Consumption of meat and fish and risk of lung cancer: results from the European Prospective Investigation into Cancer and Nutrition

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Abstract Evidence from case–control studies, but less so from cohort studies, suggests a positive association between meat intake and risk of lung cancer. Therefore, this association was evaluated in the frame of the European Prospective Investigation into Cancer and Nutrition, EPIC. Data from 478,021 participants, recruited from 10 European countries, who completed a dietary questionnaire in 1992–2000 were evaluated; 1,822 incident primary lung cancer cases were included in the present evaluation. Relative risk estimates were calculated for categories of meat intake using multi-variably adjusted Cox proportional hazard models. In addition, the continuous intake variables

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were calibrated by means of 24-h diet recall data to account for part of the measurement error. There were no consistent associations between meat consumption and the risk of lung cancer. Neither red meat (RR = 1.06, 95% CI 0.89–1.27 per 50 g intake/day; calibrated model) nor processed meat (RR = 1.13, 95% CI 0.95–1.34 per 50 g/day; calibrated model) was significantly related to an increased risk of lung cancer. Also, consumption of white meat and fish was not associated with the risk of lung cancer. These findings do not support the hypothesis that a high intake of red and processed meat is a risk factor for lung cancer.

Keywords Lung cancer · Diet · Epidemiology · Meat · Fish · EPIC

Introduction

Lung cancer is the most common cause of cancer deaths in the world, and smoking is clearly the primary risk factor. However, numerous studies have shown that diet might be etiologically important. The association between fruit and vegetables, and even more so between some nutrients provided by fruit and vegetable consumption, and lung cancer risk has been studied extensively while less emphasis has been put on other dietary factors, including foods of animal origin [1].

Three groups of carcinogens have been described that may explain a higher risk of lung cancer by high consumption of meat. High-temperature cooking of meat results in the formation of heterocyclic amines and polycyclic aromatic hydrocarbons, the latter are also present in cured and smoked meat [2–11]. N-nitroso compounds are another group of potent carcinogens, and their endogenous formation can be induced by heme iron or nitrate/nitrite from preserved meat.

On the basis of the available scientific evidence, the 2007 report of the World Cancer Research Fund (WCRF) [1] concluded that there is limited suggestive evidence for a positive association of red and processed meat consumption and risk of lung cancer. For red meat, this conclusion was based on 1 cohort and 9 case–control studies; for processed meat on 4 cohort studies and 10 case–control studies. A recent US study provided some additional evidence for a positive association between red meat intake and lung cancer risk [4], whereas another reported no

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associations between meat intake and lung cancer incidence [12]. However, several other cohort studies that were not included in the WCRF evaluation did not find statistically significant associations between meat consumption and lung cancer incidence or mortality [13–19] besides a Japanese cohort study, which reported contrasting results for the effect of ham and sausages intake on lung cancer risk by sex [20]. Concerning white meat/poultry consumption and lung cancer risk, the available literature gives no clear hint on an association [1]. For fish consumption, the body of evidence is even smaller, with the WCRF stating that no conclusion could be drawn [1].

Considering the current evidence as rather inconsistent, we evaluated the association of meat and fish consumption in a large European cohort with a wide range of dietary intakes.

Subjects and methods

Subjects

EPIC is a multi-center cohort study including more than 500,000 individuals designed to investigate the relationship between diet, lifestyle, and environmental factors and the incidence of different forms of cancer. The total cohort consists of subcohorts recruited from centers from Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and United Kingdom. Study subjects were mostly aged 25–70 years and mostly recruited from the general population residing in a given geographical area, a town, or a province. However, Spanish and Italian participants were recruited among blood donors, members of several health insurance programs, employees of several enterprises, civil servants, but also the general population. Further exceptions were the French cohort based on female members of the health insurance for state school employees, the Utrecht and Florence cohorts based on women attending breast cancer screening, and most of the Oxford cohort based on vegetarians and health-conscious volunteers. Eligible subjects were invited to participate in the study by mail or by personal contact. Those who accepted signed an informed consent form, and diet and lifestyle questionnaires were mailed to them to be filled in. Study subjects were then invited to a center for blood collection and anthropometric measurements including height and weight, and to deliver the completed diet and lifestyle questionnaires; in France, Norway, and Oxford, self-reported height and weight was assessed via questionnaire [21].

From the cohort, we excluded participants with a prevalent diagnosis of cancer of any site ($n = 23{,}633$), subjects with missing follow-up information ($n = 3{,}446$), individuals in the top and bottom 1% of the ratio of energy intake to estimated energy requirement calculated from body weight [22] to reduce the impact on the analysis of implausible extreme values ($n = 9{,}671$), participants with missing baseline information on diet and/or lifestyle ($n = 6{,}220$), and finally 49 individuals with uncertain lung cancer diagnosis; thus the analytical cohort comprised of 142,602 men and 335,825 women.

Diet and lifestyle questionnaires

Following the results of several methodological studies conducted in the early 1990s, diet was measured by country-specific instruments designed to capture local dietary habits and to provide high compliance [21]. Seven countries adopted an extensive self-administered dietary questionnaire, which can provide data on up to 300–350 food items per country. In Greece, Spain, and Ragusa, a dietary questionnaire, very similar in content to the above, was administered by direct interview. A food frequency questionnaire and a 7-day record were adopted in the United Kingdom. In Malmö, Sweden, a quantitative questionnaire combined with a 7-day menu book and an interview was used. The lifestyle questionnaires included questions on education and socioeconomic status, occupation, history of previous illness and disorders or surgical operation, lifetime history of consumption of tobacco and alcoholic beverages, and physical activity. Comparability of non-dietary questions was ensured by a set of core questions that were similar in all participating centers.

For this analysis, meats were grouped into red meat (beef, pork, mutton/lamb, horse, goat), processed meat (all meat products, including ham, bacon, sausages; small part

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of minced meat that has been bought as ready-to-eat product), white meat (equals poultry, including chicken, hen, turkey, duck, goose, rabbit (domestic), unclassified poultry), and fish (fish, fish products, crustaceans, molluscs, fish in crumbs, unclassified fish). Processed meat mainly refers to processed red meat but may contain small amounts of processed white meat as well, e.g. in sausages.

Endpoints

The follow-up is based on population cancer registries in seven of the participating countries: Denmark, Italy, Netherlands, Spain, Sweden, United Kingdom, and Norway. In France, Germany, and Greece, a combination of methods including health insurance records, cancer and pathology registries, and active follow-up through study subjects and their next-of-kin was used. Mortality data are also collected from either the cancer registry or the mortality registries at the regional or national level.

Cancer cases were identified by the end of the censoring periods ending between December 2002 and December 2005 in the EPIC centers, with the exception of Germany, Greece, and France, where the end of the follow-up was considered to be the last known contact, date of diagnosis, or date of death, whichever came first. Cancer of the lung as analyzed here was coded based on the International Classification of Diseases-Oncology (ICD-O) 2nd edition and included invasive cancers coded to C 34. According to the morphology codes of the WHO International Histological Classification of Tumours, histological types were classified into four major histological types: squamous cell carcinoma (8052, 8070–8073, 8075, and 8123), small cell carcinoma (8041–8045 and 8246), large cell carcinoma (8012, 8020–8021, and 8082), and adenocarcinoma (8140, 8143, 8200, 8211, 8230, 8250–8251, 8260, 8300, 8310, 8480–8481, 8490, and 8550). Other histological types (8010–8011, 8022, 8030–8032, 8046, 8240, 8243, 8430, 8560, 8710, 8720, 8800–8801, 9120, 9133, 9590, 9591, 9671, and 9699) and unclassified histological types of carcinomas (8000–8001 and missing histological data) were placed into a miscellaneous category. Only first incident lung cancer cases were taken into account.

Statistical methods

The analyses were performed using Cox regression and were stratified by sex, age (in 1-year categories), and center. Age was used as the primary dependent time variable in all Cox regression models. Intakes of red and processed meat as well as fish were categorized into categories of 0–9, 10–19, 20–39, 40–79, and 80+ g/day; categories for the sum of red and processed meat were 0–19, 20–39, 40–79, 80–159, 160+ g/day; categories for white meat were 0–4, 5–9, 10–19, 20–39, 40+ g/day. To adjust for lifelong tobacco smoking, we included baseline smoking status and intensity of smoking as one variable [never smokers = reference category); current cigarette smokers (3 categories: 1–14, 15–24 and 25+ cigarettes/day); former smokers who stopped less than 10 years ago, 11–20 years ago, 20+ years ago; other smokers (one category including pipe or cigar smokers and occasional smokers); missing information on smoking]. In addition, duration of smoking in 10-year categories (≤10 years = reference category, 11–20 years, 21–30 years, 31–40 years, 41–50 years, >50 years) is added as a second variable in the statistical models. We separately adjusted for amount of smoking and duration of smoking instead of using pack years of smoking to be better able to differentiate between, e.g., heavy smokers of a short duration and light smokers for a long duration [23]. Additionally, all analyses were adjusted for body weight and height, energy intake from fat and energy intake from carbohydrates and protein, intake of alcohol, consumption of fruits and vegetables (all continuous), physical activity (active, moderately active, moderately inactive, inactive, missing) [24], and education (none or primary school completed; technical/professional school; secondary school; university degree; missing). Adjustment variables were included consecutively in the models; smoking was by far the strongest confounder, but also inclusion of total energy or energy-providing nutrients (including alcohol) showed distinct effects on risk estimates. Also, education, physical activity, and fruit and vegetable consumption were shown to be potential confounders and slightly changed the risk estimates in our models. Models with mutual adjustment of all types of meat were not performed. In addition to the analyses of all lung cancer cases combined, we performed analyses for subtypes of lung cancer.

In order to improve the comparability of dietary data across the participating centers, dietary intakes from the questionnaires were calibrated using a standardized 24-h dietary recall [25, 26], thus partly correcting for over- and underestimation of dietary intakes [27, 28]. A 24-h dietary recall was collected from an 8% random sample of each center's participants. Dietary intakes were calibrated using a fixed effects linear model in which gender- and center-specific 24-h dietary recall data were regressed on the questionnaire data controlling for weight, height, age, day of the week, and season of the year. Non-consumers of red meat (2.0%), processed meat (1.9%), poultry (13.1%), and fish (5.5%) as indicated in the food frequency questionnaire were excluded from the regression calibration models and kept as zero values. Calibrated and uncalibrated data were used to estimate the association of meat consumption on a continuous scale.

Subanalyses were performed by sex and smoking status. Including a cross-product term along with the main effect terms (continuous variable) in the Cox regression model tested for interaction on the multiplicative scale. The statistical significance of the cross-product term was evaluated using the likelihood ratio test. We also examined whether excluding the first 2 years of follow-up altered the association. Heterogeneity between countries was assessed using likelihood chi-square tests. All analyses were conducted using SAS version 9.1 (SAS Institute, Cary, North Carolina).

Results

During a median follow-up time of 8.7 years, 1,822 incident lung cancers had been included in the IARC database by June 2007; 82% being histologically confirmed. Of all cases, 31.4% of all cases were adenocarcinomas, 19.8% squamous cell carcinomas, 15.6% small cell carcinomas, and 5.5% large cell carcinomas. Men and women with high red and processed meat intake were more likely to be current smokers and less likely to have a high-school degree (Table 1). BMI was higher among subjects with high red and processed meat consumption, who also consumed more alcohol but less fruits and vegetables.

Overall, there were no statistically significant associations of red or processed meat consumption with lung cancer risk (Table 2). Subjects consuming more than 80 g red meat per day had an RR = 1.19 (95% CI 0.94–1.50) compared with those consuming less than 10 g/day. The associations were not modified by sex (p-interaction = 0.22 in the calibrated model) or by smoking status (p-interaction = 0.72). Subjects that consumed more than 80 g processed meat per day did not have a higher risk of lung cancer than subjects with an intake of less than 10 g/day (RR = 0.92, 95% CI 0.73–1.17). Sex and smoking status did not modify these associations (p-interaction 0.32 and 0.07, respectively). Also, for the sum of red and processed meat, no statistically significant associations were obtained, although risk estimates were all above unity. After correction for measurement error, the relative risk of lung cancer for each 100 g increase in red and processed meat consumption was 1.18 (0.94–1.48); using the uncalibrated continuous intake data, the risk estimate was 1.07 (0.95–1.19).

White meat and fish consumption were not associated with lung cancer risk in the entire cohort (Table 2). For both food groups, there was no statistically significant effect modification by sex or smoking status (all p-interaction > 0.05). For all food groups analyzed, no statistically significant heterogeneity between countries has been observed (data not shown).

Excluding the first 2 years of follow-up from the analysis did not materially alter the observed associations (Table 2). The same effect was noted when we evaluated the associations in histologically confirmed cases (data not shown).

Analyses by histological subtypes of lung cancer revealed no statistically significant associations with meat or fish intake in the categorical models as well as in the calibrated linear models (Table 3). If anything, a tendency for a higher risk of large cell carcinoma with increasing intake of red and processed meat, and an inverse association with white meat consumption can be hypothesized; however, numbers of cases are low and confidence intervals are wide.

Discussion

In this analysis of the EPIC cohort, we did not observe a consistent elevated risk of lung cancer with high consumption of meat or an association with fish consumption.

Several mechanisms have been thought to link the consumption of meat with lung cancer risk, including high intake of total fat, saturated fat, and cholesterol [29], an increased intake [2–4] or inhalation [5] of heterocyclic amines and polycyclic aromatic hydrocarbons depending on the type of meat preparation [6, 7], an elevated intake of nitrite and/or nitrate as potential precursors of nitrosamine formation [8, 9], and enhanced intestinal/endogenous formation of *N*-nitroso compounds or lipid peroxidation products due to high intake of heme–iron [10, 11]. However, the results from prospective cohort studies that examined the association between meat consumption and the risk of lung cancer are inconsistent [4, 13–20, 30]. A mortality follow-up of the 1987 National Health Interview Survey cohort revealed a significantly increased mortality from lung cancer among subjects with high red meat intake (RR = 1.6, 95% CI 1.0–2.6, top vs. bottom quartile) [30]. Just recently, results of a US cohort showed a higher risk of lung cancer among men (RR = 1.13, 95% CI 0.97–1.32, top vs bottom quintile) and women (RR = 1.22, 95% CI 1.09–1.38, top vs bottom quintile) with high red meat consumption [4]. Intake ranges of the quintiles in this US study are roughly comparable with the intake categories in our analysis. The missing association between white meat consumption and lung cancer incidence is in accordance with the literature data [1].

Similar to meat, a high variation was also shown for fish consumption in EPIC [31]. Fish was not associated with

Table 1 Baseline characteristics of EPIC study participants by categories of the sum of red and processed meat intake in male and female EPIC participants

	Complete cohort	0–19 g/day	20–39 g/day	40–79 g/day	80–159 g/day	≥160 g/day
Men						
Number	142,602	10,365	10,335	36,458	63,827	21,617
Age at recruitment*	52.2 (±10.1)	47.2 (±13.8)	53.9 (±11.1)	52.9 (±10.3)	52.6 (±9.4)	51.6 (±8.7)
Weight (kg)*	80.8 (±12.0)	75.7 (±11.2)	78.2 (±10.9)	79.9 (±11.5)	81.7 (±11.9)	83.7 (±12.9)
Height (cm)*	174.7 (±7.3)	175.8 (±7.2)	173.3 (±7.6)	174.0 (±7.4)	174.9 (±7.2)	175.6 (±7.2)
BMI (kg/m^2)*	26.5 (±3.6)	24.5 (±3.4)	26.1 (±3.4)	26.4 (±3.5)	26.7 (±3.6)	27.2 (±3.9)
Alcohol intake (g/day)*	21.4 (±24.7)	14.0 (±17.9)	14.3 (±18.5)	16.9 (±20.5)	23.0 (±24.0)	28.4 (±28.6)
Energy from fat (kcal/day)*	868 (±304)	684 (±273)	682 (±251)	767 (±259)	895 (±270)	1,134 (±306)
Energy from other sources (kcal/day)*	1,407 (±404)	1,271 (±391)	1,200 (±387)	1,294 (±373)	1,440 (±374)	1,662 (±408)
Vegetables (g/day)*	193.1 (±151.0)	270.1 (±173.2)	213.9 (±175.0)	196.9 (±165.6)	179.5 (±138.4)	180.0 (±121.5)
Fruits (g/day)*	216.1 (±204.5)	260.8 (±232.2)	265.6 (±240.0)	239.9 (±220.6)	199.8 (±189.9)	178.7 (±169.4)
Highest school level (%)**						
None/primary school completed	30.9	9.0	29.6	30.0	32.2	37.2
Technical/professional school	24.7	18.6	20.4	23.1	25.6	27.7
Secondary school	16.0	14.5	18.2	18.5	15.5	12.0
University degree	26.5	47.7	26.7	24.9	24.8	22.0
Physical activity (%)**						
Inactive	18.4	17.5	15.2	17.6	19.6	18.0
Moderately inactive	26.3	29.0	27.9	25.6	26.4	25.0
Moderately active	32.6	37.1	30.6	30.6	32.8	33.8
Active	12.2	12.9	9.0	9.1	12.5	17.7
Smoking status (%)**						
Lifelong non-smoker	30.7	48.5	32.7	31.5	28.3	25.4
Current cigarettes (<15/day)	9.4	6.0	8.0	8.7	10.0	10.5
Current cigarettes (15–24/day)	10.0	3.7	6.7	8.0	11.1	14.3
Current cigarettes (25+/day)	5.3	1.6	3.6	4.3	5.7	7.8
Ex-smoker (≤10 years)	13.2	13.3	14.9	14.3	14.5	14.6
Ex-smoker (>10 years)	21.9	20.1	22.5	21.6	20.3	18.0
Women						
Number	335,825	44,285	49,489	130,070	102,824	9,157
Age at recruitment*	50.8 (±9.8)	46.5 (±13.2)	51.9 (±9.7)	51.4 (±9.0)	51.3 (±8.7)	50.6 (±8.4)
Weight (kg)*	65.6 (±11.7)	62.6 (±10.5)	65.0 (±11.2)	66.0 (±11.5)	66.6 (±12.1)	68.5 (±13.6)
Height (cm)*	162.3 (±6.7)	163.1 (±6.7)	161.6 (±7.0)	162.1 (±6.7)	162.5 (±6.5)	162.2 (±6.4)
BMI (kg/m^2)*	25.0 (±4.4)	23.6 (±4.0)	24.9 (±4.4)	25.1 (±4.4)	25.3 (±4.5)	26.1 (±5.1)
Alcohol intake (g/day)*	8.0 (±11.7)	7.0 (±10.2)	6.3 (±9.9)	7.5 (±11.1)	9.7 (±13.0)	12.5 (±16.6)
Energy from fat (kcal/day)*	699 (±245)	581 (±226)	599 (±216)	671 (±217)	802 (±231)	1,028 (±273)
Energy from other sources (kcal/day)*	1,187 (±342)	1,110 (±339)	1,068.6 (±321)	1,155.6 (±319)	1,289 (±335)	1,484 (±374)
Vegetables (g/day)*	218.9 (±143.3)	273.2 (±169.4)	216.1 (±151.2)	204.6 (±136.4)	212.3 (±128.5)	249.5 (±150.2)
Fruits (g/day)*	248.6 (±189.1)	278.7 (±218.9)	264.5 (±205.4)	244.9 (±185.7)	233.8 (±169.2)	235.8 (±178.1)
Highest school level (%)**						
None/primary school completed	26.2	13.0	28.2	28.1	26.8	28.1
Technical/professional school	22.0	19.4	19.2	22.6	22.8	18.8
Secondary school	26.3	22.4	25.7	26.1	26.8	27.0
University degree	23.0	36.2	22.5	19.8	20.2	21.3
Physical activity (%)**						
Inactive	13.7	17.5	11.8	12.5	14.2	16.1
Moderately inactive	31.7	34.2	28.4	28.9	34.9	41.0

Table 1 continued

	Complete cohort	0–19 g/day	20–39 g/day	40–79 g/day	80–159 g/day	≥160 g/day
Moderately active	32.9	33.1	33.8	32.7	32.7	31.1
Active	6.5	7.7	5.9	6.2	6.8	6.5
Smoking status (%)**						
Lifelong non-smoker	47.9	56.5	49.7	46.7	43.1	38.6
Current cigarettes (<15/day)	10.8	7.3	10.0	11.7	11.2	10.3
Current cigarettes (15–24/day)	6.8	3.4	5.2	6.8	8.2	9.9
Current cigarettes (25+/day)	1.5	0.7	1.2	1.4	1.9	3.2
Ex-smoker (≤10 years)	8.6	10.9	8.7	8.9	8.8	8.7
Ex-smoker (>10 years)	13.5	13.3	12.4	12.5	12.4	11.7

* Mean ± SD

** Do not add up to 100% due to missing information

lung cancer risk in the present evaluation in EPIC. This null result adds to the limited epidemiologic evidence in this field. Most case–control (summarized in [1]) and prospective studies that examined fish consumption and subsequent risk of lung cancer reported no association [14, 17, 18, 20, 30], except for a Norwegian study [16] where risk was increased only in the highest intake category ("main meals with fish", >5 times/week).

In a subanalysis, we examined whether the association between meat and fish consumption and lung cancer risk differed by subtype of lung cancer. However, there were no apparent differences between these categories. This is in agreement with some, but not all previous studies (reviewed in [12]).

The large sample size, the prospective design, and the possibility to partly correct for measurement errors by applying a calibration method, thus, improving the results of the dietary questionnaires are major strengths of our study. A methodological strength of the EPIC project as a whole is the inclusion of participants from 10 European countries with distinctly diverging dietary habits with respect to meat [32] and fish consumption [31]. A high between-person variation in diet decreases the impact of measurement error and enables the detection of only modest diet–disease relationships. A major strength of the EPIC study is the use of the calibration procedure to correct for systematic over- and underestimation of dietary intakes [27, 33]. The use of the calibration method in our study had no major effects on the risk estimates. However, the calibrated hazard ratios may still be affected to some extent by measurement error since the error structure in the reference method is not entirely independent of that in the food frequency questionnaire [34, 35]. The overall number of consumers of meat and fish in the single 24-h diet recalls per subject (approximately 75% for processed meat, 50% for red meat and fish, 25% for poultry) seems high enough to avoid introduction of additional bias during calibration.

Some limitations should be mentioned as well, which include the still small number of cases when considering histologic subtypes of lung cancer. The most important challenge in studies on diet and lung cancer risk is the adequate controlling for confounding by smoking. Although the smoking variables used in the present analysis were carefully developed and already applied in the evaluation of the association between fruits and vegetables intake and lung cancer risk in EPIC [23], the possibility of confounding by smoking can never completely be excluded. Results in lung cancer cases who have never smoked are free of this bias. However, we did not observe statistically significant effect modification by smoking status in our analyses. Case–control studies in never-/non-smokers [36, 37] and a prospective study in Seven-day Adventists [13] with only 4% current smokers did not report consistent positive associations. Furthermore, we did not take into account environmental tobacco smoking because information on environmental tobacco smoking was assessed at only 11 EPIC centers. However, when we restricted our analyses to the 214,964 participants for whom information on exposure to passive smoking was available (exposure at home or at work; yes vs. no), the results did not change appreciably (data not shown). Finally, we tested for effect modification by sex because men and women have different smoking habits and different habits concerning meat consumption. However, no statistically significant interactions were observed.

In conclusion, our results do not support the hypothesis that meat consumption is a major risk factor for lung cancer. Similarly, fish consumption was not related to the risk of lung cancer. Once a longer follow-up has yielded even larger number of cases, further testing of this hypothesis by the main histological types of lung cancer may be warranted.

Table 2 Relative risks * and 95% confidence interval for lung cancer by the sum of red and processed meat, red meat, processed meat, white meat, and fish consumption in EPIC

Red & processed meat			Red meat			Processed meat			White meat			Fish		
Intake (g/day)	Cases	RR (95% CI)	Intake (g/day)	Cases	RR (95% CI)	Intake (g/day)	Cases	RR (95% CI)	Intake (g/day)	Cases	RR (95% CI)	Intake (g/day)	Cases	RR (95% CI)
0–19	81	1 (ref.)	0–9	121	1 (ref.)	0–9	324	1 (ref.)	0–4	436	1 (ref.)	0–9	311	1 (ref.)
20–39	182	1.25 (0.95–1.65)	10–19	158	1.11 (0.87–1.42)	10–19	308	0.98 (0.82–1.16)	5–9	334	0.97 (0.83–1.12)	10–19	340	1.05 (0.90–1.23)
40–79	563	1.18 (0.92–1.52)	20–39	427	1.18 (0.95–1.46)	20–39	527	1.00 (0.85–1.17)	10–19	496	0.94 (0.82–1.08)	20–39	582	1.11 (0.95–1.29)
80–159	775	1.15 (0.89–1.49)	40–79	672	1.12 (0.91–1.39)	40–79	492	1.05 (0.88–1.26)	20–39	359	0.97 (0.83–1.13)	40–79	432	1.08 (0.91–1.28)
≥160	221	1.25 (0.92–1.69)	≥80	444	1.19 (0.94–1.50)	≥80	171	0.92 (0.73–1.17)	≥40	197	0.95 (0.79–1.14)	≥80	157	1.08 (0.86–1.36)
Continuous models		Per 100 g			Per 50 g			Per 50 g			Per 50 g			Per 50 g
Uncalibrated		1.07 (0.95–1.19)			1.02 (0.94–1.09)			1.06 (0.97–1.15)			0.95 (0.82–1.10)			1.04 (0.96 – 1.13)
Calibrated		1.18 (0.94–1.48)			1.06 (0.89–1.27)			1.13 (0.95–1.34)			0.92 (0.65–1.32)			1.10 (0.91 – 1.35)
Excluding first two years of follow-up														
Uncalibrated		1.07 (0.94–1.21)			1.01 (0.93–1.10)			1.06 (0.97–1.17)			0.94 (0.80–1.10)			1.05 (0.96 – 1.16)
Calibrated		1.18 (0.92–1.52)			1.05 (0.87–1.28)			1.15 (0.94–1.40)			0.89 (0.58–1.35)			1.13 (0.91 – 1.41)

* Stratified by sex (if appropriate), center, and age (1-year categories) and adjusted for smoking status (never, ex, current, missing), amount of cigarettes smoked (<15, 15–24, ≥25 cigarettes/day), duration of smoking (≤10, 11–20, 21–30, 31–40, >40 years), time since quit smoking in ex-smokers (<10, 10–19, ≥20 years), body weight and height, energy intake from fat and energy intake from carbohydrates and protein, intake of alcohol, consumption of fruits and vegetables (all continuous), physical activity (active, moderately active, moderately inactive, inactive, missing), and education (none or primary school completed; technical/professional school; secondary school; university degree; missing)

Table 3 Relative risks* and 95% confidence intervals for subtypes of lung cancer by the sum of red and processed meat (per 100 g/day), red meat, processed meat, white meat, and fish consumption in EPIC (continuous models per 50 g/day)

	Adeno-carcinoma (n cases = 574) RR (95% CI)	Large cell carcinoma (*n* cases = 137) RR (95% CI)	Small cell carcinoma (*n* cases = 286) RR (95% CI)	Squamous cell carcinoma (*n* cases = 363) RR (95% CI)
Red & processed meat				
Uncalibrated	1.07 (0.87–1.32)	1.20 (0.80–1.81)	1.03 (0.79–1.35)	1.07 (0.84–1.36)
Calibrated	1.25 (0.83–1.88)	1.88 (0.85–4.15)	1.11 (0.51–2.41)	1.14 (0.55–2.35)
Red meat				
Uncalibrated	1.06 (0.93–1.22)	1.04 (0.78–1.37)	1.04 (0.86–1.25)	0.97 (0.82–1.14)
Calibrated	1.21 (0.89–1.65)	1.25 (0.73–2.14)	1.13 (0.67–1.89)	0.88 (0.54–1.45)
Processed meat				
Uncalibrated	1.03 (0.87–1.21)	1.17 (0.89–1.55)	0.99 (0.81–1.22)	1.12 (0.94–1.34)
Calibrated	1.19 (0.87–1.65)	1.61 (0.86–3.02)	0.91 (0.47–1.73)	1.25 (0.70–2.22)
White meat				
uncalibrated	1.01 (0.78–1.30)	0.52 (0.28–0.95)	0.71 (0.47–1.08)	0.96 (0.71–1.30)
Calibrated	0.93 (0.45–1.94)	0.15 (0.02–1.05)	0.85 (0.14–5.33)	1.03 (0.19–5.59)
Fish				
Uncalibrated	1.11 (0.97–1.21)	1.02 (0.76–1.38)	1.22 (1.03–1.45)	0.81 (0.65–1.01)
Calibrated	1.29 (0.91–1.81)	1.12 (0.57–2.22)	1.45 (0.74–2.85)	0.72 (0.37–1.41)

* Stratified by sex (if appropriate), center, and age (1-year categories) and adjusted for smoking status (never, ex, current, missing), amount of cigarettes smoked (<15, 15–24, ≥25 cigarettes/day), duration of smoking (≤10, 11–20, 21–30, 31–40, >40 years), time since quit smoking in ex-smokers (<10, 10–19, ≥20 years), body weight and height, energy intake from fat and energy intake from carbohydrates and protein, intake of alcohol, consumption of fruits and vegetables (all continuous), physical activity (active, moderately active, moderately inactive, inactive, missing), and education (none or primary school completed; technical/professional school; secondary school; university degree; missing)

Acknowledgments The work described in the paper was carried out with the financial support of the "Europe Against Cancer" Programme of the European Commission (SANCO); Ligue contre le Cancer (France); Société 3 M (France); Mutuelle Générale de l'Education Nationale; Institut National de la Santé et de la Recherche Médicale (INSERM); Institut Gustave Roussy; Deutsche Krebshilfe; Deutsches Krebsforschungszentrum; German Federal Ministry of Education and Research; Danish Cancer Society; ISCIII of the Spanish Ministry of Health (RETICC DR06/0020); Health Research Fund (FIS) of the Spanish Ministry of Health; the Spanish Regional Governments of Andalucia, Asturias, Basque Country, Murcia and Navarra; Cancer Research UK; Medical Research Council, UK; the Stroke Association, UK; British Heart Foundation; Department of Health, UK; Food Standards Agency, UK; the Wellcome Trust, UK; Hellenic Ministry of Health; Stavros Niarchos Foundation; Hellenic Health Foundation; Italian Association for Research on Cancer; Italian National Research Council; Dutch Ministry of Public Health, Welfare and Sports (VWS), Netherlands Cancer Registry (NKR), LK Research Funds, Dutch Prevention Funds, Dutch ZON (Zorg Onderzoek Nederland), World Cancer Research Fund (WCRF), Statistics Netherlands(The Netherlands); Nordforsk; Swedish Cancer Society; Swedish Scientific Council; Regional Government of Skane and Västerbotten, Sweden.

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