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Associations of Whole and Refined Grain Intakes with Adiposity-Related Cancer Risk in the Framingham Offspring Cohort (1991–2013)

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Abstract

Case-control studies suggest that higher whole grain and lower refined grain intakes are associated with reduced cancer risk, but longitudinal evidence is limited. The objective of this prospective cohort study is to evaluate associations between whole and refined grains and their food sources in relation to adiposity-related cancer risk. Participants were adults from the Framingham Offspring cohort (N = 3,184; ≥18 yr). Diet, measured using a food frequency questionnaire, medical and lifestyle data were collected at exam 5 (1991–95). Between 1991 and 2013, 565 adiposity-related cancers were ascertained using pathology reports. Cox proportional hazards models were used to estimate adjusted hazard ratios and 95% confidence intervals for associations of whole and refined grains with risk of adiposity-related cancers combined and with risk of breast and prostate cancers in exploratory site-specific analyses. Null associations between whole and refined grains and combined incidence of adiposity-related cancers were observed in multivariable-adjusted models (HR: 0.94; 95% CI: 0.71–1.23 and HR: 0.98; 95% CI: 0.70–1.38, respectively). In exploratory analyses, higher intakes of whole grains (oz eq/day) and whole grain food sources (servings/day)

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Notes on Contributor

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Conflict of Interest Statement

The authors declare that they have no conflict of interest.

were associated with 39% and 47% lower breast cancer risk (HR: 0.61; 95% CI: 0.38–0.98 and HR: 0.53; 95% CI: 0.33–0.86, respectively). In conclusion, whole and refined grains were not associated with adiposity-related cancer risk. Whole grains may protect against breast cancer, but findings require confirmation within a larger sample and in other ethnic groups.

Introduction

Plant based diets are widely recommended for cancer prevention (1). However, the study of dietary plant foods in relation to cancer risk has focused primarily on fruit and vegetable intake (1,2), leaving the influences of other plant foods relatively less explored. There has been much interest over the years in the possible protective effect of whole grains against cancer. Whole grains represent “the intact, ground, cracked or flaked fruit of the grains, whose principal components, the starchy endosperm, germ and bran, are present in the same relative portions as they exist in the intact grain” (3). Whole grains are recommended as an integral component of a healthy diet for the prevention of obesity, diabetes, cardiovascular disease (3), and most recently colorectal cancer in the World Cancer Research Fund/ American Institute for Cancer Research’s Continuous Update Project (4). Therefore, a more comprehensive understanding of their role in chronic disease prevention, particularly in the context of other types of cancer, is of great significance. While numerous studies have linked fiber intake from grains to cancer (5), the role of whole grains as a whole-some source of measured and unmeasured dietary constituents in cancer risk is not well understood.

Whole grains contain potential anticarcinogenic agents such as antioxidants, trace minerals, phytate, phenolic acids, phytoestrogens, and fiber (6,7). By virtue of these nutrients and nonnutrients, they may reduce cancer risk through a number of mechanisms including improved glycemic control and reduced insulin resistance, reduced sex hormone concentrations, dilution of carcinogens in the colon, and fermentation into short chain fatty acids with pro-apoptotic and antineoplastic potential in addition to providing still unknown constituents that may be protective or act synergistically (6,7). Importantly, whole grains may influence cancer risk via their effect on body adiposity, as higher whole grain and lower refined grain intakes have been associated with lower body mass index (BMI), visceral and subcutaneous and adipose tissue, and obesity risk (6–9), which play an important role in cancer etiology (1).

Whole grain intake is associated with reduced cancer mortality in cohort studies (10,11), and an inverse association with cancer risk has been reported from case-control studies (12,13). Nevertheless, findings from epidemiological cohort studies have focused primarily on colorectal cancer and have produced inconsistent results (5). About 60% of whole grain intake in the US is derived from individual food items, mostly cereals, rather than mixed dishes (3). However, most existing cohort studies, particularly in the United States, do not report associations on whole grain food sources, cumulatively and individually, in relation to cancer risk. This is important due to a potential differential physiologic role for different types of grains.

Refined grain foods are nutritionally inferior to their whole grain counterparts due to the removal of the outer bran and inner germ during the milling process resulting in loss of the

nutrients and nonnutrients (14), and thus do not confer the same potential health benefits. However, refined grain intakes constitute the majority of grain consumption and exceed recommended levels, with less than 10% of US adults meeting the recommendation of consuming half of grains as whole grains based on nationally representative data (15,16). Approximately half of refined grain intake is from mixed dishes, while 20% comes from snacks and sweets and 30% is eaten as a separate food item, such as cereals, breads, or rice (3). However, similarly to whole grains, the role of refined grains and their major food sources in cancer risk is not widely studied (17–20).

In this context of biologic plausibility and limited, inconsistent existing epidemiologic evidence, the purpose of this prospective cohort study is to investigate the impact of whole and refined grains and their major food sources on combined incidence of adiposity-related cancers in an aging sample of American adults using the data from the Framingham Offspring (FOS) cohort. In exploratory analyses, associations of whole and refined grains with the most prevalent male and female site-specific cancers, breast and prostate cancers, were evaluated with the caveat of limited power. The FOS provides a unique opportunity to investigate the role of whole and refined grain intakes in cancer etiology due to the availability of comprehensive diet data on the most commonly consumed whole and refined grain foods and the ability to decipher their whole and refined grain content using the US Department of Agriculture Nutrient Database. The analysis was limited to adiposity-related cancers, which may be avertable through dietary modification due to their hypothesized association with lifestyle factors.

Methods

Study Population

The study sample consisted of participants from the FOS that represents the second familial generation of the Framingham Heart Study (FHS). Recruitment for the FOS cohort began in 1971–1975 through enrollment of 5,124 offspring of the original cohort of FHS participants and their spouses (21). Clinical exams were conducted, on average, every 4 yr and included physical examinations, anthropometric measurements, laboratory tests, and health-related questionnaires (21). The collection of dietary data was initiated during the fifth clinical exam in 1991–1995 and was available for 3,418 participants. Therefore, this was considered the baseline examination for the present analyses.

Participants with valid diet data at clinical exam 5 were included in the present analyses. Dietary information was considered valid if reported energy intakes were between 600–4,199 kcal/day and 600–3,999 kcal/day for men and women, respectively, and if less than 13 food items were left blank (22) Participants with “implausible intakes” as per these guidelines established by the FHS were excluded (n = 98). Women who were pregnant at exam 5 were removed from these analyses (n = 2). Participants with a cancer diagnosis prior to exam 5 were also excluded (n =134). Based on these inclusion and exclusion criteria, a total of 3,184 participants were included in the final analytical sample. The Institutional Review Board for Research with Human Subjects at New York University approved of all research activities (IRB #10–7319). Informed consent was obtained from all individual

participants included in the study, and research activities complied with the 1964 Helsinki Declaration.

Assessment of Dietary Intake

Habitual dietary intake over the previous year was assessed using the 126-item semi-quantitative Harvard food frequency questionnaire (FFQ), which has been previously validated by comparison with multiple diet records and shown an average de-attenuated correlation of 0.83 for dietary nutrient intakes (23). Whole grain food intake assessed by this questionnaire has been inversely associated with risks of total mortality (24) and type 2 diabetes (25), thereby also providing an indirect measure of validity of this FFQ for assessment of whole grain intakes. In the FOS, FFQs were mailed to participants for completion before the clinical exam. Participants were asked to bring the completed questionnaire with them to the study appointment for revision with trained personnel. Participants reported the frequency with which they consumed a list of foods with standard serving sizes. Intakes of whole and refined grains in addition to other dietary covariates were estimated for each individual by multiplying the reported frequency of consumption of foods by nutrient content of the portion consumed, estimated using the US Department of Agriculture Nutrient Database, and summing relevant food items (26).

Whole grain intakes were derived from the reported consumption of whole grain food sources including whole-grain cold breakfast cereal, oatmeal, dark bread, brown rice, other grains (e.g., bulgur, kasha, couscous), popcorn, bran, and wheat germ. As previously published in FHS (9,27), a serving of whole or refined grains was equivalent to a MyPyramid Equivalents Database portion unit of whole and refined grain food sources. Whole-grain food sources included whole grain cold breakfast cereal, cooked oatmeal, brown rice or other grains, dark bread, popcorn, added bran or added germ. Refined-grain food sources included refined-grain cold breakfast cereal, other cooked breakfast cereal, white bread, English muffins, bagels, muffins, biscuits, white rice, pasta, pancakes, waffles, crackers, and pizza. Cold breakfast cereals were classified as either whole grain (≥25% whole grain or bran by weight) or refined grain (<25% whole grain or bran by weight) using the definition by Jacobs et al. (28). Brand names were used to classify cold breakfast cereals as whole vs. refined grain.

Cancer Case Ascertainment

Cancers were considered adiposity-related if identified by the American Cancer Society or the National Cancer Institute as clearly or possibly linked to overweight and obesity (29,30). This definition included cancers of the gastrointestinal tract, reticuloendothelial system (blood, bone, and spleen), female reproductive tracts, genitourinary organs, and the thyroid gland. Cancer cases were obtained from the FHS cancer files, which include confirmed primary cancers ascertained from pathology reports with some diagnoses (<5%) based solely on death certificates or clinical reports without pathology reports. Self-reported or suspected diagnoses not confirmed by pathology reports were excluded from these analyses. The FHS cancer files also provided information on cancer type and date of diagnosis obtained from the patients' medical records. A total of 565 primary adiposity-related cancers occurred after exam 5. Female cancers (n =162) included breast, ovarian, endometrial, and cervical

cancers. Gastrointestinal cancers (n =102) included esophageal, colorectal, gastric, liver, gallbladder, and pancreatic cancers. Genitourinary cancers (n =220) included prostate, bladder, and renal cancers. Cancers of the reticuloendothelial system (n =65) included all cancers of the blood, bone, and spleen. The most prevalent cancers were breast (n = 124), prostate (n = 157), and colorectal cancers (n = 68).

Assessment of Covariates

Age was reported at every clinical exam and the number of years of education was reported during in-person interviewing at exam 2. Lifestyle covariates were also self-reported at each clinical exam and used to classify participants by smoking status (current/former/non-smoker) and to compute total alcohol intake (ounces per wk) and a physical activity index (PAI) (>33 = high, 30–33 = moderate and <30 = low) (31). Anthropometric measures including weight, height, and waist circumference (WC) were measured at exam 5 by trained personnel. BMI was calculated using the formula: weight (kg)/height squared (m^2). Participants were considered "normal," "overweight," and "obese" if their BMI was <25, 25–29.9, ≥30 kg/m^2, respectively (32). For WC measurements, men and women with WC >40 and >35 inches, respectively, were considered "at risk" (33). Participants were considered to have a history of chronic disease based on the presence or absence of diabetes and cardiovascular disease (CVD) at or prior to exam 5. Participants were considered to have diabetes if their fasting blood glucose was ≥126 mg/dl or if they reported receiving diabetes treatment. They were considered to have CVD as defined previously by FHS (34). Among women, menopausal status was assessed using a standardized medical history questionnaire, and hormone therapy (HT) use was ascertained by the examining physician.

Statistical Methods

Clinical, demographic, and dietary characteristics were compared across the quintiles of whole grain intake (ounce equivalents/day) using the general linear models procedure (PROC GLM). Whole and refined grain intakes in ounce equivalents per day (oz eq/day) and total whole and refined grain food intake in servings/day were categorized into quintiles for the main analyses with adiposity-related cancers combined as an outcome and categorized into tertiles for the exploratory site-specific analyses, given the limited number of breast and prostate cancers. Individual whole and refined grain foods were categorized into tertiles for all analyses, because the range of intakes was too limited to use quintiles based on the frequencies of consumption of these foods.

Cox proportional hazards regression models were used to estimate age- and multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CI) for the hypothesized associations between whole and refined grains and their food sources in relation to adiposity-related cancer risk. Exploratory site-specific analyses were conducted for breast and prostate cancers with the caveat of limited power. To evaluate grain intake and cancer risk, participants contributed years from the date at baseline (exam 5) until the date of cancer diagnosis, death, or end of follow-up period, whichever was earlier (median follow-up was 13.1 yr). Participants who were lost to follow-up or died from other causes were censored. The test for linear contrast was used to compute P-trend values for the detection of a linear trend across the quintiles of whole and refined grain consumption in the main analyses with

adiposity-related cancers. Results were considered statistically significant if *P* values were <0.05.

Multivariable regression models for all cancer outcomes were adjusted for established cancer risk factors, selected *a-priori* based on World Cancer Research Fund/American Institute of Cancer Research report (1), including age (yr), sex (male vs. female), smoking (current, former, nonsmoker), alcohol (ounces/wk), and energy intake (kcal). In the analyses restricted to breast cancer, we further adjusted for menopausal status, HT use (users vs. nonusers), age at menopause (yr), and number of live births. For all analyses, other potential confounders including history of CVD or diabetes (previous diagnosis of CVD and/or diabetes vs. no diagnosis), education (yr), physical activity (high, moderate, low), antioxidant supplement use (users vs. nonusers), fruit and vegetable intake (servings/day), and energy intake from total, trans, and saturated fat (%kcal) were tested in the models. The whole grain models were also tested for adjustment for intakes of refined grains (oz eq/day) and vice versa. These covariates were added singularly to the model and were retained in the final models if they had an impact of >10% on HRs.

To determine whether BMI and WC are confounders or modify the impact of grains on adiposity-related cancers, models were fitted with and without BMI and WC. Models were re-run by BMI (“normal” vs. “overweight and obese”) and WC strata (“normal” vs. “at risk”) if interactions with BMI and WC were statistically significant. Similarly, we tested for interactions with sex, smoking status (“ever smoker” vs. “never smoker”), and physical activity due to the potential impact of these factors on the cancer risk, which may cause the risk estimates to vary (1). A multiplicative term was introduced for these potential interactions in each model. A $P < 0.1$ was considered significant, and if present, results were reported separately in subgroups. All statistical analyses were conducted using SAS statistical software (version 9.3; SAS Institute, Cary, NC).

Results

Characteristics of the Study Population Across the Quintiles of Whole Grain Intake at Exam 5 (Ounce Equivalents/Day)

Demographic, clinical, and dietary characteristics of the study population across the quintiles of whole grain intake at exam 5 (oz eq/day) are shown in Table 1. The mean age was higher in the fifth vs. first quintile of intake (56.0 vs. 54.6 yr), as was the percentage of females (53.8 vs. 47.9%) and the number of years of education (14.5 vs. 13.4 yr) ($P \leq 0.021$). BMI and PAI were lower in the fifth vs. first quintile (27.0 vs. 27.8 kg/m^2 and 34.8 vs. 35.1, respectively ($P \leq 0.039$)) and indicated that the sample was, on average, overweight and characterized by relatively high levels of physical activity. Similarly, WC was lower across the increasing quintile categories of whole grain intake from 37.1 to 36.1 inches ($P = 0.005$).

The use of antioxidant supplements increased across the quintiles of whole grain intake (29.5% vs. 43.3%) ($P < 0.0001$). The percentage of current, former, and never smokers varied significantly across the categories of intake ($P < 0.0001$). In general, the percentage of “never” and “former” smoker was higher and that of “current” smokers was lowest among

participants who are in the highest quintile of whole grain consumption. Among women, those in the highest quintile of whole grain intake were more likely to be postmenopausal (67.1 vs. 64.9%) ($P = 0.018$) and to report HT use (12.6 vs. 7.4%) ($P = 0.002$).

In this cohort the mean intakes of whole and refined grains were 1.2 and 4.0 oz eq/day, respectively, representing approximately 22.3% of total grain intake consumed as whole grains. We also characterized the study population's dietary intakes by quintiles of whole grain intake. Participants in the highest quintile reported higher total energy intakes (2186.8 vs. 1653.3 kcal), energy intake from carbohydrate (54.4 vs. 48.7%), and energy intake from protein (16.8 vs. 16.2%) and lower energy intake from fat (25.6 vs. 28.6%) compared to those in the lowest quintile ($P < 0.0001$). Participants with higher whole grain intakes also reported higher intakes of fruits and vegetables, legumes, and fiber ($P < 0.0001$). However, they reported significantly lower intakes of alcohol (2.0 vs. 3.0 ounces/wk) ($P < 0.0001$). There were no statistically significant differences in intakes of refined grains ($P = 0.20$) or red and processed meat across the quintiles of whole grain consumption ($P = 0.27$).

Whole Grains and Cancer Risk

Whole grain intake (oz eq/day) in the highest vs. lowest quintile was not associated with combined incidence of adiposity-related cancers in age-adjusted models (HR: 0.88; 95% CI: 0.68–1.14) and models adjusted for age, sex, energy intake, alcohol, and smoking (HR: 0.94; 95% CI: 0.71–1.23) (P-trend = 0.53) (Table 2). Additional adjustment for BMI, WC, chronic diseases (CVD and diabetes), physical activity, antioxidant use, percentage energy intake from fat, fruit and vegetable, and refined grain intake did not alter these findings. Additionally, participants with higher percentage of total grains consumed as whole grains did not have a statistically significant reduction in adiposity-related cancer risk in multivariable-adjusted models (HR: 0.84; 95% CI: 0.64–1.10) (P-trend = 0.80).

In analyses of site-specific cancers (Table 3), null associations were also observed for whole grain intake and percentage of total grains consumed as whole grains in relation to prostate cancer risk in age- and multivariable-adjusted models (nonsignificant HR ranging from 1.27 to 1.47). However, for breast cancer, higher whole grain consumption was associated with a 39% reduction in risk (HR: 0.61; 95% CI: 0.38–0.98) in models adjusted for age, energy intake, smoking, alcohol, age at menopause, menopausal status, number of live births, and HT use. Additional adjustment for other potential confounders did not significantly alter these associations.

No associations were observed for total intake of whole grain foods (servings/day) in age-adjusted models (HR: 0.95; 95% CI: 0.74–1.23) and multivariable-adjusted models for adiposity-related cancers (HR: 1.03; 95% CI: 0.79–1.35) (P-trend = 0.93) (Table 2). Similarly, no associations were noted for consumption of whole grain foods and risk of prostate cancers in age- and multivariable-adjusted models (HR: 1.22; 95% CI: 0.83–1.80) (Table 3). However, consumption of whole grain food sources in the highest vs. lowest tertile of intake was associated with 47% lower breast cancer risk in multivariable-adjusted models (HR: 0.53; 95% CI: 0.33–0.86). When tertiles of individual commonly consumed whole grain foods were examined separately, there were no significant associations between whole grain cereals, brown rice, and dark bread in relation to adiposity-related cancers or

any of the site-specific cancers. However, consumption of popcorn in the highest vs. lowest tertile was associated with 25% higher risk of adiposity-related cancers in multivariable-adjusted models (HR: 1.25; 95% CI: 1.01–1.26).

Next, we tested for interactions for the associations between whole grain intake (oz eq/day) and intake of whole grain foods (servings/day) with sex, BMI, WC, physical activity, and smoking status in relation to adiposity-related cancers. There were no significant interactions by BMI, WC, or physical activity ($P \geq 0.106$). A statistically significant multiplicative interaction was observed for sex ($P = 0.007$) and smoking status ($P = 0.09$) with whole grain intake (oz eq/day) and for sex ($P = 0.01$) with intake of whole grain food sources (servings/day). However, stratified analyses by sex and smoking status ("ever" vs. "never") did not reveal any significant associations (data not shown).

Refined Grains and Cancer Risk

Similarly to the reported findings on whole grains, there was no association between refined grain intake and combined incidence of adiposity-related cancers in age-adjusted (HR: 1.00; 95% CI: 0.76–1.31) and multivariable-adjusted models (HR: 0.98; 95% CI: 0.70–1.38) (P-trend = 0.77) (Table 2). Null results were also observed for breast and prostate cancers in multivariable adjusted models (nonsignificant HR ranging from 0.76 to 1.26) (Table 3). When intakes of refined grain food sources were examined, there were also no significant associations for adiposity-related cancers or any of the site-specific cancers (nonsignificant HRs ranging from 0.70 to 1.23) (Tables 2 and 3). An investigation of individual commonly consumed refined grain foods including, refined grain cereals, white rice, white bread, baked goods, and grain desserts, in relation to cancer risk also revealed no significant associations (data not shown).

Next, we tested for interactions for the associations between refined grain intake (oz q/d) and intake of refined grain foods (servings/day) with sex, BMI, WC, physical activity and smoking status in relation to adiposity-related cancers. There were no significant interactions by physical activity level ($p \geq 0.36$). A statistically significant multiplicative interaction was observed for sex ($P \leq 0.008$), WC ($P \leq 0.014$), BMI ($P \leq 0.08$) and smoking status ($P \leq 0.05$) with both refined grain intake (oz eq/day) and intake of refined grain food sources (servings/day). However, stratified analyses by BMI and WC and by sex did not reveal any significant associations (data not shown).

Discussion

In this cohort of aging American adults, there was no overall association between intakes of whole and refined grains and their major food sources in relation to combined incidence of adiposity-related cancers. These null findings persisted after stratification by sex, BMI, WC, physical activity level, and smoking status. It is notable, that the FOS cohort reported higher whole grain intakes than the general US population. A recent analysis using National Health and Nutrition Examination Survey (NHANES) 2001–2010 (15) showed that the mean whole grain intake for adults 19–50 yr and ≥51 yr was 0.61 and 0.86 oz eq/day, respectively, which is less than the whole grain intakes reported in this study (1.2 oz eq/day). In previous analyses (35), we have shown that FOS participants at exam 5 also report moderate-to-high

levels of physical activity, lower intakes of dietary fat, higher intakes of fiber and fruits and vegetables compared to NHANES findings (3,36). Furthermore, while the FOS sample was on average overweight, the mean BMI was lower than that observed in the US population (27.4 vs. 28.7 kg/m^2) (37). Therefore, FOS participants may be healthier than the general population. Hence, the risk estimates may be attenuated, thereby underestimating the effects that could be expected in the general population.

While whole grain foods, collectively, were not associated with adiposity-related cancer risk, higher popcorn consumption was associated with 25% higher risk of these cancers. This finding of a detrimental effect on cancer risk may be due to chance, given the number of multiple comparisons for the individual whole grain food sources that were conducted in these analyses, and warrants confirmation in future studies with larger sample sizes. This can also be attributed to the marketing and purchase of large portion sizes of this snack food or to the butter, salt, and sugar that are typically added to microwave popcorn (38), which can lead to overeating and consequently obesity, an established risk factor for these cancers (39). However, in this cohort, adjustment for energy intake and measures of body adiposity did not alter these findings.

In site-specific analyses, null results were observed for refined grains in relation to breast and prostate cancers and for whole grains in relation to prostate cancer. Higher consumption of whole grains and whole grain food sources was associated with a 39% and 47% reduction in breast cancer risk, respectively. This finding may be due to chance given the limited power for these site-specific analyses, as multiple previous studies report null findings for whole grains in relation to breast cancer (reviewed in (5)). However, these findings are in agreement with a recent analysis within the Nurses Health Study II, which showed that adult intake of whole grain foods was associated with 18% lower premenopausal breast cancer risk (20). This association is biologically plausible, as whole grains are associated with lower measures of body adiposity (9,27). In this cohort, participants with higher whole grain consumption had lower BMI ($P = 0.025$) and WC ($P = 0.005$), although adjustment for these risk factors did not significantly alter HRs. Whole grains may also reduce breast cancer risk by virtue of their cereal fiber content, which has been shown to protect against breast cancer in previous studies (reviewed in (40)). Fiber is associated with lower body adiposity and serum estrogen levels (40,41), thereby potentially lowering cancer risk. However, adjustment for fiber intake also did not alter these findings. Nevertheless, whole grains are also a source of phytoestrogens, which impact sex hormone production and metabolism, thereby potentially conferring protection against hormone related cancers (6). Phytoestrogens reduce circulating estrogen levels, inhibit tumor growth and initiation, and lower early markers of risk for mammary carcinogenesis (6).

Our overall null results for adiposity-related cancers are in agreement with a recent systematic review of prospective cohort studies (5), which has shown that most studies on whole grains and cancer report no association. Nevertheless, in that review (5), approximately half of the studies on gastrointestinal cancers were suggestive of a 6–47% reduction in cancer risk with higher whole grain intakes (5). For colorectal cancer, 3 (42–44) out of 7 studies (19,42–47) reported a 6–33% reduction in risk with higher whole grain consumption. More recently, a study within the Scandinavian HELGA cohort reported 45%

lower risk of oesophageal cancer when comparing the highest vs. the lowest tertile of whole grain intakes (48). Collectively, these findings indicate that whole grains may be particularly protective against gastrointestinal cancers. However, we did not have sufficient site-specific adiposity-related cancer cases to evaluate these associations in the FOS cohort.

Prospective epidemiologic evidence on refined grains and cancer is more limited, but previous studies (17–20) are also consistently indicative of a null association, particularly for breast cancers (17,20). It is important to note that some evidence is suggestive that high intakes of grains (both whole and refined) could be a marker of a diet that is low in energy (49), which would reduce the risk of obesity and consequently cancers (50). Therefore, the null associations in this study may be attributable to a potential protective role of total grain intake in general, rather than whole grain intake specifically. However, in this cohort higher grain consumption was not associated with lower energy intakes, and in exploratory analyses on total grains and cancer, we did not find any significant associations.

Another potential explanation for the null results on refined grains is that participants in the highest quintile of refined grain intake were more likely to be younger and educated, and women were less likely to be postmenopausal and to report HT use (Supplementary Table 1). They also reported higher intakes of fruits and vegetables, legumes and fiber and had nonsignificantly lower alcohol intakes and higher whole grain intakes, which may have mitigated any potential detrimental impact of refined grains. However, adjustment for these covariates did not alter our null findings. Furthermore, there is evidence that the Harvard FFQ reportedly underestimates refined grain intake when compared with diet records (51). This may have also biased results and may explain, at least in part, the absence of an association between refined grain consumption and cancer in this study.

Another limitation is the possible misclassification and underestimation of whole grain intakes by the FFQ. Misclassification of dietary exposures is always a potential limitation of observational studies, especially when certain assumptions are made to classify foods as whole or refined grain food sources. For instance, the assumption is that foods, such as pasta and crackers, are sources of refined grains, yet it is possible that participants are consuming a whole grain variety given the increasing availability of whole grain foods. Alternatively, the assumption that dark breads are largely made from whole grain flour can also lead to measurement error and misclassification of subjects. These types of misclassification may have biased our findings toward the null.

Observational studies rely on estimates of whole grains based on data from recipes or food packaging, but whole grain content is often not reported precisely on ingredient lists (52). This limits the accuracy of whole grain estimation and potentially introduces bias to the findings of observational studies on whole grains and health. Another issue that warrants mention is our definition of whole grain foods. The US Food and Drug Administration (FDA) states that to qualify for the whole grains health claim, a product must include 51% whole grains by weight (53). However, presently, there is no universally accepted definition of whole grains (52). In this study, in consistency with previous FOS studies on whole grains (9,27), we considered cold breakfast cereals that were ≥25% whole grain by weight whole grain products using the definition by Jacobs et al. (28). While this is inconsistent with the

FDA definition, a study among British adults has shown that foods that are 51% whole grain by weight accounted for only 27% of whole grain intake (54).

Other study limitations pertain to our sample characteristics. FHS participants are primarily Caucasian. Therefore, results of this study may not be representative of the general population or generalizable to other racial and ethnic groups for which associations between nutritional factors and cancer may vary. Furthermore, while we examined whole and refined grains in relation to combined incidence of adiposity-related cancers, we were unable to investigate these associations by cancer site and subtype, with the exception of breast and prostate cancer, due to the limited number of cancer cases. Lastly, although models were adjusted for established or hypothesized medical, lifestyle, and dietary risk factors for cancer, we cannot rule out residual confounding by unknown factors.

The strengths of this study include the use of reliable measures to ascertain exposures, outcomes, and covariates. The study employed a validated widely used FFQ to measure grain consumption and other aspects of diet, and the definition of whole grain foods was clearly stated. Both absolute whole and refined grain intakes (oz eq/day) and intakes of whole and refined grain products (servings/day) were evaluated in consistency with recent recommendations for reporting whole grain intakes in observational studies (52). Cancer cases were ascertained using pathology reports and medical records. Anthropometric and lifestyle measures were obtained by trained personnel, and medical data were confirmed by the examining physician. The prospective design and long duration of follow-up for approximately 2 decades are also strengths of this study.

Currently, dietary guidance on grains recommends consuming at least half of grains as whole grains (3). The cancer prevention guidelines of the American Institute for Cancer Research recommend eating relatively unprocessed cereals with every meal and limiting the intake of refined starchy foods (1). Despite the overall lack of association between whole grain intake and adiposity-related cancer risk in this study and in most previous longitudinal studies (reviewed in (5)), in exploratory analyses, we documented that higher whole grain intakes may protect against breast cancer. Moreover, whole grains have been linked to lower risk of obesity and diabetes (41), which are in turn risk factors for some cancers (50,55). Therefore, health professionals who advise on cancer and public health initiatives need to promote the substitution of refined grains with whole grains due to their generally protective role in chronic disease prevention when consumed in the context of an overall healthy diet.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Participant characteristics at exam 5 (1991–95) by quintile categories of whole grain intakes (oz eq/day).

Whole grain intake (oz eq/day)	**<0.23 oz eq/day (*N* = 635)**	**0.23–0.59 oz eq/day (*N* = 632)**	**0.59–1.12 oz eq/day (*N* = 644)**	**1.12–1.93 oz eq/day (*N* = 643)**	**>1.93 oz eq/day (*N* = 630)**	
Characteristics	**Percentage/Mean (SD)**	**Percentage/Mean (SD)**	**Percentage/Mean (SD)**	**Percentage/Mean (SD)**	**Percentage/Mean (SD)**	***P* value**
Age (yr)	54.6 (9.7)	53.3 (9.8)	53.3 (10.0)	54.4 (9.3)	56.0 (9.6)	<0.0001
Female (%)	47.9%	51.9%	55.0%	56.6%	53.8%	0.021
Education (yr)	13.4 (2.5)	13.9 (2.6)	14.1 (2.6)	14.5 (2.6)	14.5 (2.7)	<0.0001
Physical activity	35.1 (6.6)	35.2 (6.6)	34.5 (5.8)	34.3 (5.7)	34.8 (6.2)	0.039
BMI (kg/m^2)[a]	27.8 (5.1)	27.3 (5.0)	27.5 (4.9)	27.2 (4.9)	27.0 (4.8)	0.025
Waist circumference (inches)	37.1 (5.7)	36.5 (5.7)	36.7 (5.6)	36.1 (5.5)	36.1 (5.6)	0.005
Smoking status (%)						
Current smoker	30.7%	23.8%	17.6%	13.6%	11.4%	<0.0001
Former smoker	41.4%	41.3%	45.2%	45.0%	43.4%	
Never smoker	28.0%	34.9%	37.1%	41.4%	45.3%	
Antioxidant use(%)[b]	29.5%	30.1%	38.2%	40.0%	43.3%	<0.0001
Postmenopausal (%)	64.9%	59.2%	59.4%	69.0%	67.1%	0.018
HT use (%)[1]	7.4%	8.7%	10.0%	13.2%	12.6%	0.002
Diet						
Total calories (kcal)	1653.3 (604.2)	1781.4 (611.4)	1817.6 (583.6)	1904.8 (578.8)	2186.8 (617.0)	<0.0001
Total carbohydrates (%kcal)	48.7 (9.1)	49.0 (8.5)	50.2 (8.0)	52.1 (7.6)	54.4 (7.6)	<0.0001
Total protein (%kcal)	16.2 (3.8)	16.5 (3.5)	17.2 (3.2)	17.3 (3.2)	16.8 (2.8)	<0.0001
Total fat (%kcal)	28.6 (6.6)	28.5 (5.9)	27.8 (5.5)	26.5 (5.5)	25.6 (5.9)	<0.0001
Fruits and vegetables (servings/day)	2.6 (1.7)	3.1 (2.1)	3.6 (2.0)	4.0 (2.1)	5.0 (2.9)	<0.0001
Legumes (servings/wk)	1.8 (1.7)	2.1 (1.6)	2.3 (1.8)	2.6 (1.8)	3.2 (2.7)	<0.0001
Refined grains (oz eq/day)	4.0 (2.3)	4.1 (2.1)	4.0 (2.0)	3.9 (2.0)	4.2 (2.2)	0.20
Fiber intake (g/day)	12.7 (5.4)	14.9 (5.8)	16.9 (5.5)	19.7 (6.1)	25.1 (8.9)	<0.0001
Red and processed meat (servings/wk)	5.5 (4.6)	5.5 (4.1)	5.4 (4.0)	5.0 (4.5)	5.1 (4.5)	0.27
Alcohol (oz/wk)	3.0 (4.6)	2.8 (4.1)	2.6 (4.0)	2.2 (2.9)	2.0 (3.1)	<0.0001

[a]BMI, body mass index; HT, hormone therapy.

[b]Participants were considered users of antioxidant supplements if they reported taking supplements of at least 1 of the following on the FFQ: vitamin A, vitamin C, vitamin E, selenium, beta-carotene.

Table 2.

Adjusted hazard ratios (95% confidence intervals) for adiposity-related cancers by quintile categories of whole and refined grain intakes and foods (*N* = 3,184).

Whole grain intake (oz eq/day)	<0.23	<.23–0.59	0.59–1.12	1.12–1.93	>1.93	*P for trend*
At risk (cases)	635(112)	632(105)	644(119)	643(111)	630(118)	
Age-adjusted	1.00	1.02(0.78–1.33)	1.09(0.84–1.41)	0.91(0.70–1.18)	0.88(0.68–1.14)	0.22
Multivariable-adjusted[c,d]	1.00	1.04(0.79–1.36)	1.19(0.92–1.54)	0.97(0.74–1.27)	0.94(0.71–1.23)	0.53
Whole grain foods[a] (servings/day)	<0.28	0.28–0.64	0.64–1.13	1.13–1.85	>1.85	*P for trend*
At risk (cases)	671(113)	661(110)	562(104)	652(113)	638(125)	
Age-adjusted	1.00	1.03(0.80–1.34)	1.17(0.89–1.52)	0.97(0.75–1.26)	0.95(0.74–1.23)	0.60
Multivariable-adjusted[c,d]	1.00	1.07(0.82–1.39)	1.28(0.98–1.68)	1.04(0.79–1.35)	1.03(0.79–1.35)	0.93
% Total grains as whole grains	<6.0%	6.0–14.2%	14.2–23.8%	23.8–37.0%	>37.0%	*P for trend*
At risk (cases)	639(119)	612(83)	679(132)	620(119)	634(112)	
Age-adjusted	1.00	0.84(0.64–1.12)	1.01(0.88–1.31)	1.10(0.90–1.49)	0.82(0.68–1.09)	0.38
Multivariable-adjusted[c,d]	1.00	0.86(0.65–1.15)	1.05(0.82–1.35)	1.14(0.88–1.48)	0.84(0.64–1.10)	0.80
Refined grain intake (oz eq/day)	<2.26	2.26–3.16	3.16–4.14	4.14–5.52	>5.52	*P for trend*
At risk (cases)	636(110)	655(132)	626(110)	630(111)	637(102)	
Age-adjusted	1.00	1.18(0.91–1.52)	1.12(0.85–1.44)	1.10(0.84–1.42)	1.00(0.76–1.31)	0.22
Multivariable-adjusted[c,d]	1.00	1.18(0.91–1.54)	1.14(0.86–1.51)	1.09(0.81–1.46)	0.98(0.70–1.38)	0.77
Refined grain foods (servings/day)[b]	<1.81	1.81–2.62	2.62–3.56	3.56–5.25	>5.25	*P for trend*
At risk (cases)	640(120)	634(114)	640(103)	635(116)	635(112)	
Age-adjusted	1.00	1.11(0.86–1.44)	0.84(0.64–1.09)	1.20(0.92–1.55)	0.97(0.75–1.26)	0.97
Multivariable-adjusted[c,d]	1.00	1.19(0.91–1.55)	0.89(0.68–1.18)	1.26(0.94–1.68)	0.99(0.72–1.36)	0.93

[a] Whole grain foods included whole grain cold breakfast cereal, cooked oatmeal, brown rice, other grains, dark bread, popcorn, bran and wheat germ.

[b] Refined grain foods included refined grain cold breakfast cereal and other cooked cereal, sandwiches and casseroles, white bread, English muffins or bagels, muffins or biscuits, white rice, pasta, pancakes or waffles, crackers, pizza, cookies, brownies, doughnuts, cakes, sweet rolls, pies, and chowder.

[c] Models were adjusted for age, sex, smoking, alcohol, and energy intake.

[d] Additional adjustment for BMI, WC, height, chronic diseases (CVD and diabetes), physical activity, antioxidant use, percentage energy from fat, and refined grain intake did not significantly alter these findings.

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Table 3.

Adjusted hazard ratios (95% confidence intervals) for site-specific cancers by tertile categories of whole and refined grain intakes and foods (*N* = 3,184).

	Breast cancer (*N* = 124)[c]			Prostate cancer (*N* = 157)[d]		
	At risk (cases)	Age-adjusted	Multivariable-adjusted[e,g]	At risk (cases)	Age-adjusted	Multivariable-adjusted[f,g]
Whole grain intake (oz eq/day)						
Tertile 1	560 (47)	1.00	1.00	501 (41)	1.00	1.00
Tertile 2	588 (44)	0.84 (0.56–1.27)	0.84 (0.55–1.28)	504 (53)	1.39 (0.92–2.10)	1.45 (0.96–2.19)
Tertile 3	541 (33)	0.63 (0.40–0.98)	0.61 (0.38–0.98)	490 (63)	1.42 (0.95–2.10)	1.47 (0.97–2.24)
Whole grain foods (servings/day)[a]						
Tertile 1	518 (47)	1.00	1.00	550 (54)	1.00	1.00
Tertile 2	615 (44)	0.74 (0.49–1.12)	0.75 (0.50–1.14)	459 (40)	1.00 (0.66–1.50)	0.99 (0.65–1.50)
Tertile 3	556 (33)	0.56 (0.36–0.88)	0.53 (0.33–0.86)	486 (63)	1.20 (0.83–1.74)	1.22 (0.83–1.80)
% Total grains as whole grains						
Tertile 1	543 (43)	1.00	1.00	475 (40)	1.00	1.00
Tertile 2	578 (40)	0.89 (0.58–1.37)	0.92 (0.59–1.41)	522 (60)	1.28 (0.85–1.91)	1.31 (0.87–1.97)
Tertile 3	568 (41)	0.83 (0.54–1.29)	0.79 (0.51–1.24)	498 (57)	1.21 (0.80–1.81)	1.27 (0.84–1.92)
Refined grain intake (oz eq/day)						
Tertile 1	545 (40)	1.00	1.00	495 (59)	1.00	1.00
Tertile 2	583 (40)	0.92 (0.59–1.42)	0.98 (0.61–1.56)	507 (50)	0.96 (0.66–1.40)	0.88 (0.59–1.32)
Tertile 3	561 (44)	1.04 (0.68–1.61)	1.26 (0.73–2.17)	493 (48)	0.93 (0.63–1.36)	0.76 (0.46–1.25)
Refined grain foods (servings/day)[b]						
Tertile 1	557 (41)	1.00	1.00	490 (55)	1.00	1.00
Tertile 2	570 (41)	0.90 (0.58–1.39)	1.00 (0.63–1.59)	509 (57)	1.16 (0.80–1.69)	1.04 (0.70–1.56)
Tertile 3	562 (42)	1.01 (0.65–1.55)	1.23 (0.73–2.09)	496 (45)	0.86 (0.58–1.28)	0.70 (0.42–1.17)

[a]Whole grain foods included whole grain cold breakfast cereal, cooked oatmeal, brown rice, other grains, dark bread, popcorn, bran and wheat germ.

[b]Refined grain foods included refined grain cold breakfast cereal and other cooked cereal, sandwiches and casseroles, white bread, English muffins or bagels, muffins or biscuits, white rice, pasta, pancakes or waffles, crackers, pizza, cookies, brownies, doughnuts, cakes, sweet rolls, pies, and chowder.

[c]For breast cancers, tertile cut-offs were as follows for: whole grain intake (oz eq/day): T1: 0.50, T2: 0.50–1.35. T3: >1.35; whole grain foods (servings/day): T1: <0.56, T2: 0.56–1.35, T3: >1.35; percentage of total grain as whole grains: T1: <12.34%, T2: 12.34–29.45%, T3: 29.45%; refined grain intake (oz eq/day): T1: <2.73, T2: 2.73–4.31, T3: >4.31; for refined grain food intake (servings/day): T1: <2.20, T2: 2.20–3.76, T3: >3.76.

[d] For prostate cancers, tertile cut-offs were as follows for whole grain intake (oz eq/day): T1: 0.43, T2: 0.43–1.24. T3: >1.24; whole grain foods (servings/day): T1: <0.50, T2: 0.50–1.28, T3: >1.28; percentage of total grain as whole grains: T1: <9.49%, T2: 9.49–25.25%, T3: >25.25%; refined grain intake (oz eq/day): T1: <3.00, T2: 3.00–4.88, T3: >4.88; for refined grain food intake (servings/day): T1: <2.20, T2: 2.20–3.76, T3: >3.76.

[e] Models were adjusted for age, smoking, alcohol, energy intake, menopausal status, age at menopause, hormone therapy use, and number of live births.

[f] Models were adjusted for age, smoking, alcohol, and energy intake.

[g] Additional adjustment for BMI, WC, height, chronic diseases (CVD and diabetes), physical activity, antioxidant use, percentage energy from fat, fruit and vegetable intake, and refined grain intake did not significantly alter these findings.