Dietary Fat Intake and Lung Cancer Risk: A Pooled Analysis

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A B S T R A C T

Purpose

Dietary fat may play a role in lung carcinogenesis. Findings from epidemiologic studies, however, remain inconsistent. In this pooled analysis of 10 prospective cohort studies from the United States, Europe, and Asia, we evaluated the associations of total and specific types of dietary fat with lung cancer risk.

Methods

Cox regression was used to estimate hazard ratios (HRs) and 95% CIs in each cohort. Study-specific risk estimates were pooled by random- or fixed-effects meta-analysis. The first 2 years of follow-up were excluded to address potential influence of preclinical dietary changes.

Results

Among 1,445,850 participants, 18,822 incident cases were identified (mean follow-up, 9.4 years). High intakes of total and saturated fat were associated with an increased risk of lung cancer (for highest v lowest quintile: HR, 1.07 and 1.14, respectively; 95% CI, 1.00 to 1.15 and 1.07 to 1.22, respectively; *P* for trend for both < .001). The positive association of saturated fat was more evident among current smokers (HR, 1.23; 95% CI, 1.13 to 1.35; *P* for trend < .001) than former/never smokers (*P* for interaction = .004), and for squamous cell and small cell carcinoma (HR, 1.61 and 1.40, respectively; 95% CI, 1.38 to 1.88 and 1.17 to 1.67, respectively; *P* for trend for both < .001) than other histologic types (*P* for heterogeneity < .001). In contrast, a high intake of polyunsaturated fat was associated with a decreased risk of lung cancer (HR, 0.92; 95% CI, 0.87 to 0.98 for highest v lowest quintile; *P* for trend = .02). A 5% energy substitution of saturated fat with polyunsaturated fat was associated with a 16% to 17% lower risk of small cell and squamous cell carcinoma. No associations were found for monounsaturated fat.

Conclusion

Findings from this large, international cohort consortium suggest that modifying dietary fat intake (ie, replacing saturated fat with polyunsaturated fat) may reduce lung cancer risk, particularly among smokers and for squamous cell and small cell carcinoma.

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INTRODUCTION

Lung cancer, the most common cancer in the world, accounts for about 13% of total cancer cases and 20% of cancer-related deaths worldwide annually.¹ Although the vast majority of lung cancer is explained by tobacco smoking,² dietary factors have also been suggested to influence lung cancer risk.³ The World Cancer Research Fund/American Institute for Cancer Research considers fruit and other foods containing carotenoids as probable protective factors,^{4,5} whereas red or processed meat, total fat, and butter have been

suggested as possible risk factors.⁴ Emerging evidence further indicates that specific types of fat (ie, saturated, monounsaturated, and polyunsaturated fat) may play different roles in lung carcinogenesis.⁶ Findings from epidemiologic studies, however, remain inconsistent. Several case-control studies reported that saturated fat was associated with a higher risk for lung cancer in men and in nonsmoking, white women.⁷⁻¹⁰ A few prospective cohort studies also found a positive association with saturated fat among men, especially heavy smokers^{11,12}; however, other cohort studies observed no association.¹³⁻¹⁵ Evidence linking mono- or polyunsaturated fat with lung

ASSOCIATED CONTENT

Appendix

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cancer is also inconsistent. Some case-control studies^{8,10} and prospective studies^{11,13} suggested that total unsaturated or mono-unsaturated fat is positively associated with lung cancer risk among men. In contrast, a significantly lower risk of lung cancer was linked with higher consumptions of plant-based fat (mostly unsaturated fat)¹⁵ and fish (a source of polyunsaturated fat).¹⁶ Overall, evidence from prospective cohort studies and meta-analyses is elusive regarding the association of specific types of dietary fat with lung cancer.^{11,13-15,17}

In this study, we investigated the association between dietary fat intake and the risk of lung cancer, using data pooled from 10 prospective cohort studies in the United States, Europe, and Asia. We evaluated the associations between total and specific types of dietary fat intakes and lung cancer risk overall, and by smoking status, sex, race/ethnicity, and histologic type.

METHODS

Study Populations

This analysis includes individual-level data from 10 prospective cohorts: the National Institutes of Health-AARP Study,¹⁸ Health Professionals' Follow-up Study,¹⁹ Iowa Women's Health Study,²⁰ Nurses' Health Study,²¹ Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial,²² Southern Community Cohort Study,²³ Vitamins and Lifestyle Study,²⁴ European Prospective Investigation into Cancer & Nutrition,²⁵ Shanghai Men's Health Study,²⁶ and Shanghai Women's Health Study.²⁷ All studies were approved by institutional review boards at local institutions. The current study only involved analyzing de-identified information.

In each study, we excluded participants who had a history of any cancer except nonmelanoma skin cancer, who did not report smoking status, and who reported implausible energy intake. Implausible energy intake was determined by predefined ranges in five cohorts (Health Professionals' Follow-up Study, Iowa Women's Health Study, Nurses' Health Study, Southern Community Cohort Study, and Vitamins and Lifestyle Study) or by cohort- and sex-specific ranges (beyond three standard deviations of the log-transformed mean energy intake). To minimize potential influence due to preclinical diseases and/or dietary changes, we also excluded the first 2 years of follow-up, including participants who died, developed any cancer, or were lost to follow-up within 2 years. Final study populations for our analysis are summarized in Table 1.

Dietary Assessment

Dietary information at baseline was assessed by using validated food frequency questionnaires or quantitative dietary questionnaires.²⁸⁻³⁸ Based on study-specific food composition tables, each study estimated daily intakes of total energy, carbohydrate, protein, and fat (ie, total, saturated, monounsaturated, and polyunsaturated fat).

Outcome Assessment

Incident cases of lung cancer were ascertained per each study protocol, via active and/or passive follow-up methods, including data linkage to cancer and death registries and self-reports confirmed by medical record review. Based on the International Classification of Diseases for Oncology, lung cancers were classified into five histologic types: adenocarcinoma, squamous cell carcinoma, other kinds of non-small cell carcinoma, small cell carcinoma, and others, including carcinoma not otherwise specified, sarcoma, and any kind of uncertain types.

Statistical Analysis

Hazard ratios (HRs) and 95% CIs were estimated in each cohort by fitting the Cox proportional hazards models. Proportional hazard

assumption was tested using time-by-covariate interactions and no evidence of violation was found. All models were stratified by baseline age groups and enrollment years (both in 5-year intervals). Follow-up time was treated as the time scale, calculated as the total time from 730 days (2 years) after enrollment until the date of diagnosis of any cancer, date of death, end of follow-up, or follow-up loss, whichever came first. Intakes of macronutrients were analyzed as percentages of total energy intake.³⁹ Dietary fat intakes were modeled as categorical variables using cohort- and sex-specific quintiles, with the lowest quintile as reference. Linear trend tests were conducted using the Wald test, with continuous values corresponding to the median value for each quintile. Risk estimates from each study were pooled based on their inverse variance weights. Heterogeneity across the studies was evaluated by the *Q* and *I*² statistics.⁴⁰⁻⁴² We adopted random-effects models if *P* for heterogeneity was $< .10$,⁴² or fixed-effect models when observing no evidence for heterogeneity.

Covariates were selected based on prior knowledge of putative risk factors for lung cancer and their associations with lung cancer risk in the current study. Included were age (continuous), sex, smoking status (never, former, current), smoking pack-years (continuous), family history of lung cancer, race/ethnicity (white, black, Asian, others), educational attainment (less than high school, high school graduate, vocational/professional education, college education, university graduate, graduate studies), alcohol consumption (0 g/d, > 0 to ≤ 28 g/d in men; or > 0 to ≤ 14 g/d in women; > 28 g/d in men; or > 14 g/d in women), physical activity (tertiles of leisure time or total activity measured by hours or metabolic equivalent hours), obesity status (body mass index [BMI] < 18.5 , 18.5 to 24.9, 25 to 29.9, ≥ 30 kg/m²; results remained the same if Asian-specific BMI cutoff points were used for Asian population), total vegetable intake (cohort- and sex-specific quintiles), and menopausal status in women.

We conducted all analyses using multivariate nutrient-density models that included total energy intake, percentage of energy from fat, and all aforementioned covariates.³⁹ To estimate the association for specific type of fat, saturated, monounsaturated, and polyunsaturated fats were mutually adjusted. The results can be interpreted as the substitution effects of energy from total or a particular type of fat for equivalent energy from carbohydrate and protein. Furthermore, to evaluate effect of a 5% energy substitution, we modeled specific fat intakes as continuous variables and estimated substitution effects by calculating the difference in the coefficients of the two targeted fats.⁴³

In addition, we pooled individual data into a single dataset and conducted aggregated pooled-analyses. Interactions between fat and smoking status, sex, and race/ethnicity were evaluated by likelihood ratio test. Heterogeneity across histologic types of lung cancer was evaluated. Possible nonlinear relationship between dietary fat and lung cancer was evaluated with the restricted cubic spline regression. To reduce influences due to extreme values, participants with the highest 1% of each fat intake were excluded from the analysis. A series of sensitivity analyses was conducted, including using the residual method to adjust for total energy intake, using project-wide sex-specific quintiles instead of cohort- and sex-specific cutoffs, and further adjusting for red meat intake, a major food source of total and saturated fat as well as a putative lung cancer risk factor.^{44,45}

Statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC) and STATA 12 (StataCorp, College Station, TX). All *P* values were two sided and statistical significance was set at .05.

RESULTS

Among a total of 1,445,850 participants (627,988 men and 817,862 women, after excluding the first 2 years of follow-up), 18,822 primary, incident lung cancer cases were identified over follow-up periods of 4.3 to 20.7 years. Mean intakes of total fat ranged from 15.5% to 34.9% of energy across studies. Substantially lower intakes of all types of fat were observed in Asian populations than

Table 1. Characteristics of the Cohort Studies Included in the Pooled Analysis of Dietary Fat Intake and Lung Cancer

Study	Country	Years of Study Entry	Sex of Patients	No. of Participants*	Follow-up (Years)†	Age Range at Baseline	No. of Cases	Never Smokers (%)	Dietary Intake‡				
									Energy (kcal)	Fat (%E)	SFA (%E)	MUFA (%E)	PUFA (%E)
National Health Institute-AARP Diet and Health Study	USA	1995-1997	M	276,118	7.4	50-71	5,051	26.1	2,030	27.9	9.5	11.6	6.9
Health Professionals Follow-up Study	USA	1986-1987	W	189,193	7.7	50-71	3,013	47.3	1,582	27.6	9.3	11.1	7.2
Iowa Women's Health Study	USA	1986-1986	M	45,320	17.3	32-79	930	43.7	1,989	29.1	10.9	12.2	5.9
Nurses' Health Study	USA	1984-1984	W	33,574	17.1	52-71	955	65.9	1,800	30.8	11.9	12.9	6.0
Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial	USA	1993-2004	M	75,937	20.7	37-65	1,907	43.9	1,743	31.7	12.5	12.6	6.6
				50,659	7.5	54-83	864	29.7	2,185	28.6	10.3	11.8	6.5
Southern Community Cohort Study	USA	2002-2009	W	52,627	7.8	53-82	609	57.2	1,625	27.1	9.6	10.9	6.6
			M	27,464	4.3	40-80	325	19.6	3,094	33.9	10.2	13.1	7.6
			W	40,489	4.4	40-80	291	45.1	2,222	34.4	10.3	12.9	8.2
Vitamins and Lifestyle Study	USA	2000-2002	M	31,792	7.1	50-76	468	33.3	2,234	34.9	10.9	13.2	7.9
			W	33,898	7.4	50-76	388	56.1	1,495	32.6	10.4	12.2	7.3
European Prospective Investigation into Cancer & Nutrition	Europe	1991-2001	M	136,607	9.4	19-97	1,287	33.6	2,417	32.1	13.1	13.3	5.7
			W	320,066	9.2	19-98	1,191	57.0	1,933	32.2	13.5	12.7	5.9
Shanghai Men's Health Study	China	2001-2006	M	60,028	8.1	40-75	776	30.5	1,913	16.2	4.8	7.1	4.0
Shanghai Women's Health Study	China	1996-2000	W	72,078	13.4	40-70	767	97.3	1,677	15.5	4.5	6.8	4.1
Total No. of study participants				1,445,850			18,822						

Abbreviations: M, men; MUFA, monounsaturated fat; %E, percent energy; PUFA, polyunsaturated fat; SFA, saturated fat; W, women.

*Including only participants who were eligible for the current pooled analysis.

†Mean years of total time interval from 730 days after study entry to the date of diagnosis of any cancer or the final date of last contact (ie, end of follow-up, date of death, or follow-up loss).

‡Mean values of each dietary intake.

those in the United States and European populations (Table 1; Appendix Table A1, online only).

At baseline, participants who reported a higher fat intake had a higher BMI and lower levels of education and physical activity (Table 2). Prevalence of current smoking and cumulative lifetime tobacco exposure was significantly higher among people with high fat intakes. All differences across total fat intake were statistically significant, and these patterns were consistently observed in men and women.

After adjusting for potential confounders, total and saturated fat showed significant associations with an increased risk of lung cancer (HR [95% CI] in the highest v lowest quintile, 1.07 [1.00 to 1.15] and 1.14 [1.07 to 1.22], respectively; *P* for trend for both < .001; Table 3). Conversely, polyunsaturated fat was associated with a decreased risk of lung cancer (HR [95% CI], 0.92 [0.87 to 0.98]; *P* for trend = .02). There was no evidence of heterogeneity across studies (Table 3; Appendix Fig A1, online only). When stratified by smoking status, significant associations were observed only among ever smokers (*P* for trend < .001 for total and saturated fat and *P* for trend = .03 for polyunsaturated fat). No associations were found for monounsaturated fat (Table 3).

The association of saturated fat with lung cancer risk appeared stronger among current smokers (HR [95% CI], 1.23 [1.13 to 1.35]; *P* for trend < .001; Table 4) than former and never smokers (*P* for interaction = .004), and for squamous cell carcinoma and

small cell carcinoma (HR [95% CI], 1.61 [1.38 to 1.88] and 1.40 [1.17 to 1.67], respectively; *P* for trend for both < .001) than other histologic types (*P* for heterogeneity < .001). This histologic-specific association pattern existed regardless of smoking status, although the point estimates among never smokers did not reach statistical significance. Stratified analyses on polyunsaturated fat and lung cancer did not show significant interactions except that the association seemed more evident among Asians (HR [95% CI], 0.80 [0.66 to 0.96]; *P* for trend = .03) than other races (*P* for interaction = .04; Appendix Table A2, online only).

Restricted cubic spline analyses indicated linear associations of saturated fat (positive) and polyunsaturated fat (inverse) with lung cancer (Fig 1). Given the differential association between these two fats, we evaluated isocaloric substitution effects of saturated fat with polyunsaturated fat (Table 4). Every 5% energy substitution was associated with an overall 12% lower risk of lung cancer (95% CI, 0.84 to 0.93). The beneficial effect was primarily found among current smokers and former smokers (especially those who quit smoking ≤ 10 years before). Noticeably, a 5% energy substitution was associated with a 17% lower risk of squamous cell carcinoma (95% CI, 0.74 to 0.93) and a 16% lower risk of small cell carcinoma (95% CI, 0.73 to 0.95).

Results from aggregated analyses were basically the same as main results from meta-analyses (Appendix Table A3, online only). Sensitivity analyses using residual method to control for total

Table 2. Baseline Characteristics Across Quintiles of Total Fat Intake*

Characteristic	Total Fat Intake: Energy (%)									
	Men (n = 627,988)					Women (n = 817,862)				
	Q1	Q2	Q3	Q4	Q5	Q1	Q2	Q3	Q4	Q5
Age, years	58.3	58.1	57.9	57.8	57.6	55.5	55.0	54.7	54.5	54.4
Race/ethnicity, %										
White	81.6	82.8	83.4	83.9	84.4	83.9	84.6	84.6	84.8	84.9
Black	5.0	4.7	4.5	4.4	4.2	5.2	4.9	5.0	5.0	5.1
Asian	11.6	10.9	10.6	10.4	10.2	9.7	9.5	9.4	9.3	9.2
Others	1.8	1.6	1.5	1.3	1.2	1.2	1.0	1.0	0.9	0.8
Family history of lung cancer, %	2.1	2.2	2.2	2.3	2.4	2.1	2.2	2.2	2.3	2.3
Graduate studies or higher, %	23.7	22.4	20.7	19.3	17.6	8.2	7.2	6.4	5.6	4.7
Smoking status, %										
Never smoker	30.3	30.9	30.9	30.1	26.8	56.5	57.4	57.3	57.0	56.1
Former smoker	50.9	50.0	49.0	47.9	46.6	29.3	27.6	26.6	25.5	23.6
Current smoker	18.8	19.1	20.1	22.0	26.6	14.2	15.0	16.1	17.5	20.3
Lifetime smoking exposure, pack-years	21.6	21.0	21.4	22.3	25.7	8.7	8.5	8.7	9.2	10.4
Alcohol intake, g/d	32.9	17.7	14.0	11.4	9.1	9.4	6.7	5.9	5.1	4.0
High physical activity level, %†	32.6	28.9	26.7	25.0	22.4	32.7	29.5	27.8	25.7	23.0
Body mass index, kg/m ²	26.1	26.5	26.7	26.9	27.3	25.4	25.7	25.9	26.1	26.7
Menopause, %	—	—	—	—	—	71.5	68.5	67.0	66.0	65.8
Dietary intakes per day‡										
Energy, kcal	2,082	2,080	2,147	2,227	2,311	1,649	1,726	1,790	1,853	1,895
Carbohydrate, %E	57.3	53.4	50.5	47.5	42.3	58.9	53.8	50.6	47.5	42.0
Protein, %E	14.7	15.6	15.9	16.1	16.3	15.7	16.0	16.1	16.1	16.2
Total fat, %E	19.2	25.1	28.5	31.9	37.6	20.8	26.0	29.3	32.5	38.1
Saturated fat, %E	6.7	8.9	10.2	11.5	13.3	7.8	9.9	11.1	12.3	14.0
Monounsaturated fat, %E	7.7	10.2	11.7	13.2	15.8	8.0	10.2	11.6	13.0	15.8
Polyunsaturated fat, %E	4.6	5.7	6.3	6.9	8.1	4.8	5.7	6.3	6.9	8.0
Vegetables, g	256	241	232	224	229	280	259	249	244	260

NOTE. Data are given as mean or proportion (%).

Abbreviations: —, not applicable; %E, percent energy; Q, quintile.

*Based on the cohort- and sex-specific quintiles of total dietary fat intake.

†Defined as the highest cohort- and sex-specific tertile of leisure time or total physical activity measured by hours or metabolic equivalent hours.

‡Mean values by quintiles of dietary intake of total fat.

Table 3. Risk of Lung Cancer by Quintiles of Total and Specific Types of Dietary Fat Intakes*

Type of Dietary Fatt	Energy (%)					P for Trend	P for Heterogeneity
	Q1	Q2	Q3	Q4	Q5		
All participants (N = 1,445,850)							
Total fat							
No. of cases	3,458	3,438	3,466	3,890	4,570		
HR (95% CI)	1 (ref)	1.04 (0.99 to 1.09)	1.02 (0.97 to 1.07)	1.08 (1.03 to 1.13)	1.07 (1.00 to 1.15)	< .001	.25
Saturated fat							
No. of cases	3,328	3,316	3,464	3,864	4,850		
HR (95% CI)	1 (ref)	1.02 (0.97 to 1.08)	1.05 (0.98 to 1.11)	1.08 (1.01 to 1.16)	1.14 (1.07 to 1.22)	< .001	.38
Monounsaturated fat							
No. of cases	3,400	3,485	3,581	3,889	4,467		
HR (95% CI)	1 (ref)	1.05 (0.99 to 1.11)	1.03 (0.97 to 1.10)	1.04 (0.97 to 1.12)	1.06 (0.98 to 1.14)	.31	.24
Polyunsaturated fat							
No. of cases	3,965	3,585	3,674	3,731	3,867		
HR (95% CI)	1 (ref)	0.96 (0.91 to 1.00)	0.97 (0.92 to 1.02)	0.96 (0.91 to 1.02)	0.92 (0.87 to 0.98)	.02	.33
Ever smokers (n = 793,768)							
Total fat							
No. of cases	2,945	2,972	3,051	3,380	4,172		
HR (95% CI)	1 (ref)	1.05 (1.00 to 1.10)	1.04 (0.99 to 1.10)	1.07 (1.02 to 1.13)	1.12 (1.06 to 1.17)	< .001	.45
Saturated fat							
No. of cases	2,822	2,830	3,026	3,421	4,421		
HR (95% CI)	1 (ref)	1.01 (0.95 to 1.07)	1.06 (0.99 to 1.13)	1.09 (1.02 to 1.17)	1.15 (1.07 to 1.24)	< .001	.62
Monounsaturated fat							
No. of cases	2,890	3,010	3,157	3,422	4,041		
HR (95% CI)	1 (ref)	1.06 (1.00 to 1.13)	1.05 (0.98 to 1.13)	1.03 (0.96 to 1.11)	1.06 (0.97 to 1.15)	.40	.24
Polyunsaturated fat							
No. of cases	3,461	3,119	3,228	3,277	3,435		
HR (95% CI)	1 (ref)	0.96 (0.91 to 1.01)	0.97 (0.92 to 1.03)	0.97 (0.91 to 1.03)	0.93 (0.88 to 0.99)	.03	.66
Never smokers (n = 652,082)							
Total fat							
No. of cases	513	466	415	510	398		
HR (95% CI)	1 (ref)	0.95 (0.84 to 1.08)	0.86 (0.75 to 0.98)	1.09 (0.96 to 1.24)	0.92 (0.80 to 1.05)	.89	.46
Saturated fat							
No. of cases	506	486	438	443	429		
HR (95% CI)	1 (ref)	1.08 (0.93 to 1.25)	0.96 (0.81 to 1.14)	0.95 (0.70 to 1.28)	1.03 (0.84 to 1.26)	.81	.25
Monounsaturated fat							
No. of cases	510	475	424	467	426		
HR (95% CI)	1 (ref)	0.97 (0.82 to 1.15)	0.91 (0.76 to 1.09)	1.08 (0.89 to 1.31)	1.06 (0.85 to 1.32)	.42	.86
Polyunsaturated fat							
No. of cases	504	466	446	454	432		
HR (95% CI)	1 (ref)	0.94 (0.83 to 1.08)	0.93 (0.80 to 1.07)	0.94 (0.80 to 1.09)	0.88 (0.75 to 1.04)	.28	.64

Abbreviations: HR, hazard ratio; Q, quintile; ref, reference.

*Based on the cohort- and sex-specific quintiles.

†All HRs were estimated in each cohort and then pooled by meta-analysis. Models were stratified by baseline age group and enrollment year and adjusted for age, sex, smoking status, smoking pack-years, family history of lung cancer, race/ethnicity, educational attainment, alcohol consumption, physical activity level, obesity status, intakes of total energy and vegetable, and menopausal status in women. Specific types of fat were mutually adjusted. The results indicate the risk of lung cancer when substituting energy from total or specific type of fat for equivalent energy from carbohydrate and protein.

energy intake or project-wide cutoffs for fat intakes or further adjustment for red meat intake also yielded similar results (Appendix Tables A4 to A6, online only).

DISCUSSION

In this pooled analysis of 10 prospective cohort studies, we found that high intakes of total or saturated fat were associated with an increased risk of lung cancer, particularly for squamous cell and small cell carcinoma. Specifically, the highest quintile of saturated fat intake showed a 61% higher risk for squamous cell carcinoma and a 40% higher risk for small cell carcinoma, compared with the lowest quintile. In contrast, a high intake of polyunsaturated fat was associated with a decreased risk of lung cancer. Isocaloric

replacement of saturated fat with polyunsaturated fat (5% of energy) was associated with an overall 12% lower risk of lung cancer. Monounsaturated fat was not associated with lung cancer risk. Results did not change with the use of alternative analytic approaches and in a series of sensitivity analyses.

Despite controversy, saturated fat has been suggested to play an adverse role in the development of various cancers, including lung cancer.^{11,12,46-49} Significant positive association of saturated fat and lung cancer has been observed in case-control studies⁷⁻¹⁰ as well as in several, but not all, prospective studies.¹¹⁻¹⁵ A previous pooled analysis of eight cohort studies among Western, predominantly white populations reported that a higher intake of saturated fat was associated with lung cancer risk in age-adjusted model (relative risk [RR] 1.21; 95% CI, 1.08 to 1.36 per 5% energy increase),¹⁴ although the association was attenuated after adjusting

Table 4. Risk of Lung Cancer by Quintiles of Saturated Fat Intake: Stratified Analysis

Characteristic	No. of Cases	Hazard Ratio (95% CI) by Saturated Fat Intake*, †					P for Trend	P for Interaction/ Heterogeneity	5% Substitution with PUFA‡	
		Q1	Q2	Q3	Q4	Q5				
All participants (N = 1,445,850)										
Smoking status										
Current smokers	9,119	1 (ref)	1.01 (0.93 to 1.10)	1.05 (0.96 to 1.14)	1.13 (1.03 to 1.23)	1.23 (1.13 to 1.35)	< .001	.004	0.89 (0.84 to 0.95)	
Former smokers	7,401	1 (ref)	1.03 (0.95 to 1.12)	1.11 (1.02 to 1.22)	1.15 (1.04 to 1.27)	1.17 (1.04 to 1.27)	.001		0.90 (0.83 to 0.97)	
Never smokers	2,302	1 (ref)	1.06 (0.92 to 1.22)	0.97 (0.83 to 1.14)	1.00 (0.85 to 1.19)	1.02 (0.85 to 1.23)	.63		0.90 (0.77 to 1.02)	
Sex										
Men	9,701	1 (ref)	1.09 (1.01 to 1.18)	1.15 (1.05 to 1.25)	1.16 (1.06 to 1.27)	1.25 (1.14 to 1.37)	< .001	.08	0.90 (0.84 to 0.96)	
Women	9,121	1 (ref)	0.97 (0.90 to 1.05)	1.01 (0.93 to 1.09)	1.11 (1.02 to 1.21)	1.17 (1.07 to 1.28)	< .001		0.87 (0.81 to 0.93)	
Race/ethnicity										
White	16,174	1 (ref)	1.02 (0.96 to 1.08)	1.06 (1.00 to 1.13)	1.13 (1.06 to 1.20)	1.21 (1.13 to 1.29)	< .001	.11	0.90 (0.85 to 0.94)	
Black	807	1 (ref)	1.22 (0.94 to 1.59)	1.23 (0.92 to 1.65)	1.22 (0.88 to 1.68)	1.08 (0.76 to 1.55)	.97		0.88 (0.65 to 1.11)	
Asian	1,656	1 (ref)	1.03 (0.85 to 1.23)	1.09 (0.88 to 1.35)	1.03 (0.81 to 1.32)	1.11 (0.84 to 1.47)	.56		0.89 (0.71 to 1.06)	
Histologic types										
Adenocarcinoma	7,004	1 (ref)	0.97 (0.89 to 1.06)	1.03 (0.93 to 1.13)	1.04 (0.94 to 1.15)	1.07 (0.96 to 1.18)	.11	< .001	0.93 (0.86 to 1.00)	
Squamous cell carcinoma	3,227	1 (ref)	1.23 (1.08 to 1.41)	1.36 (1.17 to 1.57)	1.44 (1.24 to 1.68)	1.61 (1.38 to 1.88)	< .001		0.83 (0.74 to 0.93)	
Other non-small cell	3,051	1 (ref)	1.11 (0.97 to 1.27)	1.12 (0.97 to 1.30)	1.22 (1.04 to 1.42)	1.32 (1.12 to 1.55)	.001		0.91 (0.81 to 1.01)	
Small cell lung carcinoma	2,497	1 (ref)	1.05 (0.90 to 1.23)	1.12 (0.95 to 1.33)	1.29 (1.09 to 1.53)	1.40 (1.17 to 1.67)	< .001		0.84 (0.73 to 0.95)	
Ever smokers (n = 793,768)										
Sex										
Men	9,143	1 (ref)	1.09 (1.01 to 1.18)	1.15 (1.05 to 1.25)	1.15 (1.05 to 1.26)	1.26 (1.14 to 1.38)	< .001	.17	0.91 (0.85 to 0.97)	
Women	7,377	1 (ref)	0.95 (0.87 to 1.03)	1.02 (0.93 to 1.12)	1.13 (1.03 to 1.25)	1.18 (1.07 to 1.30)	< .001		0.88 (0.81 to 0.94)	
Race/ethnicity										
White	14,803	1 (ref)	1.02 (0.96 to 1.08)	1.08 (1.01 to 1.15)	1.14 (1.07 to 1.23)	1.23 (1.14 to 1.32)	< .001	.24	0.89 (0.85 to 0.94)	
Black	748	1 (ref)	1.22 (0.93 to 1.60)	1.23 (0.90 to 1.68)	1.18 (0.84 to 1.65)	1.07 (0.74 to 1.55)	.95		0.87 (0.63 to 1.11)	
Asian	801	1 (ref)	0.98 (0.75 to 1.28)	1.11 (0.81 to 1.51)	1.03 (0.73 to 1.46)	1.05 (0.71 to 1.57)	.90		0.93 (0.68 to 1.17)	
Histologic types										
Adenocarcinoma	5,749	1 (ref)	0.94 (0.86 to 1.04)	1.01 (0.91 to 1.12)	1.03 (0.93 to 1.15)	1.06 (0.94 to 1.19)	.14	.001	0.95 (0.88 to 1.03)	
Squamous cell carcinoma	3,103	1 (ref)	1.22 (1.06 to 1.41)	1.33 (1.15 to 1.55)	1.44 (1.23 to 1.68)	1.59 (1.36 to 1.87)	< .001		0.83 (0.74 to 0.93)	
Other non-small cell	2,760	1 (ref)	1.13 (0.98 to 1.30)	1.18 (1.01 to 1.38)	1.25 (1.06 to 1.48)	1.35 (1.14 to 1.61)	.001		0.92 (0.80 to 1.02)	
Small cell lung carcinoma	2,419	1 (ref)	1.05 (0.90 to 1.24)	1.13 (0.95 to 1.34)	1.28 (1.08 to 1.53)	1.38 (1.15 to 1.65)	< .001		0.85 (0.74 to 0.96)	
Never smokers (n = 652,082)										
Sex										
Men	558	1 (ref)	1.07 (0.79 to 1.45)	1.07 (0.77 to 1.49)	1.14 (0.80 to 1.63)	1.02 (0.69 to 1.51)	.84	.41	0.88 (0.63 to 1.13)	
Women	1,744	1 (ref)	1.06 (0.90 to 1.25)	0.95 (0.79 to 1.14)	0.96 (0.79 to 1.17)	1.03 (0.83 to 1.26)	.71		0.91 (0.76 to 1.05)	
Race/ethnicity										
White	1,371	1 (ref)	1.05 (0.87 to 1.26)	0.91 (0.75 to 1.12)	0.98 (0.80 to 1.21)	1.00 (0.80 to 1.25)	.79	.70	0.92 (0.78 to 1.07)	
Black	59	1 (ref)	1.31 (0.55 to 3.16)	1.34 (0.49 to 5.68)	1.78 (0.60 to 5.28)	1.07 (0.29 to 3.98)	.87		1.10 (0.28 to 1.92)	
Asian	855	1 (ref)	1.07 (0.83 to 1.38)	1.08 (0.80 to 1.45)	1.02 (0.73 to 1.43)	1.16 (0.79 to 1.71)	.56		0.87 (0.62 to 1.12)	
Histologic types										
Adenocarcinoma	1,255	1 (ref)	1.09 (0.89 to 1.33)	1.04 (0.84 to 1.30)	1.01 (0.80 to 1.28)	1.01 (0.78 to 1.30)	.88	.12	0.87 (0.70 to 1.03)	
Squamous cell carcinoma	124	1 (ref)	1.45 (0.77 to 2.73)	1.89 (0.96 to 3.74)	1.53 (0.72 to 3.25)	1.92 (0.88 to 4.20)	.17		0.80 (0.30 to 1.31)	
Other non-small cell	291	1 (ref)	0.99 (0.67 to 1.46)	0.72 (0.46 to 1.14)	0.96 (0.60 to 1.53)	0.99 (0.60 to 1.63)	.80		0.95 (0.61 to 1.28)	
Small cell lung carcinoma	78	1 (ref)	0.91 (0.40 to 2.07)	0.90 (0.35 to 2.28)	1.72 (0.68 to 4.36)	2.22 (0.81 to 6.05)	.03		0.68 (0.03 to 1.35)	

Abbreviations: PUFA, polyunsaturated fat; Q, quintile; ref, references.

*Based on the cohort- and sex-specific quintiles.

†Hazard ratios were estimated in aggregated pooled analyses. Models were stratified by cohort, baseline age group, and enrollment year and adjusted for age, sex, smoking status, smoking pack-years, family history of lung cancer, race/ethnicity, educational attainment, alcohol consumption, physical activity level, obesity status, intakes of total energy and vegetable, and menopausal status in women. Specific types of fat were mutually adjusted. The results indicate the risk of lung cancer when substituting energy from saturated fat for equivalent energy from carbohydrate and protein.

‡Hazard ratios were estimated in aggregated pooled analyses. Models were stratified by cohort, baseline age group, and enrollment year and adjusted for age, sex, smoking status, smoking pack-years, family history of lung cancer, race/ethnicity, educational attainment, alcohol consumption, physical activity level, obesity status, intakes of total energy and vegetable, and menopausal status in women. The results indicate the risk of lung cancer when substituting 5% of energy from saturated fat with 5% energy from polyunsaturated fat.

Fig 1. Dose-response relationship of (A, B) saturated fat and (C, D) polyunsaturated fat intakes with lung cancer risk. Solid line indicates the hazard ratio of lung cancer and dashed line indicates the 95% CIs. The 10th percentile of saturated/polyunsaturated fat intake was set as reference, and four knot positions were fitted at the 5th, 25th, 75th, and 95th percentiles. All models were stratified by cohort, baseline age group, and enrollment year, and were adjusted for age, sex, race/ethnicity, smoking status, smoking pack-years, family history of lung cancer, educational attainment, alcohol consumption, physical activity level, obesity status, intakes of total energy and vegetable, and menopausal status in women. Specific types of fat were mutually adjusted. The results indicate the risk of lung cancer when substituting energy from saturated or polyunsaturated fat for equivalent energy from carbohydrate and protein.

for lifestyle factors and smoking history. Previous studies have also suggested that the association between saturated fat intake and lung cancer may be more evident among smokers,^{11,12} especially male smokers and heavy smokers. In the current study, we found a significant interaction between smoking status and saturated fat intake in relation to lung cancer risk. The positive association of saturated fat and the beneficial association of substituting saturated with polyunsaturated fats were primarily seen among current smokers and former smokers who quit ≤ 10 years before. Although the underlying mechanisms remain largely unknown,

potential biologic interaction between saturated fat and smoking was supported by animal studies. Nicotine-derived nitrosamine ketone (NNK) is a potent tobacco carcinogen.⁵⁰ NNK promotes lung carcinogenesis by inducing cyclooxygenase-2, disrupting arachidonic acid signaling, and activating tumorigenic pathways.⁵⁰ Noticeably, these tumor-promoting effects of NNK were found to be enhanced by a high-fat diet.^{51,52} Moreover, emerging evidence indicates that saturated fat itself may increase carcinogenesis by regulating DNA damage and inflammatory responses.^{53,54}

In our study, we found that saturated fat was primarily associated with an increased risk of squamous cell and small cell carcinoma. Overall, the highest quintile of saturated fat intake exhibited a 40% to 61% higher risk. This histologic-specific pattern was also observed among never smokers, although the point estimates did not reach statistical significance. The nonsignificant association among never smokers might be due to a small number of cases for histologic type-specific analyses. Indeed, analyses without excluding the first 2 years of follow-up showed significant associations of saturated fat with squamous cell carcinoma (HR, 2.18; 95% CI, 1.06 to 4.47; *P* for trend = .04) and small cell carcinoma (HR, 2.36; 95% CI, 0.94 to 5.93; *P* for trend = .005) among never smokers. This finding is in line with one previous report,¹⁰ but in contrast with two case-control studies that reported the positive association of saturated fat appeared stronger for adenocarcinoma.^{7,8} Considering that smoking is more strongly associated with squamous cell and small cell carcinoma than other histologic types (ie, adenocarcinoma and large cell carcinoma),⁵⁵ it is plausible that the adverse effects of saturated fat may be more pronounced for these histologic types of lung cancer. On the other hand, residual confounding from smoking could not be entirely excluded. Further studies are needed to examine the potential interplays between saturated fat intake, smoking, and different types of lung cancer, as well as the underlying biologic mechanisms.

Potential beneficial health effects of polyunsaturated fat have been widely discussed, but its association with lung cancer remains unclear. Previous cohort studies have yielded inconsistent but mostly null findings on the association between polyunsaturated fat and lung cancer.^{11-13,15} One study found a significant inverse association between a high intake of fat from plant foods, predominantly unsaturated fats, and lung cancer incidence (RR, 0.7; 95% CI, 0.5 to 0.9 for the highest v lowest quartile).¹⁵ The previously referenced pooled analysis¹⁴ found no association of polyunsaturated fat with lung cancer risk. A recent meta-analysis including eight prospective studies reported a nonsignificant, decreased lung cancer risk with high polyunsaturated fat intake (RR, 0.91; 95% CI, 0.78 to 1.06 for the highest v lowest category).¹⁷ Our current study, the largest study on this topic thus far, to our knowledge, showed polyunsaturated fat intake was inversely associated with lung cancer risk. We further found that substituting energy from saturated fat with polyunsaturated fat may reduce lung cancer risk. In vitro and in vivo studies have suggested several potential cancer inhibitory effects of polyunsaturated fat, especially n-3-polyunsaturated fat, including as an inhibitor for arachidonic acid and cyclooxygenase-2, an inflammatory mediator, and a suppressor of fatty acid synthase.^{6,51,56,57} N-3-polyunsaturated fat may also affect cytokine production and inflammatory gene expression.⁵⁷ However, the role of n-6-polyunsaturated fat in carcinogenesis remains controversial. This study could not explore potential associations for specific polyunsaturated fats because of a lack of detailed information. Future studies focused on subtypes of polyunsaturated fat and their roles in the development of lung cancer are warranted.

As with other nutritional epidemiologic studies, measurement errors in dietary assessment are a concern, although the questionnaires used in participating cohorts have been validated and shown good validity.²⁸⁻³⁸ Furthermore, most participating cohorts have only collected dietary information at baseline and the single

dietary assessment prohibited us from evaluating the influence of possible dietary changes over time. In the few cohorts that have conducted multiple dietary surveys, models using only baseline diet seemed to yield similar or weaker results compared with models using cumulative diet.^{58,59} Lack of information on subtypes of polyunsaturated fat is also a study limitation, as mentioned previously. We believe, however, that these potential measurement errors are nondifferential with respect to lung cancer status, given our prospective study design, and that our analytic strategies minimize the effect of potential bias on study results. The first 2 years of follow-up were excluded from analyses and cohort- and sex-specific cutoffs of dietary intakes were used to reduce the potential influences of reverse causation and varied dietary measures. All associations were evaluated with comprehensive adjustments for lung cancer risk factors, including smoking status and amount, dietary, and other nondietary factors, and results from sensitivity analyses were consistent with overall results. Nevertheless, we cannot rule out residual confounding by imperfectly measured covariates (eg, smoking) and unadjusted potential confounders (eg, trans-fat), nor could we distinguish the effect of fat from that of other nutrients and chemicals in fat-rich foods (eg, red meat) that may influence lung cancer risk. However, we have adjusted for total vegetable intake in our analysis, and the results did not change after further adjusting for red meat intake.

To our knowledge, this study is the largest prospective investigation on dietary fat intake and lung cancer risk to date, including six times as many cases as the previous pooled analysis¹⁴ and seven studies that have not been part of any previous pooled or meta-analyses. Moreover, our study includes diverse populations of whites, blacks, and Asians from three continents and provides evidence suggesting potentially different roles of saturated and polyunsaturated fats in the development of lung cancer.

In conclusion, findings from this large, international cohort consortium indicate that a high intake of saturated fat and a low intake of polyunsaturated fat are associated with an increased risk of lung cancer. Substituting saturated fat with polyunsaturated fat may reduce lung cancer risk, especially among smokers and for squamous cell and small cell carcinoma. Although the apparent benefit is relatively small compared with smoking avoidance and cessation, our study suggests that promoting polyunsaturated fat while reducing saturated fat intake, especially among current smokers and recent quitters, may present a modifiable dietary approach to the prevention of not only cardiovascular disease but also lung cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Dietary Fat Intake and Lung Cancer Risk: A Pooled Analysis

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Appendix

Fig A1. Risk of lung cancer associated with (A) saturated fat and (B) polyunsaturated fat intake (the highest v the lowest quintile) in each participating cohort. All models were adjusted for age, sex, smoking status, smoking pack-years, family history of lung cancer, race/ethnicity, educational attainment, alcohol consumption, physical activity level, obesity status, intakes of total energy and vegetable, and menopausal status in women. Specific types of fat were mutually adjusted. The results indicate the risk of lung cancer when substituting energy from saturated or polyunsaturated fat for equivalent energy from carbohydrate and protein. *P* for heterogeneity across studies = .38 for saturated fat and .33 for polyunsaturated fat. Abbreviations: AARP, National Institutes of Health-AARP Study (NIH-AARP); %E, percent energy; EPIC, European Prospective Investigation into Cancer & Nutrition; HPFS, Health Professionals' Follow-up Study; IWHS, Iowa Women's Health Study; NHS, Nurses' Health Study; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; SCCS, Southern Community Cohort Study; SHS, Shanghai Men's and Women's Health Studies; VITAL, Vitamins and Lifestyle Study.

Table A1. Dietary Fat Intake in the Participating Cohort Studies

Study	Energy (%)*														
	Total Fat					Saturated Fat					Monounsaturated Fat				
	Q1	Q2	Q3	Q4	Q5	Q1	Q2	Q3	Q4	Q5	Q1	Q2	Q3	Q4	Q5
National Health Institute-AARP Diet and Health Study															
Men: All participants	17.6	24.2	28.1	31.9	37.8	5.5	7.8	9.4	10.9	13.8	7.1	9.9	11.6	13.3	15.9
Lung cancer cases	17.1	24.1	28.1	32.0	38.2	5.4	7.9	9.4	10.9	14.0	7.0	9.9	11.7	13.3	16.1
Women: All participants	17.4	23.5	27.5	31.5	38.0	5.5	7.5	9.0	10.6	13.7	6.8	9.4	11.1	12.8	15.5
Lung cancer cases	17.5	23.4	27.4	31.5	38.5	5.5	7.5	9.0	10.7	14.0	6.8	9.4	11.1	12.8	15.7
Health Professionals Follow-Up Study															
All participants	20.7	26.2	29.2	32.1	37.1	7.1	9.5	10.9	12.3	14.9	8.3	10.8	12.2	13.6	15.9
Lung cancer cases	20.8	26.2	29.4	32.1	37.3	7.3	9.5	10.9	12.3	14.9	8.4	10.8	12.3	13.6	16.1
Iowa Women's Health Study															
All participants	23.4	28.1	30.9	33.6	38.2	8.6	10.5	11.7	13.0	15.6	9.4	11.6	12.9	14.2	16.4
Lung cancer cases	23.6	28.0	30.9	33.7	38.3	8.6	10.5	11.7	13.0	16.0	9.5	11.6	12.9	14.2	16.4
Nurses' Health Study															
All participants	24.0	29.0	31.8	34.6	39.3	9.0	11.1	12.4	13.7	16.2	9.2	11.4	12.7	13.9	16.0
Lung cancer cases	23.6	29.0	31.8	34.5	39.7	8.9	11.1	12.3	13.7	16.4	9.1	11.4	12.6	13.9	16.1
Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial															
Men: all participants	19.6	25.4	28.7	32.0	37.3	6.5	8.7	10.2	11.6	14.3	7.9	10.4	11.9	13.3	15.7
Lung cancer cases	19.5	25.3	28.8	32.0	37.4	6.5	8.8	10.1	11.7	14.5	7.7	10.3	11.8	13.3	15.7
Women: All participants	18.6	23.6	26.9	30.2	36.0	6.2	8.0	9.4	10.8	13.6	7.2	9.4	10.8	12.2	14.7
Lung cancer cases	18.7	23.5	26.8	29.9	35.4	6.2	8.1	9.4	10.8	13.8	7.3	9.4	10.8	12.0	14.3
Southern Community Cohort Study															
Men: All participants	23.6	31.2	34.7	37.7	42.3	6.8	9.2	10.4	11.5	13.3	8.9	11.9	13.3	14.6	16.6
Lung cancer cases	24.0	31.1	34.7	37.8	42.4	6.8	9.1	10.3	11.5	13.5	9.2	11.9	13.3	14.6	16.6
Women: All participants	25.2	31.5	34.8	37.8	42.5	7.1	9.2	10.3	11.4	13.3	9.2	11.7	13.1	14.3	16.3
Lung cancer cases	25.3	31.6	34.9	37.9	42.8	7.1	9.2	10.3	11.4	13.6	9.1	11.7	13.1	14.3	16.4
Vitamins and Lifestyle Study															
Men: All participants	23.8	30.9	35.1	39.0	45.5	6.9	9.3	10.8	12.3	14.9	8.7	11.6	13.2	14.9	17.7
Lung cancer cases	23.9	31.0	35.1	38.9	45.4	7.1	9.3	10.9	12.3	14.9	8.8	11.7	13.3	14.9	17.6
Women: All participants	21.4	28.2	32.5	36.8	44.2	6.3	8.6	10.2	11.8	14.8	7.8	10.5	12.2	13.9	16.9
Lung cancer cases	21.8	28.4	32.6	37.0	43.9	6.5	8.5	10.2	11.9	14.9	7.9	10.4	12.2	13.9	16.8
European Prospective Investigation Into Cancer & Nutrition															
Men: All participants	24.0	29.0	31.9	34.9	40.4	8.6	11.3	13.0	14.7	17.9	9.1	11.2	12.6	14.3	19.4
Lung cancer cases	24.2	28.9	32.0	35.1	40.4	8.6	11.3	13.0	14.7	18.2	9.2	11.2	12.6	14.2	19.2
Women: All participants	24.1	29.1	32.0	35.0	40.5	9.2	11.8	13.4	15.0	18.2	8.6	10.6	12.0	13.7	18.7
Lung cancer cases	24.3	29.0	32.1	35.2	40.3	9.4	11.8	13.4	15.1	18.5	8.6	10.6	12.0	13.6	17.6
Shanghai Men's Health Study															
All participants	9.7	13.2	15.7	18.3	23.8	2.6	3.8	4.6	5.6	7.5	3.8	5.5	6.7	8.2	11.4
Lung cancer cases	9.6	13.3	15.7	18.3	24.3	2.6	3.7	4.6	5.6	7.7	3.7	5.5	6.7	8.2	11.7
Shanghai Women's Health Study															
All participants	9.3	12.9	15.2	17.7	22.5	2.4	3.5	4.4	5.3	7.0	3.7	5.3	6.5	7.9	10.6
Lung cancer cases	9.1	12.8	15.3	17.7	22.7	2.3	3.5	4.4	5.3	6.9	3.6	5.3	6.5	7.9	10.7

Abbreviation: Q, quintile.

*Mean values of each quintile.

Table A2. Risk of Lung Cancer by Quintiles of Polyunsaturated Fat Intake: Stratified Analysis

Characteristic	No. of Cases	Hazard Ratio (95% CI) by Polyunsaturated Fat Intake*,†					P for Trend	P for Interaction/ Heterogeneity
		Q1	Q2	Q3	Q4	Q5		
All participants (N = 1,445,850)								
Smoking status								
Current smokers	9,119	1 (ref)	1.01 (0.95 to 1.09)	1.00 (0.93 to 1.07)	1.02 (0.95 to 1.10)	1.01 (0.94 to 1.09)	.96	.15
Former smokers	7,401	1 (ref)	0.90 (0.83 to 0.97)	0.97 (0.89 to 1.05)	0.93 (0.85 to 1.01)	0.90 (0.82 to 0.98)	.06	
Never smokers	2,302	1 (ref)	0.97 (0.85 to 1.10)	0.94 (0.82 to 1.08)	0.96 (0.83 to 1.11)	0.92 (0.79 to 1.07)	.54	
Sex								
Men	9,701	1 (ref)	0.94 (0.88 to 1.01)	0.98 (0.92 to 1.05)	0.97 (0.90 to 1.04)	0.95 (0.88 to 1.03)	.29	.30
Women	9,121	1 (ref)	0.98 (0.92 to 1.05)	0.97 (0.91 to 1.05)	0.97 (0.90 to 1.04)	0.96 (0.89 to 1.03)	.25	
Race/ethnicity								
White	16,174	1 (ref)	0.97 (0.92 to 1.02)	0.99 (0.94 to 1.04)	0.99 (0.94 to 1.05)	0.97 (0.92 to 1.03)	.31	.04
Black	807	1 (ref)	1.02 (0.80 to 1.30)	0.95 (0.73 to 1.25)	0.87 (0.65 to 1.16)	0.89 (0.64 to 1.22)	.30	
Asian	1,656	1 (ref)	0.85 (0.73 to 0.99)	0.90 (0.76 to 1.07)	0.86 (0.72 to 1.02)	0.80 (0.66 to 0.96)	.03	
Histologic types								
Adenocarcinoma	7,004	1 (ref)	1.00 (0.92 to 1.08)	1.04 (0.96 to 1.12)	1.03 (0.94 to 1.12)	0.98 (0.90 to 1.08)	.68	.80
Squamous cell carcinoma	3,227	1 (ref)	1.00 (0.90 to 1.13)	0.98 (0.87 to 1.10)	0.99 (0.88 to 1.12)	0.92 (0.81 to 1.05)	.20	
Other non-small cell	3,051	1 (ref)	0.93 (0.82 to 1.04)	0.94 (0.83 to 1.06)	0.94 (0.82 to 1.07)	0.98 (0.86 to 1.13)	.95	
Small cell lung carcinoma	2,497	1 (ref)	0.92 (0.81 to 1.05)	0.96 (0.84 to 1.10)	0.93 (0.80 to 1.07)	0.98 (0.85 to 1.14)	.63	
Ever smokers (n = 793,768)								
Sex								
Men	9,143	1 (ref)	0.92 (0.86 to 0.99)	0.97 (0.90 to 1.05)	0.96 (0.89 to 1.03)	0.94 (0.87 to 1.02)	.28	.51
Women	7,377	1 (ref)	1.00 (0.93 to 1.08)	0.99 (0.92 to 1.07)	0.99 (0.91 to 1.07)	0.97 (0.89 to 1.06)	.35	
Race/ethnicity								
White	14,803	1 (ref)	0.97 (0.92 to 1.02)	0.99 (0.93 to 1.04)	0.98 (0.93 to 1.04)	0.97 (0.91 to 1.03)	.21	.44
Black	748	1 (ref)	0.97 (0.76 to 1.25)	0.94 (0.71 to 1.24)	0.85 (0.63 to 1.16)	0.90 (0.65 to 1.25)	.36	
Asian	801	1 (ref)	0.79 (0.62 to 1.00)	0.94 (0.73 to 1.19)	0.88 (0.68 to 1.13)	0.85 (0.65 to 1.12)	.52	
Histologic types								
Adenocarcinoma	5,749	1 (ref)	1.02 (0.93 to 1.11)	1.07 (0.98 to 1.17)	1.05 (0.95 to 1.15)	1.01 (0.91 to 1.12)	.84	.90
Squamous cell carcinoma	3,103	1 (ref)	1.01 (0.90 to 1.14)	1.00 (0.88 to 1.13)	1.01 (0.89 to 1.15)	0.94 (0.82 to 1.07)	.30	
Other non-small cell	2,760	1 (ref)	0.89 (0.79 to 1.01)	0.95 (0.83 to 1.08)	0.93 (0.81 to 1.06)	0.96 (0.83 to 1.11)	.85	
Small cell lung carcinoma	2,419	1 (ref)	0.92 (0.81 to 1.05)	0.95 (0.83 to 1.09)	0.93 (0.81 to 1.08)	0.97 (0.84 to 1.13)	.60	
Never smokers (n = 652,082)								
Sex								
Men	558	1 (ref)	1.33 (1.01 to 1.76)	1.21 (0.89 to 1.63)	1.28 (0.94 to 1.75)	1.16 (0.83 to 1.62)	.59	.17
Women	1,744	1 (ref)	0.88 (0.76 to 1.03)	0.88 (0.75 to 1.03)	0.89 (0.75 to 1.05)	0.87 (0.73 to 1.03)	.32	
Race/ethnicity								
White	1,371	1 (ref)	0.99 (0.83 to 1.17)	0.98 (0.82 to 1.17)	1.03 (0.86 to 1.24)	1.06 (0.87 to 1.28)	.50	.03
Black	59	1 (ref)	2.05 (0.82 to 5.14)	1.23 (0.43 to 3.51)	1.12 (0.36 to 3.51)	0.79 (0.22 to 2.87)	.59	
Asian	855	1 (ref)	0.90 (0.73 to 1.12)	0.87 (0.69 to 1.10)	0.84 (0.66 to 1.08)	0.75 (0.57 to 0.98)	.02	
Histologic types								
Adenocarcinoma	1,255	1 (ref)	0.93 (0.77 to 1.11)	0.89 (0.74 to 1.08)	0.93 (0.76 to 1.13)	0.87 (0.70 to 1.07)	.54	.40
Squamous cell carcinoma	124	1 (ref)	0.90 (0.53 to 1.52)	0.57 (0.31 to 1.07)	0.69 (0.37 to 1.29)	0.65 (0.34 to 1.25)	.14	
Other non-small cell	291	1 (ref)	1.27 (0.88 to 1.83)	0.85 (0.56 to 1.29)	1.04 (0.68 to 1.58)	1.25 (0.81 to 1.92)	.41	
Small cell lung carcinoma	78	1 (ref)	0.97 (0.47 to 1.99)	1.42 (0.69 to 2.93)	0.77 (0.32 to 1.88)	1.28 (0.53 to 3.08)	.90	

Abbreviations: Q, quintile; ref, reference.

*Based on the cohort- and sex-specific quintiles.

†Hazard ratios were estimated in aggregated pooled analyses. Models were stratified by cohort, baseline age group, and enrollment year and adjusted for age, sex, smoking status, smoking pack-years, family history of lung cancer, race/ethnicity, educational attainment, alcohol consumption, physical activity level, obesity status, intakes of total energy and vegetable, and menopausal status in women. Specific types of fat were mutually adjusted. The results indicate the risk of lung cancer when substituting energy from polyunsaturated fat for equivalent energy from carbohydrate and protein.

Dietary Fat Intake and Lung Cancer Risk

Table A3. Aggregated Pooled Analyses: Association of Lung Cancer With Total and Specific Types of Dietary Fat Intakes*

	Energy (%)					
Type of Dietary Fatt†	Q1	Q2	Q3	Q4	Q5	P for Trend
All participants (N = 1,445,850)						
Total fat						
No. of cases	3,458	3,438	3,466	3,890	4,570	
HR (95% CI)	1 (ref)	1.04 (0.99 to 1.09)	1.03 (0.98 to 1.08)	1.09 (1.04 to 1.14)	1.11 (1.06 to 1.17)	< .001
Saturated fat						
No. of cases	3,328	3,316	3,464	3,864	4,850	
HR (95% CI)	1 (ref)	1.03 (0.98 to 1.09)	1.08 (1.02 to 1.14)	1.14 (1.07 to 1.21)	1.22 (1.14 to 1.30)	< .001
Monounsaturated fat						
No. of cases	3,400	3,485	3,581	3,889	4,467	
HR (95% CI)	1 (ref)	1.03 (0.97 to 1.09)	0.99 (0.93 to 1.05)	0.99 (0.92 to 1.06)	1.00 (0.93 to 1.07)	.64
Polyunsaturated fat						
No. of cases	3,965	3,585	3,674	3,731	3,867	
HR (95% CI)	1 (ref)	0.96 (0.92 to 1.01)	0.98 (0.93 to 1.03)	0.97 (0.93 to 1.03)	0.95 (0.91 to 1.01)	.14
Ever smokers (n = 793,768)						
Total fat						
No. of cases	2,945	2,972	3,051	3,380	4,172	
HR (95% CI)	1 (ref)	1.05 (1.00 to 1.10)	1.05 (0.99 to 1.10)	1.08 (1.02 to 1.13)	1.12 (1.07 to 1.18)	< .001
Saturated fat						
No. of cases	2,822	2,830	3,026	3,421	4,421	
HR (95% CI)	1 (ref)	1.02 (0.97 to 1.09)	1.09 (1.02 to 1.16)	1.15 (1.08 to 1.23)	1.23 (1.14 to 1.31)	< .001
Monounsaturated fat						
No. of cases	2,890	3,010	3,157	3,422	4,041	
HR (95% CI)	1 (ref)	1.04 (0.98 to 1.10)	1.00 (0.93 to 1.07)	0.98 (0.91 to 1.05)	0.99 (0.92 to 1.07)	.39
Polyunsaturated fat						
No. of cases	3,461	3,119	3,228	3,277	3,435	
HR (95% CI)	1 (ref)	0.96 (0.91 to 1.01)	0.98 (0.93 to 1.04)	0.98 (0.92 to 1.03)	0.96 (0.91 to 1.02)	.18
Never smokers (n = 652,082)						
Total fat						
No. of cases	513	466	415	510	398	
HR (95% CI)	1 (ref)	0.95 (0.84 to 1.08)	0.87 (0.76 to 0.99)	1.10 (0.97 to 1.25)	0.92 (0.81 to 1.06)	.96
Saturated fat						
No. of cases	506	486	438	443	429	
HR (95% CI)	1 (ref)	1.06 (0.92 to 1.22)	0.97 (0.83 to 1.14)	1.00 (0.85 to 1.19)	1.02 (0.85 to 1.23)	.63
Monounsaturated fat						
No. of cases	510	475	424	467	426	
HR (95% CI)	1 (ref)	0.98 (0.85 to 1.14)	0.92 (0.78 to 1.09)	1.06 (0.88 to 1.27)	1.03 (0.84 to 1.25)	.41
Polyunsaturated fat						
No. of cases	504	466	446	454	432	
HR (95% CI)	1 (ref)	0.97 (0.85 to 1.10)	0.94 (0.82 to 1.08)	0.96 (0.83 to 1.10)	0.92 (0.79 to 1.07)	.54

Abbreviations: HR, hazard ratio; Q, quintile; ref, reference.

*Based on the cohort- and sex-specific quintiles.

†HRs were estimated in aggregated pooled-analyses. Models were stratified by cohort, baseline age group, and enrollment year and adjusted for age, sex, smoking status, smoking pack-years, family history of lung cancer, race/ethnicity, educational attainment, alcohol consumption, physical activity level, obesity status, intakes of total energy and vegetable, and menopausal status in women. Specific types of fat were mutually adjusted. The results indicate the risk of lung cancer when substituting energy from total or specific type of fat for equivalent energy from carbohydrate and protein.

Table A4. Sensitivity Analysis Using the Residual Method for Energy Adjustment*

	Energy-Adjusted Fat Intake (g/d)						
Type of Dietary Fatt	Q1	Q2	Q3	Q4	Q5	P for Trend	P for Heterogeneity
All participants (N = 1,445,850)							
Total fat							
No. of cases	3,460	3,380	3,440	3,965	4,577		
HR (95% CI)	1 (ref)	1.01 (0.95 to 1.08)	0.99 (0.93 to 1.06)	1.09 (1.04 to 1.14)	1.07 (1.00 to 1.15)	< .001	.53
Saturated fat							
No. of cases	3,317	3,276	3,470	3,872	4,887		
HR (95% CI)	1 (ref)	1.02 (0.97 to 1.08)	1.05 (0.99 to 1.12)	1.10 (1.03 to 1.17)	1.15 (1.07 to 1.23)	< .001	.18
Monounsaturated fat							
No. of cases	3,401	3,414	3,624	3,918	4,465		
HR (95% CI)	1 (ref)	1.02 (0.96 to 1.08)	1.03 (0.96 to 1.10)	1.03 (0.96 to 1.10)	1.04 (0.96 to 1.13)	.31	.33
Polyunsaturated fat							
No. of cases	3,955	3,546	3,714	3,748	3,859		
HR (95% CI)	1 (ref)	0.95 (0.90 to 0.99)	0.98 (0.93 to 1.03)	0.97 (0.92 to 1.02)	0.93 (0.87 to 0.98)	.07	.39
Ever smokers (n = 793,768)							
Total fat							
No. of cases	2,939	2,930	3,032	3,450	4,169		
HR (95% CI)	1 (ref)	1.04 (0.99 to 1.09)	1.03 (0.98 to 1.09)	1.09 (1.04 to 1.15)	1.11 (1.05 to 1.17)	< .001	.68
Saturated fat							
No. of cases	2,812	2,789	3,040	3,431	4,448		
HR (95% CI)	1 (ref)	1.01 (0.96 to 1.08)	1.07 (1.00 to 1.14)	1.11 (1.03 to 1.19)	1.15 (1.07 to 1.24)	< .001	.57
Monounsaturated fat							
No. of cases	2,889	2,940	3,202	3,460	4,029		
HR (95% CI)	1 (ref)	1.03 (0.97 to 1.09)	1.05 (0.98 to 1.12)	1.03 (0.96 to 1.11)	1.05 (0.96 to 1.14)	.34	.43
Polyunsaturated fat							
No. of cases	3,455	3,099	3,242	3,298	3,426		
HR (95% CI)	1 (ref)	0.95 (0.90 to 1.00)	0.98 (0.92 to 1.03)	0.97 (0.91 to 1.03)	0.93 (0.87 to 0.99)	.09	.67
Never smokers (n = 652,082)							
Total fat							
No. of cases	521	450	408	515	408		
HR (95% CI)	1 (ref)	0.90 (0.79 to 1.02)	0.93 (0.73 to 0.95)	1.08 (0.95 to 1.22)	0.91 (0.80 to 1.05)	.91	.39
Saturated fat							
No. of cases	505	487	430	441	439		
HR (95% CI)	1 (ref)	1.07 (0.93 to 1.24)	0.98 (0.77 to 1.24)	0.99 (0.73 to 1.36)	1.00 (0.75 to 1.35)	.53	.08
Monounsaturated fat							
No. of cases	512	474	422	458	436		
HR (95% CI)	1 (ref)	0.96 (0.82 to 1.12)	0.88 (0.74 to 1.06)	1.01 (0.83 to 1.23)	1.04 (0.84 to 1.29)	.64	.37
Polyunsaturated fat							
No. of cases	500	447	472	450	433		
HR (95% CI)	1 (ref)	0.93 (0.82 to 1.07)	1.01 (0.88 to 1.17)	0.96 (0.82 to 1.12)	0.91 (0.77 to 1.07)	.63	.45

Abbreviations: HR, hazard ratio; Q, quintile; ref, reference.

*Based on the cohort- and sex-specific quintiles.

†HRs were estimated in each cohort and then pooled by meta-analysis. Models were stratified by baseline age group and enrollment year and adjusted for age, sex, smoking status, smoking pack-years, family history of lung cancer, race/ethnicity, educational attainment, alcohol consumption, physical activity level, obesity status, intakes of total energy and vegetable, and menopausal status in women. Specific types of fat were mutually adjusted. The results indicate the risk of lung cancer when substituting energy from total or specific type of fat for equivalent energy from carbohydrate and protein.

Dietary Fat Intake and Lung Cancer Risk

Table A5. Sensitivity Analysis Using the Same Sex-Specific Quintile Cut Points for All Cohorts*

	Energy (%)					P for Trend	P for Heterogeneity
Type of Dietary Fatt	Q1	Q2	Q3	Q4	Q5		
All participants (N = 1,445,850)							
Total fat							
No. of cases	3,612	3,686	3,545	3,841	4,138		
HR (95% CI)	1 (ref)	1.05 (0.97 to 1.14)	1.06 (1.01 to 1.13)	1.12 (1.06 to 1.18)	1.14 (1.08 to 1.21)	< .001	.60
Saturated fat							
No. of cases	3,511	3,757	3,981	3,783	3,790		
HR (95% CI)	1 (ref)	1.06 (0.99 to 1.14)	1.16 (1.07 to 1.25)	1.15 (1.06 to 1.25)	1.20 (1.09 to 1.31)	< .001	.69
Monounsaturated fat							
No. of cases	3,476	3,384	3,526	4,197	4,239		
HR (95% CI)	1 (ref)	1.01 (0.95 to 1.08)	0.99 (0.92 to 1.07)	1.06 (0.98 to 1.16)	1.03 (0.89 to 1.19)	.65	.08
Polyunsaturated fat							
No. of cases	3,355	3,505	3,869	4,011	4,082		
HR (95% CI)	1 (ref)	0.98 (0.93 to 1.04)	0.97 (0.92 to 1.03)	0.96 (0.90 to 1.02)	0.95 (0.88 to 1.01)	.09	.68
Ever smokers (n = 793,768)							
Total fat							
No. of cases	2,602	3,322	3,219	3,497	3,880		
HR (95% CI)	1 (ref)	1.09 (1.00 to 1.18)	1.07 (1.01 to 1.13)	1.12 (1.05 to 1.19)	1.15 (1.08 to 1.22)	< .001	.34
Saturated fat							
No. of cases	2,525	3,354	3,584	3,512	3,545		
HR (95% CI)	1 (ref.)	1.05 (0.98 to 1.12)	1.13 (1.04 to 1.23)	1.13 (1.04 to 1.24)	1.17 (1.06 to 1.29)	< .001	.83
Monounsaturated fat							
No. of cases	2,563	2,991	3,180	3,860	3,926		
HR (95% CI)	1 (ref)	1.00 (0.94 to 1.08)	1.00 (0.88 to 1.14)	1.09 (0.96 to 1.25)	1.02 (0.86 to 1.22)	.81	.01
Polyunsaturated fat							
No. of cases	2,572	3,057	3,477	3,646	3,768		
HR (95% CI)	1 (ref)	1.00 (0.94 to 1.06)	0.99 (0.93 to 1.06)	0.97 (0.91 to 1.04)	0.96 (0.89 to 1.03)	.14	.43
Never smokers (n = 652,082)							
Total fat							
No. of cases	1,010	364	326	344	258		
HR (95% CI)	1 (ref.)	0.87 (0.74 to 1.03)	0.99 (0.82 to 1.18)	1.13 (0.94 to 1.37)	1.04 (0.85 to 1.29)	.73	.62
Saturated fat							
No. of cases	986	403	397	271	245		
HR (95% CI)	1 (ref)	1.12 (0.91 to 1.37)	1.34 (1.03 to 1.75)	1.20 (0.88 to 1.64)	1.27 (0.89 to 1.83)	.68	.23
Monounsaturated fat							
No. of cases	913	393	346	337	313		
HR (95% CI)	1 (ref)	1.07 (0.83 to 1.36)	1.03 (0.76 to 1.40)	1.01 (0.70 to 1.45)	1.16 (0.78 to 1.72)	.41	.28
Polyunsaturated fat							
No. of cases	783	448	392	365	314		
HR (95% CI)	1 (ref)	0.90 (0.79 to 1.03)	0.81 (0.64 to 1.03)	0.88 (0.73 to 1.06)	0.89 (0.72 to 1.11)	.46	.33

Abbreviations: HR, hazard ratio; Q, quintile; ref, reference.

*Based on the sex-specific quintiles derived from one single dataset.

†HRs were estimated in each cohort and then pooled by meta-analysis. Models were stratified by baseline age group and enrollment year and adjusted for age, sex, smoking status, smoking pack-years, family history of lung cancer, race/ethnicity, educational attainment, alcohol consumption, physical activity level, obesity status, intakes of total energy and vegetable, and menopausal status in women. Specific types of fat were mutually adjusted. The results indicate the risk of lung cancer when substituting energy from total or specific type of fat for equivalent energy from carbohydrate and protein.

Table A6. Sensitivity Analysis Further Adjusting for Red Meat Intake*

	Energy (%)					P for Trend	P for Heterogeneity
Type of Dietary Fatt	Q1	Q2	Q3	Q4	Q5		
All participants (N = 1,445,850)							
Total fat							
No. of cases	3,458	3,438	3,466	3,890	4,570		
HR (95% CI)	1 (ref)	1.01 (0.97 to 1.07)	0.99 (0.94 to 1.04)	1.03 (0.98 to 1.09)	1.03 (0.96 to 1.11)	.10	.19
Saturated fat							
No. of cases	3,328	3,316	3,464	3,864	4,850		
HR (95% CI)	1 (ref)	1.01 (0.95 to 1.07)	1.03 (0.97 to 1.09)	1.08 (1.00 to 1.14)	1.13 (1.05 to 1.21)	< .001	.33
Monounsaturated fat							
No. of cases	3,400	3,485	3,581	3,889	4,467		
HR (95% CI)	1 (ref)	1.04 (0.98 to 1.10)	1.01 (0.95 to 1.08)	1.00 (0.93 to 1.08)	1.00 (0.92 to 1.09)	.75	.60
Polyunsaturated fat							
No. of cases	3,965	3,585	3,674	3,731	3,867		
HR (95% CI)	1 (ref)	0.95 (0.91 to 1.00)	0.97 (0.92 to 1.02)	0.97 (0.92 to 1.02)	0.94 (0.89 to 0.99)	.09	.66
Ever smokers (n = 793,768)							
Total fat							
No. of cases	2,945	2,972	3,051	3,380	4,172		
HR (95% CI)	1 (ref)	1.03 (0.97 to 1.08)	1.01 (0.96 to 1.07)	1.03 (0.97 to 1.09)	1.07 (1.00 to 1.12)	.06	.48
Saturated fat							
No. of cases	2,822	2,830	3,026	3,421	4,421		
HR (95% CI)	1 (ref)	1.00 (0.94 to 1.06)	1.04 (0.97 to 1.11)	1.07 (1.00 to 1.15)	1.14 (1.06 to 1.22)	< .001	.50
Monounsaturated fat							
No. of cases	2,890	3,010	3,157	3,422	4,041		
HR (95% CI)	1 (ref)	1.05 (0.99 to 1.12)	1.04 (0.94 to 1.15)	1.01 (0.90 to 1.12)	1.01 (0.92 to 1.10)	.72	.47
Polyunsaturated fat							
No. of cases	3,461	3,119	3,228	3,277	3,435		
HR (95% CI)	1 (ref)	0.96 (0.91 to 1.01)	0.97 (0.92 to 1.03)	0.97 (0.92 to 1.03)	0.95 (0.89 to 1.01)	.14	.93
Never smokers (n = 652,082)							
Total fat							
No. of cases	513	466	415	510	398		
HR (95% CI)	1 (ref)	0.95 (0.83 to 1.08)	0.85 (0.74 to 0.97)	1.06 (0.92 to 1.22)	0.88 (0.75 to 1.02)	.53	.61
Saturated fat							
No. of cases	506	486	438	443	429		
HR (95% CI)	1 (ref)	1.07 (0.92 to 1.24)	0.95 (0.80 to 1.13)	0.94 (0.69 to 1.27)	1.03 (0.84 to 1.26)	.84	.20
Monounsaturated fat							
No. of cases	510	475	424	467	426		
HR (95% CI)	1 (ref)	0.97 (0.82 to 1.13)	0.91 (0.75 to 1.10)	1.05 (0.85 to 1.29)	1.01 (0.79 to 1.28)	.73	.89
Polyunsaturated fat							
No. of cases	504	466	446	454	432		
HR (95% CI)	1 (ref)	0.95 (0.83 to 1.08)	0.93 (0.81 to 1.08)	0.94 (0.81 to 1.10)	0.90 (0.76 to 1.06)	.42	.56

Abbreviations: HR, hazard ratio; Q, quintile; ref, reference.

*Based on the cohort- and sex-specific quintiles

†HRs were estimated in each cohort and then pooled by meta-analysis. Models were stratified by baseline age group and enrollment year and adjusted for age, sex, smoking status, smoking pack-years, family history of lung cancer, race/ethnicity, educational attainment, alcohol consumption, physical activity level, obesity status, intakes of total energy, vegetable, and red meat, and menopausal status in women. Specific types of fat were mutually adjusted. The results indicate the risk of lung cancer when substituting energy from total or specific type of fat for equivalent energy from carbohydrate and protein.