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Association of whole grain food consumption with lung cancer risk: a prospective cohort study

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Abstract

Background Whether the intake of whole grain foods can protect against lung cancer is a long-standing question of considerable public health import, but the epidemiologic evidence has been limited. Therefore we aim to investigate the relationship between whole grain food consumption and lung cancer in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) cohort.

Methods Diet was assessed with a self-administered Diet History Questionnaire (DHQ) at baseline. All incident lung cancer cases were pathologically verified. Hazard ratios and 95% confidence intervals for lung cancer risk associated with whole grain food consumption were estimated by Cox proportional hazards regression.

Results During a median follow-up of 12.2 years, a total of 1,706 incident lung cancer events occurred, including 1,473 (86.3%) cases of non-small cell lung cancer (NSCLC) and 233 (13.7%) of small cell lung cancer (SCLC). After multivariate adjustment, comparing the highest quarter of consumption of whole grain foods to the lowest quarter, a 16% lower rate (HR 0.84, 95% CI 0.73–0.98) of lung cancer risks and a 17% lower rate (HR 0.83, 95% CI 0.69–0.98) for NSCLC were found, but no significant difference was shown for SCLC (HR 0.95, 95% CI 0.63–1.44). These results were consistently observed after a large range of subgroup and sensitivity analyses. A linear dose-response pattern was shown for lung cancer, NSCLC, and SCLC (P for non-linearity > 0.05).

Conclusions In this large prospective cohort study, whole grain food consumption was associated with reduced lung cancer and NSCLC. Our findings suggest a potential protective role of whole grain foods against lung cancer.

Keywords Whole grain foods, Lung cancer, Non-small cell lung cancer, Small cell lung cancer, Cohort study

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What we already know about this topic

1. Epidemiological studies have found associations between the consumption of whole grain foods and a decreased risk of obesity, diabetes, cardiovascular disease, and several kinds of cancers.
2. The longitudinal relationship between whole grain foods and lung cancer and its subtypes remains poorly understood.

What this article tells us that is new

1. A higher consumption of whole grain foods was independently associated with a decreased risk for lung cancer, and non-small cell lung cancer (NSCLC), but not small cell lung cancer (SCLC) compared with those in the lowest quarter.
2. A linear dose-response pattern was shown for lung cancer, NSCLC but not for SCLC.

Introduction

Lung cancer stands as one of the most prevalent cancers globally, burdened with the heaviest toll in terms of morbidity and mortality, constituting 11.4% of all cancer cases and a staggering 18.0% of cancer-attributed fatalities [1–3]. Despite therapeutic advances, it remains the primary cause of tumor-related deaths, posing a significant global health burden [4]. Hence, the identification of factors that may prevent lung cancer is crucial in terms of public health policy, though smoking is the primary risk factor [5]. One potential modifiable risk factor that has been hypothesized to be associated with lung cancer incidence is the diet which was suggested to influence the risks of several chronic diseases by growing epidemiological evidence [6].

Acknowledging the intricate biological interplay among various dietary components, the adoption of a comprehensive whole-diet approach and the investigation of specific dietary patterns have been suggested as advantageous in elucidating diet's contribution to disease progression. Whole-grain foods, mirroring the natural proportions of bran, germ, and endosperm found in unprocessed grains, exhibit superior nutritional density compared to refined grains [7]. These grains serve as vital sources of vitamins, minerals, fatty acids, antioxidants, dietary fiber, and phytochemicals [8]. Their nutrient-rich profile, including both essential and non-essential components, may diminish the risks of chronic diseases and cancer via diverse mechanisms, such as enhancing glycemic control and mitigating insulin resistance, among others [9]. In more detail, whole grains contribute to a healthy gut microbiome, are rich in phytochemicals that counteract oxidative stress and inflammation, help regulate insulin levels to decrease insulin resistance, and generate short-chain fatty acids (SCFAs), all of which collectively serve to diminish the risks of cancer [10–12]. Therefore, whole grains are recommended as an integral component of a healthy diet to prevent obesity, diabetes, cardiovascular disease, and most recently colorectal cancer based on various cohort studies [13, 14]. However, few studies have explored the associations between whole grain food intake and lung cancer and its subtype risks in the community population [9, 10].

Within this framework of biological plausibility, amidst limited epidemiologic evidence and the escalating burden of lung cancer, our prospective cohort study aims to delve into the influence of whole grain foods and their primary sources on the cumulative incidence of lung cancer in an aging American adult cohort. Leveraging the robust Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial data, characterized by extensive longitudinal tracking and meticulous examination of dietary habits and medical histories, we hypothesize that whole grain consumption is inversely related to lung cancer risk.

Methods

Study population

The design of the PLCO Cancer Screening Trial has been previously described [15]. In brief, participants aged 55 to 74 were enrolled and randomly assigned to either the intervention (screening) group or the control group at 10 screening centers across the U.S. between November 8, 1993, and July 2, 2001. Those in the intervention group received screenings for prostate, lung, colorectal, and ovarian cancers during specified study years, while the control group received standard care. All participants completed a Baseline Questionnaire (BQ) covering demographic, lifestyle, anthropometric factors, and medical and reproductive histories at study entry, along with diet information evaluated by the Diet History Questionnaire (DHQ) starting in 1998. Cancer diagnosis data were collected through 2009, and mortality data were tracked until 2018. The PLCO Cancer Screening Trial was approved by the institutional review boards at all study sites, complied with the Declaration of Helsinki, and all participants provided written informed consent for both the original and ancillary studies. The current project, which involves the use of PLCO data for secondary analysis, has been approved by the National Cancer Institute's Cancer Data Access System (PLCO-1547) and the Institutional Review Board of Chongqing University Cancer Hospital (CZLS2024123-A).

In our research, participants who completed the BQ at the study entry and the DHQ which was offered to both arms of the trial starting in 1998 were included. Exclusion criteria included: individuals who did not complete the BQ had a personal history of lung cancer or any other

cancer before completing the BQ, did not complete a valid DHQ (please refer to the dietary assessment section), and did not have an active follow-up after enrollment. A flow chart was seen in Fig. 1 and the detail of population selection was seen in supplement eTable1 which was summarized by the National Cancer Institute (NCI).

Dietary assessment

Dietary data were collected using the DHQ, which consisted of 156 questions regarding the frequency of consumption of various foods, beverages, supplements, and other items over the past year(see supplement eMethod for timeline). The daily intake of each food item was estimated by multiplying the reported consumption frequency by the portion size. Nutrient intake was calculated using responses from the DHQ, with the nutrient values for each food item multiplied by the frequency and summed across all responses. Nutrient composition databases were generated using the DietCalc software, based on data from the United States Department of Agriculture's 1994–96 Continuing Survey of Food Intakes by Individuals and the University of Minnesota's Nutrition Data System for Research [16]. A valid DHQ was defined as the completion of the questionnaire with a completion date before the date of death, containing fewer than 8 missing or multiple frequency responses, and not having extreme energy intake (top and bottom 1% of each sex group) [17]. Healthy Eating Index-2015(HEI-2015), a measure of diet quality, was calculated using the method

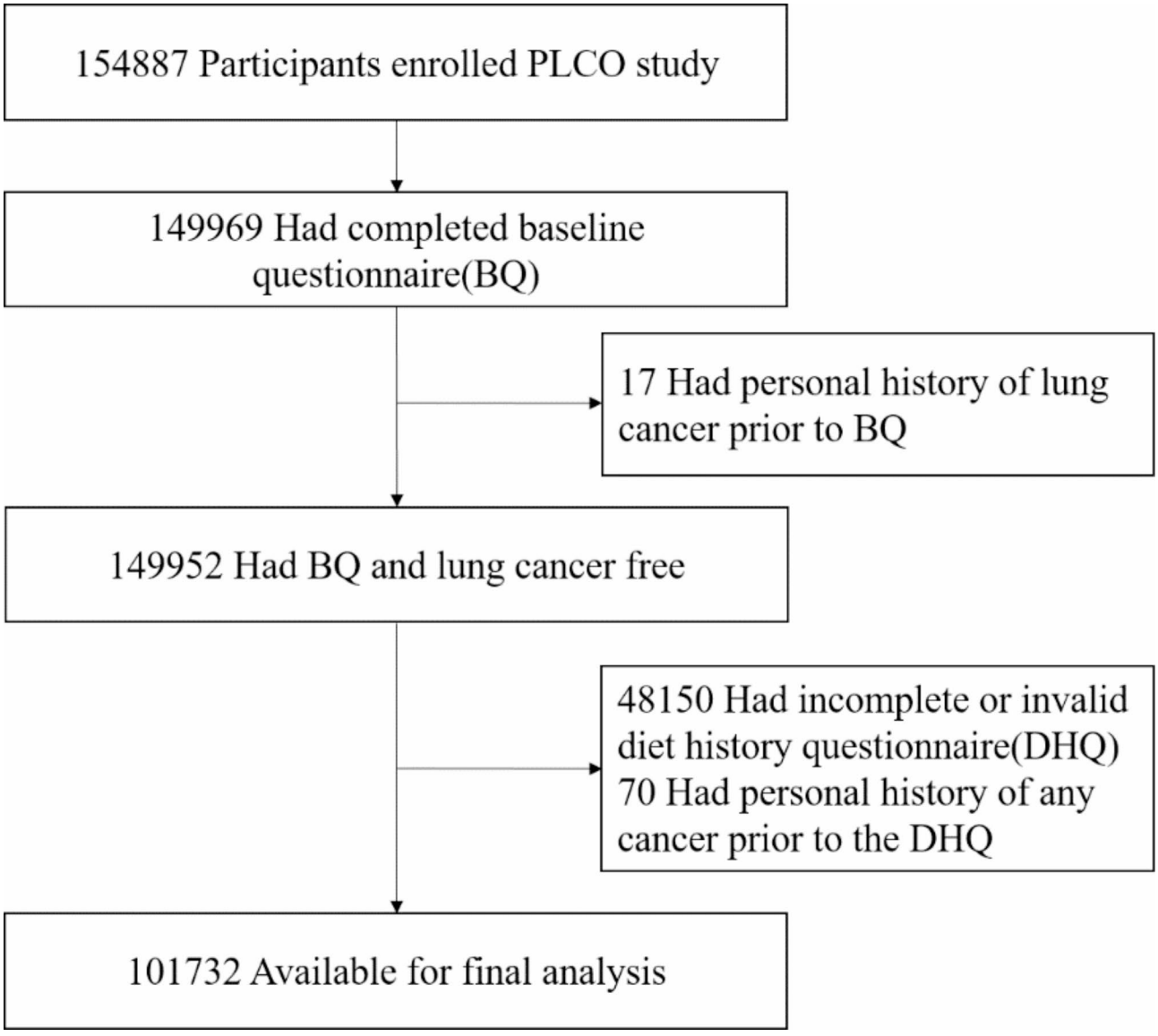

Fig. 1 Flowchart of study sample in the PLCO study
Abbreviations: PLCO, prostate, lung, colorectal, and ovarian

described in the literature [18, 19]. In brief, the HEI-2015 assesses adherence to the 2015–2020 Dietary Guidelines for Americans (DGA) through 13 dietary components, scoring from 0 (nonadherence) to 100 (optimal adherence). Components are divided into two categories: nine adequacy components that score higher with increased intake, and four moderation components that score higher with reduced intake. Scores are calculated per 1,000 kcal/day, except for saturated fats and fatty acids. Fatty acids are assessed as the ratio of unsaturated to saturated fatty acids. The maximum score for individual components ranges from 5 to 10 points (see supplement eMethod). The food and nutrient intakes reported in the DHQ were validated against four 24-hour dietary recalls and other established food frequency questionnaires [20, 21].

Assessment of whole grain food consumption

Whole grain intake (g/day) was estimated based on the dry weight of whole grain ingredients in all grain-based foods (e.g., bread, pasta, breakfast cereals). Foods and ingredients classified as whole grains included whole grain bread or rolls, oatmeal, cold breakfast cereals, rice or other cooked grains, granola bars, meal replacement bars, crackers, bagels, muffins, corn chips, popcorn, rice, and rice milk.

Ascertainment of lung cancer

In this study, the primary endpoint was lung cancer incidence. Participants self-reported lung cancer diagnoses through annual questionnaires. Lung cancer incidence was initially identified through study screenings, self-reports in annual updates, reports from family members, and data linkages to local cancer registries and the National Death Index database. For the current analysis, all lung cancer cases were confirmed via pathological reports and classified into histological subtypes according to the International Classification of Diseases for Oncology, 2nd Edition (ICD-O-2) morphology, including non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) [15]. Notably, carcinoid lung cancer was not deemed a target for lung cancer screening in the PLCO trial.

Assessment of other variables

Demographic, medical history and other risk factor information were extracted through BQ. Hypertension was defined as systolic blood pressure > 140 mm Hg, diastolic blood pressure > 90 mm Hg, or the use of antihypertensive medications. Diabetes mellitus was defined as fasting glucose > 7 mmol/L or the use of antidiabetic therapy. The data collected included sex, baseline age, body mass index (BMI, calculated as weight in kilograms divided by height in meters squared), smoking status (current and former, or never), employment status (working, retired, or unemployed), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, or others), family history of any cancer (yes or no), family history of lung cancer (yes or no), physical activity level (less than once per month or more than once per month), marital status (single, married, or no longer married), and educational attainment (no high school diploma, high school diploma, some college, college degree or postgraduate degree).

Statistical analysis

The baseline characteristics of the study population were presented by the quartile of whole grain food consumption. Test of differences across consumption quarters was performed by one-way ANOVA for continuous variables and Chi-square test for categorical variables.

Individual follow-up time was defined as a period from entry (baseline examination) until the time of lung cancer occurrence (diagnosis) or censoring was defined as the exit of the study due to other causes or death, loss to follow-up, or the end of the study. Multivariable Cox proportional hazard regression was used to estimate hazard ratios (HR) and 95% confidence intervals (CI) between whole grain food consumption and lung cancer risk with the lowest quarter as the reference category. Tests for a linear trend in lung cancer risk across different levels of whole grain food consumption were conducted by assigning the median value to each category and considering these values as continuous variables in the multi-adjusted Cox proportional hazard model. In multivariable adjustment, potential confounder selection was based on existing literature and deferred to statistical criteria. Based on these criteria, model 1 was adjusted for sex, age, race, and family history of lung cancer; model 2 was further adjusted for prevalent hypertension, prevalent diabetes, smoking status, total energy intake, alcohol consumption, HEI-2015 score, employment status, marital status, physical activity status, and BMI. The proportionality of hazards was verified using the Schoenfeld residuals method. The increase in HR with every 1-standard deviation(SD) increase in whole grain food consumption was also estimated.

The proportional hazards assumption was assessed using Schoenfeld residuals. Kaplan-Meier curves, adjusted for confounding factors, were used to describe lung cancer risk concerning whole grain food consumption. Subgroup analyses were also conducted to evaluate the heterogeneity of findings, stratified by age (≥ 65 vs. <65 years), sex (male vs. female), family history of lung cancer (yes vs. no), BMI (≥ 25 vs. <25 kg/m^2), smoking status (current and former vs. never), and alcohol consumption(≥ median vs. < median). The P-value for

interaction was obtained through a likelihood ratio test, comparing models with and without interaction terms.

Additionally, restricted cubic spline Cox regression models with knots at the 5th, 35th, 65th, and 95th percentiles of consumption were used to assess the potential dose-response and non-linear associations, with 0 servings/day as the reference. Non-linearity was tested using a likelihood ratio test, comparing the model with only the linear term against the model including both linear and cubic spline terms.

All analyses were conducted using Stata version 15 (StataCorp, College Station, Texas, USA) and SPSS 23.0 (SPSS Inc., Chicago, IL, USA). A two-sided P-value < 0.05 was considered statistically significant. All analyses followed a predefined statistical analysis plan (available upon request).

Patient and public involvement

No participants were consulted in formulating the research question, defining outcomes, or planning the study's design and execution. Nor were they solicited for insights on interpreting or reporting the findings. Due to the complex nature of the data, we lacked access to patients or members of the public with the requisite statistical and methodological skills to analyze or interpret the current results. However, the study's outcomes will be communicated to participants and the general public via the cohort website, public events, and press releases.

Results

Characteristics of the study population

A total of 101,732 participants (50,187 men and 51,545 women) were included in the present study, with a mean age of 62.5 years and an average whole grain food consumption of 17.7 g/day (see Table 1). Compared to participants in the lowest quartile of whole grain consumption, those in the highest quartile were more likely to be older, male, non-smokers, non-Hispanic, single, retired, engage in more physical activity, had diabetes, a higher level of education, higher HEI-2015 scores, and a lower BMI, but not hypertension, a family history of lung cancer. On average, they also consumed more carbohydrates, protein, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, fruits, vegetables, dietary fiber, added sugars, sodium, potassium, calcium, and magnesium, had more total caloric intake, but a lower intake of alcohol, and red meat(all P-values < 0.001) (see Table 1).

Lung cancer events

During a median follow-up of 12.2 (interquartile range, 10.5–13.6) years (1,213,533 person-years), a total of 1,706 incident lung cancer events occurred, including 1,473 (86.3%) cases of NSCLC and 233 (13.7%) of SCLC. No significant difference in lung cancer subtypes and stages was observed among different categories of whole grain food consumption (see Table 2).

Whole grain food consumption and risk for lung cancer

After adjusting for sex, age, race, family history of lung cancer, hypertension, diabetes, smoking status, total energy intake, alcohol consumption, HEI-2015 score, employment status, marital status, physical activity, and BMI using Cox regression analysis, participants in the highest quartile of whole grain intake had a 16% lower risk of lung cancer (HR 0.84, 95% CI 0.73–0.98) and a 17% lower risk of NSCLC (HR 0.83, 95% CI 0.69–0.98) compared to those in the lowest quartile. However, no significant difference was observed for SCLC (HR 0.95, 95% CI 0.63–1.44) (see Table 3). After full adjustment, each SD increase in whole grain food consumption was associated with a reduced risk of lung cancer (HR 0.91, 95% CI 0.86–0.98) and NSCLC (HR 0.91, 95% CI 0.85–0.98), but not for SCLC (HR 0.94, 95% CI 0.81–1.11) (see supplement eFigure 1). Figure 2 presents cumulative incidence curves for lung cancer, NSCLC, and SCLC, stratified by whether whole grain consumption was above or below the median, adjusted for age and sex.

Subgroup analyses were performed by repeating the multivariable-adjusted Cox regression models across different strata, comparing the highest and lowest quartiles of whole grain consumption. No significant interactions were observed for predefined stratification factors such as age, sex, family history of lung cancer, BMI, smoking status, or alcohol consumption(P for interaction > 0.05) (see Table 4).

In the overall study population, whole grain consumption was found to be associated with risks of lung cancer, NSCLC, and SCLC in a linear dose-response manner (P for non-linearity > 0.05) (see Fig. 3).

Discussion

Findings from this aging American adults' cohorts showed that higher whole grain intake was significantly associated with a lower risk of lung cancer and NSCLC, but not for SCLC after considering a range of potential confounders encompassing crucial risk factors on lung cancer and the overall dietary quality. These findings persisted after subgroup analyses by age, sex, family history of lung cancer, BMI, smoking status, and alcohol consumption. Dose-response analyses revealed that with increased intake of whole grain foods, the rate of lung cancer incidence decreased in a linear inverse way. Our findings support the hypothesis that the intake of whole grain foods could be a dietary factor that decreases the risk of lung cancer.

Table 1 Baseline characteristics of the study population according to whole grain food consumption

Characteristic	Quarters of whole grain food consumption, g/day				Full Sample	*P*-value
	Q1 (< 1.0)	Q2 (6.3 < 13.3)	Q3 (13.3-<23.2)	Q4 (≥ 23.2)		
No. of participants	25,435	25,432	25,434	25,431	101,732	
Age(year)	61.8 ± 5.2	62.4 ± 5.2	62.7 ± 5.3	63.1 ± 5.3	62.5 ± 5.3	< 0.001
Male, n (%)	11,699(46.0)	11,603(45.6)	12,931(50.8)	13,954(54.9)	50,187(49.3)	< 0.001
Study arm (intervention, n, %)	12,766(50.2)	12,935(50.9)	13,168(51.8)	13,321(52.4)	52,190(51.3)	< 0.001
BMI (kg/m^2)	27.4 ± 4.9	27.4 ± 4.8	27.2 ± 4.7	27.0 ± 4.8	27.2 ± 4.8	< 0.001
Physical activity, n (%)						< 0.001
Less than once/month	2430(9.6)	1982(7.8)	1760(6.9)	1600(6.3)	7772(7.6)	
More than once/month	15,022(59.0)	16,489(64.8)	16,818(66.1)	16,550(65.1)	64,879(63.8)	
Unknown	7983(31.4)	6961(27.4)	6856(27.0)	7281(28.6)	29,081(28.6)	
Current and former smoking, n(%)	14,784(58.1)	13,296(52.3)	12,827(50.4)	12,573(49.4)	53,480(52.6)	< 0.001
Prevalent diabetes mellitus, n(%)	1416(5.6)	1590(6.3)	1736(6.8)	2140(8.4)	6882(6.8)	< 0.001
Prevalent hypertension, n(%)	8600(33.8)	8272(32.5)	8160(32.1)	8262 (32.5)	33,294(32.7)	< 0.001
Family history of any cancer, n(%)	14,215(55.9)	14,415(56.7)	14,275(56.1)	14,225(55.9)	57,130(56.2)	0.253
Family history of lung cancer, n(%)	2906(11.4)	2655(10.4)	2712(10.7)	2624(10.3)	10,897(10.7)	< 0.001
Employment, n (%)						< 0.001
Working	11,105(43.7)	10,162(40.0)	9705(38.2)	9420(37.0)	40,392(39.7)	
Retired	9893(38.9)	10,737(42.1)	11,521(45.3)	12,037(47.4)	44,188(43.4)	
Unemployed	4329(17.0)	4417(17.4)	4078(16.0)	3868(15.2)	16,692(16.4)	
Unknown	108(0.4)	116(0.5)	130(0.5)	106(0.4)	460(0.5)	
Education, n (%)						< 0.001
No high school degree	1761(6.9)	1364(5.4)	1369(5.4)	1706(6.7)	6200(6.1)	
High school degree	9920(39.0)	9202(36.2)	8760(34.4)	8820(34.7)	36,702(36.1)	
Some college	5620(22.1)	5565(21.9)	5334(21.0)	5263(20.7)	21,782(21.4)	
College degree or postgraduate	8134(32.0)	9301(36.5)	9971(39.2)	9642(37.9)	37,048(36.4)	
Marital status, n (%)						< 0.001
Single	788(3.1)	764(3.0)	766(3.0)	890(3.5)	3208(3.2)	
Married	19,638(77.2)	20,234(79.6)	20,251(79.6)	19,621(77.2)	79,744(78.4)	
No longer married	4966(19.5)	4389(17.3)	4366(17.2)	4876(19.2)	18,597(18.3)	
Unknown	43(0.2)	45(0.2)	51(0.2)	44(0.2)	183(0.2)	
Race						< 0.001
Non-Hispanic White	22,771(89.6)	23,550(92.6)	23,686(93.2)	22,621(89.0)	92,628(91.1)	
Non-Hispanic Black	669(2.6)	628(2.4)	722(2.8)	1336(5.2)	3355(3.3)	
Hispanic	431(1.7)	345(1.4)	313(1.2)	380(1.5)	1469(1.4)	
Others	1564(6.1)	909(3.6)	713(2.8)	1094(4.3)	4280(4.2)	
Total caloric intake (Cal/d)	1547.1 ± 724.4	1642.0 ± 680.2	1783.5 ± 682.6	1971.1 ± 758.7	1735.9 ± 729.9	< 0.001
Healthy Eating Index-2015	61.2 ± 9.6	65.7 ± 9.0	68.3 ± 8.7	70.8 ± 8.7	66.5 ± 9.7	< 0.001
Alcohol consumption (g/day)	11.7 ± 29.2	9.7 ± 24.3	8.7 ± 20.6	7.2 ± 18.6	9.3 ± 23.6	< 0.001
Macronutrients intake						
Carbohydrates(g/d)	182.4 ± 85.0	204.5 ± 78.4	231.8 ± 81.7	266.7 ± 95.7	221.4 ± 91.1	< 0.001
Protein(g/d)	57.8 ± 29.0	63.0 ± 27.8	69.0 ± 28.4	76.4 ± 32.1	66.6 ± 30.2	< 0.001
SFA(g/d)	20.1 ± 12.0	19.5 ± 11.5	19.1 ± 11.1	20.9 ± 12.1	19.9 ± 11.7	< 0.001
MUFA(g/d)	23.8 ± 13.4	23.1 ± 12.9	22.5 ± 12.5	24.9 ± 13.8	23.6 ± 13.2	< 0.001
PUFA(g/d)	13.1 ± 7.6	13.4 ± 7.2	14.2 ± 7.3	15.5 ± 8.0	14.1 ± 7.6	< 0.001
Food consumption						< 0.001
Fruit(g/d)	209.9 ± 200.9	252.9 ± 194.9	289.2 ± 203.2	340.9 ± 239.9	273.2 ± 215.9	< 0.001
Vegetable(g/d)	242.8 ± 173.3	262.9 ± 164.3	288.5 ± 173.4	337.3 ± 209.1	282.9 ± 184.3	< 0.001
Whole grain foods(g/d)	3.0 ± 1.9	9.7 ± 2.0	17.6 ± 2.9	40.6 ± 19.3	17.7 ± 17.3	< 0.001
Red meat(g/d)	63.6 ± 55.1	61.2 ± 50.6	61.2 ± 49.7	60.4 ± 53.0	61.6 ± 52.2	< 0.001
Dietary fiber(g/d)	13.4 ± 6.8	16.1 ± 6.6	19.2 ± 7.3	23.2 ± 9.2	18.0 ± 8.4	< 0.001
Added sugar(tsp/d)	11.8 ± 10.6	11.9 ± 8.7	12.8 ± 8.5	13.6 ± 9.0	12.5 ± 9.3	< 0.001
Mineral intake						< 0.001
Sodium(mg/d)	2364.7 ± 1150.2	2570.9 ± 1102.9	2824.7 ± 1128.4	2732.3 ± 1212.9	2364.7 ± 1150.2	< 0.001

Table 1 (continued)

Characteristic	Quarters of whole grain food consumption, g/day				Full Sample	*P*-value
	Q1 (< 1.0)	Q2 (6.3 < 13.3)	Q3 (13.3-<23.2)	Q4 (≥ 23.2)		
Potassium(mg/d)	2771.5 ± 1143.4	3074.1 ± 1116.6	3384.0 ± 1165.1	3747.7 ± 1341.5	3244.3 ± 1248.6	< 0.001
Calcium(mg/d)	593.4 ± 355.1	701.9 ± 362.6	801.8 ± 386.8	897.6 ± 436.3	748.7 ± 402.8	< 0.001
Magnesium(mg/d)	265.0 ± 113.3	299.1 ± 109.1	337.7 ± 114.1	385.4 ± 134.9	321.8 ± 126.5	< 0.001

Continuous variables were expressed as mean ± SD and categorical variables as number and percentage. Abbreviations: BMI, body mass index; SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids

Table 2 Lung cancer of whole grain food consumption categories

Outcome	Quarters of whole grain food consumption, g/day				Full Sample	*P*-value
	Q1 (< 1.0)	Q2 (6.3 < 13.3)	Q3 (13.3-<23.2)	Q4 (≥ 23.2)		
Lung cancer in follow-up, n	534/25,435	429/25,432	381/25,434	362/25,431	1706/101,732	< 0.001
Non-small cell lung cancer, n (%)	463(86.7)	372(86.7)	326(85.6)	312(86.2)	1473(86.3)	0.958
Small cell lung cancer, n (%)	71(13.3)	57(13.3)	55(14.4)	50(13.8)	233(13.7)	
Lung cancer stage						0.344
Stage I and II, n (%)	204(38.2)	158(36.8)	118(31.0)	118(32.6)	598(35.1)	
Stage III and IV, n (%)	258(48.3)	214(49.9)	207(54.3)	193(53.3)	872(51.1)	
Small cell lung cancer, n (%)	72(13.5)	57(13.3)	56(14.7)	51(14.1)	236(13.8)	

Categorical variables as numbers and percentages

Table 3 Cox proportional hazard ratios for lung cancer of whole grain food consumption categories

Variables	Quarters of whole grain food consumption, g/day				*P* for trend
	Q1 (< 1.0)	Q2 (6.3 < 13.3)	Q3 (13.3-<23.2)	Q4 (≥ 23.2)	
No. of participants	25,435	25,432	25,434	25,431	
Lung cancer					
No. of events	534	429	381	362	
Person-years	298028.1	303195.5	306396.4	305913.2	
Rate per 1000 person-years	1.8	1.4	1.2	1.2	
Unadjusted	1.00 (reference)	0.78(0.69–0.89)	0.69(0.60–0.78)	0.65(0.57–0.74)	< 0.001
Model 1	1.00 (reference)	0.84(0.75–0.94)	0.72(0.65–0.81)	0.67(0.60–0.76)	< 0.001
Model 2	1.00 (reference)	0.93(0.83–1.06)	0.86(0.75–0.99)	0.84(0.73–0.98)	< 0.001
Non-small cell lung cancer					
No. of events	463	372	326	312	
Person-years	297425.1	302775.9	306005.3	305562.6	
Rate per 1000 person-years	1.6	1.2	1.1	1.0	
Unadjusted	1.00 (reference)	0.78(0.68–0.90)	0.68(0.59–0.78)	0.65(0.56–0.75)	< 0.001
Model 1	1.00 (reference)	0.85(0.75–0.97)	0.72(0.63–0.81)	0.68(0.60–0.77)	< 0.001
Model 2	1.00 (reference)	0.93(0.76–1.15)	0.86(0.66–1.05)	0.83(0.69–0.98)	< 0.001
Small cell lung cancer					
No. of events	71	57	55	50	
Person-years	294525.1	300454.0	303836.2	303611.0	
Rate per 1000 person-years	0.2	0.2	0.2	0.2	
Unadjusted	1.00 (reference)	0.78(0.55–1.11)	0.74(0.52–1.06)	0.67(0.47–0.97)	0.032
Model 1	1.00 (reference)	0.86(0.63–1.18)	0.79(0.58–1.09)	0.78(0.59–0.96)	0.004
Model 2	1.00 (reference)	1.05(0.75–1.52)	1.06(0.73–1.57)	0.95(0.63–1.44)	0.187

Values are hazard ratios (95% confidence intervals)

Model 1: Adjusted for sex, age, race, and family history of lung cancer

Model 2: Adjusted for model 1 plus, prevalent hypertension, prevalent diabetes, smoking status, total energy intake, alcohol consumption, HEI-2015 score, employment status, marital status, physical activity status, and BMI

Abbreviations: HEI-2015, Healthy Eating Index-2015; BMI, body mass index

Interpretation and comparison with other studies

Whole grain foods contain numerous potential anti-carcinogenic agents, including antioxidants, trace minerals, phytate, phenolic acids, phytoestrogens, and fiber [22]. These components may significantly reduce cancer risk through various mechanisms, such as improving glycemic control and reducing insulin resistance, lowering sex hormone levels, diluting colon carcinogens, and

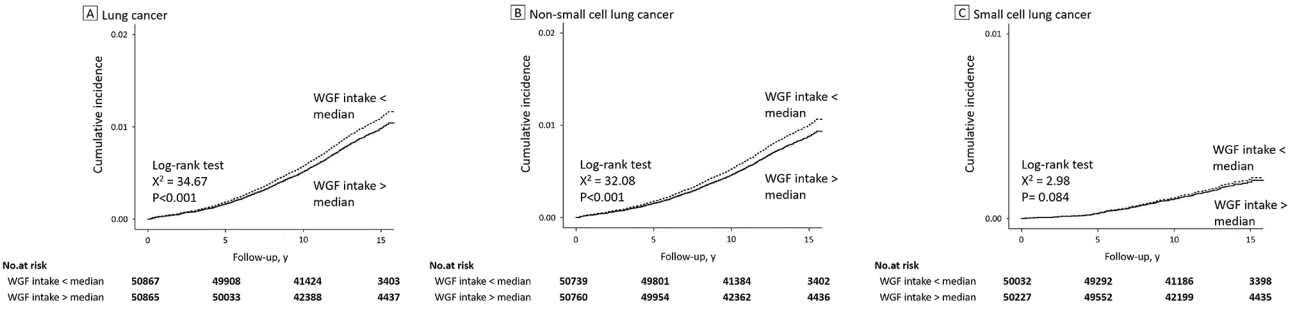

Fig. 2 Adjusted cumulative incidence of lung cancer based on whole grain food consumption
Data are for the hazard ratio (HR) of (**A**) lung cancer, (**B**) non-small cell lung cancer, and (**C**) small cell lung cancer. The reference level was set at 0 serving/day. The dotted lines represent the upper and lower bounds of the 95% confidence interval of HR. Multivariate adjustments were made for sex, age, race, family history of lung cancer, prevalent hypertension, prevalent diabetes, smoking status, total energy intake, alcohol consumption, HEI-2015 score, employment status, marital status, physical activity status, and BMI
Abbreviations: WFG, whole grain food

Table 4 Subgroup analyses for association between consumption of whole grain foods and lung cancer (highest versus lowest quarter of consumption)

Subgroup variables	Lung cancer		Non-small cell lung cancer		Small cell lung cancer	
	HR (95% CI)	*P* for interaction	HR (95% CI)	*P* for interaction	HR (95% CI)	*P* for interaction
Age (years)						
≥65	0.78(0.66–0.95)	0.846	0.69(0.57–0.85)	0.197	1.07(0.64–1.95)	0.178
<65	1.13(0.83–1.51)		1.09(0.82–1.48)		0.70(0.29–1.74)	
Sex						
Male	0.83(0.68–0.99)	0.753	0.80(0.66–0.99)	0.754	0.93(0.53–1.63)	0.157
Female	0.88(0.69–1.15)		0.84(0.63–1.09)		0.99(0.59–2.11)	
Family history of lung cancer						
Yes	1.01(0.68–1.50)	0.158	1.06(0.70–1.62)	0.874	1.05(0.68–1.65)	0.178
No	0.82(0.69–0.98)		0.78(0.64–0.93)		0.85(0.49–1.47)	
BMI (kg/m^2)						
≥25	0.91(0.75–1.05)	0.478	0.88(0.72–1.11)	0.844	1.07(0.74–1.56)	0.357
<25	0.82(0.62–0.96)		0.72(0.55–0.94)		0.87(0.56–1.53)	
Smoking						
Current and former	0.88(0.75–1.03)	0.874	0.86(0.72–1.03)	0.792	1.04(0.69–1.59)	0.357
Never	0.80(0.56–0.97)		0.79(0.51–0.93)		0.85(0.48–1.27)	
Alcohol consumption						
≥median	0.92(0.75–1.07)	0.175	0.89(0.71–1.11)	0.471	1.06(0.75–1.55)	0.531
< median	0.78(0.58–0.92)		0.73(0.56–0.95)		0.85(0.51–1.35)	

Adjusted for sex, age, race, family history of lung cancer, prevalent hypertension, prevalent diabetes, smoking status, total energy intake, alcohol consumption, HEI-2015 score, employment status, marital status, physical activity status, and BMI

Abbreviations: HEI-2015, Healthy Eating Index-2015; BMI, body mass index

fermenting into short-chain fatty acids with pro-apoptotic and antineoplastic properties. Additionally, whole grains might contain other protective or synergistic components that are not yet fully understood. A meta-analysis has indicated that a high intake of whole grain foods may offer protection against gastric cancer. At the same time, the consumption of refined cereals could be a risk factor for the same [23]. Moreover, consumption of whole grain foods has been inversely associated with the risks of developing various types of cancer, including esophageal cancer, liver cancer, endometrial cancer, oral and pharyngeal cancer, pancreatic cancer, bladder cancer, breast cancer, and small intestinal cancer [24–31]. While quite limited prior studies have reported on the association between whole grain foods and lung cancer and its subtypes. A cross-sectional study based on the PLCO cohort concluded that carbohydrates and fiber from fruits, vegetables, and whole grains were associated with a lower lung cancer risk, whereas refined carbohydrates from processed foods like soft drinks might elevate the risk [32]. However, the study had limitations, including not accounting for lung cancer subtypes, insufficient adjustments, and not being conducted prospectively. In line with our findings, the NIH-AARP Diet and Health Study demonstrated that higher consumption of whole grains and fruits was significantly inversely associated

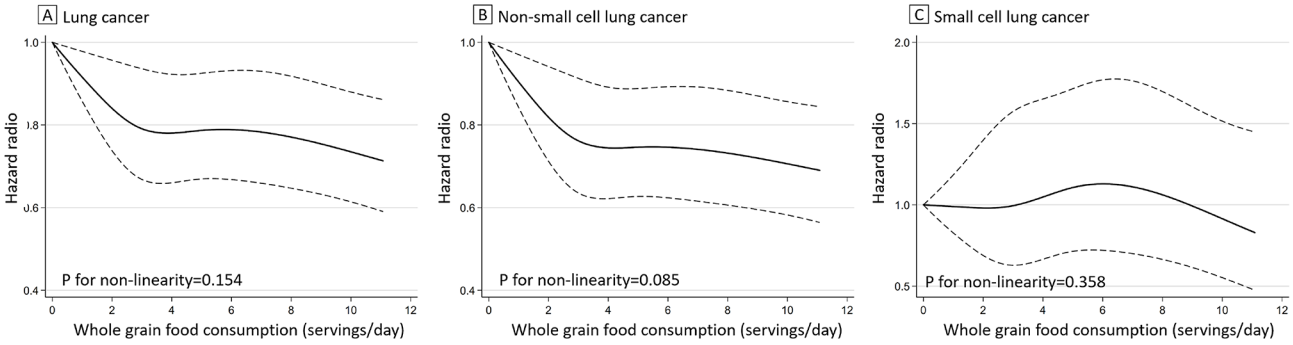

Fig. 3 Adjusted dose-response associations between whole grain food consumption and risk of lung cancer
Data are for the cumulative incidence of (**A**) lung cancer, (**B**) non-small cell lung cancer, and (**C**) small cell lung cancer among participants with and without whole grain food consumption greater than the median. Adjustments were made for age and sex
Abbreviations: HEI-2015, Healthy Eating Index-2015; BMI, body mass index

with lung cancer risk for several dietary indices, such as HEI-2010 and AHEI-2010, particularly among former smokers [33]. Additionally, a pooled analysis of 10 prospective cohorts, involving 1,445,850 adults from studies conducted in the United States, Europe, and Asia, found that dietary fiber—primarily from whole grains in a typical mixed diet—was associated with a reduced risk of lung cancer after adjusting for known risk factors and among non-smokers [34]. Epidemiological evidence based on 416,588 participants from the UK Biobank with a median follow-up of 7.13y illustrated that dietary fiber was inversely associated with the risk of lung cancer [35]. However, more recently, whole grains have been recommended for reasons beyond their fiber content, whereas recommendations for whole grain intake have typically formed part of dietary fiber in the past [36]. To our knowledge, this study is one of the few prospective analyses to have identified an association between whole grain food consumption and an increased risk of lung cancer, including two major subtypes. This finding is attributed to our enhanced dietary assessment methods and the use of robust clinical outcomes aligned with standardized diagnostic procedures, along with a large sample size and relatively long follow-up period. However, no association was found between whole grain consumption and SCLC. One possible explanation is that the limited number of SCLC cases may have been insufficient to detect a protective effect. Additionally, residual confounding factors might have obscured any potential beneficial effects.

Multiple plausible hypotheses could elucidate our observed findings. Firstly, whole grain foods have demonstrated a notable capacity to reduce systemic inflammation, a crucial factor in lung cancer development. This effect may stem from the absorption of colonic small-chain fatty acids, which are renowned for their anti-inflammatory properties (inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A reductase) and anti-tumorigenic effects [37, 38]. Secondly, whole grains are abundant sources of fermentable carbohydrates, including dietary fiber, resistant starch, and oligosaccharides, which could be generated into short-chain fatty acids by gut microbiota [39]. Emerging evidence has suggested that the beneficial effects of short-chain fatty acids on host immunity and metabolism are not restricted to the gut but reach various organs, including the lungs [40]. Moreover, previous animal research has shown that the inclusion of fermentable fiber in the diet has the potential to reshape the immune environment in the lungs by altering the composition of gut and lung microbiota, potentially exerting a protective effect against cancer [41]. Thirdly, Those individuals who consume a higher intake of whole grain foods tend to have a generally healthier lifestyle, accompanied by increased energy intake [9, 42–44]. This is due to the slower digestion and absorption of carbohydrates, which leads to increased feelings of satiety, improved glycaemic control, and lower insulin concentrations. These factors have long been identified as risk factors in cancer development. Finally, Whole grains contain many antioxidants, including vitamins, trace minerals, and non-nutrients such as phenolic acids, lignans, phytoestrogens, and antinutrients such as phytic acid. These constituents can effectively delay or slow down the oxidation of oxidizable substrates, making them vital in the prevention of cancer [45–47].

Strengths and limitations of this study

The strengths of our study include a relatively large sample size from multiple centers across the U.S., a prospective population-based design with long-term follow-ups, and thorough information on potential confounders. Comprehensive dietary assessments, standardized protocols for outcome evaluation, and a diverse set of sensitivity analyses further enhance the robustness and credibility of our results. Nevertheless, we acknowledge several limitations. Firstly, the observational nature of this study precluded determining causality and

eliminating residual confounding from unmeasured variables, but the fact that significant findings were observed following comprehensive adjustments for covariates and in a dose-response manner underscores the robustness of the conclusions. Secondly, although the data were acquired prospectively, dietary information was collected cross-sectionally which might not reflect long-term dietary habits and the change of diet during the follow-up was not recorded or analyzed. Besides, self-reported DHQs were typically prone to response and/or recall bias, and measurement errors cannot be ruled out. Hence, the associations were examined based on ranking instead of absolute intake levels. Thirdly, the limited number of incident events could adversely impact the analytical power of these analyses, resulting in broader confidence intervals for risk estimates and should be interpreted with utmost caution. Fourthly, even after adjustment for lifestyles people who had higher whole grain or fiber intake were more likely to have a healthier diet and lifestyle overall, which might contribute to the reduced risk. Finally, the present study sample consisted mostly of Caucasians, and this may limit the generalizability of our results to other racial/ethnic populations or geographic regions. Further investigation is needed to re-evaluate the association among diverse populations based on a more precise and dynamic dietary intake evaluation.

Conclusions and policy implications

In this large prospective population-based analysis, after adjusting for a wide range of known or putative lung cancer risk factors, we found that consumption of whole grain foods was associated with reduced risk of lung cancer, NSCLC, but not SCLC. Although further large-scale longitudinal investigation is needed to replicate these findings, disentangle the underlying mechanisms, and determine specific dietary components associated with benefits in diverse racial/ethnic populations, our study suggests a potential novel health benefit of increasing whole grain food intake in lung cancer prevention.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12935-025-03634-z.

Supplementary Material 1

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Author contributions
All authors read and approved the final manuscript. Study concept and design: All authors; Acquisition, analysis, or interpretation of data: Wang. Drafting of the manuscript: Wang and Zhao. Critical revision of the manuscript for important intellectual content: Wu and Zhou. Statistical analysis: Wang. Obtained funding: Wu and Wang. Supervision: Wu and Zhou.

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Data availability
Data described in the manuscript, code book, and analytic code will not be made available because the authors are prohibited from distributing or transferring the data and codebooks on which their research was based to any other individual or entity under the terms of an approved NCI Research Proposal and Data and Materials Distribution Agreement through which the authors obtained these data.

Declarations

Ethics approval and consent to participate
Not applicable.

Competing interests
The authors declare no competing interests.

Ethical standards
The study procedures followed were by the ethical standards of the Institutional Review Board and the Principles of the Declaration of Helsinki.

Declaration of generative AI and AI-assisted technologies in the writing process
During the preparation of this work the authors used ChatGPT to enhance readability and refine language. After using this tool, the authors reviewed and edited the content as needed and took full responsibility for the content of the publication.

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