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Dietary Fat and Risk of Lung Cancer in a Pooled Analysis of Prospective Studies¹

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Abstract

Lung cancer rates are highest in countries with the greatest fat intakes. In several case-control studies, positive associations have been observed between lung cancer and intakes of total and saturated fat, particularly among nonsmokers. We analyzed the association between fat and cholesterol intakes and lung cancer risk in eight prospective cohort studies that met predefined criteria. Among the 280,419 female and 149,862 male participants who were followed for up to 6–16 years, 3,188 lung cancer cases were documented. Using the Cox proportional hazards model, we calculated study-specific relative risks that were adjusted for smoking history and other potential risk factors. Pooled relative risks were computed using a random effects model. Fat intake was not associated with lung cancer risk. For an increment of

5% of energy from fat, the pooled multivariate relative risks were 1.01 [95% confidence interval (CI), 0.98–1.05] for total, 1.03 (95% CI, 0.96–1.11) for saturated, 1.01 (95% CI, 0.93–1.10) for monounsaturated, and 0.99 (95% CI, 0.90–1.10) for polyunsaturated fat. No associations were observed between intakes of total or specific types of fat and lung cancer risk among never, past, or current smokers. Dietary cholesterol was not associated with lung cancer incidence [for a 100-mg/day increment, the pooled multivariate relative risk was 1.01 (95% CI, 0.97–1.05)]. There was no statistically significant heterogeneity among studies or by sex. These data do not support an important relation between fat or cholesterol intakes and lung cancer risk. The means to prevent this important disease remains avoidance of smoking.

Introduction

Although cigarette smoking is the primary cause of lung cancer with RRs³ exceeding 20 for comparisons of current *versus* never smokers, diet has been hypothesized to influence lung cancer risk (1–3). Rates of lung cancer are highest in countries with the greatest consumption of fat, even after adjusting for population rates of cigarette smoking (4–6). In most case-control studies, risks of lung cancer have been elevated 1.5- to 3-fold among persons with the highest compared with the lowest intakes of total and saturated fat (7–13). A particularly strong positive association between saturated fat intake and lung cancer was seen among nonsmoking women in one of these investigations (9). However, in another case-control study of 587 female lung cancer cases, dietary fat was unrelated to risk of lung cancer, even among nonsmokers (14). Prospective data examining the association between fat intake and lung cancer risk have been limited. A 40–60% increase in lung cancer risk has been reported for high *versus* low intakes of total and saturated fat in studies from Finland (15) and Norway (16) and in men, but not women, in a United States cohort (17). Only the results for the men in the United States cohort were statistically significant (17). No relationship with dietary fat has been observed in three other cohort studies (18–20). Animals fed diets high in either saturated or unsaturated fat have developed more lung cancers than animals fed lower fat diets, but these effects could not be separated from those of total energy intake because the animals on the high-fat diets had higher calorie intakes (21, 22). On the basis of the available epidemiological and animal data, a major review of diet and cancer (3) concluded that diets high in total or saturated fat may possibly increase the risk of lung cancer; the data for monounsaturated and polyunsaturated fat were inconclusive (3).

The association between cholesterol intake and lung cancer risk also has varied. Dietary cholesterol has been positively

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³ The abbreviations used are: RR, relative risk; CI, confidence interval.

Table 1 Characteristics of the cohort studies included in the pooled analysis of fat intake and lung cancer

Study (sex) ^a	Follow-up period	Baseline cohort	Age range (years)	No. of cases ^b	Mean (SD) total fat intake, % energy	RRs (95% CI) for 5% of energy increase in total fat intake	
						Age-adjusted	Multivariate-adjusted ^c
Adventist Health Study (F)	1976–1982	17,990	25–100	20	37.4 (3.8)	0.88 (0.47–1.64)	0.78 (0.36–1.66)
Adventist Health Study (M)	1976–1982	12,526	25–99	31	37.2 (3.0)	1.40 (0.83–2.35)	0.85 (0.47–1.54)
α -Tocopherol β -Carotene Cancer Prevention Study (M) ^d	1985–1996	6,771	50–69	298	39.0 (5.4)	1.15 (1.04–1.28)	1.13 (1.01–1.27)
Canadian National Breast Screening Study (F)	1980–1993	56,837	40–60	149	43.0 (6.2)	1.12 (0.98–1.27)	1.05 (0.90–1.22)
Health Professionals Follow-Up Study (M)	1986–1996	44,350	32–79	244	31.9 (6.3)	1.09 (0.98–1.20)	1.03 (0.92–1.16)
Iowa Women's Health Study (F)	1986–1996	33,828	52–71	433	34.1 (5.7)	1.06 (0.97–1.15)	0.99 (0.90–1.08)
Netherlands Cohort Study (F)	1986–1992	62,412	54–70	128	39.1 (5.7)	1.03 (0.88–1.21)	1.04 (0.87–1.25)
Netherlands Cohort Study (M)	1986–1993	58,279	54–70	828	38.9 (5.9)	0.94 (0.87–1.01)	0.98 (0.88–1.07)
New York State Cohort (F)	1980–1987	21,045	15–107	130	34.0 (3.9)	1.11 (0.89–1.39)	0.95 (0.75–1.21)
New York State Cohort (M)	1980–1987	27,936	15–107	392	35.4 (4.8)	1.36 (1.22–1.52)	1.08 (0.94–1.23)
Nurses' Health Study (a) (F)	1980–1986	88,307	34–67	156	38.9 (7.9)	1.01 (0.92–1.12)	0.95 (0.85–1.06)
Nurses' Health Study (b) (F) ^e	1986–1996	68,318	40–67	379	32.7 (5.7)	1.10 (1.01–1.20)	0.99 (0.90–1.09)
Total/Pooled RR (95% CI)		430,281		3,188		1.09 (1.02–1.16)	1.01 ^f (0.98–1.05)

^a Men (M) and women (F) within the same cohort are presented separately.

^b After excluding participants with incomplete smoking data, implausible values for energy intake, or previous cancer (other than nonmelanoma skin cancer) diagnosis.

^c Adjusted for age, education (<high school graduate, high school graduate, >high school graduate), body mass index (<23, 23–<25, 25–<30, \geq 30 kg/m²), alcohol intake (0, >0–<5, 5–<15, 15–<30, and \geq 30 g/day), total fruit and vegetable intake (quintiles), energy intake (continuous), smoking status (never, past, current), smoking duration for past smokers (continuous), smoking duration for current smokers (continuous), and amount smoked for current smokers (continuous).

^d Only the placebo group of the α -Tocopherol β -Carotene Cancer Prevention Study was included in this analysis. The RRs were adjusted for age, education, body mass index, alcohol intake, total fruit and vegetable intake, energy intake, smoking duration, and amount smoked. The categories are defined in footnote c.

^e The participants in the baseline cohort for the Nurses' Health Study (b) are included in the Nurses' Health Study (a).

^f $P = 0.53$ for overall pooled RR. Test for between-study heterogeneity: $P = 0.68$.

associated with lung cancer risk in several case-control studies (8, 10, 12, 23), but a statistically significant association has not been observed in others (7, 9, 14). A positive relationship between cholesterol intake and lung cancer incidence was observed in the prospective Western Electric Study (24), and a marginally statistically significant 30% higher risk of lung cancer was observed in the Nurses' Health Study for women in the highest *versus* lowest quintile of cholesterol intake (20). However, in other cohort studies, no association has been found (15–20, 25). Because of the mixed findings, which included a number of positive studies and no study showing a significant decrease in risk, a review of the available evidence concluded that diets high in cholesterol possibly increase the risk of lung cancer (3).

To examine the relation of lung cancer with intakes of total and specific types of fat and cholesterol with greater statistical power than was available in any one study, we analyzed the primary data from 8 prospective cohort studies included in the Pooling Project of Prospective Studies of Diet and Cancer (Pooling Project). This large collection of data allowed a detailed analysis of fat intake over a wide range of intakes and allowed analyses by smoking status and histological type of lung cancer.

Materials and Methods

Study Population. The Pooling Project was initially established to evaluate diet and breast cancer associations (26). For the breast cancer analyses, eight prospective studies (27–34) were identified that met the following predefined criteria: (a) at least 200 incident breast cancer cases; (b) assessment of long-term dietary intake; and (c) a validation study of the diet assessment method or a closely related instrument. In this analysis, with lung cancer as the outcome, additional criteria for inclusion of studies were at least 50 incident lung cancer cases

and assessment of smoking history at baseline. The New York University Women's Health Study (31) and Sweden Mammography Cohort (30), both of which were included in our breast cancer analyses, were excluded from the lung cancer analyses because they did not assess smoking history at baseline. We added two cohorts of men which met the inclusion criteria: the placebo group of the α -Tocopherol β -Carotene Cancer Prevention Study (35) and the Health Professional's Follow-up Study (Ref. 36; Table 1). The person-time experienced during follow-up of the Nurses' Health Study was divided into two independent segments for analysis. The 1980–1986 follow-up period is referred to as Nurses' Health Study (a) and the 1986–1996 follow-up period is referred to as Nurses' Health Study (b). Following the underlying theory of survival analysis, blocks of person-time in different time periods are statistically independent, regardless of the extent to which they are derived from the same people (37). Thus, pooling estimates from these two time periods is equivalent to using a single time period but takes advantage of the enhanced exposure assessment in 1986 compared with 1980.

Dietary Assessment. In each cohort, diet was assessed at baseline using a food frequency questionnaire developed for that study population. The number of food items on the questionnaires ranged from 45 in the Adventist Health Study to 276 in the α -Tocopherol β -Carotene Cancer Prevention Study. Portion sizes were not given in two studies; participants specified portion sizes in three studies; and portion sizes were specified on the questionnaires in the remaining studies. Intakes of total, saturated, monounsaturated, and polyunsaturated fat, cholesterol, energy, and other nutrients were calculated by each study from the reported food intakes. The polyunsaturated fat intake data corresponded to linoleic acid for the Adventist Health Study and to total polyunsaturated fat for the remaining studies.

Assessment of Nondietary Risk Factors. Information on smoking history, education, height, weight, and other potential risk factors was collected at baseline in each study using self-administered questionnaires designed for that particular study. For smoking history, each study assessed whether individuals had ever smoked or were current smokers. Among smokers, the number of cigarettes smoked per day and the years smoked were assessed.

Identification of Lung Cancer Outcomes. Each study ascertained incident lung cancers using one or more of the following methods: follow-up questionnaires and subsequent medical record review (20, 35, 36, 38), linkage with a cancer registry (17, 34, 35, 38–40), or linkage with a death registry (17, 20, 34, 36). We categorized lung cancers into adenocarcinomas, squamous cell carcinomas, small cell carcinomas, and other carcinomas based on International Classification of Diseases for Oncology morphology codes (41) or the histological classification provided by the original study investigators.

Statistical Analysis. For each cohort, after applying the exclusion criteria used by that study, we further excluded participants if they reported energy intakes greater or less than three SDs from the study-specific \log_e -transformed mean energy intake of the baseline population, or reported a history of cancer (except nonmelanoma skin cancer) at baseline, or were missing information on smoking habits.

Each study was analyzed using the Cox proportional hazards model. Because dietary questionnaires were processed for only a sample of noncases, the Canadian National Breast Screening Study and the Netherlands Cohort Study were analyzed as case-cohort studies (42) using Epicure software (43). The remaining studies were each analyzed using SAS PROC PHREG (44). Because most studies included only one sex, studies including both women and men were analyzed as two separate cohorts. Follow-up time was calculated from the date the baseline questionnaire was returned until the date of lung cancer diagnosis, date of death, or end of follow-up, whichever came first.

We analyzed associations for intakes of total fat and each type of fat as a percentage of total calories. Cholesterol intake was energy-adjusted using the residual method (45). Fat and cholesterol intakes were analyzed as continuous and categorical variables. Study- and sex-specific quartiles were assigned based on the distributions in the subcohorts in the Canadian National Breast Screening Study and Netherlands Cohort Study and in the total baseline populations of the remaining cohorts. For the analyses of categories of total fat intake using identical intake cut points across studies, we defined the reference category as 30 to <35% of energy from fat so that each cohort would have sufficient numbers of participants in the comparison group. To calculate the *P* for the test for trend across categories, participants were assigned the median value of their category of intake, and this variable was entered as a continuous term in the regression model. For each study, we adjusted for age by including the age at baseline and the year that the baseline questionnaire was returned as stratification variables. In the multivariate analyses, smoking history, education, body mass index, alcohol consumption, total fruit and vegetable consumption, and energy intake were included as covariates because they may be potential confounders of the dietary associations. For each covariate, comparable categories were defined in each study (see Table 1). An indicator variable for missing responses for measured covariates within a study was created, when applicable. Two-sided 95% CIs were calculated.

After analyzing each study separately, we calculated sum-

mary RRs using the random-effects model developed by DerSimonian and Laird (46); the study-specific estimates were weighted by the inverse of their variance. We tested for heterogeneity among studies using the asymptotic DerSimonian and Laird *Q* statistic (46).

Additional analyses for specific types of fat were conducted by including saturated, monounsaturated, and polyunsaturated fat and protein and alcohol intakes in the same multivariate model, in addition to the other covariates. In this model, the RRs for the specific types of fat are adjusted for each other and have the interpretation of being compared with an identical decrease in the percentage of energy from carbohydrates (47).

We tested whether associations between fat and cholesterol intakes and lung cancer risk were modified by sex and smoking status using the meta-regression model proposed by Stram (48).

We also evaluated associations between fat and cholesterol intakes with adenocarcinomas, small cell carcinomas, and squamous cell carcinomas. Collectively these three histological types represented at least 60% of the cases in each study. We tested whether the associations differed by histological type using a two-degree-of-freedom squared Wald test for the null hypothesis that there is no difference between \log_e rate ratios for the three histological types (49).

Results

Among the 280,419 women and 149,862 men who formed the baseline populations for this analysis, 3,188 cases of lung cancer (1,395 in women and 1,793 in men) were diagnosed over follow-up periods of up to 6–16 years (Table 1). Overall, there were 278 lung cancers diagnosed among never smokers, 996 among past smokers, and 1,914 among current smokers. Mean fat intake among the cohorts ranged from 32 to 43% of energy.

Total Fat. In the age-adjusted analyses of each cohort (Table 1), treating total fat intake as a continuous variable, a weak but statistically significant positive association with lung cancer was observed in three cohorts (the α -Tocopherol β -Carotene Cancer Prevention Study, the Nurses' Health Study (b), and among men in the New York State Cohort). The pooled RR was 1.09 (95% CI, 1.02–1.16) for an increment of 5% of energy from fat. Adjusting for education, alcohol consumption, body mass index, total fruit and vegetable intake, and total energy intake, generally, did not materially change the study-specific RRs. After additional adjustment for smoking history, the strongest and only statistically significant positive association was seen in the α -Tocopherol β -Carotene Cancer Prevention Study. The RRs for the remaining studies were generally close to 1.0. The pooled RR was 1.01 (95% CI, 0.98–1.05) for an increment of 5% of energy from fat. The test for heterogeneity among studies was not significant ($P = 0.68$), which indicated that the differences in RRs among the cohorts were compatible with random variation. The RR for an increment in total fat intake of 5% of energy was 0.99 (95% CI, 0.94–1.04) among women and 1.04 (95% CI, 0.98–1.11) among men; the test for heterogeneity by sex was nonsignificant ($P = 0.17$). Because tests for heterogeneity by cohort and sex were not statistically significant in additional analyses, we will present only the overall pooled results for the remaining analyses.

When total fat intake was analyzed as quartiles, no association between fat intake and lung cancer risk was observed (Table 2).

We considered the possibility that the risk of lung cancer varied only at the extremes of fat intake by defining categories

Table 2 Pooled multivariate-adjusted RRs^a (95% CI) of lung cancer by quartiles of total and specific types of fat and cholesterol intakes

Nutrient	Quartile of Intake				P, test for trend	P, test for between-study heterogeneity (quartile 4)
	1	2	3	4		
Total fat	1.00	1.04 (0.93–1.17)	1.00 (0.83–1.19)	1.04 (0.92–1.17)	0.67	0.66
Saturated fat	1.00	0.94 (0.81–1.10)	0.99 (0.87–1.11)	1.01 (0.89–1.14)	0.57	0.40
Monounsaturated fat	1.00	1.02 (0.90–1.15)	1.02 (0.88–1.19)	1.03 (0.89–1.19)	0.67	0.23
Polyunsaturated fat	1.00	1.02 (0.88–1.18)	0.99 (0.89–1.10)	0.97 (0.86–1.09)	0.65	0.37
Cholesterol	1.00	1.02 (0.89–1.18)	1.03 (0.90–1.17)	1.06 (0.94–1.20)	0.31	0.35

^a RRs adjusted for same covariates as in Table 1.

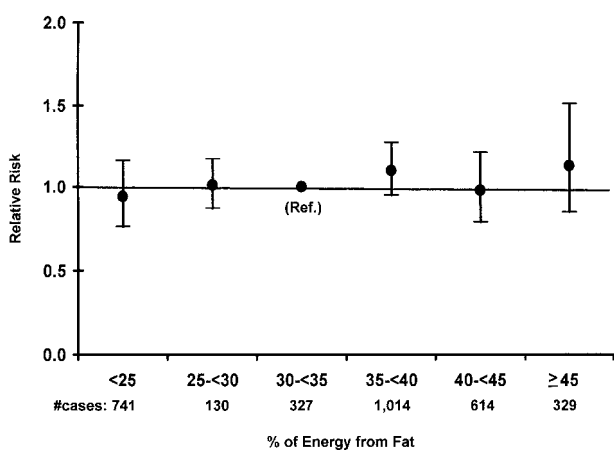


Fig. 1. Pooled multivariate RRs of lung cancer (with 95% CIs) by total fat intake among 430,281 women and men. Reference category is 30 to <35% of energy from fat.

using identical absolute intake cut points across studies. Both the female and male cohorts of the Adventist Health Study were excluded from these analyses because of small numbers. We did not find any suggestion of reduced risk with fat intakes below 25% of energy or increased risk with fat intakes over 45% of energy compared with fat intakes between 30 and <35% of energy (Fig. 1).

Specific Types of Fat and Cholesterol. In the age-adjusted analyses, saturated and monounsaturated fat intakes were positively associated with the risk of lung cancer, and polyunsaturated fat intake was not associated with risk (Table 3). The associations were slightly attenuated but still statistically significant after adjustment for education, body mass index, alcohol consumption, total fruit and vegetable intake, and energy intake. After further adjustment for smoking, the association for each type of fat was more attenuated and no longer statistically significant. Greater saturated, monounsaturated, and polyunsaturated fat intakes were not significantly associated with higher lung cancer risk in any of the individual cohorts in the multivariate analyses. Dietary cholesterol was not associated with lung cancer risk in the multivariate analyses.

When analyzed as quartiles, there was little evidence of an association between intakes of each of the specific types of fat or cholesterol and lung cancer risk (Table 2). We also found no significant associations for total and specific types of fat after excluding cases diagnosed during the first two years of follow-up in the continuous or categorical analyses (results not shown). Results were similar when we did not control for energy intake (results not shown) or when fat intakes were expressed as grams per day (results not shown). Models that

controlled for smoking using smoking status only; or a 10-level variable that accounted for smoking status, amount smoked, and years smoked; or smoking pack-years (results not shown), each yielded RRs for the dietary variables that were similar to or less attenuated than those observed for the multivariate models presented that adjusted for smoking status, duration of smoking, and amount smoked.

When intakes of saturated, monounsaturated, and polyunsaturated fat were mutually adjusted by including them simultaneously in the multivariate model as continuous variables, none of the types of fat was significantly associated with lung cancer risk (results not shown).

Analyses by Smoking Status. Because a previous study reported a remarkably strong positive association of lung cancer with intakes of total and saturated fat among never smokers (9), we examined the relationship between intakes of total and specific types of fat and cholesterol by smoking status (Table 4). We found no suggestion of a positive relation between intakes of total or saturated fat and risk of lung cancer among never smokers in any study, and the upper boundary of the 95% CIs for the pooled estimates for total and saturated fat were both less than 1.25. Similarly, no associations were observed for total and saturated fat intakes among either past or current smokers in the pooled analyses. Monounsaturated fat, polyunsaturated fat, and cholesterol intakes were not associated with lung cancer risk within any of the smoking strata. None of the associations was significantly different across the smoking strata.

Analyses by Histological Type of Lung Cancer. In analyses relating intakes of total fat, specific types of fat, and cholesterol to risks of small cell carcinomas ($n = 536$ cases), squamous cell carcinomas ($n = 894$ cases), and adenocarcinomas ($n = 953$ cases), we found no significant associations for any of the histological types examined (results not shown). In addition, there was no evidence that the associations varied significantly by histological type (results not shown).

Discussion

In this pooled analysis of prospective data from 280,419 women and 149,862 men, we found no evidence of an association between intakes of total, saturated, monounsaturated, and polyunsaturated fat and cholesterol intakes and the risk of lung cancer. The findings of this pooled analysis are not consistent with the relatively strong positive associations observed between intakes of total and saturated fat and lung cancer risks in most (7–13), but not all (14), case-control studies. Notably, the upper boundary of the CIs for comparisons of the highest versus lowest quartiles of intake (1.17 for total fat and 1.14 for saturated fat) exclude the 1.5- to 3-fold increases in risk observed in most case-control studies (7–13). However, our results are compatible with the findings for total and saturated fat intakes

Table 3 Pooled age- and multivariate-adjusted RRs of lung cancer for specific types of dietary fat (for 5% of energy increases) and cholesterol (for 100 mg/day increases)

Nutrient	Age-adjusted		Multivariate-adjusted		
	RR (95% CI)	P	RR ^a (95% CI)	P	P, test for between-study heterogeneity
Saturated fat	1.21 (1.08–1.36)	0.001	1.03 (0.96–1.11)	0.35	0.60
Monounsaturated fat	1.20 (1.06–1.37)	0.005	1.01 (0.93–1.10)	0.75	0.41
Polyunsaturated fat	0.93 (0.84–1.03)	0.19	0.99 (0.90–1.10)	0.91	0.54
Cholesterol	1.06 (1.02–1.10)	0.003	1.01 (0.97–1.05)	0.61	0.81

^a RRs adjusted for same covariates as in Table 1.

Table 4 Pooled multivariate-adjusted RRs of lung cancer for intakes of total and specific types of fat (for 5% of energy increases) and cholesterol (for 100 mg/day increases), stratified by smoking status

Nutrient	Smoking status			P, test for between-study heterogeneity caused by smoking status
	Current ^{a,b} (1907 cases)	Past ^{a,c} (973 cases)	Never ^a (257 cases)	
Total fat	1.01 (0.96–1.06)	1.01 (0.93–1.10)	1.03 (0.91–1.17)	0.87
Saturated fat	1.02 (0.92–1.13)	1.10 (0.91–1.33)	0.97 (0.74–1.27)	0.75
Monounsaturated fat	1.02 (0.88–1.19)	0.98 (0.83–1.15)	1.07 (0.81–1.43)	0.74
Polyunsaturated fat	0.98 (0.85–1.13)	0.88 (0.69–1.12)	1.22 (0.88–1.70)	0.18
Cholesterol	0.99 (0.93–1.05)	1.06 (0.99–1.13)	1.00 (0.87–1.15)	0.37

^a Adjusted for education (<high school graduate, high school graduate, >high school graduate), body mass index (<23, 23–<25, 25–<30, ≥30 kg/m²), alcohol intake (0, >0–<5, 5–<15, 15–<30 and ≥30 g/day), total fruit and vegetable intake (quintiles), and energy intake (continuous).

^b Also adjusted for smoking duration (continuous) and amount smoked (continuous).

^c Also adjusted for smoking duration (continuous).

from the cohort studies that did not meet the inclusion criteria for this analysis (15, 16, 18).

A limitation of our study is that fat intake is measured with error by food frequency questionnaires. The discrepancy in the results in our study compared with the case-control studies could have occurred if the diet assessment methods used in the case-control studies measured fat intake more accurately and precisely than did the food frequency questionnaires used in the cohort studies included in our analysis, thereby resulting in an underestimate of the true association in the cohort studies. However, in the validation studies (50–57), correlations between fat intakes estimated by the food frequency questionnaire and either multiple diet records or 24-hour recalls were generally between 0.4 and 0.6 for total and saturated fat. The validity of total fat measurement by food frequency questionnaires also has been confirmed in comparisons with blood lipid measurements (58, 59). In addition, a self-administered food frequency questionnaire (similar to the one used in the Canadian National Breast Screening Study) performed just as well or slightly better than a detailed interviewer-administered diet history when both were compared with 7-day diet records (52). Thus, a likely explanation for the discordant results from the cohort and case-control studies is a combination of selection and recall biases in the case-control investigations. In particular, if health-conscious individuals, who may tend to avoid dietary fat, are more likely to participate as controls in case-control studies than individuals who are less health conscious and who may have higher fat diets, a spurious positive association could be observed between fat intake and lung cancer risk.

As in any study, we cannot exclude an effect of dietary fat on lung cancer risk beyond the ranges of fat consumed in these populations or with long latency periods. However, we were able to evaluate a wide range of fat intakes because of the large sample size and substantial variability in intakes among popu-

lations. Also, the follow-up periods in the cohorts encompassed the time period typically assessed in the case-control studies that have suggested a positive association.

In summary, these data do not support an important relationship between fat or cholesterol intake and lung cancer risk. The means to prevent this important disease remains avoidance of smoking.

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