, 95% CI, 0.72-0.96, *P* for trend=0.009) but not CRC-specific mortality (HR, 0.82, 95% CI, 0.60-1.13, *P* for trend=0.22).

Whole grain intake after diagnosis and survival

Whole grain consumption was associated with lower CRC-specific mortality, with the multivariable HR per 20-g/day increment of 0.72 (95% CI, 0.59-0.88, *P* for trend=0.002) (Table 3). This association was attenuated after adjusting for total fiber intake (HR=0.77, 95% CI, 0.62-0.96, *P* for trend=0.02). Similar, but weaker, attenuation was observed for all-cause mortality, with the HR changing from 0.88 (95% CI, 0.80-0.97, *P* for trend=0.008) to 0.91 (0.83-1.01, *P* for trend=0.08) after including fiber in the multivariable model.

Fiber intake and survival within subgroups

In an exploratory analysis, we examined whether the association between total fiber intake and mortality differed by other predictors of cancer prognosis, including sex, age, smoking status, alcohol consumption, BMI, physical activity, aspirin use, and dietary glycemic load (eTable 5). We observed a statistically significant interaction with alcohol consumption for CRC-specific mortality (*P*=0.05) and with regular aspirin use for all-cause mortality (*P*=0.01): the inverse association of fiber intake with mortality was restricted to low alcohol consumer and non-regular aspirin users. However, given the multiple testing and limited

event numbers, these findings should be interpreted cautiously. No other statistically significant interaction was detected.

DISCUSSION

To our knowledge, this is the first prospective study examining the prognostic influence of fiber intake among CRC patients. We found that patients with higher intake of fiber, especially that from cereals, had a lower rate of CRC-specific and all-cause mortality. Patients who increased their intake from their levels before diagnosis experienced a modest reduction in mortality. Higher consumption of whole grains was also associated with better survival, and this beneficial association was partly mediated by fiber. Our findings provide novel evidence for the potential benefit of increasing fiber and whole grain consumption among CRC patients.

Substantial evidence supports the protective effect of high fiber intake for CRC prevention. According to a recent meta-analysis of 25 prospective studies, each 10-gram increment in daily intake of total and cereal fiber was associated with approximately 10% lowered risk of developing CRC.[31] This agrees with the well-established data from animal studies that high-fiber diets promote apoptosis and suppress colorectal tumor development.[32–34] Our current study adds to the existing literature and suggests that the effect of high fiber intake may extend beyond protection against cancer incidence and contribute to better prognosis after cancer is established.

Higher intake of fiber, especially cereal fiber, has been linked to improved insulin sensitivity,[35] lipid profile,[36] endothelial function, and reduced inflammation.[37] Emerging, albeit limited, evidence suggests that hyperinsulinemia and markers of insulin resistance and inflammation predict worse survival in CRC patients,[38,39] and may mediate the adverse metabolic effect of obesity and physical inactivity on CRC recurrence and death.[23,40] Therefore, higher fiber intake after CRC diagnosis may improve patients' survival by mitigating the tumor-promoting effect of hyperinsulinemia and inflammation.

Bacterial fermentation of fiber also produces butyrate, which has been increasingly implicated in modulation of the tumor microenvironment.[41] Although butyrate is a major energy source for normal colonocytes, it is metabolized to a lesser extent in cancer cells due to the Warburg effect and accumulates in the nucleus of cancerous colonocytes, in which it functions as an inhibitor of histone deacetylase to epigenetically regulate expression of numerous genes responsible for tumor growth, angiogenesis, migration, and chemoresistance.[41] Moreover, butyrate may influence CRC prognosis by modulating the function of tumor-infiltrating immune cells, including regulatory T cells[42,43] and macrophages,[44] which have been increasingly recognized for their critical roles in tumor-host interactions and cancer prognosis.[45,46]

Consistent with these data, we found that patients who consumed higher fiber after diagnosis had substantially lower rate of death. The beneficial association appeared to differ by fiber sources with cereal fiber showing the strongest association. These findings are further supported by the favorable survival in relation to high consumption of whole grain, a rich

source of cereal fiber. Concordant with our findings, previous studies support the importance of fiber sources. Compared with fiber from other sources, cereal fiber and whole grains have been most consistently associated with lower incidence of colorectal neoplasia,[31,47–50] type 2 diabetes,[51,52] cardiovascular disease,[52,53] and total mortality.[52,54] Although the exact reasons remain unclear, it is possible that the generally high fiber content of cereals, especially whole grains, may contribute to the more pronounced benefit, whereas the amount of fiber consumed from fruits may be too low for an association with health outcomes to be observed. Alternatively, other components in cereals and whole grains may contribute to their favorable effects, such as vitamins, minerals, phenols, and phytoestrogens.[55–57] However, in the current study, adjusting for fiber intake indeed attenuated the association between whole grain and lower mortality, suggesting that fiber may be an important contributor for the protective effect of whole grains.[58]

Advantages of the current study include the prospective design, detailed collection of pre- and post-diagnostic diet and lifestyle information, standardized medical record review of self-reported CRC and deaths, and long-term follow-up. Moreover, the detailed covariate data collected in parallel with fiber intake allowed for rigorous control for confounding by various predictors of cancer survival.

There are limitations that are worth noting. First, detailed treatment data were largely unavailable in the cohorts. However, among a subset of patients with chemotherapy data, fiber intake did not differ by the use of chemotherapy. Moreover, during the time period of the study, adjuvant treatment was largely standardized and primarily correlated with disease stage. Thus, our ability to control for stage in our analyses minimized any potential confounding by treatment. In addition, because all participants were health professionals, any difference in access to adjuvant chemotherapy is minimized. Second, beyond cause of mortality, data on cancer recurrences were unavailable in our cohorts. Nevertheless, because the median survival for metastatic CRC was approximately 10 to 12 months during much of the period of this study,[59] CRC-specific mortality should be a reasonable surrogate for cancer-specific outcomes. Third, the number of CRC-specific deaths is relatively small, and therefore further large-scale studies are needed.

Finally, as an observational study, residual confounding cannot be excluded, although we observed similar results through multivariable adjustment and propensity score analysis. Our findings need to be validated by further studies, including possible clinical trials. Of note, previous observational data regarding the favorable influence of other lifestyle factors on CRC survival have been subsequently confirmed in randomized trials. For example, in support of the beneficial association with CRC survival for physical activity[60] and high intake of vitamin D[61] and marine omega-3 fatty acid[62] in prospective cohort studies, randomized clinical trials have documented a positive influence of exercise intervention on patients' quality of life and functional capacity;[63–66] the benefit of preoperative omega-3 fatty acid therapy on reducing tumor vascularity and prolonging patients' survival;[67] and the effect of high-dose vitamin D supplementation on improved survival in metastatic CRC patients.[68] These robust data indicate the critical role of prospective observational studies in identification of modifiable lifestyle factors for improvement of cancer survival.

In conclusion, higher intake of fiber and whole grains after CRC diagnosis is associated with lower rate of death from that disease and other causes. Our findings provide support for the nutritional recommendations of maintaining sufficient fiber intake among CRC survivors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Disclosure

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Key Points

Question

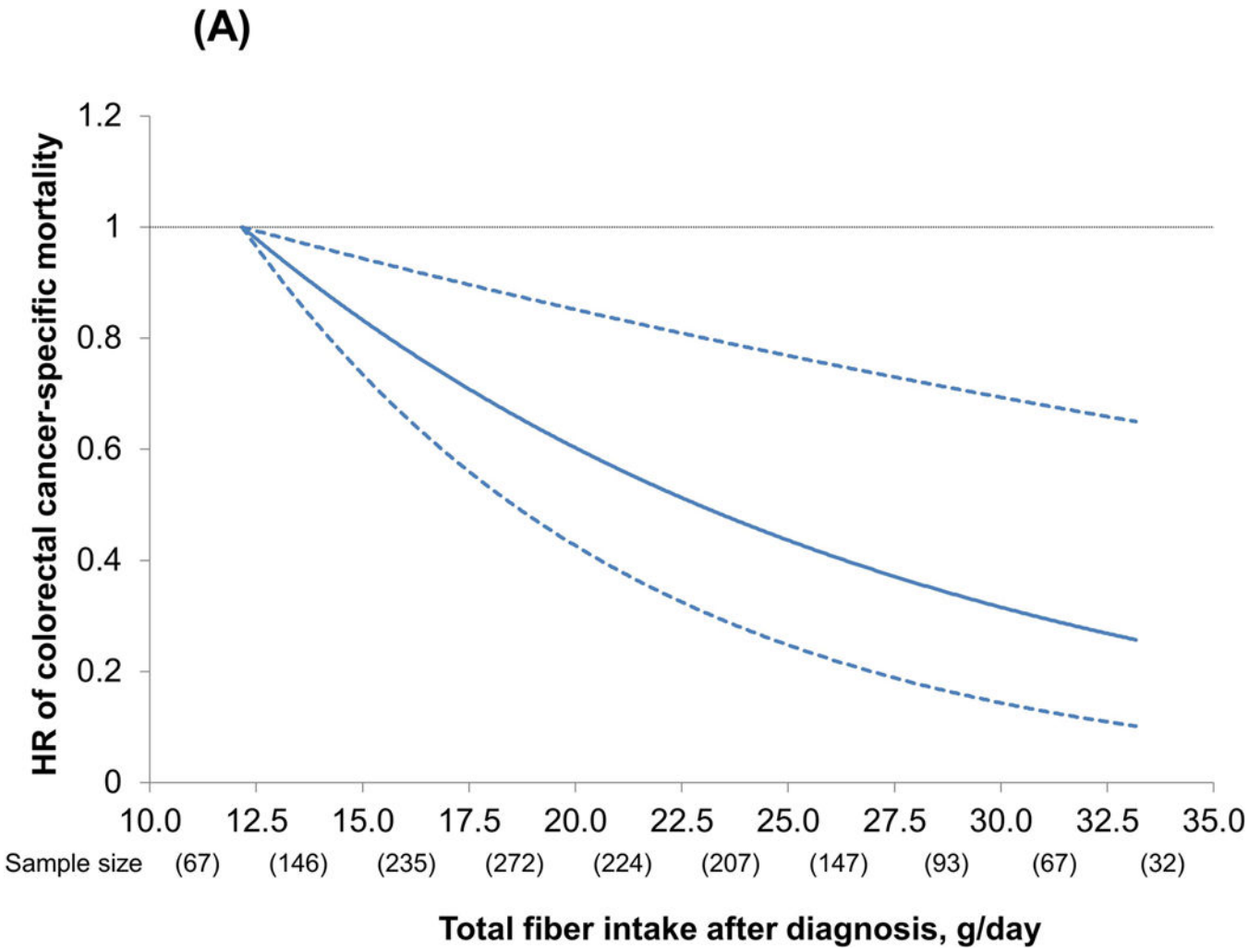
Is fiber intake after colorectal cancer diagnosis associated with mortality?

Findings

In this prospective cohort study that included 1,575 patients with stage I to III colorectal cancer, higher intake of fiber, especially that from cereals, was associated with lower risk of colorectal cancer-specific and overall mortality. Patients who increased their fiber intake after diagnosis from levels before diagnosis showed better survival. Higher intake of whole grains was also associated with favorable survival.

Meaning

Higher fiber intake after the diagnosis of non-metastatic colorectal cancer may reduce the risk of colorectal cancer-specific and overall mortality.



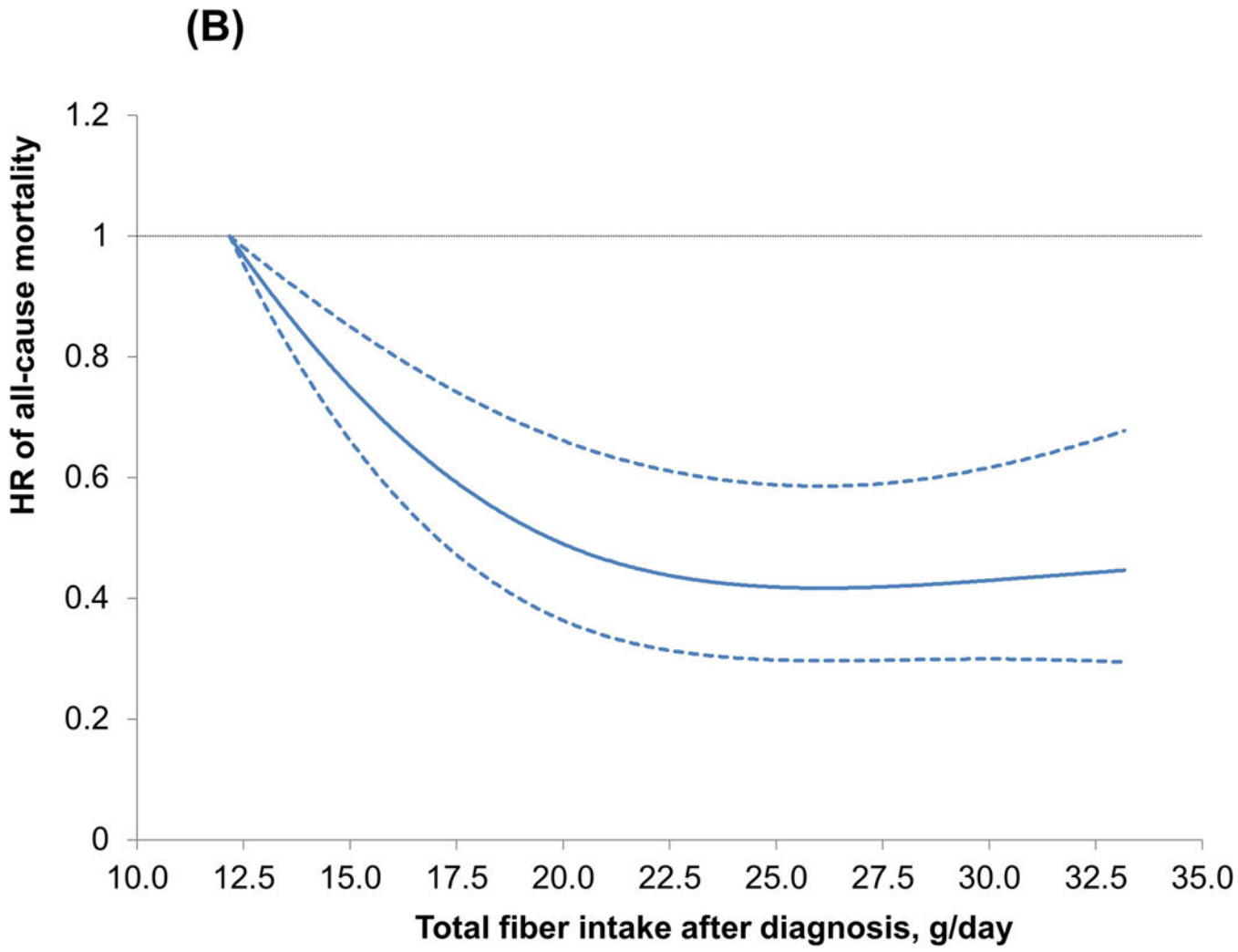


Figure 1.

Dose-response relationship between post-diagnostic fiber intake and colorectal cancer-specific mortality (A) and all-cause mortality (B) among colorectal cancer patients. Dashed lines represent the 95% confidence intervals of the hazard ratio (HR). Multivariable model was adjusted for the same set of covariates as in Table 1. For colorectal cancer-specific mortality, no spline variable was selected and *P* for linearity = 0.004; for all-cause mortality, there was a non-linear relationship with *P* = 0.007 for non-linearity and *P*<0.001 for the overall significance. Sample size within each interval of fiber intake (containing the lower limit but not the upper limit) is shown below the X-axis in panel (A). For example, there are 67 patients with fiber intake of ≤10 and >12.5 g/day. Twenty-five and 61 patients with fiber intake of <10 and ≥35 g/day are not shown, respectively.

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Table 1

Total fiber intake and its change after diagnosis in relation to mortality among colorectal cancer patients (n=1,575)*

Post-diagnostic total fiber intake	Quartile 1	Quartile 2	Quartile 3	Quartile 4	HR (95% CI) per 5 g/day	*P* for trend
Colorectal cancer-specific mortality						
Median intake (interquartile range), g/day	14.4 (12.8 to 15.8)	18.2 (16.9 to 20.8)	22.2 (20.1 to 24.8)	28.9 (25.2 to 32.2)		
No. of events (n=174)	56	40	40	38		
No. of person-years (n=14,210)	3,335	3,614	3,475	3,786		
Mortality rate (per 1,000 person-years)	16.8	11.1	11.5	10.0		
Age, sex, stage-adjusted HR (95% CI) †	1 (referent)	0.68 (0.49-0.96)	0.55 (0.39-0.78)	0.63 (0.45-0.89)	0.83 (0.72-0.95)	0.006
Multivariable-adjusted HR (95% CI) ‡	1 (referent)	0.72 (0.50-1.03)	0.48 (0.32-0.71)	0.54 (0.35-0.85)	0.78 (0.65-0.93)	0.006
All-cause mortality						
No. of events (n=773)	223	185	180	185		
Mortality rate (per 1,000 person-years)	66.9	51.2	51.8	48.9		
Age, sex, stage-adjusted HR (95% CI) †	1 (referent)	0.76 (0.65-0.90)	0.69 (0.58-0.82)	0.66 (0.56-0.78)	0.87 (0.82-0.92)	<0.001
Multivariable-adjusted HR (95% CI) ‡	1 (referent)	0.76 (0.63-0.91)	0.71 (0.58-0.87)	0.64 (0.51-0.80)	0.86 (0.79-0.93)	<0.001
Change in total fiber intake after diagnosis	Decrease of ≥2.0 g/day	Change of <2.0 g/day	Increase of 2.0-4.9 g/day	Increase of ≥5 g/day	HR (95% CI) per 5 g/day	*P* for trend
Colorectal cancer-specific mortality						
Median intake (interquartile range), g/day	−4.9 (-7.2 to -3.1)	0.1 (-0.9 to 1.1)	3.2 (2.5 to 4.1)	7.7 (6.0 to 10.0)		
No. of events (n=174)	52	64	29	29		
No. of person-years (n=14,209)	4,322	3,873	3,087	2,927		
Mortality rate (per 1,000 person-years)	12.0	16.5	9.4	9.9		
Age, sex, stage-adjusted HR (95% CI) †	1.36 (1.00-1.84)	1 (referent)	1.02 (0.70-1.49)	0.99 (0.68-1.44)	0.88 (0.80-0.98)	0.02
Multivariable-adjusted HR (95% CI) ‡	1.65 (1.17-2.34)	1 (referent)	1.08 (0.73-1.61)	0.91 (0.60-1.38)	0.82 (0.72-0.93)	0.002
All-cause mortality						
No. of events (n=773)	230	257	160	126		
Mortality rate (per 1,000 person-years)	53.2	66.4	51.8	43.0		
Age, sex, stage-adjusted HR (95% CI) †	1.10 (0.95-1.29)	1 (referent)	1.07 (0.90-1.28)	0.77 (0.64-0.93)	0.92 (0.88-0.97)	0.001
Multivariable-adjusted HR (95% CI) ‡	1.17 (0.99-1.39)	1 (referent)	1.04 (0.87-1.24)	0.67 (0.55-0.83)	0.86 (0.81-0.92)	<0.001

Abbreviation: CI, confidence interval; HR, hazard ratio.

*Post-diagnostic intake was assessed at least 6 months but no more than 4 years after diagnosis to minimize the influence of active treatment.

†Cox proportional hazards regression model stratified by age groups at diagnosis (<60, 60-64, 65-69, 70-74, and ≥75 years), sex, and cancer stage (I, II, III, and unspecified), with additional adjustment for age at diagnosis (continuous).

‡Further adjusted for year of diagnosis (continuous), tumor grade of differentiation (1-3 and unspecified), subsite (proximal colon, distal colon, rectum and unspecified), pre-diagnostic fiber intake (in quartiles), post-diagnostic alcohol consumption (<0.15, 0.15-1.9, 2.0-7.4, ≥7.5 g/d), pack-years of smoking (0, 1-15, 16-25, 26-45, >45), BMI (<23, 23-24.9, 25-27.4, 27.5-29.9, ≥30 kg/m^2), physical activity (women: <5, 5-11.4, 11.5-21.9, ≥22 MET-hours/week; men: <7, 7-14.9, 15-24.9, ≥25 MET-hours/week), regular use of aspirin (≥2 tablets per week), glycemic load (in quartiles), and consumption of total fat, folate, calcium, and vitamin D (in quartiles).

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Table 2

Post-diagnostic intake of fiber from different food sources and mortality among colorectal cancer patients (n=1,575)*

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	HR (95% CI) per 5 g/day	*P* for trend
CRC-specific mortality (n=174)						
Cereal fiber						
Median intake (interquartile range), g/day	3.3 (2.7 to 3.8)	5.1 (4.6 to 5.6)	7.0 (6.4 to 7.6)	10.2 (9.1 to 12.2)		
No. of events	52	47	40	35		
Age, sex, stage-adjusted HR (95% CI) †	1 (referent)	0.80 (0.58-1.10)	0.71 (0.50-1.00)	0.60 (0.42-0.85)	0.68 (0.53-0.89)	0.004
Multivariable-adjusted HR (95% CI) ‡	1 (referent)	0.75 (0.53-1.06)	0.66 (0.45-0.97)	0.57 (0.38-0.86)	0.67 (0.50-0.90)	0.007
Vegetable fiber						
Median intake (interquartile range), g/day	3.3 (2.7 to 3.8)	5.1 (4.6 to 5.5)	6.9 (6.1 to 7.6)	10.1 (8.6 to 12.3)		
No. of events	55	33	43	43		
Age, sex, stage-adjusted HR (95% CI) †	1 (referent)	0.51 (0.36-0.74)	0.57 (0.40-0.79)	0.67 (0.48-0.93)	0.81 (0.62-1.05)	0.11
Multivariable-adjusted HR (95% CI) ‡	1 (referent)	0.51 (0.34-0.75)	0.65 (0.45-0.95)	0.65 (0.44-0.98)	0.82 (0.60-1.13)	0.22
Fruit fiber						
Median intake (interquartile range), g/day	1.8 (1.2 to 2.2)	3.4 (2.9 to 3.7)	5.1 (4.5 to 5.6)	7.8 (6.8 to 9.9)		
No. of events	40	47	42	45		
Age, sex, stage-adjusted HR (95% CI) †	1 (referent)	1.06 (0.74-1.51)	0.94 (0.65-1.35)	0.94 (0.65-1.34)	0.91 (0.68-1.22)	0.53
Multivariable-adjusted HR (95% CI) ‡	1 (referent)	1.13 (0.77-1.66)	1.00 (0.67-1.51)	0.95 (0.61-1.46)	0.91 (0.64-1.28)	0.58
All-cause mortality (n=773)						
Cereal fiber						
No. of events	215	198	180	180		
Age, sex, stage-adjusted HR (95% CI) †	1 (referent)	0.78 (0.66-0.92)	0.74 (0.63-0.88)	0.68 (0.57-0.80)	0.77 (0.68-0.87)	<0.001
Multivariable-adjusted HR (95% CI) ‡	1 (referent)	0.79 (0.67-0.94)	0.76 (0.63-0.91)	0.69 (0.57-0.84)	0.78 (0.68-0.90)	<0.001
Vegetable fiber						
No. of events	207	207	176	183		
Age, sex, stage-adjusted HR (95% CI) †	1 (referent)	0.78 (0.66-0.93)	0.76 (0.64-0.90)	0.72 (0.61-0.86)	0.83 (0.73-0.93)	0.002
Multivariable-adjusted HR (95% CI) ‡	1 (referent)	0.85 (0.71-1.02)	0.81 (0.68-0.98)	0.74 (0.61-0.91)	0.83 (0.72-0.96)	0.009
Fruit fiber						

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	HR (95% CI) per 5 g/day	*P* for trend
No. of events	189	195	175	214		
Age, sex, stage-adjusted HR (95% CI) †	1 (referent)	0.96 (0.81-1.14)	0.82 (0.69-0.98)	0.80 (0.67-0.94)	0.83 (0.72-0.95)	0.005
Multivariable-adjusted HR (95% CI) ‡	1 (referent)	1.06 (0.88-1.27)	0.93 (0.77-1.13)	0.93 (0.76-1.13)	0.92 (0.78-1.08)	0.29

Abbreviation: CI, confidence interval; HR, hazard ratio.

*Post-diagnostic intake was assessed at least 6 months but no more than 4 years after diagnosis to minimize the influence of active treatment.

†Cox proportional hazards regression model stratified by age groups at diagnosis (<60, 60-64, 65-69, 70-74, and ≥75 years), sex, and cancer stage (I, II, III, and unspecified), with additional adjustment for age at diagnosis (continuous).

‡Further adjusted for year of diagnosis (continuous), tumor grade of differentiation (1-3 and unspecified), subsite (proximal colon, distal colon, rectum and unspecified), pre-diagnostic fiber intake (in quartiles), post-diagnostic alcohol consumption (<0.15, 0.15-1.9, 2.0-7.4, ≥7.5 g/d), pack-years of smoking (0, 1-15, 16-25, 26-45, >45), BMI (<23, 23-24.9, 25-27.4, 27.5-29.9, ≥30 kg/m^2), physical activity (women: <5, 5-11.4, 11.5-21.9, ≥22 MET-hours/week; men: <7, 7-14.9, 15-24.9, ≥25 MET-hours/week), regular use of aspirin (≥2 tablets per week), glycemic load, and consumption of total fat, folate, calcium, and vitamin D (in quartiles). Mutual adjustment was conducted by adjusting for fiber intake from other sources (i.e., except the one under examination).

Table 3

Post-diagnostic intake of whole grains and mortality among colorectal cancer patients (n=1,575)

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	HR (95% CI) per 20 g/day[†]	*P* for trend
CRC-specific mortality (n=174)						
Median intake (interquartile range), g/day	9.3 (5.8 to 11.7)	21.5 (18.5 to 24.5)	33.7 (30.2 to 37.0)	52.7 (46.9 to 62.9)		
No. of events	55	45	44	30		
HR (95% CI)[‡]	1 (referent)	0.76 (0.54-1.07)	0.67 (0.46-0.99)	0.50 (0.32-0.77)	0.72 (0.59-0.88)	0.002
HR (95% CI), adjusted for fiber intake	1 (referent)	0.80 (0.56-1.13)	0.74 (0.49-1.11)	0.57 (0.35-0.92)	0.77 (0.62-0.96)	0.02
All-cause mortality (n=773)						
No. of events	237	193	180	163		
HR (95% CI)[‡]	1 (referent)	0.86 (0.73-1.02)	0.87 (0.72-1.05)	0.75 (0.61-0.92)	0.88 (0.80-0.97)	0.008
HR (95% CI), adjusted for fiber intake	1 (referent)	0.89 (0.75-1.06)	0.91 (0.75-1.11)	0.81 (0.65-1.01)	0.91 (0.83-1.01)	0.08

Abbreviation: CI, confidence interval; HR, hazard ratio.

[*] Post-diagnostic intake was assessed at least 6 months but no more than 4 years after diagnosis to minimize the influence of active treatment.

[†] The unit of increment is approximately one standard deviation.

[‡] Cox proportional hazards regression model stratified by age groups at diagnosis (<60, 60-64, 65-69, 70-74, and ≥75 years), sex, and cancer stage (I, II, III, and unspecified), with additional adjustment for age at diagnosis (continuous), year of diagnosis (continuous), tumor grade of differentiation (1-3 and unspecified), subsite (proximal colon, distal colon, rectum and unspecified), pre-diagnostic intake of the food under examination (in quartiles), post-diagnostic alcohol consumption (<0.15, 0.15-1.9, 2.0-7.4, ≥7.5 g/d), pack-years of smoking (0, 1-15, 16-25, 26-45, >45), BMI (<23, 23-24.9, 25-27.4, 27.5-29.9, ≥30 kg/m^2), physical activity (women: <5, 5-11.4, 11.5-21.9, ≥22 MET-hours/week; men: <7, 7-14.9, 15-24.9, ≥25 MET-hours/week), regular use of aspirin (≥2 tablets per week), glycemic load, and consumption of total fat, folate, calcium, and vitamin D (in quartiles).