博士論文

Consumption of coffee and antioxidant vitamins and risk of lung cancer in Japan

（日本人におけるコーヒーおよび抗酸化ビタミン摂取と肺がんリスクに関する研究）

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Abstract

要旨

Objective: The associations between consumption of antioxidant-rich diet namely coffee and antioxidant vitamins – retinol, vitamin C, vitamin E, alpha-carotene and beta-carotene – and lung cancer risk on the Japanese population were examined.

Methods: Two analytic cohorts were generated from the Japan Public Health Center-based Prospective (JPHC) Study; a total of 87,079 Japanese men (41,727) and women (45,352) aged 40-69 years and 79,705 men (38,207) and women (41,498) aged 45-74 years were included in the analyses of coffee and antioxidant vitamins, respectively. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated by multivariable-adjusted Cox proportional hazards models with further analyses by histological type and smoking status.

Results: During 17.0 years of follow-up time, 1,668 lung cancer cases were newly diagnosed in the cohort of coffee while 1,690 cases were identified during 15.5 years of follow-up in the cohort of antioxidant vitamins. While coffee consumption was not associated with lung cancer risk in general, there was a significant increase in the risk for small cell carcinoma (HR, 3.52; 95% CI, 1.49-8.28; p_{trend} = <0.001; comparing non-drinkers with ≥5 cups/day). Higher retinol intake was positively associated with overall lung cancer risk in men (HR, 1.26; 95% CI, 1.05-1.51; p_{trend} = 0.003; comparing the lowest with the highest intake) and the risk estimates were higher in small cell carcinoma (HR, 1.92; 95% CI, 1.13-3.24; p_{trend} = <0.001). No associations were observed for other antioxidant vitamins or in women.

Conclusion: While this prospective study suggests that habitual consumption of coffee is not associated with overall lung cancer risk, a significant increase in the risk of small cell carcinoma was observed. Higher consumption of retinol may be associated with an increased risk of lung cancer in men, especially with small cell carcinoma, although confirmation is required.

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List of Abbreviations

AICR	American Institute for Cancer Research
BMI	body mass index
CI	confidence interval
DNA	deoxyribonucleic acid
FFQ	food frequency questionnaire
HR	hazard ratio
IARC	International Agency for Research on Cancer
JPHC Study	The Japan Public Health Center-based Prospective Study
PHC	public health center
WCRF	World Cancer Research Fund
WHO	World Health Organization

Chapter 1. Introduction

1.1. Background

1.1.1. Trends in lung cancer incidence

Lung cancer was once a quite rare disease. Ever since mechanization and mass marketing popularized tobacco smoking toward the end of the 19th century, lung cancer has become a global epidemic.[1] Lung cancer has been the most common cancer worldwide for several decades, accounting for 13% of newly diagnosed cases (1.8 million cases) and 19% of cancer mortality (1.6 million deaths) in 2012.[2] Notably, 67% (1.2 million) of the cases are estimated to have occurred in men, with the highest incidence rates observed in Central and Eastern Europe, followed by Eastern Asia. The incidence rates in women are substantially lower and exhibit different geographical pattern, mainly due to different historical exposure to cigarette smoking habit.[3] Despite a considerable decrease in smoking prevalence, particularly in high-income countries, the burden of disease attributable to lung cancer is expected to persist worldwide for the next few decades.[4,5]

In Japan, lung cancer has been ranked first for cancer deaths since 1998 and third for cancer incidence.[6] While lung cancer incidence in men has plateaued for several decades, it has been gradually increasing in women, reflecting a little decrease in or even unchanged smoking prevalence.[5,6] The small gap between its morbidity and mortality implies a low survival rate, highlighting the importance of primary prevention for lung cancer.

Histologically, adenocarcinoma, small cell carcinoma and squamous cell carcinoma are the major types of lung cancer; the incidence rates of small cell and squamous cell carcinomas have leveled off since late 1980s in Japan while that of adenocarcinoma has been on the rise.[7] Cigarette smoking is more strongly associated with the carcinogenesis of small cell and squamous cell carcinomas than adenocarcinoma. This partially explains the gender difference in the incidence, but a determining factor for the increasing adenocarcinoma remains unclear.[7,8] Similar trends are observed worldwide in which the incidence of adenocarcinoma surpassed those of small cell and squamous cell carcinomas.[8,9]

1.1.2. Lung cancer risk factors

Smoking is the principal cause of lung cancer.[10,11] While tobacco use is estimated to be responsible for 90% of lung cancer cases in men and 80% in women worldwide,[12] the fraction has remained at 68% in men and 24% in women in Japan,[13] increasing the significance of non-smoking factors in managing lung cancer risk. Lung cancer incidence among never smokers was in fact observed to be higher in South East Asia than elsewhere.[14] The disparity in the attributable fraction can be explained by international variation in the prevalence of smoking and passive smoking. It also reflects geographical differences in environmental factors such as exposure to indoor radon, arsenic contamination in drinking water, air pollution as well as dietary factors.[13,15-17] Furthermore, there is convincing evidence of strong association between the intake of high-dose β-carotene supplements in smokers and the risk of lung cancer.[18]

1.1.3. Protective factors for lung cancer

Although some cases of lung cancer occur in the absence of known risk factors, elimination of tobacco smoking and avoidance of second hand smoke are undeniably the best strategies to prevent lung cancer. Avoiding exposure to environmental factors such as radon and other carcinogenic chemicals could also lower the risk of lung cancer. In a comprehensive report by the World Cancer Research Fund (WCRF)/American Institute for Cancer Research (AICR), the expert panel concluded that the evidence suggesting protective effects of non-starchy vegetables, foods containing selenium and quercetin, and beverages such as coffee and tea are limited.[18] Nevertheless, there is consistent and ample evidence from a recent meta-analysis that consumption of fruits and vegetables containing carotenoids decrease the risk of lung cancer.[19]

1.2. Rationale and objectives

1.2.1. Antioxidant intake and lung cancer

Although smoking is the predominant cause of lung cancer, the incidence of lung cancer among non-smokers has been increasing, especially among women.[20-22] This suggests the presence of risk factors other than smoking and highlights the importance of elucidating non-smoking-related factors such as diet. Historically, the notion that antioxidant-rich foods such as fruits and vegetables may decrease lung cancer risk led to the implementation of large randomized clinical trials in Finland (the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study)[23] and the United States (the Beta Carotene and Retinol Efficacy

Trial (CARET).[24] These revealed an elevated risk of lung cancer among smokers and/or participants with asbestos exposure who took daily supplementation of β-carotene and/or retinol. Dietary intake of vitamin C, in contrast, has been suggested to decrease the lung cancer risk but the findings were observed mainly in the United States.[25-31] Higher intakes of vitamins A, E and carotenoids were also found to have protective effects, especially for smokers, whereas evidence on the specific dietary antioxidants remains inconclusive and limited, particularly in Asian populations.[32-37]

While prospective studies of fruits and vegetable intake and lung cancer risk have been widely conducted in Europe and North America, there has been one study in Japan, which found a null result.[19,38-41] Moreover, a comprehensive evaluation of the existing evidence in the WCRF/AICR report concluded that the evidence regarding an association between dietary antioxidants and lung carcinogenesis is not convincing.[18] Despite differences in smoking prevalence and dietary patterns between Japan and other regions, including China, no prospective study has investigated the direct association between dietary antioxidants and cancer risk in Japan.

Potential mechanisms behind the observed associations are that fruits, vegetables and grains are all abundant in antioxidant vitamins, which neutralize free radicals. Free radical-induced damage to deoxyribonucleic acid (DNA) has been hypothesized to play a role in carcinogenesis.[42] Vitamin A, the generic term for a group of liposoluble vitamins which include retinol, α- and β-carotene, is vital for maintaining epithelial tissues such as mucus membranes and lung tissues, and supporting immune function.[43] Over two-thirds of daily vitamin A consumption in the Japanese diet comes from plant-based foods.[44] Vitamin C, one of the most common antioxidants, plays a key role in blocking carcinogenesis by protecting cells from oxidative DNA damage.[45] Vitamin E, another group of liposoluble antioxidant nutrients consisting of tocopherols and tocotrienols, acts by blocking propagation of free radical reactions.[33]

Coffee is another rich dietary source of antioxidants and it is one of the most widely consumed beverages around the world, including Japan.[46,47] The biochemically active compounds such as chlorogenic acids and caffeine contained in coffee have been hypothesized to play a role in carcinogenesis by preventing oxidative damage to DNA and cell components.[48-52] Hence, it comes as no surprise that epidemiological investigation on health effects of coffee drinking has been extensive. A number of studies have reported inverse associations between coffee intake and some cancers as well as reduced mortality.[49,53-60] However, lung cancer appears to be an exception. The leading risk factor for lung cancer is smoking, and smoking and coffee drinking are positively associated behaviors.[61] The majority of the studies on coffee and lung cancer risk which found positive associations have indeed indicated a strong possibility of inadequate control for smoking.[62,63] In a large-scale prospective cohort study in the United States, coffee drinking was found to have a positive association with mortality in age-adjusted models. After adjusting for smoking status and other potential confounders, coffee consumption was significantly associated with reduced risk of mortality.[57] Therefore, adjustment for tobacco smoking remains a major and critical issue in these studies, as it may confound the associations.[61-67] While recent findings from a meta-analysis of 17 studies[62] and a large prospective cohort study[61] reported an elevated risk of lung cancer, no significant association was observed in their stratified analyses among non-smokers. In addition, very few studies have explored the association by histological type, despite the fact that smoking is closely linked to squamous cell and small cell carcinomas[68] whereas the majority of diagnoses in never smokers are adenocarcinoma.[22] Moreover, only one hospital-based case-control study[69] and two small-scale prospective cohort studies[60,70] with either limited information on exposure or small numbers of cases have been conducted in Japan.

1.2.2. Main objectives

Smoking is undoubtedly the leading cause of lung cancer. Nevertheless, there are certainly other risk factors contributing to lung carcinogenesis in smokers as well as in never-smokers. Approximately one-third and three-quarters of lung cancer cases in Japanese men and women, respectively, are in fact caused by factors other than smoking,[13] which motivates the exploration of the association between antioxidant-rich diet and lung cancer risk on the Japanese population. This thesis concentrates on coffee and antioxidant vitamins as rich sources of dietary antioxidants and aims to:

1. Investigate basic characteristics of coffee and antioxidant vitamin intake with lung cancer risk factors;
2. Assess lung cancer risk by levels of coffee and antioxidant vitamin intake; and
3. Examine risk differences by gender, histological type of lung cancer and smoking status.

1.2.3. Organization of thesis

Chapter 1 of the thesis provides the background on risk and protective factors for lung cancer followed by the rationale and objectives of the study. In this thesis, in pursuit of exploring the association between antioxidant-rich diet and lung cancer risk in Japan, coffee intake and dietary consumption of antioxidant vitamins are focused. Chapter 2 introduces the study methods, materials and the results on coffee drinking and lung cancer risk. Chapter 3 presents the details of the study and its results on antioxidant vitamin intake and lung cancer risk. The results of each study are discussed in comparison with other studies, and the strengths and limitations of the each study are also examined in Chapters 2 and 3. Chapter 4 summarizes the thesis and considers the implications for future research.

Chapter 2. Coffee and lung cancer risk

2.1. Study design and population

2.1.1. Study design

The Japan Public Health Center-based prospective Study (JPHC Study) is a 30-year ongoing cohort study designed to explore the association between potentially modifiable factors and incidence of diseases. Further details of the study have been described in a previous publication.[71] In brief, all registered residents aged 40 to 59 years from five public health center (PHC) areas (Iwate-Ninohe, Akita-Yokote, Nagano-Saku, Tokyo-Katsushika, and Okinawa-Chubu) were recruited in 1990 as Cohort I. Cohort II was subsequently established in 1993 and included all residents aged 40 to 69 years in six PHC areas (Niigata-Nagaoka, Ibaraki-Mito, Osaka-Suita, Kochi-Chuohigashi, Nagasaki-Kamigoto, and Okinawa-Miyako) to elucidate risk factors for not only cancers but also cardiovascular diseases.[72] Study locations for Cohort I were selected based on regional variation in gastric cancer mortality observed in a preceding study and Cohort II was determined considering distribution of study locations and feasibility.[73] Geographical distribution of the JPHC Study areas and the number of study participants are presented in Figure 1.

At baseline, a self-administered questionnaire was distributed to a total of 140,420 registered residents (68,722 men and 71,698 women) aged 40 to 69 years in 11 PHC areas nationwide between 1990 and 1994. Blood samples and health checkup data were also collected from those who volunteered. The 5-year and 10-year follow-up questionnaires were administered to update information on daily living and health conditions.[71]

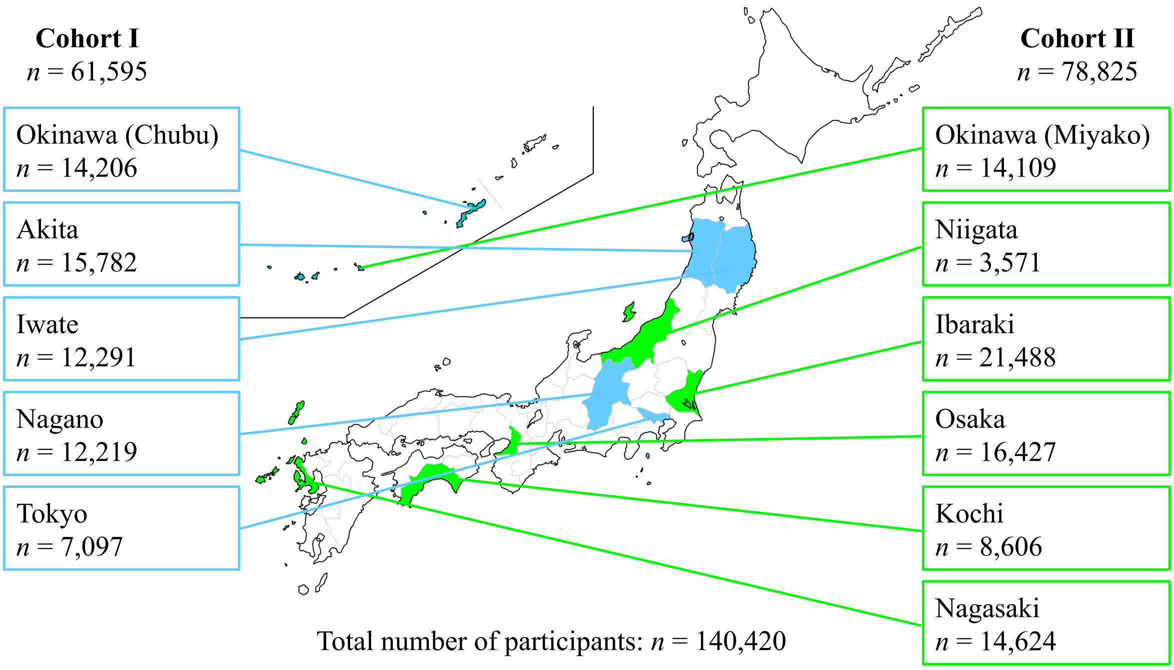

Figure 1. Map of the Japan Public Health Center-based prospective Study areas
Source: Tsugane and Sawada[71]

2.1.2. Study population

Participants from the Tokyo-Katsushika (*n* = 7,097) and Osaka-Suita (*n* = 16,427) PHC areas were not included in the present study due to the unavailability of complete data on cancer incidence. A total of 299 participants with either non-Japanese nationality (*n* = 51), pre-commencement emigration outside the study area (*n* = 170), incorrect birth date (*n* = 4), or duplicate registration (*n* = 4) were regarded as ineligible. People who had late report of emigration before the start of follow-up period or were lost to follow-up (*n* = 455) were further excluded.

Of 94,917 eligible participants who returned the completed self-administered baseline questionnaire (response rate 81.7%), those who reported a past history of cancer at any site were not included (*n* = 1,915). After excluding subjects with extreme caloric intake (±2.5% of the distribution, *n* = 4,407) and missing data on covariates including coffee intake and cigarette smoking (*n* = 1,516), 41,727 men and 45,352 women were included in the analytic cohort. Figure 2 outlines the study flow to acquire the final study sample. This study was approved by the institutional review boards of the National Cancer Center (approval number: 13-021) and the University of Tokyo (approval number: 10508).

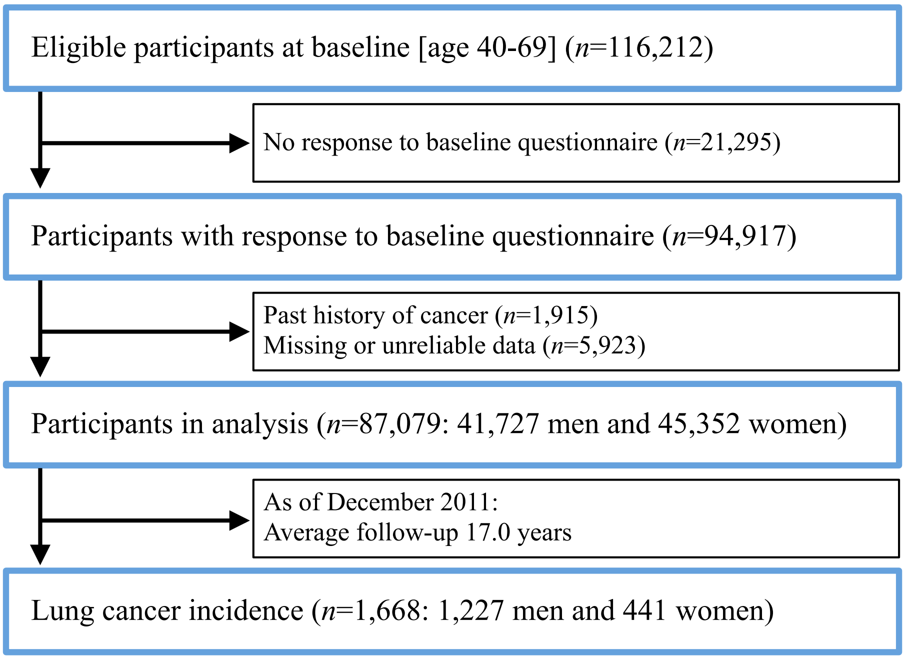

Figure 2. Study flow of analysis of coffee

2.2. Exposure variables

2.2.1. Assessment of coffee intake

At baseline, a self-administered questionnaire was distributed to all participants, to collect information on sociodemographic characteristics, medical history, and behaviors including physical activity, alcohol consumption, and smoking. Data on anthropometric measurements, blood pressures, urinalysis and hematological examination were extracted from health checkup data sponsored mostly by local governments or delegated companies in some cases.[73]

Dietary intake of coffee was measured through a self-administered food frequency questionnaire (FFQ). The FFQ used at baseline for Cohort I was a revised version of a questionnaire adopted in the preceding study and included 44 food items, which was then modified slightly for Cohort II to improve frequency and proportion categories. Validity and reproducibility of each of the FFQs, including comparability between the two FFQs, were tested by comparing food consumption measured by dietary records and the FFQ and between two identical FFQs, respectively, in subsamples of 201 participants from Cohort I and 392 participants from Cohort II. Further details of dietary assessment in the JPHC Study have been reported in previous papers.[74,75] In brief, baseline FFQ for both Cohort I and II inquired about coffee intake, along with green tea, oolong tea, black tea, juice and soft drinks, using the same six categories as follows: almost never, 1-2, 3-4 times/week, and almost everyday, which was further divided into 1-2, 3-4, and ≥5 cups/day. Coffee consumption at the time of baseline was used as an exposure and, due to small number of participants, occasional drinkers (1-2 and 3-4 times/week) were merged into one group (<1 cup/day) in this study. Different types of coffee (caffeinated or decaffeinated) were not included in the questionnaire although decaffeinated coffee is seldom consumed in Japan. Spearman rank correlation coefficients between the dietary records and coffee intake estimated from the FFQ were 0.59 for men and 0.51 for women.[76]

2.2.2. Other covariates

The following covariates have been previously reported to have associations with lung cancer incidence and thus the results were adjusted for them: body mass index (BMI),[77-79] dietary intakes of fish,[69,80] vegetables and fruits,[38,70,81] isoflavone,[82,83] smoking status,[84,85] alcohol consumption,[86] and physical activity.[87,88] BMI was calculated by dividing weight in kilograms by height in meters squared from the baseline survey. In the baseline FFQ for both cohorts, the following food items were included regarding the intakes of fish: fish and shellfishes, dried fish, salted fish, salted roe, salted fish guts, and sea-urchin paste; vegetables: green vegetables, yellow vegetables, other vegetables, pickles, and vegetable juice; and fruits: fresh fruits and fruit juice.

In addition to dietary habits, study participants were asked to report their behaviors in the questionnaire. For smoking status, participants were asked whether they are never, past or current smokers. In the baseline questionnaire, age of smoking initiation and cessation, and number of cigarettes smoked per day were also asked for past and current smokers. To explore potential variance by smoking status and estimate cumulative smoking exposure, pack-years were generated by multiplying the average number of cigarette packs (assuming 20 cigarettes per pack) smoked per day with the number of years smoked.

For alcohol consumption, choices for drinking frequency were: hardly ever, 1-3 days/month, 1-2, 3-4, 5-6 days/week, or every day in the Cohort I baseline questionnaire whereas the questionnaire for Cohort II inquired about current drinking status as: never, former, or current drinkers. Former and current drinkers were then asked to report the frequency of alcohol intake from: 1-3 days/month, 1-2, 3-4 days/week, or almost every day. To produce a consistent variable for baseline survey, drinking status was defined as follows: non-drinkers included people who reported 'hardly ever' in Cohort I and 'never/former' in Cohort II; current drinkers included those who answered to drink more than 1-3 days/month. In the JPHC study, one standard drink is approximated to contain 23 grams of ethanol for 180 mL (one *gou*) of *sake*, 36 grams of ethanol for 180 mL of *shochu/awamori*, 23 grams of ethanol for 633 mL (a large bottle) of beer, 10 grams of ethanol for 30 mL of whisky, and 6 grams of ethanol for 60 mL of wine. Daily alcohol consumption for current drinkers was then estimated by multiplying the amount (in grams) of ethanol contained in each type of alcohol drinks consumed per day.

Physical activity was measured by consistent frequency in all of the questionnaires as the following: almost none, 1-3 times/month, 1-2, 3-4 times/week, or almost every day. Tea is a common choice of beverage along with coffee in Japan and has been reported to have free radical scavenging activity and chemopreventive effects on lung cancer.[89,90] Consumption of tea namely green tea, Chinese (oolong) tea, and black tea, was assessed in the baseline FFQ as follows: almost never, 1-2, 3-4 times/week, and almost everyday, which was further divided into 1-2, 3-4, and ≥5 cups/day.

2.3. Follow-up and identification of lung cancer cases

Participants were followed from the date of baseline survey (1990-1994) until the date of lung cancer diagnosis, death, moving out of the study area, or the end of follow-up

(December 31, 2011) for the analysis of coffee, whichever occurred first. Death certificates were used with the permission of the Ministry of Health, Labor, and Welfare to confirm cause of death with the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision.[91]

Identification of lung cancer cases was conducted through patient notification from major local hospitals in each PHC area and record linkage with data from population-based cancer registries. Death certificates were used to supplement information on diagnosis in 6.6% of all lung cancer cases. Lung cancer cases were microscopically confirmed in 87% of the cases and coded using the International Classification of Diseases for Oncology, Third Edition (C34.0-34.9).[92] Histological type were classified into adenocarcinoma, squamous cell carcinoma, small cell carcinoma, and other types according to the World Health Organization (WHO)'s classification of lung tumors.[93] For participants who had multiple incidences of lung cancer, only the first incidence was used.

2.4. Statistical analysis

Multivariable Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for lung cancer risk by consumption of coffee. Participants were divided into five groups according to coffee intake (do not drink coffee, drink <1 cup/day, 1-2, 3-4, and ≥5 cups/day), with non-drinkers as the referent group. In primary analysis, risk estimates for overall lung cancer incidence and histological type (adenocarcinoma, squamous cell carcinoma, small cell carcinoma, and any other types of lung carcinoma) were determined using three models, which were adjusted for potential confounders. The first model (Model 1[a]) was adjusted for age (continuous), PHC area (9), and gender for histological analysis. The second model (Model 2[a]) was additionally adjusted for smoking status (never, former: <10, 10-19, ≥20 years of smoking cessation, current: 1-19, 20-29, 30-39, 40-49, 50-59, ≥60 pack-years). The third model (Model 3[a]) was further adjusted for BMI (<18.5, 18.5-24.9, 25.0-29.9, ≥30 kg/m^2), physical activity (almost never, <3 days/month, 1-2, 3-4 days/week, almost everyday), alcohol consumption (never/former, <1 time/week, <23, 23-45, 46-68, 69-91, ≥92 grams of ethanol/day), consumption of green, oolong, and black tea (almost never, <1 cup/week, ≥1 cup/day), and energy-adjusted intakes of fruits, vegetables, and isoflavone (continuous).

To further examine the effect of residual confounding by smoking, secondary analysis was stratified by gender and detailed smoking categories, namely smoking status (never, former and current) and smoking intensity by cumulative smoking exposure in male current and former smokers by pack-years (light smokers: ≤19.9 or heavy smokers: ≥20.0). For instance, 1 pack-year is equivalent to smoking 1 pack containing 20 cigarettes per day for 1 year, or 2 packs per day for 6 months. A cut-off for light and heavy smokers was chosen in reference to a definition published in the WHO Bulletin.[94] Secondary analysis in women was performed by smoking status (never and current) since 92.9% of female participants were never-smokers and only 1.3% were former smokers.

Covariates in Model 1[a] and Model 3[a] from the primary analysis, except for smoking status, were employed for the secondary analysis. In order to maintain sample size in scarcely populated categories in subanalysis, HRs were estimated by merging coffee intake into three groups as follows: almost never, <3 cups/day or ≥3 cups/day. *P*-values for trend were calculated by assigning scores for coffee intake (0 for the lowest consumption group to 4 for the highest) and including them in the regression models as a continuous variable. *P*-values for interaction were computed using likelihood-ratio tests comparing Cox proportional hazards models with and without cross-product terms for the combination of lung cancer subtypes and coffee intake or smoking status and coffee intake, with coffee as a continuous term. All covariates were assessed at baseline and dietary intake was adjusted for total energy intake using a residual method suggested by Willet.[95]

In order to energy-adjust nutrients, the mean logarithmic energy was calculated for men and women separately. A constant of 0.01 was added before taking the natural log to eliminate zero and negative values and then the coefficient of energy (slope) and the constant (intercept) for each nutrient for each gender were obtained. Finally, the nutrient residuals were computed from the log-transformed energy-adjusted nutrients. The following formulae indicate the mathematical process employed in this study:

Calories of intake = (mean log-transformed energy) * (slope: logarithmic intake of nutrient regressed on the logarithmic energy) + (intercept: constant)

Energy-adjusted log-transformed calories = calories of intake + nutrient residuals

Using Schoenfeld residuals, a test of the proportional hazards assumption indicated that it had not been violated. To avoid potential bias due to undiagnosed lung cancer, sensitivity analysis was conducted after excluding lung cancer cases that were diagnosed within the first five years from baseline, and produced a similar direction of associations as the main analyses. All statistical analyses were performed with Stata MP version 14.0 (StataCorp, College Station, Texas US).

2.5. Results

2.5.1. Basic characteristics of study participants

During an average follow-up of 17.0 years (1,481,887 person-years), a total of 1,668 participants (1,227 men and 441 women) were newly diagnosed with lung cancer. Of histologically confirmed cases, 43.7% were adenocarcinoma (*n* = 729). Two thirds of the study participants reported drinking coffee routinely while one third were non-drinkers (Table 1). Compared with non-drinkers, coffee drinkers were much more likely to smoke cigarettes. Male coffee drinkers tended to consume less alcohol while female coffee drinkers were likely to report higher alcohol consumption. Coffee drinkers also tended to consume lower levels of fruits, vegetables, and fish, but not meat. Both male and female coffee drinkers were less likely to have diabetes. Green tea was consumed more among coffee non-drinkers whereas black tea was consumed less. While female coffee drinkers were likely to drink more Chinese tea than non-drinkers, the consumption rate did not notably vary in men.

Table 1. Basic characteristics of study participants according to consumption of coffee

Characteristics	Men (n = 41,727) No Coffee	< 1 Cup/day	1-2 Cups/day	3-4 Cups/day	≥ 5 Cups/day	P*
Number of participants	13,191	12,767	10,414	3,921	1,434	
Number of lung cancer cases	403	370	296	109	49	
Age (years), mean (SD)	53.7 (7.7)	52.0 (7.7)	50.6 (7.8)	48.4 (7.3)	48.9 (7.4)	<0.001
Body mass index, mean (SD)	23.5 (2.9)	23.6 (2.8)	23.5 (2.8)	23.4 (2.9)	23.3 (3.1)	<0.001
Diabetes, %	8.6	6.3	4.7	4.1	3.9	<0.001
Current smoker, %	43.4	50.0	56.2	69.6	76.9	<0.001
Physical activity almost daily, %	6.1	4.9	4.8	4.3	5.5	<0.001
Dietary intake[+]						
Total energy intake (kcal/day), mean (SD)	1952 (552)	1953 (551)	1901 (516)	1881 (512)	1919 (527)	<0.001
Fruits (g/day), mean (SD)	27 (30)	27 (26)	27 (28)	26 (27)	28 (37)	<0.001
Vegetables (g/day), mean (SD)	47 (45)	45 (46)	44 (42)	40 (39)	44 (53)	<0.001
Isoflavone (mg/day), mean (SD)	18 (10)	17 (9)	16 (9)	15 (9)	15 (9)	<0.001
Alcohol consumption (g/week), mean (SD)	205 (218)	186 (209)	174 (201)	157 (197)	154 (220)	<0.001
Green tea >1 time/day, %	75.6	75.2	74.5	70.1	65.1	<0.001
Chinese tea >1 time/day, %	10.4	8.7	11.8	9.3	10.9	<0.001
Black tea >1 time/day, %	1.7	1.6	3.2	2.6	3.8	<0.001

Characteristics	Women (n = 45,352) No Coffee	< 1 Cup/day	1-2 Cups/day	3-4 Cups/day	≥ 5 Cups/day	P*
Number of participants	15,202	13,554	12,573	3,155	868	
Number of lung cancer cases	163	139	103	23	13	
Age (years), mean (SD)	55.1 (7.7)	52.4 (7.8)	50.0 (7.5)	47.3 (6.6)	48.2 (7.3)	<0.001
Body mass index, mean (SD)	23.7 (3.3)	23.6 (3.1)	23.4 (3.1)	23.2 (3.0)	23.4 (3.2)	<0.001
Diabetes, %	4.9	2.5	2.0	1.3	1.3	<0.001
Current smoker, %	4.2	4.0	6.3	13.1	23.6	<0.001
Physical activity almost daily, %	5.8	4.4	4.4	3.2	5.6	<0.001
Dietary intake[+]						
Total energy intake (kcal/day), mean (SD)	1221 (305)	1248 (304)	1247 (296)	1230 (297)	1295 (322)	<0.001
Fruits (g/day), mean (SD)	102 (75)	100 (66)	95 (67)	89 (75)	90 (90)	<0.001
Vegetables (g/day), mean (SD)	112 (92)	106 (82)	103 (84)	92 (81)	93 (92)	<0.001
Isoflavone (mg/day), mean (SD)	26 (13)	24 (12)	23 (11)	22 (12)	20 (12)	<0.001
Alcohol consumption (g/week), mean (SD)	10 (54)	11 (54)	11 (50)	17 (82)	19 (58)	<0.001
Green tea >1 time/day, %	77.1	77.8	74.7	66.4	66.6	<0.001
Chinese tea >1 time/day, %	12.1	11.0	14.0	13.7	20.3	<0.001
Black tea >1 time/day, %	1.8	1.8	4.5	3.4	5.0	<0.001

SD denotes standard deviation. The body mass index is the weight divided by the square of the height in meters.
[+]All values for dietary intake are energy-adjusted.
*ANOVA or χ^2 test

2.5.2. Lung cancer incidence by consumption of coffee

In the model adjusted for age and PHC area, coffee consumption was associated with an increased risk of lung cancer incidence (HR, 1.88; 95% CI, 1.39-2.54; p_{trend} = <0.001 for men; HR, 2.06; 95% CI, 1.16-3.67; p_{trend} = 0.253 for women; comparing non-drinkers with ≥5 cups/day) (Table 2). However, participants who routinely consumed coffee also tended to be smokers, and after adjusting for smoking, the association was notably attenuated (HR, 1.14; 95% CI, 0.83-1.55; p_{trend} = 0.405 for men; HR, 1.55; 95% CI, 0.86-2.79; p_{trend} = 0.839 for women; comparing non-drinkers with ≥5 cups/day). Similar associations were also observed for histological type. The highest hazard was seen for small cell carcinoma, with HR for the highest level of coffee intake being reduced by three-quarters after adjustment for tobacco smoking and other confounders, without significant effect modification by histological type ($p_{interaction}$ 0.331 for men; $p_{interaction}$ 0.169 for women). The risk of small cell carcinoma was even higher in a further analysis of histological types by gender although cautious interpretation is required due to small case numbers (Table 3).

Table 2. Hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between coffee intake and lung cancer risk

	Coffee intake					P_{trend}	P_{int}
	No Coffee	**< 1 Cup/day**	**1-2 Cups/day**	**3-4 Cups/day**	**≥ 5 Cups/day**		
Lung cancer (all)							
Men							0.331
Number of cases	403	370	296	109	49	—	—
Model 1[a]	1.00	1.07 (0.93-1.23)	1.27 (1.09-1.48)	1.54 (1.24-1.91)	1.88 (1.39-2.54)	<0.001	—
Model 2[a]	1.00	0.95 (0.82-1.10)	1.05 (0.89-1.23)	1.02 (0.82-1.28)	1.14 (0.83-1.55)	0.405	—
Model 3[a]	1.00	1.03 (0.88-1.22)	1.11 (0.93-1.22)	1.05 (0.82-1.34)	1.16 (0.82-1.63)	0.285	—
Women							0.169
Number of cases	163	139	103	23	13	—	—
Model 1[a]	1.00	1.08 (0.86-1.36)	1.00 (0.77-1.30)	1.08 (0.69-1.70)	2.06 (1.16-3.67)	0.253	—
Model 2[a]	1.00	1.08 (0.86-1.36)	0.95 (0.73-1.24)	0.90 (0.56-1.43)	1.55 (0.86-2.79)	0.839	—
Model 3[a]	1.00	1.06 (0.82-1.36)	0.94 (0.70-1.25)	0.90 (0.55-1.48)	1.49 (0.79-2.83)	0.942	—
Adenocarcinoma							
Number of cases	266	216	176	46	25	—	—
Model 1[a]	1.00	0.97 (0.81-1.16)	1.10 (0.90-1.33)	1.06 (0.77-1.46)	1.66 (1.09-2.51)	0.087	—
Model 2[a]	1.00	0.91 (0.76-1.09)	0.97 (0.80-1.19)	0.83 (0.59-1.16)	1.21 (0.79-1.86)	0.829	—
Model 3[a]	1.00	0.95 (0.78-1.16)	1.01 (0.81-1.26)	0.80 (0.56-1.16)	1.13 (0.70-1.83)	0.778	—
Squamous cell carcinoma							
Number of cases	107	106	76	30	16	—	—
Model 1[a]	1.00	1.20 (0.91-1.57)	1.31 (0.97-1.77)	1.80 (1.19-2.73)	2.55 (1.50-4.35)	<0.001	—
Model 2[a]	1.00	1.06 (0.80-1.40)	1.06 (0.78-1.45)	1.10 (0.71-1.70)	1.45 (0.84-2.49)	0.303	—
Model 3[a]	1.00	1.14 (0.83-1.55)	1.10 (0.78-1.55)	1.04 (0.63-1.69)	1.24 (0.66-2.32)	0.578	—
Small cell carcinoma							
Number of cases	28	61	37	21	9	—	—
Model 1[a]	1.00	2.60 (1.66-4.08)	2.28 (1.38-3.77)	4.50 (2.51-8.06)	5.39 (2.51-11.58)	<0.001	—
Model 2[a]	1.00	2.47 (1.56-3.93)	1.88 (1.12-3.16)	2.83 (1.54-5.17)	2.62 (1.16-5.90)	0.003	—
Model 3[a]	1.00	2.51 (1.47-4.30)	2.35 (1.33-4.17)	3.48 (1.79-6.73)	3.52 (1.49-8.28)	<0.001	—
Other							
Number of cases	165	126	110	35	12	—	—
Model 1[a]	1.00	0.93 (0.74-1.17)	1.17 (0.92-1.51)	1.33 (0.92-1.94)	1.27 (0.70-2.29)	0.072	—
Model 2[a]	1.00	0.87 (0.68-1.10)	1.00 (0.77-1.29)	0.94 (0.64-1.38)	0.83 (0.46-1.38)	0.707	—
Model 3[a]	1.00	0.94 (0.72-1.23)	1.00 (0.75-1.35)	0.99 (0.65-1.50)	1.02 (0.55-1.88)	0.958	—

P_{int}: $P_{interaction}$
Model 1[a]: age (continuous), study area (9 public health center areas)
Model 2[a]: age (continuous), gender (for histological analysis), study area (9 public health center areas), smoking status (never, former: <10, 10-19, and ≥20 years of smoking cessation, current: 1-19, 20-29, 30-39, 40-49, 50-59, ≥60 pack-years)
Model 3[a]: age (continuous), gender (for histological analysis), study area (9 public health center areas), smoking status (never, former: <10, 10-19, and ≥20 years of smoking cessation, current: 1-19, 20-29, 30-39, 40-49, 50-59, ≥60 pack-years), body-mass index (<18.5, 18.5-24.9, 25.0-29.9, ≥30 kg/m^2), physical activity (almost never, <3 days/month, 1-2 days/week, 3-4 days/week, almost everyday), alcohol consumption (never/former, <1 time/week, <23, 23-45, 46-68, 69-91, ≥92 g of ethanol/day), consumption of green tea, Chinese tea, and black tea (almost never, <1 cup/week, ≥1 cup/day), energy-adjusted intake of fruit, vegetables, and isoflavone (continuous).

Table 3. Hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between coffee intake and lung cancer risk: subanalysis of lung cancer subtypes by gender

Lung cancer	Coffee intake					P_{trend}
	No Coffee	< 1 Cup/day	1-2 Cups/day	3-4 Cups/day	≥ 5 Cups/day	
Adenocarcinoma						
Men						
Number of cases	146	115	109	32	17	—
Model 1[a]	1.00	0.89 (0.69-1.13)	1.21 (0.94-1.56)	1.12 (0.76-1.66)	1.63 (0.98-2.70)	0.048
Model 2[a]	1.00	0.77 (0.60-0.99)	1.01 (0.78-1.31)	0.78 (0.52-1.17)	1.06 (0.62-1.80)	0.770
Model 3[a]	1.00	0.84 (0.64-1.11)	1.09 (0.82-1.44)	0.76 (0.48-1.20)	1.00 (0.55-1.81)	0.831
Women						
Number of cases	120	101	67	14	8	—
Model 1[a]	1.00	1.06 (0.81-1.38)	0.90 (0.65-1.22)	0.89 (0.50-1.58)	1.72 (0.83-3.56)	0.975
Model 2[a]	1.00	1.06 (0.81-1.39)	0.86 (0.62-1.18)	0.87 (0.50-1.55)	1.67 (0.80-3.48)	0.818
Model 3[a]	1.00	1.07 (0.79-1.43)	0.84 (0.59-1.20)	0.85 (0.46-1.60)	1.48 (0.63-3.45)	0.659
Squamous cell carcinoma						
Men						
Number of cases	99	95	68	29	15	—
Model 1[a]	1.00	1.14 (0.86-1.52)	1.26 (0.92-1.73)	1.83 (1.20-2.80)	2.49 (1.44-4.32)	<0.001
Model 2[a]	1.00	1.00 (0.75-1.35)	1.01 (0.73-1.41)	1.15 (0.74-1.79)	1.41 (0.81-2.48)	0.322
Model 3[a]	1.00	1.11 (0.80-1.53)	1.08 (0.75-1.55)	1.10 (0.67-1.81)	1.19 (0.62-2.30)	0.563
Women						
Number of cases	8	11	8	1	1	—
Model 1[a]	1.00	1.80 (0.72-4.52)	1.67 (0.59-4.68)	1.03 (0.12-8.69)	3.42 (0.41-28.46)	0.316
Model 2[a]	1.00	1.62 (0.63-4.12)	1.47 (0.53-4.11)	NA	1.28 (0.15-11.05)	0.914
Model 3[a]	1.00	1.42 (0.49-4.09)	1.29 (0.40-4.13)	NA	1.16 (0.13-10.69)	0.763
Small cell carcinoma						
Men						
Number of cases	24	58	32	17	6	—
Model 1[a]	1.00	2.84 (1.76-4.57)	2.32 (1.36-3.98)	4.05 (2.14-7.66)	4.10 (1.65-10.14)	<0.001
Model 2[a]	1.00	2.72 (1.66-4.45)	1.94 (1.11-3.39)	2.60 (1.34-5.06)	2.00 (0.74-5.38)	0.026
Model 3[a]	1.00	2.91 (1.62-5.22)	2.49 (1.32-4.69)	3.25 (1.55-6.81)	2.82 (1.00-7.94)	0.005
Women						
Number of cases	4	3	5	4	3	—
Model 1[a]	1.00	0.92 (0.20-4.13)	1.68 (0.43-6.61)	6.86 (1.55-30.33)	15.24 (3.17-73.24)	<0.001
Model 2[a]	1.00	0.91 (0.20-4.09)	1.33 (0.34-5.17)	3.40 (0.77-15.07)	4.34 (0.86-21.96)	0.040
Model 3[a]	1.00	0.55 (0.08-3.10)	1.16 (0.29-4.68)	4.30 (0.94-19.80)	4.07 (0.74-22.49)	0.033
Other						
Men						
Number of cases	134	102	87	31	11	—
Model 1[a]	1.00	0.90 (0.66-1.17)	1.14 (0.87-1.51)	1.37 (0.92-2.05)	1.32 (0.71-2.46)	0.085
Model 2[a]	1.00	0.82 (0.63-1.07)	0.95 (0.72-1.27)	0.93 (0.62-1.41)	0.85 (0.46-1.60)	0.665
Model 3[a]	1.00	0.92 (0.68-1.24)	0.94 (0.68-1.31)	0.97 (0.62-1.53)	1.06 (0.56-2.02)	0.947
Women						
Number of cases	31	24	23	4	1	—
Model 1[a]	1.00	1.00 (0.58-1.71)	1.18 (0.67-2.08)	1.00 (0.34-2.94)	0.87 (0.12-6.46)	0.766
Model 2[a]	1.00	1.05 (0.61-1.81)	1.12 (0.63-2.00)	0.79 (0.27-2.37)	0.51 (0.07-3.92)	0.798
Model 3[a]	1.00	0.97 (0.53-1.77)	1.14 (0.61-2.14)	0.83 (0.27-2.55)	0.67 (0.09-5.12)	0.937

Model 1[a]: age (continuous), study area (9 public health center areas)
Model 2[a]: age (continuous), gender (for histological analysis), study area (9 public health center areas), smoking status (never, former: <10, 10-19, and ≥20 years of smoking cessation, current: 1-19, 20-29, 30-39, 40-49, 50-59, ≥60 pack-years)
Model 3[a]: age (continuous), gender (for histological analysis), study area (9 public health center areas), smoking status (never, former: <10, 10-19, and ≥20 years of smoking cessation, current: 1-19, 20-29, 30-39, 40-49, 50-59, ≥60 pack-years), body-mass index (<18.5, 18.5-24.9, 25.0-29.9, ≥30 kg/m^2), physical activity (almost never, <3 days/month, 1-2 days/week, 3-4 days/week, almost everyday), alcohol consumption (never/former, <1 time/week, <23, 23-45, 46-68, 69-91, ≥92 g of ethanol/day), consumption of green tea, Chinese tea, and black tea (almost never, <1 cup/week, ≥1 cup/day), energy-adjusted intake of fruit, vegetables, and isoflavone (continuous).

2.5.3. Further analysis by smoking status

Approximately half of male participants in the analysis of coffee were current smokers, whereas 92.9% of female participants were never-smokers (Table 4). In stratified analyses by smoking strata, current and former male smokers were examined by pack-years. A higher level of coffee intake among male heavy smokers who had ≥20.0 pack-years of tobacco exposure was associated with an increased risk of lung cancer (HR, 1.30; 95% CI, 1.04-1.63; p_{trend} = 0.014, comparing non-drinkers with ≥3 cups/day), whereas no substantial effect modification by smoking status was observed in either men or in women ($p_{interaction}$ = 0.266 for men; $p_{interaction}$ = 0.243 for women). While tea is also commonly consumed in Japan and is known to have antioxidant properties such as free radical scavenging effects, a separate analysis on tea including green tea, Chinese (oolong) tea, and black tea and lung cancer did not find a significant association (Table 5). Sensitivity analysis, which excluded lung cancer cases diagnosed within the first five years from baseline, produced a similar direction of associations as the main analyses.

Table 4. Hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between coffee intake and lung cancer risk: subanalysis by smoking status

	Coffee intake			P_{trend}	P_{int}
	No Coffee	< 3 Cups/day	≥ 3 Cups/day		
Men					0.266
Never-smokers					
Number of cases	40	40	7	—	—
Model 1[a]	1.00	0.75 (0.48-1.17)	1.20 (0.53-2.71)	0.587	—
Model 3[a]	1.00	0.81 (0.49-1.33)	1.41 (0.58-3.46)	0.940	—
Former smokers					
Number of cases	75	105	8	—	—
Model 1[a]	1.00	1.11 (0.82-1.50)	0.85 (0.41-1.78)	0.802	—
Model 3[a]	1.00	1.25 (0.90-1.74)	0.88 (0.40-1.95)	0.461	—
Current smokers					
Number of cases	288	521	143	—	—
Model 1[a]	1.00	1.04 (0.90-1.20)	1.18 (0.96-1.46)	0.155	—
Model 3[a]	1.00	1.12 (0.95-1.32)	1.24 (0.99-1.57)	0.058	—
Light smokers *					
Number of cases	38	58	4	—	—
Model 1[a]	1.00	1.14 (0.75-1.73)	0.61 (0.21-1.73)	0.876	—
Model 3[a]	1.00	1.35 (0.83-2.18)	0.92 (0.31-2.68)	0.500	—
Heavy smokers *					
Number of cases	325	568	147	—	—
Model 1[a]	1.00	1.08 (0.94-1.24)	1.29 (1.05-1.58)	0.023	—
Model 3[a]	1.00	1.16 (0.99-1.35)	1.30 (1.04-1.63)	0.014	—
Women					0.243
Never-smokers					
Number of cases	147	204	24	—	—
Model 1[a]	1.00	1.01 (0.81-1.25)	1.14 (0.72-1.79)	0.716	—
Model 3[a]	1.00	1.00 (0.79-1.28)	1.13 (0.70-1.84)	0.759	—
Current smokers					
Number of cases	14	35	12	—	—
Model 1[a]	1.00	1.42 (0.76-2.67)	1.39 (0.61-3.14)	0.380	—
Model 3[a]	1.00	1.27 (0.66-2.45)	1.38 (0.58-3.28)	0.441	—

P_{int}: $P_{interaction}$
Model 1[a]: age (continuous), study area (9 public health center areas)
Model 3[a]: age (continuous), study area (9 public health center areas), body-mass index (<18.5, 18.5-24.9, 25.0-29.9, ≥30 kg/m^2), physical activity (almost never, <3 days/month, 1-2 days/week, 3-4 days/week, almost everyday), alcohol consumption (never/former, <1 time/week, <23, 23-45, 46-68, 69-91, ≥92 g of ethanol/day), consumption of green tea, Chinese tea, and black tea (almost never, <1 cup/week, ≥1 cup/day), energy-adjusted intake of fruit, vegetables, and isoflavone (continuous).
*Models included current and former smokers who were categorized into light (≤19.9 pack-years) and heavy (≥20.0 pack-years) smokers. Pack-years is the number of cigarette packs (assuming 20 cigarettes per pack) smoked per day, multiplied by years of consumption.

Table 5. Hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between tea intake and lung cancer risk

	Tea intake			P_{trend}
	No tea	< 3 Cup/day	≥ 3 Cups/day	
Green tea				
Number of cases	173	160	1,318	—
Model 1[a]	1.00	0.90 (0.72-1.11)	1.00 (0.85-1.18)	0.687
Model 3[a]	1.00	1.01 (0.79-1.30)	1.09 (0.90-1.32)	0.928
Chinese (oolong) tea				
Number of cases	1,120	288	154	—
Model 1[a]	1.00	0.86 (0.76-0.98)	0.98 (0.82-1.16)	0.235
Model 3[a]	1.00	0.87 (0.76-0.99)	0.99 (0.83-1.18)	0.310
Black tea				
Number of cases	1,392	212	35	—
Model 1[a]	1.00	0.90 (0.78-1.04)	0.98 (0.70-1.37)	0.253
Model 3[a]	1.00	0.92 (0.80-1.07)	1.02 (0.72-1.44)	0.476

Model 1[a]: age (continuous), study area (9 public health center areas)
Model 3[a]: age (continuous), study area (9 public health center areas), gender, body-mass index (<18.5, 18.5-24.9, 25.0-29.9, ≥30 kg/m^2), smoking status (never, former: <10, 10-19, and ≥20 years of smoking cessation, current: 1-19, 20-29, 30-39, 40-49, 50-59, ≥60 pack-years), alcohol consumption (never/former, <1 time/week, <23, 23-45, 46-68, 69-91, ≥92 g of ethanol/day), physical activity (almost never, <3 days/month, 1-2 days/week, 3-4 days/week, almost everyday), coffee intake (almost never, <1 cup/day, 1-2 cups/day, 3-4 cups/day, ≥5 cups/day), energy-adjusted intake of fruit, vegetables, and isoflavone (continuous).

2.6. Discussion

2.6.1. Comparison with preceding studies

This prospective cohort study in Japan demonstrated that coffee consumption was not associated with overall lung cancer risk after adjustment for smoking and other potential confounders. However, an increased risk of small cell carcinoma was observed. Given the strong association with lung cancer and smoking, residual confounding by smoking is a major concern in lung cancer research and a likely explanation for the significant positive association among smokers in this study. The majority of coffee drinkers in fact tended to be smokers. While the possibility of incomplete adjustment for smoking cannot be ruled out, there was no statistically significant interaction with cancer subtypes or smoking status. An updated meta-analysis of five cohort and 12 case-control studies indicated that recently published studies consistently reported a positive association of coffee intake with lung cancer incidence despite a reduction in the risk of other types of cancers, including prostate, bladder, colorectal, and liver cancers.[62] The positive associations were consistent not only in case-control but also prospective cohort studies, whereas many were detected among smokers, suggesting the possibility of inadequate control for smoking.[61,96,97] Furthermore, the possibility of passive inhalation of cigarette smoke by non-smokers should also be considered. Presence or absence of passive smoking at home and work was included in a separate model in an attempt to assess environmental exposure, although the period and intensity of exposure could not be measured due to lack of data availability. While this analysis may have only partially captured the influence of passive smoking, the risk estimates were not substantially altered (data not shown). Coffee intake among non-smokers was not found to be associated with lung cancer risk in the present study, which is consistent with the majority of recent studies.[61,62]

In the stratified analyses by subtype of lung cancer, the risk of small cell carcinoma among coffee drinkers remained evident even after adjustment for smoking and other confounding covariates. This finding was congruent with a recent large-scale prospective cohort study in the United States wherein coffee intake was positively associated with small cell carcinoma.[61] Smoking has been closely linked with small cell and squamous cell carcinomas in previous studies.[68,98] A similar association was found in the present study, with approximately 92% of small cell carcinoma (126/137 cases) in men observed among heavy smokers with ≥20.0 pack-years. The steep increase in the risk of these subtypes of lung carcinoma could be explained by residual confounding by smoking. The oncogenic mechanism of an association between small cell carcinoma and coffee intake has yet to be elucidated, but one possible pathway might be through the activity of *TP53* and *RB1*, the tumor suppressor genes that play a crucial role in the oncogenesis of small cell carcinoma.[99] Contrary to its chemopreventive components,[48-50,100,101] coffee has been recently discovered to contain gallic acid and pyrogallol, which are considered responsible for DNA-damaging activities involving *TP53*.[102] Further research is required to examine the potential impact of coffee intake on the etiology of lung cancer of different subtypes.

2.6.2. Limitations and strengths

Some limitations of the analysis of coffee include the unavailability of information on types of coffee (caffeinated or decaffeinated), preparation methods (drip, instant, canned, espresso etc.), duration of coffee consumption, and cumulative intake of coffee as well as caffeine, although consumption of decaffeinated coffee is infrequent in Japan. Although estimation of caffeine content from coffee and tea may be technically possible, without detailed information on types of the beverages, it would likely be a very rough estimate. In the Standard Tables of Food Composition in Japan (5th revised and enlarged ed.), the amount of caffeine contained in 10 grams of coffee power for filtered coffee was estimated to be more or less the same as in 2 grams of instant coffee granules; *gyokuro* contains eight times more caffeine than *sencha* (both green tea but cultivated with different method).[103] Furthermore, a recent prospective cohort study that investigated the effect of caffeine intake on cancer risk found no association with lung cancer.[65] While average coffee drinking in Japan has increased by less than two tablespoons (24.2 mL) over the past decade,[104] coffee intake was evaluated at baseline by a single self-reported measurement, and the possibility of misclassification cannot be ruled out. However, such misclassification due to fluctuation in habitual coffee consumption during follow-up period would likely have occurred non-differentially, and might have attenuated the results toward the null. Moreover, participants who reported a history of cancer at any site were excluded and a sensitivity analysis excluding participants with newly diagnosed lung cancer was conducted, which would minimize bias from ongoing or undiagnosed illnesses. This might in turn introduce a selection bias in the study population who are alive and free of cancer at baseline since duration of coffee consumption could not be measured and the initiation of coffee drinking behavior among coffee drinkers likely occurred prior to the administration of the FFQ; this type of bias is unexceptional in cohort studies and often unavoidable.[61,105,106] Further analysis of those who were excluded due to missing data on exposure variable and covariates showed no significant differences, suggesting non-differential loss. Additionally, cumulative exposure to cigarette smoking was taken into consideration as pack-years, but more detailed data on smoking, such as depth of inhalation or nicotine dose was unavailable and thus adjustment for tobacco use was likely imperfect. Another uncontrolled yet potential confounder includes socioeconomic factors that might have influenced the consumption of coffee. As information on income was not collected in the questionnaire, occupation (professional or office workers, sales clerks or service industries, farmers, manual laborers or unemployed) at baseline was included in the additional analysis as a proxy for financial status and yielded similar risk estimates.

Allowing for these limitations, this is the first population-based prospective cohort study to investigate the association between coffee intake and lung cancer incidence in Japan. The main strengths of our study include its high response rate (81.7%), long follow-up period and negligible number of lost participants (0.4%), and negligible recall bias due to its prospective design. Misclassification of lung cancer cases was also less likely because of the rate of microscopic diagnosis and limited reliance on death certificate notification.

Chapter 3. Antioxidant vitamins and lung cancer risk

3.1. Study design and population

The JPHC Study is used to explore the association between dietary consumption of antioxidant vitamins and lung cancer risk. Details of the study are described in Chapter 2. Due to the unavailability of complete data on cancer incidence, participants from the Tokyo-Katsushika (*n* = 7,097) and Osaka-Suita (*n* = 16,427) PHC areas were not included in the present study. There were a total of 299 ineligible participants with either non-Japanese nationality (*n* = 51), pre-commencement emigration outside the study area (*n* = 170), incorrect birth date (*n* = 4), or duplicate registration (*n* = 4). Further, people who deceased or moved out of the study area before the 5-year follow-up survey were excluded (*n* = 9,027).

For the analysis of antioxidant vitamins, of 91,218 participants who returned a completed self-administered 5-year follow-up questionnaire (response rate 84.7%), those with missing data on cigarette smoking (*n* = 4,218) as well as those who reported extreme caloric intake (±2.0% of the distribution, *n* = 4,542) or a past history of cancer at any site (*n* = 2,753) were further excluded. The final analytic cohort consisted of 38,207 men and 41,498 women.

Figure 3 shows the study flow to acquire the final study sample. This study was also approved by the institutional review boards of the National Cancer Center (approval number: 13-021) and the University of Tokyo (approval number: 10508).

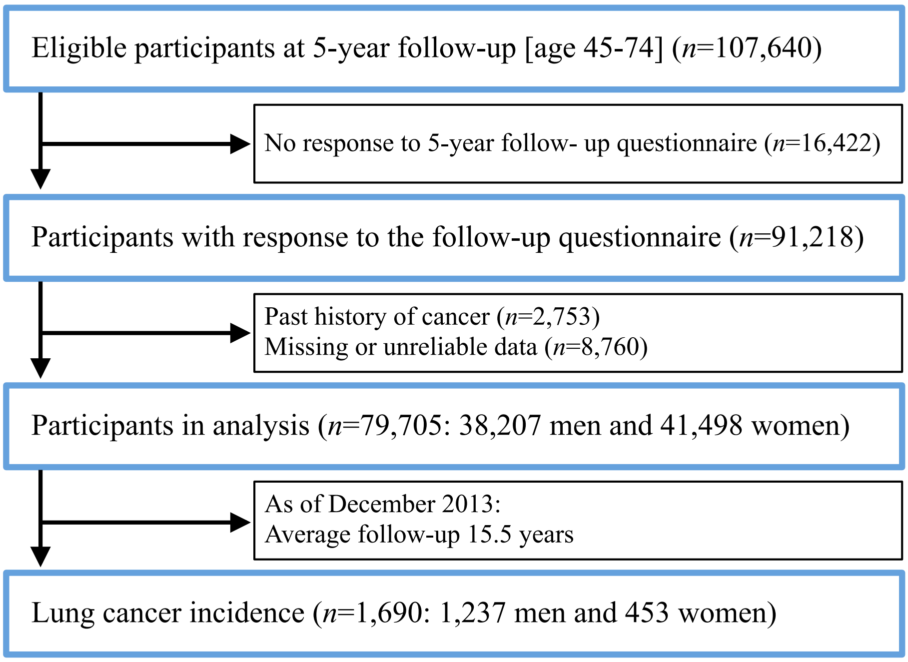

Figure 3. Study flow of analysis of antioxidant vitamins

3.2. Exposure variables

3.2.1. Assessment of antioxidant vitamin intake

Dietary measurement of antioxidant vitamins was conducted through the validated self-administered FFQ. In the JPHC Study, follow-up surveys were conducted quinquennially after the baseline survey to update information on daily living and health conditions. Since the 5-year and 10-year follow-up questionnaires collected more comprehensive information on dietary intake than the baseline questionnaire, the 5-year follow-up survey was used as the starting point to assess dietary consumption of major antioxidant vitamins, namely retinol, vitamin C, vitamin E (sum of α-, β-, γ- and δ-tocopherols), α-carotene, and β-carotene. Lycopene and cryptoxanthin are other types of carotenoids that have shown to reduce the risk of lung cancer;[107] it could not be added to the current study due to its low validity and deficient information. In the FFQ for 5-year follow-up survey, participants were asked to report an average frequency and portion size of 138 food and beverage items consumed in the past year. Average frequency was recorded with nine categories of never, 1-3 times/month, 1-2, 3-4, 5-6 times/week, once/day, 2-3, 4-6, and ≥7 times/day. Standard portions were indicated for each food item in three categories: small (50% smaller), medium (same as standard), and large (50% larger). Consumption of seasonal vegetables and fruits was calculated by asking about the frequency of intake, with consideration to the length of each season. Intake of individual food items in gram/day was obtained by multiplying the frequency by the relative portion sizes.

Daily nutritional intake was then calculated with reference to the Standard Tables of Food Composition in Japan (5th revised and enlarged ed.). Index nutrient contents in various foods per 100 grams and the amount of each antioxidant vitamin from each food item were estimated.[108] Vitamin intake from supplements was not included as an exposure in this study but was incorporated into statistical models since approximately 11% and 16% of male and female participants, respectively, reported some form of supplement use, which details were not comprehensively asked in the questionnaires. Validity of the questionnaire was evaluated in subsamples of 215 and 350 participants for Cohort I and II, respectively, by comparing data obtained through the FFQ and dietary records for 14 or 28 days (1-week dietary records measured quarterly) and produced energy-adjusted Spearman rank correlation coefficients for retinol, vitamin C, α-, β-, γ- and δ-tocopherols, α- and β-carotenes of 0.37, 0.43, 0.37, 0.35, 0.33, 0.44, 0.51 and 0.40 for men and 0.39, 0.30, 0.50, 0.40, 0.42, 0.47, 0.48 and 0.33 for women, respectively, in Cohort I and 0.43, 0.48, 0.24, 0.25, 0.20, 0.42, 0.47 and 0.46 for men and 0.49, 0.47, 0.37, 0.27, 0.43, 0.49, 0.53 and 0.48 for women, respectively, in Cohort II.[109] Reproducibility of the questionnaire was assessed from subsamples of 209 and 289 participants from Cohort I and II, respectively, by repeating identical FFQs at one-year interval and resulted in energy-adjusted correlation coefficients for retinol, vitamin C, α-, β-, γ- and δ-tocopherols, α- and β-carotenes of 0.52, 0.67, 0.65, 0.60, 0.62, 0.67, 0.48 and 0.43 for men and 0.41, 0.49, 0.49, 0.61, 0.62, 0.68, 0.42 and 0.46 for women, respectively, in Cohort I and 0.68, 0.58, 0.58, 0.62, 0.58, 0.63, 0.46 and 0.54 for men and 0.64, 0.48, 0.35, 0.55, 0.50, 0.46, 0.49 and 0.52 for women, respectively, in Cohort II.[75,109,110] Tables 6 and 7 provide the top five food items contributing to the consumption of retinol, vitamin C, α- and β-carotenes in men and women, respectively, from dietary records used in the present study. Details of vitamin E intake were not reported.[111,112]

Table 6. Top 5 foods for antioxidant vitamin intake in men from dietary records in the JPHC Study

Retinol		Vitamin C	
Food item	**mcg/day**	**Food item**	**mg/day**
Swine liver	168.6	Raw cabbage	11.9
Raw chicken egg (whole)	72.5	Raw spinach	7.4
Chicken liver	67.4	Raw Japanese persimmon	6.9
Milk	28.1	Raw potato	6.2
Raw sablefish	20.6	Raw bitter gourd	6.2
α-carotene		**β-carotene**	
Food item	**mcg/day**	**Food item**	**mcg/day**
Raw carrot	400.1	Raw carrot	1,138.6
Raw tomato	19.1	Raw spinach	355.1
Raw leaf mustard	13.8	Raw Chinese chive	112.0
Raw mango	5.5	Salted *Nozawana*	103.4
Raw bitter gourd	3.9	Raw *Komatsuna*	92.6

Sources: Kobayashi et al.[112] and Sasaki et al.[111]

Table 7. Top 5 foods for antioxidant vitamin intake in women from dietary records in the JPHC Study

Retinol		Vitamin C	
Food item	**mcg/day**	**Food item**	**mg/day**
Chicken liver	96.6	Raw cabbage	10.5
Swine liver	88.0	Raw Japanese persimmon	8.8
Raw chicken egg (whole)	60.6	Raw spinach	7.6
Milk	32.3	Raw broccoli	6.4
Raw sablefish	14.2	Satsuma mandarin	5.9
α-carotene		**β-carotene**	
Food item	**mcg/day**	**Food item**	**mcg/day**
Raw carrot	369.8	Raw carrot	1,052.4
Raw tomato	25.9	Raw spinach	361.4
Raw leaf mustard	8.7	Raw Chinese chive	102.7
Raw mango	7.1	Raw pumpkin	93.5
Raw bitter gourd	2.8	Raw *Komatsuna*	92.5

Sources: Kobayashi et al.[112] and Sasaki et al.[111]

3.2.2. Other covariates

In the 5-year follow-up FFQ, salted fish, dried fish, canned tuna, salmon or trout, bonito or tuna, cod or flat fish, sea bream, horse mackerel or sardine, mackerel pike or mackerel, dried small fish, roe, eel, squid, octopus, prawn, short-necked clam or crab shell, freshwater snails, *chikuwa* (fish paste product), and *kamaboko* (fish paste product) were included as fish and shellfishes; carrot, spinach, pumpkin, sweet pepper, tomato, Chinese chive, garland chrysanthemum, *komatsuna*, broccoli, snap bean, *chingensai*, leaf mustard, chard or Swiss chard, mugwort, cabbage, Chinese radish, onion, cucumber, Chinese cabbage, bean sprout, lettuce, bitter gourd, loofah, tomato juice, salted pickles of green leafy vegetables, salted pickles of Chinese radish, pickled Chinese cabbage, pickled cucumber, and pickled egg plant were denoted as vegetables; and papaya, mandarin orange, other oranges, apple, persimmon, strawberries, grapes, melon, water melon, peach, pear, kiwifruit, pineapple, banana, pickled plum, orange juice, and apple juice were categorized as fruits. Baseline FFQ for both cohorts inquired about intake of pulses (*miso* or fermented soybean paste, soybeans, *tofu*, *abura-age* or deep-fried *tofu*, *natto* or fermented soybeans, and other legumes excluding soybean) and the 5-year follow-up FFQ additionally asked about intakes of soymilk, *miso* soup, *yushi-dofu* (pre-drained *tofu*), and *koya-dofu* (freeze-dried *tofu*). Isoflavone intake was calculated by adding genistein and daidzein content of each food items with reference to the food composition table.[108]

Along with dietary habits, participants were also asked to report their behaviors. In the 5-year follow-up questionnaire, participants were asked whether they are never, past or current smokers for smoking status. Current smokers were further asked about the number of cigarettes smoked per day. Information on the age of smoking initiation and cessation was incorporated from the baseline survey and the number of cigarettes from the 5-year follow-up survey was used to generate pack-years.

Alcohol intake in the 5-year follow-up questionnaire was assessed with frequency choices of: hardly ever, 1-3 days/month, 1-2, 3-4, 5-6 days/week, or every day. Participants were asked to choose the most usual combination of alcohol consumed in one day from: *sake*, *shochu*/*awamori*, beer, whisky or wine. Weekly alcohol consumption was then estimated by multiplying the amount (in grams) of ethanol contained in each type of alcohol drinks consumed per day by frequency.

3.3. Follow-up and identification of lung cancer cases

Participants were followed from the date of the 5-year follow-up survey (1995) until censored on the date of lung cancer diagnosis, death, migration, or the end of follow up (December 31, 2013) for the analysis of antioxidant vitamins, whichever happened first. Death certificates were used with the permission of the Ministry of Health, Labor, and Welfare to confirm cause of death with the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision.[91]

Lung cancer cases were identified through patient notification from major local hospitals in each PHC area and record linkage with data from population-based cancer registries. Death certificates were used to supplement information on diagnosis in 7% of all lung cancer cases. Microscopic confirmation of lung cancer accounted for 79.3% of the cases and coded using the International Classification of Diseases for Oncology, Third Edition (C34.0-34.9).[92] Histological type were categorized as adenocarcinoma, squamous cell carcinoma, small cell carcinoma, and other types according to the World Health Organization (WHO)'s classification of lung tumors.[93] In the case of participants having multiple incidences of lung cancer, only the first incidence was used.

3.4. Statistical analysis

Multivariable Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for lung cancer risk by consumption of antioxidant vitamins. Participants were divided into four groups according to antioxidant vitamin intake, with the lowest consumption group as the reference. Primary analysis was conducted by gender and histological type and included the following covariates: age (continuous) and PHC area (9) in the first model (Model 1[b]); smoking status (never or 1-19, 20-29, 30-39, 40-49, 50-59, ≥60 pack-years for current and former smokers) in the second model (Model 2[b]); and alcohol consumption (0, 1-149, 150-299, 300-449, ≥450 g of ethanol/week), vitamin supplement use (yes or no), energy-adjusted intakes of fruits, vegetables, fish, and isoflavone (continuous) in the final model (Model 3[b]). Further, to test for a linear dose-response association, an additional analysis was performed with continuous variables of the exposures (per 10 mcg/day intakes of retinol, α-carotene and β-carotene, and 1 mg/day intakes of vitamin C and vitamin E) with covariates in the final model (Model 3[b]).

To explore potential variance by smoking status and estimate cumulative smoking exposure, secondary analysis was performed by strata of smoking status (never, former and current) using the same covariates included in Model 1[b] and Model 3[b] from the primary analysis. Information on age of smoking initiation and cessation from the baseline survey was incorporated since it was asked only at baseline and not on subsequent follow-up questionnaires. Pack-years were calculated for current and former smokers at the time of the 5-year follow-up survey by multiplying the average number of cigarette packs (assuming 20 cigarettes per pack) smoked per day with the number of years smoked (light smokers: ≤19.9

or heavy smokers: ≥20.0). Secondary analysis in women was conducted in current and never-smokers as never-smokers comprised 93.7% of the total female participants and 0.8% were former smokers. *P*-values for trend were calculated by assigning scores for the median values for each antioxidant intake and including them in the regression models as a continuous variable. *P*-values for interaction were calculated using likelihood-ratio tests comparing Cox proportional hazards models with and without cross-product terms for the combination of lung cancer subtypes and antioxidant intake or smoking status and antioxidant intake, with antioxidant vitamins as continuous terms. All covariates, except for the partial information used to calculate pack-years, were assessed at the 5-year follow-up survey and dietary factors were adjusted by total energy intake. Details of energy-adjustment are discussed in Chapter 2.

Using Schoenfeld residuals, a test of the proportional hazards assumption demonstrated that it had not been violated. Sensitivity analysis was conducted after excluding lung cancer cases that were diagnosed within the first five years from 5-year follow-up to avoid potential bias due to undiagnosed lung cancer, and produced a similar direction of associations as the main analyses. All statistical analyses were performed with Stata MP version 14.0

(StataCorp, College Station, Texas US).

3.5. Results

3.5.1. Basic characteristics of study participants

Over the course of 1,233,096 person-years (average of 15.5 years) of follow-up, a total of 1,690 participants (1,237 men and 453 women) were newly diagnosed with lung cancer. Of the 1,340 cases with specified histology, more than half were adenocarcinomas (*n* = 724). Dietary intake of retinol ranged from a mean of 105 mcg/day in the lowest quarter to 1,121 mcg/day in the highest quarter in men and 122 mcg/day to 1,183 mcg/day in women. While vitamin C intake ranged from a mean of 33 mg/day below the lowest quartile to 137 mg/day above the highest quartile in men and 76 mg/day to 257 mg/day in women, vitamin E intake ranged from a mean of 10 mg/day in the lowest quarter to 24 mg/day in the highest quarter in men and 16 mg/day to 32 mg/day in women. Intake of α-carotene ranged from a mean of 53 mcg/day below the lowest quartile to 767 mcg/day above the highest quartile in men and 161 mcg/day to 1,642 mcg/day in women, while intake of β-carotene ranged from a mean of 610 mcg/day in the lowest quarter to 3,980 mcg/day in men and 1,590 mcg/day to 7,798 mcg/day in women. Participants with a higher intake of antioxidant vitamins tended to drink and smoke less, and consumed more vegetables and fruits overall (Table 8).

Table 8. Basic characteristics of study participants according to consumption of antioxidant vitamins

	Men (*n* = 38,207)					Women (*n* = 41,498)				
	Lowest	**Second**	**Third**	**Highest**	***P ****	**Lowest**	**Second**	**Third**	**Highest**	***P ****
Retinol										
Number of participants	9,552	9,552	9,552	9,551		10,375	10,374	10,375	10,374	
Age (years), mean (SD)	58.0 (7.7)	57.7 (7.7)	57.3 (7.6)	57.8 (7.7)	0.428	59.1 (7.7)	57.8 (7.8)	57.4 (7.6)	57.5 (7.6)	0.035
BMI (kg/m), mean (SD)	23.6 (2.9)	23.6 (2.9)	23.6 (2.9)	23.6 (2.9)	0.247	23.7 (3.3)	23.4 (3.1)	23.6 (3.1)	23.6 (3.2)	<0.001
Current smokers, %	48.8	45.7	48.6	48.4	<0.001	5.1	5.0	5.1	6.5	<0.001
Alcohol intake (g/week), mean (SD)	240 (285)	208 (262)	210 (237)	154 (198)	<0.001	14 (85)	12 (65)	12 (53)	11 (48)	<0.001
Dietary intake[+]										
Total energy intake (kcal/day), mean (SD)	2164 (669)	2257 (720)	2296 (618)	2019 (629)	<0.001	1850 (599)	1901 (613)	1977 (559)	1760 (544)	<0.001
Fish (g/day), mean (SD)	70 (48)	75 (47)	73 (44)	85 (48)	<0.001	90 (56)	91 (55)	86 (49)	96 (51)	<0.001
Meat (g/day), mean (SD)	47 (40)	52 (39)	57 (36)	81 (47)	<0.001	50 (43)	52 (38)	58 (36)	79 (45)	<0.001
Vegetables (g/day), mean (SD)	134 (102)	136 (87)	133 (82)	141 (86)	<0.001	255 (161)	243 (134)	235 (130)	235 (130)	<0.001
Fruits (g/day), mean (SD)	87 (85)	92 (81)	88 (74)	94 (76)	<0.001	281 (215)	256 (178)	245 (170)	241 (173)	<0.001
Isoflavone (mg/day), mean (SD)	36 (30)	36 (27)	36 (24)	37 (24)	<0.001	45 (37)	42 (29)	42 (27)	43 (28)	<0.001
Retinol (mcg/day), mean (SD)	105 (43)	264 (56)	499 (81)	1121 (662)	<0.001	122 (45)	274 (53)	519 (89)	1183 (686)	<0.001
Vitamin C										
Number of participants	9,552	9,552	9,552	9,551		10,375	10,374	10,375	10,374	
Age (years), mean (SD)	55.5 (7.1)	56.8 (7.4)	58.3 (7.6)	60.2 (7.8)	<0.001	56.5 (7.5)	57.4 (7.6)	58.4 (7.7)	59.4 (7.7)	0.042
BMI (kg/m), mean (SD)	23.7 (3.0)	23.6 (2.9)	23.6 (2.9)	23.6 (2.8)	<0.001	23.7 (3.3)	23.6 (3.2)	23.5 (3.1)	23.5 (3.1)	<0.001
Current smokers, %	57.7	50.4	45.0	38.4	<0.001	7.9	5.3	4.2	4.2	<0.001
Alcohol intake (g/week), mean (SD)	327 (319)	219 (238)	163 (199)	104 (155)	<0.001	24 (107)	12 (51)	8 (38)	6 (27)	<0.001
Dietary intake[+]										
Total energy intake (kcal/day), mean (SD)	2238 (695)	2243 (860)	2186 (654)	2069 (629)	<0.001	1881 (634)	1892 (586)	1891 (558)	1826 (555)	<0.001
Fish (g/day), mean (SD)	64 (46)	76 (45)	81 (47)	82 (48)	<0.001	83 (56)	93 (52)	95 (51)	92 (52)	<0.001
Meat (g/day), mean (SD)	59 (46)	62 (42)	61 (42)	56 (41)	<0.001	71 (50)	63 (42)	56 (37)	49 (35)	<0.001
Vegetables (g/day), mean (SD)	69 (38)	112 (47)	149 (64)	214 (114)	<0.001	143 (69)	210 (85)	263 (107)	352 (177)	<0.001
Fruits (g/day), mean (SD)	35 (29)	66 (41)	97 (53)	163 (104)	<0.001	123 (85)	202 (100)	271 (127)	427 (234)	<0.001
Isoflavone (mg/day), mean (SD)	31 (28)	35 (26)	38 (25)	40 (26)	<0.001	40 (34)	42 (30)	44 (28)	45 (29)	<0.001
Vitamin C (mg/day), mean (SD)	33 (10)	58 (7)	83 (9)	137 (36)	<0.001	76 (20)	124 (12)	168 (15)	257 (61)	<0.001

Continued on next page

	Men (n = 38,207)					Women (n = 41,498)				
	Lowest	**Second**	**Third**	**Highest**	***P* ***	**Lowest**	**Second**	**Third**	**Highest**	***P* ***
Vitamin E										
Number of participants	9,552	9,552	9,552	9,551		10,375	10,374	10,375	10,374	
Age (years), mean (SD)	56.4 (7.5)	57.1 (7.6)	58.0 (7.6)	59.3 (7.7)	0.008	57.7 (8.0)	57.4 (7.7)	57.9 (7.5)	58.8 (7.6)	<0.001
BMI (kg/m²), mean (SD)	23.4 (2.9)	23.5 (2.8)	23.6 (2.9)	23.8 (2.9)	0.006	23.5 (3.2)	23.5 (3.1)	23.6 (3.1)	23.8 (3.2)	<0.001
Current smokers, %	58.1	50.6	45.2	37.6	<0.001	7.7	5.0	4.5	4.5	<0.001
Alcohol intake (g/week), mean (SD)	340 (330)	220 (231)	159 (189)	99 (150)	<0.001	26 (113)	10 (41)	8 (36)	6 (27)	<0.001
Dietary intake⁺										
Total energy intake (kcal/day), mean (SD)	2215 (676)	2246 (669)	2209 (662)	2066 (652)	0.004	1855 (632)	1915 (570)	1915 (556)	1803 (570)	<0.001
Fish (g/day), mean (SD)	55 (36)	72 (40)	83 (45)	92 (57)	<0.001	75 (47)	90 (46)	97 (50)	101 (62)	<0.001
Meat (g/day), mean (SD)	43 (31)	57 (36)	65 (43)	72 (52)	<0.001	52 (39)	61 (39)	62 (41)	63 (48)	<0.001
Vegetables (g/day), mean (SD)	75 (44)	111 (52)	145 (64)	214 (113)	<0.001	148 (74)	204 (83)	254 (98)	362 (176)	<0.001
Fruits (g/day), mean (SD)	62 (68)	85 (74)	100 (77)	114 (87)	<0.001	232 (198)	255 (174)	262 (167)	275 (199)	<0.001
Isoflavone (mg/day), mean (SD)	22 (12)	30 (15)	38 (19)	55 (38)	<0.001	26 (15)	36 (18)	44 (22)	64 (44)	<0.001
Vitamin E (mg/day), mean (SD)	10 (2)	15 (1)	18 (1)	24 (5)	<0.001	16 (3)	21 (1)	25 (1)	32 (6)	<0.001
α-carotene										
Number of participants	9,552	9,552	9,552	9,551		10,375	10,374	10,375	10,374	
Age (years), mean (SD)	56.8 (7.6)	57.0 (7.5)	57.9 (7.6)	59.2 (7.8)	0.001	57.6 (7.8)	57.5 (7.5)	57.8 (7.6)	58.8 (7.8)	<0.001
BMI (kg/m²), mean (SD)	23.5 (2.9)	23.6 (2.9)	23.6 (2.9)	23.7 (2.9)	0.129	23.5 (3.2)	23.5 (3.1)	23.6 (3.2)	23.7 (3.2)	<0.001
Current smokers, %	57.4	50.4	45.9	37.8	<0.001	7.2	5.2	4.9	4.3	<0.001
Alcohol intake (g/week), mean (SD)	262 (294)	221 (247)	187 (233)	144 (203)	<0.001	21 (94)	13 (65)	10 (48)	6 (32)	<0.001
Dietary intake⁺										
Total energy intake (kcal/day), mean (SD)	2190 (704)	2261 (650)	2246 (691)	2039 (602)	<0.001	1895 (624)	1951 (607)	1920 (547)	1723 (528)	<0.001
Fish (g/day), mean (SD)	68 (48)	75 (43)	79 (46)	81 (50)	<0.001	87 (55)	92 (49)	93 (50)	92 (56)	<0.001
Meat (g/day), mean (SD)	60 (46)	58 (39)	61 (41)	62 (45)	<0.001	62 (47)	60 (39)	59 (39)	58 (43)	<0.001
Vegetables (g/day), mean (SD)	83 (62)	114 (65)	142 (70)	207 (104)	<0.001	164 (107)	209 (106)	249 (109)	346 (159)	<0.001
Fruits (g/day), mean (SD)	73 (75)	89 (78)	96 (78)	103 (83)	<0.001	248 (201)	256 (177)	260 (178)	259 (185)	<0.001
Isoflavone (mg/day), mean (SD)	33 (29)	35 (25)	37 (25)	39 (26)	<0.001	41 (34)	42 (29)	43 (28)	46 (31)	<0.001
α-carotene (mcg/day), mean (SD)	53 (28)	151 (31)	291 (53)	767 (551)	<0.001	161 (79)	402 (70)	695 (106)	1642 (1082)	<0.001

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	Men (n = 38,207)					Women (n = 41,498)				
	Lowest	**Second**	**Third**	**Highest**	***P* ***	**Lowest**	**Second**	**Third**	**Highest**	***P* ***
β-*carotene*										
Number of participants	9,553	9,551	9,552	9,551		10,375	10,374	10,375	10,374	
Age (years), mean (SD)	56.1 (7.4)	57.1 (7.5)	58.1 (7.6)	59.6 (7.8)	<0.001	57.2 (7.8)	57.3 (7.6)	58.1 (7.6)	59.2 (7.7)	0.006
BMI (kg/m^2), mean (SD)	23.5 (2.9)	23.6 (2.8)	23.6 (2.9)	23.7 (2.9)	0.007	23.6 (3.2)	23.5 (3.1)	23.6 (3.1)	23.7 (3.2)	0.002
Current smokers, %	58.0	51.2	44.9	37.4	<0.001	7.6	5.4	4.7	4.0	<0.001
Alcohol intake (g/week), mean (SD)	288 (308)	217 (241)	180 (222)	129 (185)	<0.001	23 (103)	12 (54)	9 (40)	6 (32)	<0.001
Dietary intake⁺										
Total energy intake (kcal/day), mean (SD)	2201 (696)	2240 (674)	2228 (660)	2067 (629)	<0.001	1886 (634)	1929 (589)	1895 (543)	1779 (558)	<0.001
Fish (g/day), mean (SD)	64 (46)	75 (44)	81 (45)	83 (51)	<0.001	83 (54)	92 (49)	95 (51)	93 (56)	<0.001
Meat (g/day), mean (SD)	58 (46)	59 (41)	60 (40)	60 (44)	<0.001	66 (48)	61 (40)	58 (39)	54 (41)	<0.001
Vegetables (g/day), mean (SD)	64 (38)	107 (44)	145 (55)	230 (104)	<0.001	130 (68)	197 (73)	256 (89)	385 (157)	<0.001
Fruits (g/day), mean (SD)	57 (56)	83 (68)	102 (82)	119 (92)	<0.001	198 (158)	253 (175)	278 (186)	295 (206)	<0.001
Isoflavone (mg/day), mean (SD)	31 (29)	35 (25)	37 (24)	41 (26)	<0.001	39 (34)	42 (29)	44 (28)	47 (30)	<0.001
β-carotene (mcg/day), mean (SD)	610 (231)	1246 (175)	1957 (254)	3980 (2085)	<0.001	1590 (522)	2885 (333)	4184 (446)	7798 (3586)	<0.001

SD, standard deviation; BMI, body mass index

⁺ All values for dietary intake are energy-adjusted

* ANOVA or χ^2 test

3.5.2. Lung cancer incidence by consumption of antioxidant vitamins

In multivariable models adjusted for age, PHC area and other confounding covariates in the analysis of antioxidant vitamins, only the positive association between retinol intake and lung cancer risk among men remained evident (HR, 1.26; 95% CI, 1.05-1.51; p_{trend} = 0.003; comparing the lowest intake with the highest) (Table 9). In women, while statistically non-significant, consumption of vitamin C, α-carotene and β-carotene were positively associated whereas retinol and vitamin E were negatively associated with overall lung cancer risk; the corresponding multivariable-adjusted HRs comparing the lowest intake with the highest were 1.37 for vitamin C (95% CI, 0.92-2.05; p_{trend} = 0.138), 1.33 for α-carotene (95% CI, 0.98-1.80; p_{trend} = 0.064), 1.48 for β-carotene (95% CI, 1.03-2.13; p_{trend} = 0.089), 0.82 for retinol (95% CI = 0.61-1.09; p_{trend} = 0.072), and 0.87 for vitamin E (95% CI, 0.58-1.30; p_{trend} = 0.115). Similar associations were observed for histological type of lung cancer, particularly with the association between high retinol intake and lung cancer largely driven by small cell carcinoma toward the opposite directions for men and women (HR, 1.92; 95% CI, 1.13-3.24; p_{trend} = <0.001; $p_{interaction}$ = 0.194 for men, HR, 0.15; 95% CI, 0.02-1.24; p_{trend} = <0.096; $p_{interaction}$ = 0.046 for women).

Table 9. Hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between consumption of antioxidant vitamins and lung cancer risk

	Men (n = 38,207)						
	Lowest	**Second**	**Third**	**Highest**	P_{trend}	P_{int}	**10 mcg cont. HR (95% CI)**
Retinol							
Lung cancer (all)							
Number of cases	300	296	305	336	—	—	—
Model 1[b]	1.00	1.05 (0.89-1.23)	1.13 (0.97-1.33)	1.25 (1.06-1.46)	0.001	—	—
Model 2[b]	1.00	1.11 (0.97-1.31)	1.14 (0.97-1.35)	1.30 (1.10-1.53)	<0.001	—	—
Model 3[b]	1.00	1.09 (0.91-1.31)	1.20 (1.00-1.44)	1.26 (1.05-1.51)	0.003	0.194	1.00 (1.000-1.002)
Adenocarcinoma							
Number of cases	96	98	94	102	—	—	—
Model 1[b]	1.00	1.09 (0.82-1.45)	1.11 (0.83-1.48)	1.22 (0.91-1.62)	0.226	—	—
Model 2[b]	1.00	1.16 (0.87-1.41)	1.05 (0.78-1.41)	1.26 (0.95-1.69)	0.208	—	—
Model 3[b]	1.00	1.12 (0.82-1.54)	1.12 (0.82-1.55)	1.20 (0.87-1.66)	0.574	—	—
Squamous cell carcinoma							
Number of cases	95	73	82	87	—	—	—
Model 1[b]	1.00	0.83 (0.61-1.13)	0.95 (0.70-1.28)	1.00 (0.74-1.35)	0.327	—	—
Model 2[b]	1.00	0.86 (0.63-1.19)	1.00 (0.73-1.36)	1.04 (0.76-1.41)	0.205	—	—
Model 3[b]	1.00	0.86 (0.61-1.21)	1.00 (0.72-1.39)	0.95 (0.68-1.34)	0.470	—	—
Small cell carcinoma							
Number of cases	31	35	40	49	—	—	—
Model 1[b]	1.00	1.18 (0.73-1.92)	1.42 (0.88-2.27)	1.78 (1.13-2.81)	0.001	—	—
Model 2[b]	1.00	1.35 (0.81-2.25)	1.59 (0.97-2.60)	1.97 (1.22-3.19)	0.001	—	—
Model 3[b]	1.00	1.20 (0.69-2.10)	1.52 (0.89-2.59)	1.92 (1.13-3.24)	<0.001	—	—
Other							
Number of cases	78	90	89	98	—	—	—
Model 1[b]	1.00	1.19 (0.88-1.61)	1.27 (0.94-1.73)	1.36 (1.00-1.84)	0.085	—	—
Model 2[b]	1.00	1.23 (0.90-1.67)	1.26 (0.92-1.72)	1.37 (1.01-1.87)	0.061	—	—
Model 3[b]	1.00	1.28 (0.90-1.82)	1.40 (0.98-1.99)	1.47 (1.03-2.09)	0.065	—	—
α-carotene							
Lung cancer (all)							
Number of cases	333	306	298	300	—	—	—
Model 1[b]	1.00	0.89 (0.76-1.04)	0.79 (0.68-0.93)	0.72 (0.61-0.85)	0.008	—	—
Model 2[b]	1.00	0.97 (0.83-1.14)	0.90 (0.77-1.06)	0.88 (0.74-1.04)	0.258	—	—
Model 3[b]	1.00	1.00 (0.84-1.20)	0.89 (0.74-1.07)	0.89 (0.72-1.09)	0.533	0.254	1.00 (0.997-1.001)
Adenocarcinoma							
Number of cases	96	102	102	90	—	—	—
Model 1[b]	1.00	1.05 (0.80-1.39)	1.00 (0.76-1.32)	0.82 (0.61-1.10)	0.293	—	—
Model 2[b]	1.00	1.08 (0.81-1.44)	1.10 (0.82-1.46)	0.95 (0.71-1.29)	0.765	—	—
Model 3[b]	1.00	1.17 (0.85-1.61)	1.16 (0.84-1.61)	1.04 (0.71-1.51)	0.725	—	—
Squamous cell carcinoma							
Number of cases	94	92	78	73	—	—	
Model 1[b]	1.00	0.95 (0.71-1.26)	0.74 (0.54-1.00)	0.63 (0.46-0.86)	0.135	—	—
Model 2[b]	1.00	1.13 (0.84-1.52)	0.85 (0.62-1.17)	0.80 (0.58-1.11)	0.481	—	—
Model 3[b]	1.00	1.17 (0.85-1.61)	0.81 (0.57-1.16)	0.71 (0.48-1.06)	0.216	—	—

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	Lowest	Second	Third	Highest	P_{trend}	P_{int}	10 mcg cont. HR (95% CI)
Small cell carcinoma							—
Number of cases	49	37	34	35	—	—	—
Model 1[b]	1.00	0.75 (0.49-1.14)	0.62 (0.40-0.97)	0.64 (0.41-1.00)	0.422	—	—
Model 2[b]	1.00	0.80 (0.52-1.25)	0.72 (0.45-1.13)	0.81 (0.51-1.28)	0.933	—	—
Model 3[b]	1.00	0.70 (0.43-1.14)	0.53 (0.31-0.92)	0.74 (0.42-1.30)	0.820	—	—
Other							
Number of cases	94	75	84	102	—	—	—
Model 1[b]	1.00	0.74 (0.54-1.00)	0.72 (0.54-0.97)	0.72 (0.54-0.96)	0.055	—	—
Model 2[b]	1.00	0.78 (0.57-1.07)	0.83 (0.61-1.12)	0.86 (0.64-1.16)	0.260	—	—
Model 3[b]	1.00	0.84 (0.59-1.20)	0.88 (0.62-1.25)	0.99 (0.68-1.45)	0.844	—	—
β-carotene							
Lung cancer (all)							
Number of cases	304	326	291	316	—	—	—
Model 1[b]	1.00	0.99 (0.85-1.16)	0.78 (0.67-0.92)	0.77 (0.66-0.91)	0.009	—	—
Model 2[b]	1.00	1.08 (0.92-1.27)	0.92 (0.78-1.08)	0.95 (0.80-1.12)	0.513	—	—
Model 3[b]	1.00	1.08 (0.90-1.29)	0.86 (0.70-1.05)	0.93 (0.73-1.18)	0.887	0.264	1.00 (0.999-1.001
Adenocarcinoma							
Number of cases	96	98	100	96	—	—	—
Model 1[b]	1.00	0.96 (0.72-1.27)	0.91 (0.68-1.20)	0.82 (0.61-1.09)	0.300	—	—
Model 2[b]	1.00	1.00 (0.75-1.34)	1.00 (0.75-1.34)	0.95 (0.71-1.28)	0.844	—	—
Model 3[b]	1.00	1.01 (0.73-1.39)	0.92 (0.65-1.32)	0.99 (0.64-1.52)	0.652	—	—
Squamous cell carcinoma							
Number of cases	79	106	75	77	—	—	
Model 1[b]	1.00	1.25 (0.94-1.68)	0.77 (0.56-1.06)	0.72 (0.52-0.99)	0.091	—	—
Model 2[b]	1.00	1.42 (1.05-1.92)	0.95 (0.68-1.31)	0.89 (0.64-1.25)	0.550	—	—
Model 3[b]	1.00	1.38 (0.99-1.93)	0.85 (0.58-1.24)	0.70 (0.44-1.11)	0.227	—	—
Small cell carcinoma							—
Number of cases	45	41	30	39	—	—	—
Model 1[b]	1.00	0.83 (0.55-1.27)	0.56 (0.35-0.88)	0.69 (0.45-1.07)	0.592	—	—
Model 2[b]	1.00	0.92 (0.59-1.42)	0.62 (0.38-1.01)	0.90 (0.57-1.41)	0.640	—	—
Model 3[b]	1.00	0.80 (0.49-1.30)	0.47 (0.26-0.86)	0.79 (0.41-1.52)	0.715	—	—
Other							
Number of cases	84	81	86	104	—	—	—
Model 1[b]	1.00	0.85 (0.63-1.15)	0.79 (0.58-1.06)	0.79 (0.58-1.06)	0.062	—	—
Model 2[b]	1.00	0.95 (0.69-1.30)	0.93 (0.68-1.27)	0.99 (0.73-1.34)	0.419	—	—
Model 3[b]	1.00	1.03 (0.72-1.49)	1.05 (0.72-1.54)	1.24 (0.78-1.95)	0.839	—	—
	Lowest	**Second**	**Third**	**Highest**	P_{trend}	P_{int}	**1 mg cont. HR (95% CI)**
Vitamin C							
Lung cancer (all)							
Number of cases	255	291	345	346	—	—	—
Model 1[b]	1.00	0.99 (0.84-1.18)	1.01 (0.85-1.19)	0.87 (0.74-1.03)	0.527	—	—
Model 2[b]	1.00	1.05 (0.89-1.25)	1.15 (0.97-1.36)	1.05 (0.88-1.25)	0.138	—	—
Model 3[b]	1.00	1.02 (0.84-1.24)	1.16 (0.94-1.42)	1.02 (0.79-1.32)	0.035	0.803	1.00 (1.000-1.005

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	Lowest	Second	Third	Highest	P_{trend}	P_{int}	1 mg cont. HR (95% CI)
Adenocarcinoma							
Number of cases	78	90	122	100	—	—	—
Model 1[b]	1.00	1.05 (0.77-1.42)	1.21 (0.91-1.62)	0.91 (0.67-1.23)	0.688	—	—
Model 2[b]	1.00	1.12 (0.82-1.53)	1.36 (1.01-1.83)	1.02 (0.75-1.41)	0.951	—	—
Model 3[b]	1.00	1.16 (0.81-1.65)	1.50 (1.03-2.18)	1.31 (0.81-2.10)	0.111	—	—
Squamous cell carcinoma							
Number of cases	69	76	97	95	—	—	—
Model 1[b]	1.00	0.98 (0.70-1.35)	1.04 (0.76-1.43)	0.90 (0.65-1.23)	0.791	—	—
Model 2[b]	1.00	0.99 (0.71-1.38)	1.15 (0.83-1.58)	1.06 (0.76-1.47)	0.312	—	—
Model 3[b]	1.00	0.97 (0.67-1.41)	1.16 (0.79-1.72)	0.97 (0.59-1.58)	0.450	—	—
Small cell carcinoma							
Number of cases	34	46	32	43	—	—	—
Model 1[b]	1.00	1.17 (0.75-1.83)	0.72 (0.44-1.18)	0.85 (0.53-1.35)	0.383	—	—
Model 2[b]	1.00	1.26 (0.79-2.02)	0.89 (0.54-1.48)	1.14 (0.70-1.84)	0.683	—	—
Model 3[b]	1.00	1.16 (0.68-1.96)	1.00 (0.54-1.84)	1.21 (0.58-2.55)	0.341	—	—
Other							
Number of cases	74	79	94	108	—	—	—
Model 1[b]	1.00	0.85 (0.62-1.17)	0.90 (0.66-1.22)	0.81 (0.60-1.10)	0.953	—	—
Model 2[b]	1.00	0.92 (0.66-1.28)	1.03 (0.75-1.40)	1.00 (0.73-1.36)	0.206	—	—
Model 3[b]	1.00	0.86 (0.59-1.24)	0.91 (0.62-1.35)	0.77 (0.47-1.25)	0.396	—	—
Vitamin E							
Lung cancer (all)							
Number of cases	304	295	320	318	—	—	—
Model 1[b]	1.00	0.88 (0.75-1.03)	0.89 (0.76-1.04)	0.81 (0.69-0.95)	0.006	—	—
Model 2[b]	1.00	0.93 (0.79-1.09)	1.03 (0.87-1.21)	0.98 (0.83-1.15)	0.727	—	—
Model 3[b]	1.00	0.95 (0.78-1.15)	0.98 (0.80-1.21)	0.92 (0.70-1.21)	0.815	0.939	0.99 (0.976-1.019
Adenocarcinoma							
Number of cases	96	96	110	88	—	—	—
Model 1[b]	1.00	0.94 (0.71-1.25)	1.04 (0.79-1.37)	0.79 (0.59-1.07)	0.209	—	—
Model 2[b]	1.00	0.97 (0.72-1.30)	1.14 (0.86-1.51)	0.92 (0.68-1.25)	0.790	—	—
Model 3[b]	1.00	1.00 (0.71-1.40)	1.11 (0.77-1.61)	0.82 (0.50-1.35)	0.637	—	—
Squamous cell carcinoma							
Number of cases	79	86	84	88	—	—	—
Model 1[b]	1.00	0.96 (0.71-1.30)	0.88 (0.65-1.20)	0.84 (0.62-1.15)	0.336	—	—
Model 2[b]	1.00	0.98 (0.71-1.34)	1.04 (0.76-1.43)	0.98 (0.71-1.36)	0.770	—	—
Model 3[b]	1.00	0.88 (0.61-1.25)	0.85 (0.57-1.26)	0.74 (0.44-1.24)	0.900	—	—
Small cell carcinoma							
Number of cases	43	36	33	43	—	—	—
Model 1[b]	1.00	0.78 (0.50-1.22)	0.66 (0.41-1.04)	0.85 (0.55-1.32)	0.252	—	—
Model 2[b]	1.00	0.83 (0.53-1.31)	0.76 (0.47-1.23)	1.07 (0.68-1.68)	0.920	—	—
Model 3[b]	1.00	0.87 (0.51-1.47)	0.89 (0.49-1.62)	1.08 (0.50-2.35)	0.924	—	—
Other							
Number of cases	87	76	92	100	—	—	—
Model 1[b]	1.00	0.76 (0.56-1.04)	0.84 (0.62-1.12)	0.77 (0.57-1.04)	0.030	—	—
Model 2[b]	1.00	0.86 (0.63-1.18)	0.99 (0.73-1.34)	0.99 (0.73-1.34)	0.521	—	—
Model 3[b]	1.00	1.01 (0.70-1.47)	1.03 (0.68-1.55)	1.25 (0.75-2.08)	0.793	—	—

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	Women (n = 41,498)						
	Lowest	**Second**	**Third**	**Highest**	P_{trend}	P_{int}	**10 mcg cont. HR (95% CI)**
Retinol							
Lung cancer (all)							
Number of cases	133	109	120	91	—	—	—
Model 1[b]	1.00	0.96 (0.74-1.24)	1.10 (0.86-1.42)	0.85 (0.65-1.12)	0.129	—	—
Model 2[b]	1.00	0.97 (0.75-1.25)	1.11 (0.86-1.42)	0.83 (0.63-1.10)	0.009	—	—
Model 3[b]	1.00	1.01 (0.78-1.32)	1.16 (0.90-1.51)	0.82 (0.61-1.09)	0.072	0.046	1.00 (0.996-1.000)
Adenocarcinoma							
Number of cases	89	82	91	72	—	—	—
Model 1[b]	1.00	1.07 (0.79-1.45)	1.23 (0.91-1.65)	0.99 (0.72-1.37)	0.289	—	—
Model 2[b]	1.00	1.08 (0.79-1.45)	1.23 (0.91-1.66)	0.98 (0.71-1.35)	0.236	—	—
Model 3[b]	1.00	1.11 (0.81-1.51)	1.29 (0.95-1.75)	0.96 (0.69-1.34)	0.237	—	—
Squamous cell carcinoma							
Number of cases	7	9	5	4	—	—	—
Model 1[b]	1.00	1.48 (0.55-4.00)	0.85 (0.26-2.72)	0.68 (0.20-2.39)	0.622	—	—
Model 2[b]	1.00	1.62 (0.60-4.40)	0.87 (0.27-2.78)	0.68 (0.19-2.36)	0.521	—	—
Model 3[b]	1.00	1.76 (0.62-5.03)	0.99 (0.30-3.31)	0.58 (0.14-2.38)	0.425	—	—
Small cell carcinoma							
Number of cases	7	4	7	1	—	—	—
Model 1[b]	1.00	0.63 (0.18-2.16)	1.01 (0.34-2.94)	0.14 (0.02-1.13)	0.075	—	—
Model 2[b]	1.00	0.69 (0.20-2.40)	1.08 (0.37-3.17)	0.14 (0.02-1.12)	0.073	—	—
Model 3[b]	1.00	0.83 (0.23-2.96)	1.09 (0.35-3.40)	0.15 (0.02-1.24)	0.096	—	—
Other							
Number of cases	30	14	17	14	—	—	—
Model 1[b]	1.00	0.58 (0.30-1.10)	0.81 (0.44-1.47)	0.66 (0.34-1.26)	0.739	—	—
Model 2[b]	1.00	0.57 (0.30-1.09)	0.78 (0.43-1.43)	0.64 (0.33-1.23)	0.689	—	—
Model 3[b]	1.00	0.62 (0.32-1.19)	0.83 (0.45-1.53)	0.63 (0.32-1.24)	0.623	—	—
α-carotene							
Lung cancer (all)							
Number of cases	97	95	126	135	—	—	
Model 1[b]	1.00	0.97 (0.73-1.28)	1.20 (0.92-1.57)	1.23 (0.94-1.60)	0.107	—	
Model 2[b]	1.00	0.98 (0.74-1.31)	1.25 (0.96-1.64)	1.29 (0.99-1.69)	0.068	—	
Model 3[b]	1.00	0.99 (0.74-1.32)	1.19 (0.90-1.58)	1.33 (0.98-1.80)	0.064	0.797	1.00 (0.999-1.002)
Adenocarcinoma							
Number of cases	69	73	94	98	—	—	—
Model 1[b]	1.00	1.04 (0.75-1.45)	1.25 (0.91-1.71)	1.26 (0.92-1.72)	0.129	—	—
Model 2[b]	1.00	1.04 (0.75-1.45)	1.27 (0.93-1.74)	1.28 (0.94-1.76)	0.109	—	—
Model 3[b]	1.00	1.09 (0.76-1.50)	1.30 (0.93-1.82)	1.43 (0.99-2.05)	0.025	—	—
Squamous cell carcinoma							
Number of cases	3	8	7	7	—	—	—
Model 1[b]	1.00	2.68 (0.71-10.11)	2.36 (0.61-9.16)	2.36 (0.60-9.27)	0.792	—	—
Model 2[b]	1.00	2.86 (0.76-10.82)	2.74 (0.70-10.70)	2.87 (0.73-11.32)	0.626	—	—
Model 3[b]	1.00	3.12 (0.81-12.03)	2.17 (0.49-9.56)	3.73 (0.81-17.23)	0.469	—	—
Small cell carcinoma							
Number of cases	4	2	3	10	—	—	
Model 1[b]	1.00	0.47 (0.09-2.59)	0.68 (0.15-3.06)	2.06 (0.63-6.75)	0.510	—	—
Model 2[b]	1.00	0.55 (0.10-3.02)	0.81 (0.18-3.67)	2.51 (0.76-8.31)	0.398	—	—
Model 3[b]	1.00	0.63 (0.10-3.83)	1.02 (0.20-5.27)	2.61 (0.60-11.34)	0.627	—	—

Continued on next page

	Lowest	Second	Third	Highest	P_{trend}	P_{int}	10 mcg cont. HR (95% CI)
Other							
Number of cases	21	12	22	20	—	—	
Model 1[b]	1.00	0.57 (0.28-1.15)	0.98 (0.54-1.78)	0.82 (0.44-1.53)	0.787	—	
Model 2[b]	1.00	0.58 (0.28-1.17)	1.01 (0.55-1.85)	0.86 (0.46-1.61)	0.736	—	
Model 3[b]	1.00	0.54 (0.26-1.10)	0.78 (0.41-1.49)	0.67 (0.33-1.38)	0.857	—	
β-*carotene*							
Lung cancer (all)							
Number of cases	88	107	129	129	—	—	—
Model 1[b]	1.00	1.25 (0.94-1.66)	1.37 (1.04-1.80)	1.29 (0.98-1.71)	0.194	—	—
Model 2[b]	1.00	1.27 (0.96-1.69)	1.42 (1.08-1.87)	1.37 (1.04-1.81)	0.125	—	—
Model 3[b]	1.00	1.24 (0.92-1.68)	1.45 (1.07-1.97)	1.48 (1.03-2.13)	0.089	0.362	1.00 (0.999-1.001)
Adenocarcinoma							
Number of cases	64	79	100	91	—	—	—
Model 1[b]	1.00	1.25 (0.90-1.74)	1.44 (1.05-1.98)	1.24 (0.90-1.72)	0.267	—	—
Model 2[b]	1.00	1.25 (0.90-1.74)	1.47 (1.07-2.02)	1.27 (0.92-1.77)	0.221	—	—
Model 3[b]	1.00	1.25 (0.88-1.78)	1.62 (1.14-2.32)	1.55 (1.01-2.38)	0.024	—	—
Squamous cell carcinoma							
Number of cases	6	7	7	5	—	—	
Model 1[b]	1.00	1.57 (0.51-4.80)	1.33 (0.42-4.19)	0.92 (0.26-3.22)	0.645	—	—
Model 2[b]	1.00	1.79 (0.58-5.49)	1.51 (0.47-4.78)	1.19 (0.34-4.19)	0.859	—	—
Model 3[b]	1.00	1.81 (0.56-5.83)	1.35 (0.35-5.12)	1.03 (0.18-5.81)	0.778	—	—
Small cell carcinoma							—
Number of cases	3	3	2	11	—	—	—
Model 1[b]	1.00	1.00 (0.20-4.96)	0.65 (0.11-3.89)	3.32 (0.91-12.09)	0.167	—	—
Model 2[b]	1.00	1.12 (0.22-5.54)	0.67 (0.11-4.04)	4.28 (1.16-15.77)	0.142	—	—
Model 3[b]	1.00	1.56 (0.25-9.66)	1.07 (0.14-8.29)	5.65 (0.95-33.72)	0.785	—	—
Other							
Number of cases	15	18	20	22	—	—	—
Model 1[b]	1.00	1.18 (0.60-2.35)	1.21 (0.62-2.36)	1.25 (0.64-2.42)	0.680	—	—
Model 2[b]	1.00	1.21 (0.61-2.40)	1.25 (0.64-2.46)	1.31 (0.67-2.56)	0.638	—	—
Model 3[b]	1.00	1.06 (0.52-2.15)	1.01 (0.48-2.11)	1.06 (0.45-2.51)	0.969	—	—
	Lowest	**Second**	**Third**	**Highest**	P_{trend}	P_{int}	**1 mg cont. HR (95% CI)**
Vitamin C							
Lung cancer (all)							
Number of cases	82	116	125	130	—	—	—
Model 1[b]	1.00	1.30 (0.98-1.72)	1.29 (0.97-1.72)	1.28 (0.96-1.70)	0.149	—	—
Model 2[b]	1.00	1.35 (1.02-1.80)	1.36 (1.02-1.81)	1.35 (1.01-1.79)	0.091	—	—
Model 3[b]	1.00	1.30 (0.96-1.75)	1.31 (0.94-1.81)	1.37 (0.92-2.05)	0.138	0.499	1.00 (0.999-1.004)
Adenocarcinoma							
Number of cases	56	91	92	95	—	—	—
Model 1[b]	1.00	1.52 (1.09-2.12)	1.40 (1.00-1.97)	1.37 (0.97-1.93)	0.424	—	—
Model 2[b]	1.00	1.55 (1.11-2.16)	1.42 (1.01-2.00)	1.41 (1.00-1.98)	0.350	—	—
Model 3[b]	1.00	1.57 (1.10-2.24)	1.44 (0.97-2.13)	1.56 (0.97-2.51)	0.387	—	—
Squamous cell carcinoma							
Number of cases	6	5	8	6	—	—	—
Model 1[b]	1.00	0.80 (0.24-2.66)	1.23 (0.42-3.65)	0.90 (0.28-2.92)	0.869	—	—
Model 2[b]	1.00	0.92 (0.28-3.06)	1.55 (0.52-4.60)	1.08 (0.33-3.46)	0.715	—	—
Model 3[b]	1.00	0.78 (0.21-2.98)	1.93 (0.54-6.92)	1.43 (0.26-7.74)	0.317	—	—

Continued on next page

	Lowest	Second	Third	Highest	P_{trend}	P_{int}	1 mg cont. HR (95% CI)
Small cell carcinoma							
Number of cases	2	2	7	8	—	—	
Model 1[b]	1.00	1.15 (0.16-8.25)	4.26 (0.86-21.02)	5.19 (1.05-25.69)	0.003	—	—
Model 2[b]	1.00	1.39 (0.19-9.92)	5.47 (1.11-27.02)	5.89 (1.21-28.73)	0.012	—	—
Model 3[b]	1.00	0.70 (0.06-7.96)	5.23 (0.94-29.05)	5.57 (0.77-40.19)	0.054	—	—
Other							
Number of cases	18	18	18	21	—	—	
Model 1[b]	1.00	0.78 (0.40-1.51)	0.75 (0.39-1.44)	0.83 (0.44-1.58)	0.727	—	—
Model 2[b]	1.00	0.82 (0.42-1.58)	0.79 (0.41-1.52)	0.86 (0.45-1.63)	0.732	—	—
Model 3[b]	1.00	0.70 (0.34-1.40)	0.58 (0.27-1.24)	0.60 (0.24-1.54)	0.980	—	—
Vitamin E							
Lung cancer (all)							
Number of cases	105	125	112	111	—	—	—
Model 1[b]	1.00	1.24 (0.96-1.62)	1.08 (0.83-1.42)	1.02 (0.78-1.35)	0.538	—	—
Model 2[b]	1.00	1.30 (1.00-1.69)	1.13 (0.86-1.48)	1.05 (0.80-1.39)	0.635	—	—
Model 3[b]	1.00	1.22 (0.92-1.62)	1.06 (0.77-1.44)	0.87 (0.58-1.30)	0.115	0.931	0.98 (0.954-1.005)
Adenocarcinoma							
Number of cases	71	93	93	77	—	—	—
Model 1[b]	1.00	1.38 (1.01-1.89)	1.34 (0.98-1.83)	1.06 (0.76-1.48)	0.436	—	—
Model 2[b]	1.00	1.41 (1.03-1.93)	1.36 (0.99-1.87)	1.06 (0.76-1.48)	0.448	—	—
Model 3[b]	1.00	1.43 (1.02-2.00)	1.45 (1.00-2.09)	1.15 (0.71-1.86)	0.531	—	—
Squamous cell carcinoma							
Number of cases	4	10	4	7	—	—	—
Model 1[b]	1.00	2.58 (0.80-8.28)	1.00 (0.25-4.06)	1.73 (0.49-6.10)	0.763	—	—
Model 2[b]	1.00	3.23 (1.00-10.42)	1.19 (0.29-4.85)	2.01 (0.57-7.13)	0.898	—	—
Model 3[b]	1.00	3.11 (0.90-10.74)	1.15 (0.25-5.36)	1.44 (0.22-9.47)	0.471	—	—
Small cell carcinoma							
Number of cases	3	4	4	8	—	—	—
Model 1[b]	1.00	1.28 (0.29-5.75)	1.22 (0.27-5.50)	2.19 (0.56-8.55)	0.256	—	—
Model 2[b]	1.00	1.65 (0.36-7.49)	1.50 (0.33-6.82)	2.78 (0.70-11.04)	0.248	—	—
Model 3[b]	1.00	2.09 (0.36-12.01)	1.68 (0.28-10.25)	2.11 (0.28-15.78)	0.268	—	—
Other							
Number of cases	27	18	11	19	—	—	—
Model 1[b]	1.00	0.69 (0.38-1.26)	0.42 (0.21-0.85)	0.69 (0.37-1.27)	0.808	—	—
Model 2[b]	1.00	0.71 (0.39-1.30)	0.43 (0.21-0.87)	0.71 (0.38-1.31)	0.822	—	—
Model 3[b]	1.00	0.53 (0.28-1.01)	0.28 (0.13-0.60)	0.26 (0.10-0.67)	0.105	—	—

P_{int}: $P_{interaction}$

10 mcg/1 mg cont. HR: continuous HR per unit (10 mcg increase for retinol, α- and β-carotene, 1 mg increase for vitamins C and E)

Model 1[b]: age (continuous), study area (9 public health center areas)

Model 2[b]: age (continuous), study area (9 public health center areas), smoking status (never or 1-19, 20-29, 30-39, 40-49, 50-59, ≥60 pack-years for current and former smokers)

Model 3[b]: age (continuous), study area (9 public health center areas), smoking status (never or 1-19, 20-29, 30-39, 40-49, 50-59, ≥60 pack-years for current and former smokers), alcohol consumption (0, 1-149, 150-299, 300-449, ≥450 g of ethanol/week), vitamin supplements use (yes or no), and energy-adjusted intakes of fish, isoflavone, vegetables, and fruits (continuous)

3.5.3. Further analyses by smoking status

In the analysis of antioxidant vitamins, current and former smokers accounted for 87% of lung cancer cases among men, whereas more than 88% of cases in women were among never smokers (Table 10). To explore the effect of potential residual confounding by smoking, a subgroup analysis was conducted within detailed smoking strata including pack-years among current and former male smokers. No significant associations were observed between lung cancer and antioxidant vitamin intake in male never and former smokers. Among male current smokers, a positive association was found between lung cancer and consumption of retinol (HR, 1.22; 95% CI, 0.99-1.50; p_{trend} = 0.030; comparing the lowest intake with the highest) and vitamin C (HR, 1.19; 95% CI, 0.88-1.59; p_{trend} = 0.003). The positive associations remained only among light smokers for retinol (HR, 1.63; 95% CI, 0.70-3.81; p_{trend} = 0.002; comparing the lowest intake with the highest) and heavy smokers for vitamin C (HR, 1.19; 95% CI, 0.90-1.57; p_{trend} = 0.006). Interestingly, there was an inverse association between high α-carotene intake and the cancer risk among male light smokers (HR, 0.29; 95% CI, 0.09-0.93; p_{trend} = 0.041; comparing the lowest intake with the highest). Contrary to what was observed among men, the highest level of retinol intake was associated with a lower hazard ratio of lung cancer among female current smokers (HR, 0.51; 95% CI, 0.18-1.40; p_{trend} = 0.033; comparing the lowest intake with the highest). No associations were observed in every other examined stratum. Interactions were examined in all aforementioned stratified analyses; none of these were statistically significant, except for an interaction between histological type and retinol intake in women (results shown in Tables 9 and 10).

Sensitivity analyses, which excluded lung cancer cases diagnosed within the first five years of follow-up produced a similar direction of associations as the main analyses. Figures 4 and 5 present overview of risk estimates for overall lung cancer incidence by consumption of antioxidant vitamins in men and women, respectively.

Table 10. Hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between consumption of antioxidant vitamins and lung cancer risk: subanalysis by smoking status

	Lowest	Second	Third	Highest	P_{trend}	P_{int}	Lowest	Second	Third	Highest	P_{trend}	P_{int}
			Retinol						**α-carotene**			
Men (n = 38,207)												
Never smokers												
Number of cases	46	38	37	45	—	—	28	38	53	47	—	—
Model 1[b]	1.00	0.87 (0.56-1.34)	0.96 (0.62-1.48)	1.12 (0.73-1.70)	0.156	—	1.00	1.10 (0.68-1.80)	1.26 (0.80-2.00)	0.80 (0.50-1.30)	0.486	—
Model 3[b]	1.00	1.05 (0.65-1.70)	1.11 (0.69-1.80)	1.16 (0.71-1.90)	0.342	0.408	1.00	1.34 (0.77-2.33)	1.31 (0.75-2.26)	0.84 (0.46-1.55)	0.749	0.123
Former smokers												
Number of cases	48	53	45	50	—	—	40	46	49	61	—	—
Model 1[b]	1.00	1.13 (0.76-1.68)	1.07 (0.71-1.62)	1.15 (0.77-1.73)	0.453	—	1.00	0.98 (0.64-1.49)	0.93 (0.62-1.42)	0.99 (0.66-1.50)	0.110	—
Model 3[b]	1.00	1.13 (0.71-1.79)	1.38 (0.87-2.19)	1.40 (0.88-2.23)	0.330	—	1.00	1.00 (0.62-1.61)	1.00 (0.62-1.62)	0.93 (0.55-1.57)	0.158	—
Current smokers												
Number of cases	206	205	223	241	—	—	265	222	196	192	—	—
Model 1[b]	1.00	1.14 (0.94-1.38)	1.19 (0.99-1.45)	1.29 (1.06-1.55)	0.011	—	1.00	0.95 (0.80-1.14)	0.82 (0.68-0.98)	0.85 (0.70-1.03)	0.043	—
Model 3[b]	1.00	1.09 (0.89-1.35)	1.21 (0.98-1.48)	1.22 (0.99-1.50)	0.030	—	1.00	0.98 (0.81-1.20)	0.81 (0.65-1.00)	0.90 (0.71-1.14)	0.239	—
Light smokers*												
Number of cases	10	9	10	20	—	—	17	13	13	6	—	—
Model 1[b]	1.00	0.91 (0.37-2.26)	1.17 (0.48-2.85)	1.97 (0.91-4.30)	<0.00	—	1.00	0.79 (0.38-1.63)	0.68 (0.32-1.41)	0.35 (0.14-0.92)	0.050	—
Model 3[b]	1.00	0.83 (0.32-2.21)	1.00 (0.38-2.64)	1.63 (0.70-3.81)	0.002	—	1.00	0.94 (0.41-2.13)	0.64 (0.27-1.51)	0.29 (0.09-0.93)	0.041	—
Heavy smokers*												
Number of cases	244	249	258	271	—	—	288	255	232	247	—	—
Model 1[b]	1.00	1.14 (0.95-1.36)	1.17 (0.98-1.40)	1.24 (1.04-1.48)	0.063	—	1.00	0.94 (0.80-1.11)	0.82 (0.69-0.97)	0.86 (0.72-1.03)	0.243	—
Model 3[b]	1.00	1.11 (0.91-1.35)	1.25 (1.02-1.51)	1.24 (1.02-1.51)	0.071	—	1.00	0.98 (0.81-1.18)	0.83 (0.68-1.01)	0.91 (0.73-1.13)	0.740	—

	Lowest	Second	Third	Highest	P_{trend}	P_{int}	Lowest	Second	Third	Highest	P_{trend}	P_{int}
Women[a] (n = 41,498)												
Never smokers												
Number of cases	122	92	103	81	—	—	84	81	115	118	—	—
Model 1[b]	1.00	0.89 (0.68-1.17)	1.06 (0.81-1.38)	0.86 (0.64-1.14)	0.262	—	1.00	0.94 (0.69-1.27)	1.25 (0.94-1.66)	1.22 (0.92-1.63)	0.185	—
Model 3[b]	1.00	0.94 (0.71-1.24)	1.11 (0.84-1.47)	0.86 (0.64-1.16)	0.275	0.317	1.00	0.96 (0.70-1.31)	1.23 (0.91-1.66)	1.32 (0.95-1.84)	0.102	0.897
Current smokers												
Number of cases	11	15	14	7	—	—	11	10	10	16	—	—
Model 1[b]	1.00	1.64 (0.75-3.58)	1.45 (0.65-3.21)	0.54 (0.21-1.41)	0.032	—	1.00	1.14 (0.48-2.69)	1.06 (0.45-2.51)	1.75 (0.79-3.86)	0.039	—
Model 3[b]	1.00	1.68 (0.77-3.69)	1.51 (0.68-3.37)	0.51 (0.18-1.40)	0.033	—	1.00	1.13 (0.48-2.70)	0.88 (0.35-2.18)	1.54 (0.64-3.73)	0.162	—
			Vitamin C						**β-carotene**			
Men (n = 38,207)												
Never smokers												
Number of cases	28	35	55	48	—	—	30	40	42	54	—	—
Model 1[b]	1.00	0.94 (0.57-1.55)	1.22 (0.77-1.94)	0.80 (0.49-1.29)	0.921	—	1.00	1.11 (0.69-1.78)	0.90 (0.56-1.44)	0.87 (0.56-1.37)	0.754	—
Model 3[b]	1.00	0.79 (0.45-1.38)	1.02 (0.59-1.78)	0.51 (0.25-1.04)	0.677	0.420	1.00	1.25 (0.73-2.14)	0.80 (0.45-1.43)	0.89 (0.47-1.69)	0.748	0.204
Former smokers												
Number of cases	23	47	55	71	—	—	35	50	42	69	—	—
Model 1[b]	1.00	1.49 (0.90-2.45)	1.31 (0.80-2.14)	1.31 (0.81-2.12)	0.488	—	1.00	1.15 (0.75-1.77)	0.77 (0.49-1.21)	1.08 (0.71-1.63)	0.326	—
Model 3[b]	1.00	1.65 (0.92-2.95)	1.65 (0.90-3.02)	1.64 (0.81-3.35)	0.406	—	1.00	1.17 (0.71-1.92)	0.80 (0.46-1.37)	1.14 (0.62-2.10)	0.311	—
Current smokers												
Number of cases	204	209	235	227	—	—	239	236	207	193	—	—
Model 1[b]	1.00	1.05 (0.87-1.28)	1.10 (0.91-1.34)	1.10 (0.91-1.34)	0.097	—	1.00	1.03 (0.86-1.24)	0.91 (0.76-1.10)	0.89 (0.74-1.08)	0.145	—
Model 3[b]	1.00	1.04 (0.83-1.29)	1.16 (0.92-1.47)	1.19 (0.88-1.59)	0.003	—	1.00	1.02 (0.83-1.25)	0.87 (0.69-1.09)	0.88 (0.66-1.16)	0.544	—
Light smokers*												
Number of cases	15	7	11	16	—	—	13	12	14	10	—	—
Model 1[b]	1.00	0.51 (0.21-1.25)	0.64 (0.29-1.40)	0.87 (0.42-1.80)	0.316	—	1.00	0.88 (0.30-1.94)	0.97 (0.45-2.07)	0.75 (0.32-1.75)	0.218	—
Model 3[b]	1.00	0.54 (0.20-1.47)	0.59 (0.22-1.58)	0.81 (0.24-2.76)	0.353	—	1.00	1.04 (0.43-2.50)	1.08 (0.43-2.72)	0.48 (0.13-1.80)	0.138	—
Heavy smokers*												
Number of cases	212	249	279	282	—	—	261	274	235	252	—	—
Model 1[b]	1.00	1.10 (0.92-1.32)	1.09 (0.91-1.31)	1.05 (0.87-1.26)	0.382	—	1.00	1.03 (0.87-1.22)	0.85 (0.71-1.01)	0.88 (0.74-1.05)	0.256	—
Model 3[b]	1.00	1.11 (0.90-1.37)	1.20 (0.96-1.51)	1.19 (0.90-1.57)	0.006	—	1.00	1.02 (0.84-1.23)	0.82 (0.66-1.02)	0.90 (0.70-1.17)	0.971	—

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	Lowest	Second	Third	Highest	P_{trend}	P_{int}	Lowest	Second	Third	Highest	P_{trend}	P_{int}
Women[a] (n = 41,498)												
Never smokers												
Number of cases	72	103	110	113	—	—	78	90	117	113	—	—
Model 1[b]	1.00	1.27 (0.94-1.72)	1.27 (0.94-1.71)	1.23 (0.91-1.67)	0.171	—	1.00	1.15 (0.85-1.56)	1.36 (1.02-1.82)	1.24 (0.92-1.66)	0.273	—
Model 3[b]	1.00	1.22 (0.88-1.69)	1.22 (0.86-1.72)	1.28 (0.83-1.97)	0.108	0.586	1.00	1.13 (0.82-1.56)	1.43 (1.03-1.98)	1.39 (0.94-2.05)	0.081	0.937
Current smokers												
Number of cases	9	12	11	15	—	—	9	14	9	15	—	—
Model 1[b]	1.00	2.12 (0.90-4.98)	1.84 (0.74-4.58)	2.50 (1.07-5.87)	0.246	—	1.00	2.48 (1.05-5.86)	1.27 (0.49-3.33)	2.70 (1.12-6.48)	0.133	—
Model 3[b]	1.00	2.10 (0.86-5.14)	1.83 (0.67-5.02)	2.60 (0.85-7.95)	0.707	—	1.00	2.44 (1.01-5.87)	1.18 (0.41-3.40)	2.87 (0.94-8.82)	0.460	—
Vitamin E												
Men (n = 38,207)												
Never smokers												
Number of cases	35	39	39	53	—	—						
Model 1[b]	1.00	0.84 (0.53-1.32)	0.73 (0.46-1.15)	0.72 (0.46-1.13)	0.109	—						
Model 3[b]	1.00	0.92 (0.53-1.60)	0.87 (0.48-1.58)	0.89 (0.43-1.84)	0.643	0.555						
Former smokers												
Number of cases	38	51	54	53	—	—						
Model 1[b]	1.00	1.11 (0.73-1.69)	1.01 (0.66-1.53)	0.86 (0.56-1.32)	0.179	—						
Model 3[b]	1.00	1.27 (0.77-2.09)	1.09 (0.62-1.89)	1.03 (0.51-2.07)	0.524	—						
Current smokers												
Number of cases	231	205	227	212	—	—						
Model 1[b]	1.00	0.92 (0.76-1.11)	1.07 (0.89-1.29)	1.05 (0.87-1.27)	0.563	—						
Model 3[b]	1.00	0.95 (0.76-1.17)	1.02 (0.80-1.30)	0.98 (0.72-1.34)	0.763	—						
Light smokers*												
Number of cases	12	10	14	13	—	—						
Model 1[b]	1.00	0.82 (0.35-1.91)	1.06 (0.48-2.31)	0.95 (0.42-2.14)	0.945	—						
Model 3[b]	1.00	1.07 (0.42-2.71)	0.81 (0.28-2.38)	0.84 (0.21-3.33)	0.653	—						
Heavy smokers*												
Number of cases	257	246	267	252	—	—						
Model 1[b]	1.00	0.94 (0.79-1.12)	1.02 (0.86-1.21)	0.96 (0.80-1.14)	0.557	—						
Model 3[b]	1.00	0.98 (0.80-1.20)	1.03 (0.82-1.29)	0.96 (0.72-1.29)	0.945	—						

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	Lowest	Second	Third	Highest	P_{trend}	P_{int}
Women[a] (n = 41,498)						
Never smokers						
Number of cases	95	111	96	96	—	—
Model 1[b]	1.00	1.20 (0.91-1.58)	1.01 (0.76-1.35)	0.97 (0.72-1.30)	0.506	—
Model 3[b]	1.00	1.14 (0.85-1.54)	0.96 (0.69-1.33)	0.81 (0.53-1.25)	0.216	NA
Current smokers						
Number of cases	8	13	14	12	—	—
Model 1[b]	1.00	2.39 (0.99-5.77)	2.44 (1.01-5.89)	1.74 (0.69-4.40)	0.919	—
Model 3[b]	1.00	2.33 (0.93-5.84)	1.14 (0.86-6.05)	1.37 (0.38-4.94)	0.276	—

P_{int}: $P_{interation}$
Model 1[b]: age (continuous), study area (9 public health center areas)
Model 3[b]: age (continuous), study area (9 public health center areas), alcohol consumption (0, 1-149, 150-299, 300-449, ≥450 g of ethanol/week), vitamin supplements use (yes or no), and energy-adjusted intakes of fish, isoflavone, vegetables, and fruits (continuous).
*Models included both current and former smokers who were categorized into light (≤19.9 pack-years) and heavy (≥20.0 pack-years) smokers. Pack-years is the number of cigarette packs (assuming 20 cigarettes per pack) smoked per day, multiplied by years of consumption.

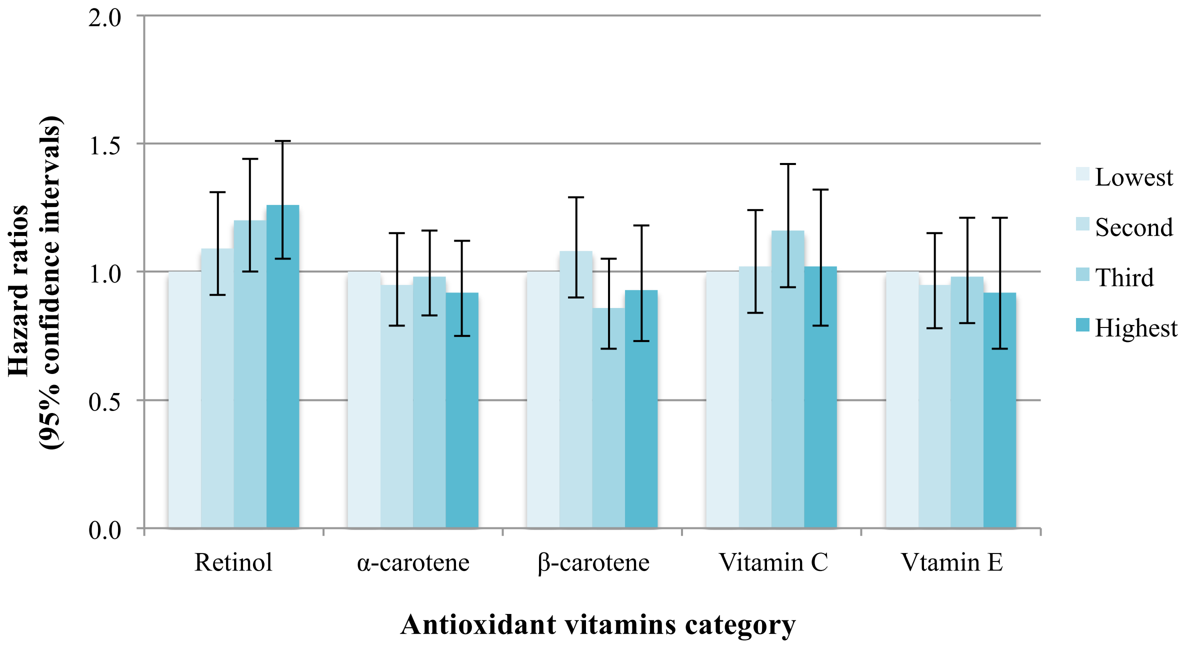

Figure 4. Overview of hazard ratios and 95% confidence intervals for overall lung cancer according to consumption of antioxidant vitamins in men

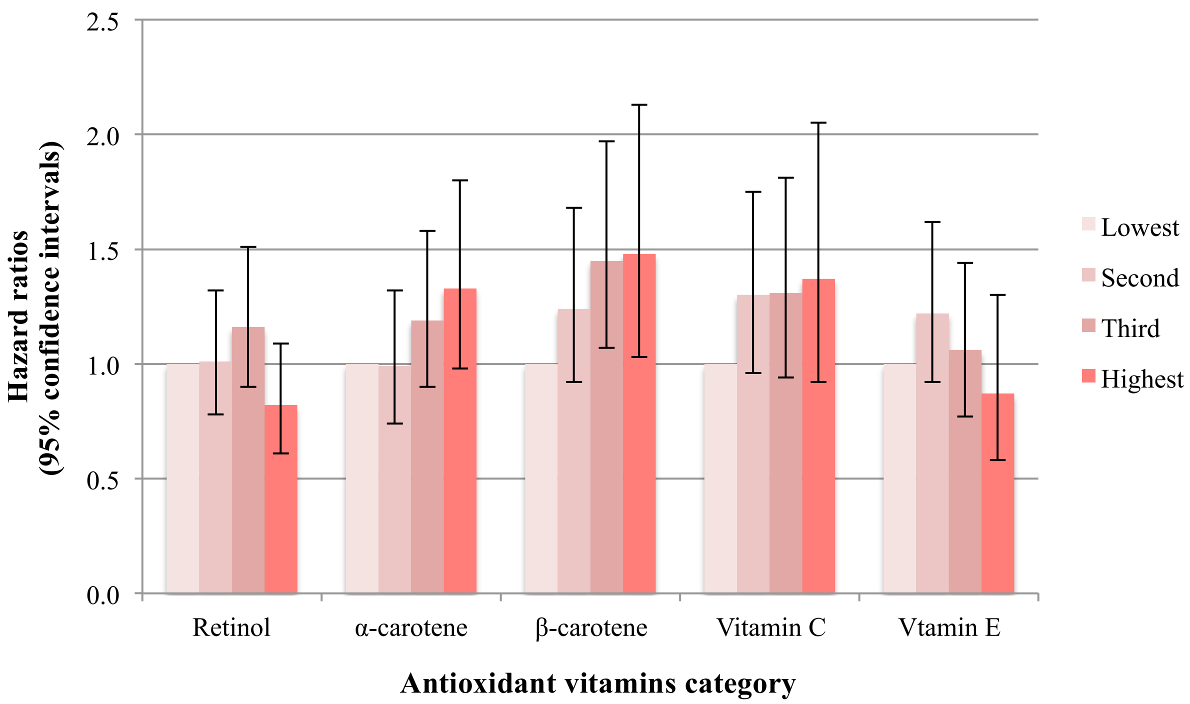

Figure 5. Overview of hazard ratios and 95% confidence intervals for overall lung cancer according to consumption of antioxidant vitamins in women

3.6. Discussion

3.6.1. Comparison with preceding studies

In this prospective cohort study, higher consumption of retinol was positively associated with lung cancer risk in men, especially with small cell carcinoma. While this finding of a positive association agrees with studies of retinol supplement use,[113,114] other cohort studies on dietary retinol intake observed no association.[32,115] This may be attributable to the level of retinol consumption, given that mean retinol intake in the highest category in our study (1,121 mcg for men and 1,183 mcg for women) was much higher than that in a study with dietary retinol intake (251.7 mcg)[32] and somewhat comparable to the highest group in a study with retinol supplementation (>1,200 mcg).[113] The difference in the level of consumption might indeed also explain the null result with β-carotene in the present study. Previous randomized controlled trials of β-carotene supplementation, which reported an increased lung cancer risk, had much higher levels of consumption (ranging from 20 mg[23] to 30 mg[24]) than in our study (3.98 mg for men and 7.80 mg for women), suggesting the possibility that the activities of certain antioxidant nutrients conflict at supranutritional levels. Although the oncogenic mechanisms of the harmful effects of antioxidants have not been completely elucidated, it has been suggested that a high-dose intake of certain antioxidants may act as conditional pro-oxidants under high oxidative stress and exposure to lung irritants such as tobacco smoking and asbestos; and that the activity of an antioxidant is dependent on its redox potential in connection with other pro- and anti-oxidants in its microenvironment.[113,116] While a recent meta-analysis reported a protective effect of vitamin C in studies from the United States but not in those from Europe or Asia,[25] this study found no significant association between vitamin C intake and lung cancer risk. In the analytic cohort of antioxidant vitamins, 87% of the present lung cancer cases in men and 12% in women were in fact among current and past smokers. Furthermore, consistent with the previously established link between small cell and squamous cell carcinomas and cigarette smoking in Japan,[68,98] over 90% of small cell (142/155 cases) and squamous cell carcinomas (308/337 cases) in men were observed among current and past smokers. The significant positive association among current smokers suggests the possibility of incomplete control for smoking, although estimated risks were higher among light than among heavy smokers. This should be interpreted with caution since information on pack-years was unavailable in one-third of male smokers. On the other hand, despite limited number of lung cancer cases in women, these findings were less likely biased by residual confounding given the low prevalence of smoking among women in this cohort.

This study also found no associations between consumption of vitamin E and pro-vitamin A carotenoids, namely α-carotene and β-carotene, and lung cancer risk, which are consistent with the WCRF/AICR report.[18] While consumption of foods containing carotenoids has been shown to decrease the risk of lung cancer,[18,32] this association was not seen in a previous JPHC study due to the small number of lung cancer cases[38]. Further, retinol intake was associated with an increased risk of lung cancer in men whereas the risk estimates among women showed the opposite. This might be in part attributable to the smaller number of lung cancer cases in women and different consumption levels of the antioxidant vitamins. There is accumulating epidemiologic evidence showing gender differences in susceptibility to lung cancer.[117] Previous study has found a lower level of DNA repair capacity in women leading to a higher level of DNA damage and mutation in the lung tissue.[118] In addition, several genetic mutations such as *KRAS*, *HER2* or *EGFR* mutations were found to occur more frequently in non-small cell lung cancer of women than men.[119,120] This might partly explain the risk difference between men and women although no significant associations among women were observed in the present study, which accordingly warrants further evaluation.

3.6.2. Limitations and strengths

In the analysis of antioxidant vitamins, the 5-year follow-up survey was used, but it was missing information on age of smoking initiation and cessation. Further, the specific details of smoking, such as the presence of passive smoking, depth of inhalation or nicotine dose, which would have helped control the effects of tobacco exposure, were not inquired in the questionnaire. Furthermore, detailed information on vitamin intake through supplements was not available in the FFQ and thus could not be included in the analyses. Nevertheless, the questionnaires did ask whether participants took vitamin supplements, which a tenth of the participants reported using, and this was included in the final model as a covariate. While the FFQ was previously validated against dietary records for 28 days (1-week dietary records measured quarterly) or 14 days[121] and its reproducibility was guaranteed by repeating the same FFQs at a one-year interval,[110] it might produce a less accurate estimation of dietary intake than the 24-hour recall method. Measurement of exposures was conducted once at 5-year follow-up survey and thus the possibility of misclassification cannot be ruled out. Although retinol had a relatively lower validity compared to the rest of exposure variables, the validity and reproducibility of our FFQ were evaluated as adequate,[75,110,121] and were comparable with those in other large-scale prospective cohort studies.[32,37,122] It should be also noted that the FFQ validity and reproducibility heavily depends on the type of food or nutrient, and having a low validity for a specific nutrient might reflect larger measurement errors. Moreover, given the marginal change in the consumption of antioxidant vitamins,[104] such misclassification would be independent of lung cancer diagnosis and likely non-differential, and might accordingly have led to underestimation of the true effect. Additionally, participants who reported a history of any cancer prior to the 5-year follow-up survey were excluded and a sensitivity analysis excluding lung cancer cases diagnosed within the first five years of the follow-up period was performed, which would likely minimize bias from undiagnosed or ongoing illnesses. On the other hand, this might have led to a selection bias if the exclusion is related to lung cancer outcome. Yet, further analysis with those excluded for missing covariates showed that there were no substantial differences in the risk estimates, suggesting the loss of the missing data in this study at random. Also, there is a possibility of uncontrolled confounding factors such as exposure to radon or socioeconomic status that might influence consumption of antioxidant vitamins. A nation-wide survey on indoor radon in Japan revealed that mean concentrations of indoor radon decreased over the past few decades.[123] Whilst its effect may not have been extensive, radon remains as the prominent risk factor for lung cancer.[16] Moreover, since information on income was not available in the baseline or follow-up questionnaire, occupation at 5-year follow-up was included in the additional analysis, which did not alter the risk estimates significantly.

Despite these limitations, this is the first and only population-based prospective cohort study to investigate the association between consumption of antioxidant nutrients and lung cancer incidence in Japan. The main strengths of the study include its prospective design, high response rate and long follow-up period. The possibility of recall bias was negligible because exposure data were collected before diagnosis. Misclassification of lung cancer cases was also less likely because of the rate of microscopic diagnosis and limited reliance on death certificate notification. Stratified analyses by histological type and smoking status yielded novel insights into the potential mechanism by which each antioxidant vitamin influences the pathogenesis of lung cancer differently.

3.6.3. Recommendations for future studies

Considering the limitations and strengths of the study, following are two recommendations for future JPHC Study:

1. Detailed information on smoking behavior is crucial in determining true effects of exposures in not only lung cancer research but also an extensive range of epidemiological studies since smoking increases risks for cardiovascular and respiratory diseases, cancers as well as for birth defects and miscarriage.[10] Therefore, repeating questions such as age of smoking initiation and cessation, and presence of passive smoking at home or work in follow-up surveys and further adding questions on nicotine dose would improve the quality of the study.

2. Validity and reproducibility of the FFQ vary depending on types of food or nutrient. While comprehensive questionnaires will allow complete collection of data, such extensive survey could become burdensome for study participants and likely lower response rate. Hence, employing better methods to conduct the FFQ more frequently – e.g., utilize IT devices to record foods and beverages consumed in the dietary record method and repeat it every two years – can improve the validity of the study.

Chapter 4. Conclusion

The present study found no substantial risk of lung cancer based on consumption of antioxidant-rich diet such as vitamins C and E, and α- and β-carotenes. However, a positive association between coffee intake and small cell carcinoma was observed. It is also indicated that a high level of retinol intake in men may be associated with the increased cancer risk. Nevertheless, residual confounding due to smoking cannot be ruled out since the positive association was evident with small cell carcinoma and among current smokers. The possible influence of excessive intake of retinol needs to be explored. Consequently, specific policy implications may not be drawn from this study. Further studies that capture more detailed quantitative information on tobacco smoking would help clarify the impact of antioxidant-rich diet and residual confounding on lung carcinogenesis. While smoking still has a substantial effect on lung cancer incidence and on mortality worldwide, studying the non-smoking-related factors not only highlights the significant price of smoking but also plays a part in understanding the mechanisms that might reduce lung cancer morbidity and mortality.

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Appendices

Appendix 1. Summary of previous cohort studies

	Study	Location, study period	Age	Cases/cohort	Exposure range	RR/OR (95% CI)	Adjustments
Coffee	Guertin 2016	US, 1995-2006	50-71 y	9,196/457,366	Non-drinkers vs. ≥6 cups/day	1.29 (1.15-1.45)	Age, sex, smoking status, number of cigarettes smoked per day, use of pipe/cigars, race/ethnicity, body mass index, level of education, alcohol consumption, health status, total energy intake, nutrient density-adjusted fruit intake, nutrient density-adjusted vegetable intake, supplement use, current marital status, physical activity, history of cardiovascular disease, diabetes, and family history of cancer
	Hashibe 2015	US, 1992-2011	55-74 y	1,137/96,024	<1 cup/day vs. ≥2 cups/day	1.10 (0.94-1.28)	Age, sex, race, education, smoking status, smoking frequency, smoking duration, and time since stopping smoking for past smokers
	Bae 2013	Korea, 1993-2008	40-59 y	93/7,009	Non-drinker vs. ≥7 cups/week	1.89 (0.94-4.30)	None
	Khan 2004	Japan, 1984-2002	40+ y	51/3,158	Non-drinkers vs. drinkers	0.70 (0.40-1.40) for men 2.10 (0.50-8.00) for women	Age and smoking
	Fu 1997	Japan, 1985-1995	40+ y	161/24,489	Non-drinkers vs. drinkers	2.02 (1.34-3.05) for men 0.92 (0.44-1.93) for women	Smoking, consumption of tea, vegetables, fruits, and alcohol
	Stensvold 1994	Norway, 1977-1990	35-54 y	125/42,973	≤4 cups/day vs. ≥7 cups/day	2.29 (1.38-3.80)	Age, sex, cigarettes per day, county of residence

RR: relative risk; OR: odds ratio, CI: confidence interval

	Study	Location, study period	Age	Cases/cohort	Exposure range (mcg/day)	RR/OR (95% CI)	Adjustments
Carotenoids	Takata 2013	China, 2002-2009	40-74 y men	359/61,491	Q1: 1,449.8 vs. Q4: 5,025.5 (median)	0.64 (0.46-0.88)	Age, smoking status, years of smoking, number of cigarettes per day, total caloric intake, education, body mass index, consumption of tea, history of chronic bronchitis, and family history of lung cancer among first-degree relatives
	Wright 2004	Finland, 1985-1999	50-69 y men	1,787/27,111	Q1: 2,832 vs. Q5: 8,320 (mean)	0.96 (0.91-1.02)	Age, number of cigarettes per day, number of years of smoking, intervention assignment, body mass index, educational level, and energy intake
	Yuan 2003	Singapore, 1993-2000	45-74 y	482/62,392	Q1: 23 vs. Q5: 376 for α-carotene Q1: 583 vs. Q5: 2,473 for β-carotene (median, /1,000 kcal)	1.06 (0.79-1.42) for α-carotene 1.00 (0.74-1.35) for β-carotene	Age, sex, dialect group, year of interview, education level, body mass index, number of cigarettes per day, number of years smoked, number of years since quitting
	Neuhouser 2003	US, 1989-2001	45-69 y	742/14,120	Q1: ≤5,425 vs. Q5: ≥13,244 (mean)	0.90 (0.64-1.37)	Age, sex, smoking status, total pack-years of smoking, asbestos exposure, race/ethnicity, and enrollment center
	Holick 2002	Finland, 1985-1998	50-69 y men	1,644/27,084	Q1: <2,770 vs. Q5: >6,792 (median)	0.84 (0.72-0.99)	Age, years smoked, cigarettes per day, intervention assignment, supplement use, energy intake, cholesterol, and fat
	Michaud 2000	US, 1984-1996 (W) 1986-1996 (M)	30-55 y women 40-75 y men	519/77,283 275/46,924	Q1: 8,002 vs. Q4: 30,251 for women Q1: 7,802 vs. Q5: 33,253 for men (median)	0.69 (0.46-1.03) for women 0.64 (0.37-1.13) for men	Age, smoking status, age at start of smoking, quintiles of energy intake, and time period
	Voorrips 2000	Netherlands, 1986-1992	55-69 y men	939/58,279	Q1: 198 vs. Q5: 1,300 for α-carotene Q1: 1,480 vs. Q5: 4,729 for β-carotene (median)	0.89 (0.65-1.23) for α-carotene 0.85 (0.63-1.18) for β-carotene	Age, smoking status, years of smoking, number of cigarettes per day, educational level, family history of lung cancer, socioeconomic status, and energy intake

RR: relative risk; OR: odds ratio; CI: confidence interval
*Previous studies since 2000 are shown

	Study	Location, study period	Age	Cases/cohort	Exposure range	RR/OR (95% CI)	Adjustments
Vitamin A	Takata 2013	China, 2002-2009	40-74 y men	359/61,491	Q1: 359.4 vs. Q4: 1,046.1 (mcg RE/day, median)	0.63 (0.44-0.88)	Age, years of smoking, number of cigarettes smoked per day, smoking status, total caloric intake, education body mass index, consumption of tea, history of chronic bronchitis, and family history of lung cancer among first-degree relatives
	Yuan 2003	Singapore, 1993-2000	45-74 y	482/62,392	Q1: 1,513 vs. Q5: 5,507 (IU/1,000 kcal, median)	0.90 (0.66-1.22)	Age, sex, dialect group, year of interview, education level, body mass index, number of cigarettes per day, number of years smoked, number of years since quitting
	Holick 2002	Finland, 1985-1998	50-69 y men	1,644/27,084	Q1: <717 vs. Q5: >2,138 (mcg/day, median)	0.96 (0.82-1.13)	Age, years smoked, cigarettes per day, supplement use, intervention assignment, energy intake, cholesterol, and fat
Vitamin C	Takata 2013	China, 2002-2009	40-74 y	359/61,491	Q1: 46.2 vs. Q4: 150.4 (mg/day)	0.84 (0.61-1.16)	Age, years of smoking, number of cigarettes smoked per day, smoking status, total caloric intake, education body mass index, consumption of tea, history of chronic bronchitis, and family history of lung cancer among first-degree relatives
	Yuan 2003	Singapore, 1993-2000	45-74 y	482/62,392	Q1: 19 vs. Q5: 102 (mg/1,000 kcal, median)	0.81 (0.59-1.09)	Age, sex, dialect group, year of interview, education level, body mass index, number of cigarettes per day, number of years smoked, number of years since quitting
	Neuhouser 2003	US, 1989-2001	45-69 y	742/14,120	Q1: ≤35 vs. Q5: ≥110 (mg/day, mean)	0.66 (0.47-0.94)	Age, sex, smoking status, total pack-years of smoking, asbestos exposure, race/ethnicity, and enrollment center
	Voorrips 2000	Netherlands, 1986-1992	55-69 y men	939/58,279	Q1: 51 vs. Q3: 138 (mg/day, median)	0.64 (0.54-0.77)	Age, smoking status, years of smoking, number of cigarettes per day, educational level, family history of lung cancer, socioeconomic status, and energy intake
Vitamin E	Roswall 2010	Denmark, 1993-2006	50-64 y	721/55,557	Q1: ≤6.2 vs. Q4: ≥9.9 (mg/day, median)	0.59 (0.44-0.77)	Intake of three other micronutrients as well as supplemental intake, smoking status, smoking duration, smoking intensity, smoking cessation, passive smoking, work exposure
	Yuan 2003	Singapore, 1993-2000	45-74 y	482/62,392	Q1: 2.5 vs. Q5: 5.3 (mg/1,000 kcal, median)	1.04 (0.77-1.42)	Age, sex, dialect group, year of interview, education level, body mass index, number of cigarettes per day, number of years smoked, number of years since quitting
	Voorrips 2000	Netherlands, 1986-1992	55-69 y men	939/58,279	Q1: 7 vs. Q5: 24 (mg/day, median)	1.15 (0.80-1.65)	Age, smoking status, years of smoking, number of cigarettes per day, educational level, family history of lung cancer, socioeconomic status, and energy intake

RR: relative risk; OR: odds ratio; CI: confidence interval
*Previous studies since 2000 are shown

Appendix 2. Ethical approval

（様式６-1）

2015年06月19日

研究倫理審査委員会結果通知書

国立研究開発法人国立がん研究センター理事長　殿

国立研究開発法人国立がん研究センター研究倫理審査委員会委員長

研究計画に関する申請あるいは報告について、当センターの手順書に基づき審査を行い、以下のとおり判定した。

研究課題番号	2001-021
研究課題名	多目的コホート研究(JPHC Study)
研究責任者	がん予防・検診研究センター　がん予防・検診研究センター　津金　昌一郎
適用となる倫理指針	□人を対象とする医学系研究に関する倫理指針 □臨床研究に関する倫理指針　■疫学研究に関する倫理指針 □ヒトゲノム・遺伝子解析研究に関する倫理指針 □その他
研究計画書等に関する情報	研究計画書の作成日：2015年06月16日　第2015/06/16版（バージョン） 説明同意文書の作成日：－　第－版（バージョン）
申請/報告の種別	□研究計画の新規申請　■研究計画の変更申請 □実施状況報告　□安全性情報に関する報告 □研究に関する不適切事案に関する報告 □その他
審査方法・判断方法	□通常（合議）審査（委員会開催日：　年　月　日） ■迅速審査（適用条件：委員会手順書第12条第1項第1号　軽微な変更） □研究倫理審査委員会委員長決裁 □あらかじめ指名する者による審査不要の判断※ □
委員会判定日（上記※の場合を除く）	2015年06月19日　判定　■承認　□条件付き承認　□却下　□保留（継続審査）　□差し戻し　□非該当　□その他
付帯条件・勧告	
判定が承認以外の場合の理由、その他の意見	
備考	変更内容：　研究協力者追加 審査対象文書：研究実施計画書

（様式６-2）

2015年06月25日

研究許可申請に関する指示・決定通知書

津金　昌一郎　殿

国立研究開発法人国立がん研究センター理事長

（押印省略）

貴殿から申請のあった上記の研究について、以下のとおり決定したので、通知する。

判定	■許可　□不許可　□差し戻し　□非該当 □その他
当センターにおける研究期間	自：1990年04月01日 至：2024年03月31日

Appendix 3. Example of a food frequency questionnaire at baseline (selected pages)[124]

COHORT I QUESTIONNAIRE

NAME:
SEX:
ADDRESS:
TELEPHONE NUMBER:

YELLOW FORM – GENERAL MEDICAL BACKGROUND QUESTIONS

Please answer the following questions concerning your past medical history and present health status.

1. Have you ever been diagnosed with any of the following diseases? Please circle all that apply.

	None
Diabetes, stroke, hypertension, myocardial infarction/angina pectoris, asthma, chronic bronchitis, allergy, kidney disease, cystitis, chronic hepatitis/liver cirrhosis, peptic gastric/duodenal ulcer, biliary stone, others (________________________________) cancer (stomach, lung, colorectum, liver, breast, uterine, others:_________________________)	

2. Have your parents/immediate family had any of the following diseases?

	Father	Mother	Brothers	Sisters	Spouse
(Example) Diabetes	○				
Diabetes					
Stroke					
Hypertension					
Myocardial infarction/angina pectoris					
Chronic hepatitis/liver cirrhosis					
Gastric/duodenal ulcer					
Cancer (site)	( )	( )	( )	( )	( )

3. Have you ever received a blood transfusion?

0. No	1. Yes

4. Are you currently taking any medications prescribed by your physician?

No	Yes

If yes, please check any of the following drugs you are currently taking

Drugs for hypertension, drugs for decreasing the blood cholesterol level, drugs for diabetes, drugs for gout, others (please specify ____)

5. How often do you take vitamin supplements?

0. Seldom	1. 1-4 days per week	2. Almost every day

If 1 or 2, please check which kinds of vitamins you take.

Vitamin B compound, Vitamin C, Vitamin E, Vitamin A, Multi-vitamin, others (   )

6. Have you undergone a medical examination or screening test within the past year?

No	Yes

If yes, please check any of the following you have undergone.

Blood pressure, blood test, electrocardiogram, funduscopy, chest X-ray, sputum examination, gastric X-ray, gastric endoscopy, occult blood test, colon x-ray, colonoscopy

7. What are your height and body weight?

Height ☐☐☐ cm Weight ☐☐☐ kg

8. Has your body weight changed more than 5 kg since you were 20 years old?

1. Decreased	2. Not changed	3. Increased

9. How often do you participate in sports or physical exercise?

0. Almost never	1. 1-3 days a month	2. 1-2 days a week	3. 3-4 days a week	5. Almost every day

PURPLE FORM – SMOKING AND DRINKING QUESTIONS

Please answer the following questions concerning smoking and alcohol drinking.

1. Have you ever been a smoker'?

0. No	1. Yes

If yes, how old were you when you began smoking? [ ][ ] years old

Do you currently smoke cigarettes?

0. No	1. Yes	2. Occasionally

If you no longer smoke, how old were you when you quit smoking?

If yes, how many cigarettes a day do you smoke? [ ][ ][ ] Cigarette s /day

2. Have you ever lived with a smoker for more than 10 years?

0. No	Yes

If yes, how old were you when you were living with them?

1. Younger than 20 years old	2. Older than 20 years old	3. Both

3. How often are you exposed to passive smoking (more than 1 hour /day) outside the home, such as at work?

0. Almost never	1. 1-3 days a month	2. 1-4 days a week	3. Almost every day

4. How often do you drink alcoholic beverages such as Japanese sake, shochu, awamori, beer, whisky, brandy, or wine?

0. Almost never	1. 1-3 days a month	2. 1-2 days a week	3. 3-4 days a week	4. 5-6 days a week	5. Every-day

If you drink more than 1-2 days a week,
how much do you drink, on average, every day?

Japanese sake	_____ go (180ml)
Shochu, awamori	_____ go (180ml)
*Beer (large 633ml)	_____ bottles
Whisky (30ml)	_____ cups
Others ________________	________ ml

*For beer, please convert medium bottles (500 ml) to 0.8 bottle and small bottles (350 ml) to 0.6 bottle.

Do you smoke more cigarettes than usual while drinking alcohol?

0. Do not smoke	1. Smoke as usual	2. More than usual

5. Do you blush soon after drinking alcohol?

1. Yes	2. Probably yes	3. No change	4. Don't know

6. Does your heart beat faster than usual or do you get a headache soon after drinking alcohol?

1. Yes	2. Probably yes	3. No change	4. Don't know

GREEN FORM – BASELINE
DIETARY QUESTIONS

Please answer the following questions concerning your usual food intake.

1. How many days per week do you eat the following meals? Indicate the frequency with a circle.

	Seldom	1-2 days/week	3-4 days/week	Almost every day
Breakfast (not just coffee or juice)	0	1	2	3
Dinner at home	0	1	2	3
Between-meal snacks	0	1	2	3

2. On average, how many bowls (normal size) of rice do you eat per day?

0. Less than one per day	1. Approximately _______________ bowls a day

3. How often do you drink miso soup? (Check one)

0. Almost never	1. 1-2 days/week	2. 3-4 days/week	3. Almost daily

↓

If almost daily, how many bowls on average do you drink per day?

________Bowls/day

4. Circle your food preferences/dislikes.

Preferences/Dislikes	Like very much	Like a little	Dislike
Food rich in oil	1	2	3
Spicy foods	1	2	3
Very salty foods	1	2	3
Sour food	1	2	3
Sweets, such as desserts	1	2	3
Hot foods and drinks	1	2	3

5. Circle the way you most commonly prepare the foods you eat most.

	Raw	Boil	Grill	Deep-fry	Stir-fry	Other
Meats	1	2	3	4	5	6
Fish and shellfish	1	2	3	4	5	6
Vegetables	1	2	3	4	5	6

6. How often do you have fried foods such as stir-fry or deep-fry?

0. Almost never	1. 1-2 days/week	2. 3-4 days/week	3. Almost daily

7. Do you avoid the burned/charred parts of fish or meat?

0. No	1. Yes

8. Circle the frequency with which you eat (or do not eat) each of the following foods:

Frequency	Almost never	1-2 days /week	3-4 days /week	Almost daily
Noodles (not instant)	0	1	2	3
Breads (including Japanese confection breads, sandwiches)	0	1	2	3
Butter or margarine	0	1	2	3
Fruits	0	1	2	3
Green vegetables (spinach, garland, chrysanthemum leaves, etc.)	0	1	2	3
Yellow vegetables (carrots, pumpkin, squash, etc.)	0	1	2	3
Other vegetables (Chinese cabbage, radish, tomato, cucumber, etc.)	0	1	2	3
Dressings and mayonnaise	0	1	2	3
Pickles (salty or salty rice-bran paste)	0	1	2	3
Mushrooms	0	1	2	3
Potatoes (sweet potatoes, potatoes, etc.)	0	1	2	3
Seaweeds (wakame, nori, kombu, etc.)	0	1	2	3
Soybean and soybean products (tofu, deep-fried tofu, fermented soybeans, etc.)	0	1	2	3
Other legumes (broad beans, etc.)	0	1	2	3
Eggs	0	1	2	3
Milk and dairy products (except cheeses)	0	1	2	3
Cheese	0	1	2	3
Beef	0	1	2	3
Pork	0	1	2	3
Chicken	0	1	2	3
Bacon, ham, sausage	0	1	2	3
Liver	0	1	2	3
Fresh fish and shellfish	0	1	2	3
Dried fish (mezashi, etc.) and salted fish (salted salmon, etc.)	0	1	2	3
Salted roe (cod or salmon roe, etc.)	0	1	2	3
Salted fish guts and salted sea urchin	0	1	2	3

9. Are you careful about your salt intake?

0. No	1. Yes

10. Are you careful about your cholesterol intake?

0. No	1. Yes

2. Do you eat many green and yellow vegetables?

0. No	1. Yes

3. Are you careful about your fat intake?

1. No	2. Yes

4. Compared to average, how would you describe the volume of food you typically eat in a meal?

1. Much less	2. Less	3. Same	4. More	5. Much more

5. How would you describe your usual meals?

1. Eat until half-full	2. Eat until 80% full	3. Eat until full

6. Circle the frequency of your average consumption of each of the following beverages:

Frequency	Almost never	1-2 days/ week	3-4 days/ week	Almost daily Cups/glasses/cans/bottles		
				1-2/day	3-4/day	≥5/day
Japanese tea (green tea)	0	1	2	3	4	5
Chinese tea (oolong tea)	0	1	2	3	4	5
Black tea	0	1	2	3	4	5
Other teas	0	1	2	3	4	5
Coffee	0	1	2	3	4	5
Milk	0	1	2	3	4	5
Cola, carbonated soft drinks	0	1	2	3	4	5
100% fruit juice	0	1	2	3	4	5
Vegetable juice	0	1	2	3	4	5

7. How many teaspoons of sugar do you use per cup of coffee or black tea?
(If you do not take sugar, please indicate “0”)

☐☐ teaspoons

COHORT II QUESTIONNAIRE

NAME:
SEX:
ADDRESS:
TELEPHONE NUMBER:

YELLOW FORM – GENERAL MEDICAL BACKGROUND QUESTIONS

Please answer the following questions concerning your past medical history and present health status.

1. Have you ever been diagnosed with any of the following diseases? Please circle all that apply

1. None
2. stroke 3. myocardial infarction 4. hypertension 5. diabetes mellitus 6. hyperlipidemia 7. gout 8. asthma 9. allergy 10. kidney disease 11. chronic hepatitis or liver cirrhosis 12. peptic ulcer 13. biliary stone 14. stomach cancer 15. lung cancer 16. colorectal cancer 17. liver cancer 18. breast cancer 19. uterine cancer 20. other kinds of cancer (______________)

2. Have you experienced any of these symptoms within the past year?

● abrupt chest pain lasting for more than 10 seconds	1. No	2. Yes
● arrhythmia	1. No	2. Yes
● sudden feeling of thickness of the tongue	1. No	2. Yes
● numb hands and feet	1. No	2. Yes
● intermittent claudication	1. No	2. Yes

3. Have your parents had any of the following diseases?

1. stroke 2. diabetes mellitus 3. heart disease, 4. cancer (site:)

Have your siblings had any of the following diseases?

1. stroke 2. diabetes mellitus 3. heart disease, 4. cancer (site:)

4. Have you ever received a blood transfusion?

1. No	2. Yes

5. Are you currently taking any medications prescribed by your physician?

1. No	2. Yes

If yes, please check any of the following drugs you are currently taking:

1. Drugs for hypertension, 2. Drugs for decreasing blood lipid level, 3. Drugs for diabetes mellitus, 4. Drugs for gout, 5. Drugs for angina pectoris, 6. Unknown drugs, 7. Other drugs (____________________)

6. How often do you take vitamin supplements?

1. Almost never
2. 1 to 4 days per week
3. 3. Nearly every day

Please check which kinds of vitamins you take.

1. Vitamin B compound	2. Vitamin C	3. Vitamin E	4. Vitamin A
5. Multi-vitamins	6. Other ( )		

7. Have you undergone a medical examination or screening test within the past year?

1. No	2. Yes

8. Have you had your blood pressure taken within the past year?

1. No	2. Yes

If yes, how would you describe your blood pressure?

1. High	2. Not high	3. Don't know

Please record your most recent blood pressure measurement.

Systolic:				mmHg
Diastolic:				mmHg
	0. Don't remember			

9. Have you ever had your serum total cholesterol measured?

1. No	2. Yes

If yes, how would you describe your most recent blood cholesterol level?

1. High, 2. Not high
3. Don't know

Please provide your most recent serum total cholesterol value.

			mg/dl	0. Don't remember

10. What are your height and body weight?

Height [| |] cm Weight [| |] kg

11. What was your body weight when you were 20 years old?

			kg	0. Don't remember

12. How often do you participate in sports or physical exercise?

0. Almost never	1. 1-3 days a month	2. 1-2 days a week	3. 3-4 days a week	5. Almost every day

PURPLE FORM – SMOKING AND DRINKING QUESTIONS

Please answer the following questions concerning smoking and alcohol drinking.

1. Do you currently smoke cigarettes?

1. No	2. Yes

If yes,

how many cigarettes a day do you smoke ? [ ][ ][ ] Cigarettes /day

how old were you when you began smoking? [ ][ ] years old

If you no longer smoke, but smoked before,

how old were you when you quit smoking? [ ][ ] years old

how many cigarettes per day did you smoke? [ ][ ][ ] Cigarettes /day

how old were you when you began smoking? [ ][ ] years old

2. When you were a primary school or a middle school student, was there anyone who smoked in your family?

1. No	2. Yes

3. How often are you exposed to passive smoking outside the house?

1. Almost never	2. 1-3 days a month	3. 1-4 days a week	4. Almost every day

4. Do you drink alcoholic beverages?

1. No	2. I did but have stopped	3. Yes

How often do you drink Japanese sake, shochu, awamori, beer, whisky, brandy, or wine? (If you have stopped drinking, please write down how often you drank before stopping).

1. Almost never	2. 1-3 days a month	3. 1-4 days a week	4. Almost every day

On average, how much of the following do you drink every day:

Japanese sake [ ][ ] go Shochu [ ][ ] go Awamori [ ][ ] go

Beer (large) [ ][ ] bottles Beer (medium -500ml) [ ][ ] bottles Beer (small -350ml) [ ][ ] bottles Wine [ ][ ] glasses

Whisky, brandy, or vodka [ ][ ] cups

(If you have stopped drinking, please write down how often you drank before stopping)

- How many days per month do you drink at social events? [ ][ ] days
- In sum, what kind of beverages and how much of each kind do you drink at social events?

Japanese sake [ ][ ] go Shochu [ ][ ] go Awamori [ ][ ] go

Beer (large) [ ][ ] bottles Beer (medium -500ml) [ ][ ] bottles Beer (small -350ml) [ ][ ] bottles Wine [ ][ ] glasses

Whisky, brandy, or vodka [ ][ ] cups

(If you have stopped drinking, please write down how often you drank before stopping)

- Do you drink strong alcoholic drinks such as whiskey, brandy, and awamori?

1. No	2. Occasionally	3. Often

- Do you smoke more cigarettes than usual while drinking alcohol?

1. Do not smoke while drinking	2. Smoke as usual	3. More than usual

5. Do you blush soon after drinking alcohol?

1. Yes	2. No	3. Not sure

6. Does any part of your body except your face become red soon after drinking alcohol?

1. Yes	2. No	3. Not sure

7. Do you feel any throbbing of blood vessels in the brain or develop a headache soon after drinking alcohol?

1. Yes	2. No	3. Not sure

8. Does your heart beat faster than usual soon after drinking alcohol?

1. Yes	2. No	3. Not sure

GREEN FORM – BASELINE
DIETARY QUESTIONS

Please answer the following questions concerning your usual food intake.

1. How do you like the following kinds of food? Please check.

Preferences/Dislikes	Like very much	Like a little	Dislike
Food rich in oil	1	2	3
Very salty foods	1	2	3
Very sweet foods	1	2	3
Sour food	1	2	3
Sweets, such as desserts	1	2	3
Hot foods and drinks	1	2	3

2. Which kind of cooking method do you use most often use when you cook the following foods? Please check one of the following methods.

	Raw	Boil	Grill	Deep-fry	Saute
Meats	1	2	3	4	5
Fish and shellfish	1	2	3	4	5
Green vegetables	1	2	3	4	5
Carrots	1	2	3	4	5

3. How often do you have the following kinds of foods? Please check.

Frequency	Almost never	1-2 days /week	3-4 days /week	Almost every day
Fried food	1	2	3	4
Mayonnaise	1	2	3	4
Dressing	1	2	3	4
Ketchup	1	2	3	4

4. On average, how many bowls (normal size) of rice do you have per day?

1. Almost never have rice
2. Approximately [|] bowls a day

5. How often do you have miso soup?

Almost never	1-2 days /week	3-4 days /week	Almost every day

If almost every day, how many cups on average do you have a day? [|] cups

6. Please describe your usual dietary habits. Check how many times you usually eat each food item. When your intake varies by season, write the number of times this month.

Frequency	Almost never	Seldom	1-2 days /week	3-4 days /week	Almost every day
Chicken	1	2	3	4	5
Beef	1	2	3	4	5
Pork	1	2	3	4	5
Ham, sausage, bacon	1	2	3	4	5
Liver	1	2	3	4	5
Fresh fish (sashimi, boiled fish, grilled fish	1	2	3	4	5
Dried fish, dried salted salmon	1	2	3	4	5
Minced fish products	1	2	3	4	5
Canned fish	1	2	3	4	5
Pickled fish	1	2	3	4	5
Whitebait	1	2	3	4	5
Seaweed (kelp, wakame, etc)	1	2	3	4	5
Green vegetables	1	2	3	4	5
Carrots	1	2	3	4	5
Tomato	1	2	3	4	5
Potato	1	2	3	4	5
Bean curd	1	2	3	4	5
Natto	1	2	3	4	5
Tsukemono, nozawana	1	2	3	4	5
Other kinds of tsukemono	1	2	3	4	5
Apples	1	2	3	4	5
Oranges	1	2	3	4	5
Egg	1	2	3	4	5
Milk	1	2	3	4	5
Cheese	1	2	3	4	5
Yogurt	1	2	3	4	5
Butter	1	2	3	4	5
Margarine	1	2	3	4	5
Bread	1	2	3	4	5
Noodles (except instant noodles)	1	2	3	4	5
Instant noodles	1	2	3	4	5
Dessert	1	2	3	4	5
Japanese dessert	1	2	3	4	5

Portion size: How would you describe your average portion size of the following foods? Please look at the following photo examples of food. If the amount is about half that of the example, please choose 'less than the example'; if more than one and a half times the example, please choose 'more than the example'.

	Less than the example	Similar to the example	More than the example
Chicken	1	2	3
Beef	1	2	3
Pork	1	2	3
Liver	1	2	3
Fish	1	2	3
Dried Fish	1	2	3
Whitebait	1	2	3
Spinach	1	2	3
Carrot	1	2	3
Tomato	1	2	3
Potato	1	2	3
Bean Curd	1	2	3
Natto	1	2	3
Apple	1	2	3
Orange	1	2	3
Egg	1	2	3
Milk	1	2	3
Butter or margarine	1	2	3

7. Please choose the three kinds of fish you most often eat.

1. horse mackerel 2. sardines 3. mackerel 4. pacific saury 5. herring
6. sea bream 7. flat fish 8. cod and pollack 9. barracuda 10. atka mackerel
11. tuna 12. yellowtail 13. cultured yellowtail 14. skipjack and frigate mackerel 15.salmon
16. masu 17. conger eel 18. octopus 19. squid and cuttlefish 20. crabs
21. prawns, lobsters and shrimps 22. carp 23. smelt 24. eel 25. Other ( )

8. Do you eat parts of fish or meat burned by cooking?

1. Do not eat	2. Eat

9. Are you careful about your salt intake?

1. No	2. Yes

10. Are you careful about your cholesterol intake such as from egg or meat?

1. No	2. Yes

11. Are you careful about your intake of animal fat such as from butter or bacon?

1. No	2. Yes

12. Do you eat a lot of green and yellow vegetables?

1. No	2. Yes

13. How would you describe the size of your dinner?

1. Do not overeat	2. Eat until full	3. Overeat

14. Do you pay attention to nutritional balance in your diet?

1. Yes, I pay attention	2. I rarely pay attention	3. I do not pay attention

15. Please check the frequency of your average consumption of the following beverages

Frequency	Almost never	1-2 days/ week	3-4 days/ week	Almost daily Cups/glasses/cans/bottles		
				1-2/day	3-4/day	≥5/day
Japanese tea (green tea)	0	1	2	3	4	5
Chinese tea (oolong tea)	0	1	2	3	4	5
Black tea	0	1	2	3	4	5
Coffee	0	1	2	3	4	5
Cola, carbonated soft drinks	0	1	2	3	4	5
100% fruit juice	0	1	2	3	4	5
Vegetable juice	0	1	2	3	4	5

16. Are you able to sleep soon after drinking coffee?

1. No	2. Yes

17. Do you take sugar in coffee or black tea?

1. No	2. Yes

Appendix 4. Example of a food frequency questionnaire at 5-year follow-up (selected pages)[124]

Health Promotion Questionnaire

If you found an error in your name or address, please correct it with a red pen.

The Ministry of Health and Welfare: The Japan Public Health Center-based prospective Study on Cancer and Cardiovascular Disease Research Group

National Cancer Center

National Cardiovascular Center

We may call to ask you some questions regarding the contents of what you have filled in. Please provide your phone number below if you do not mind.

☎ ______ – ______

Please do not fill in anything here.

Do not fill in

Before starting the questionnaire

The Epidemiology Research Group of the Ministry of Health, Labor and Welfare is working on research on "How do I prevent adult illnesses such as cancer, stroke, myocardial infarction, etc.?" In this context, we carried out the "Health Promotion Questionnaire" from 1990 to 1991 targeting people who were born from 1930 through 1949 who live in the cities, towns and villages of five health center districts throughout the nation.

Five years have passed since the survey, and we are carrying out a second questionnaire to find out whether there have been any changes in lifestyle or health status of people during this interval, and also details about the state of your dietary life. We would like to ask your cooperation now that you understand the background of this survey.

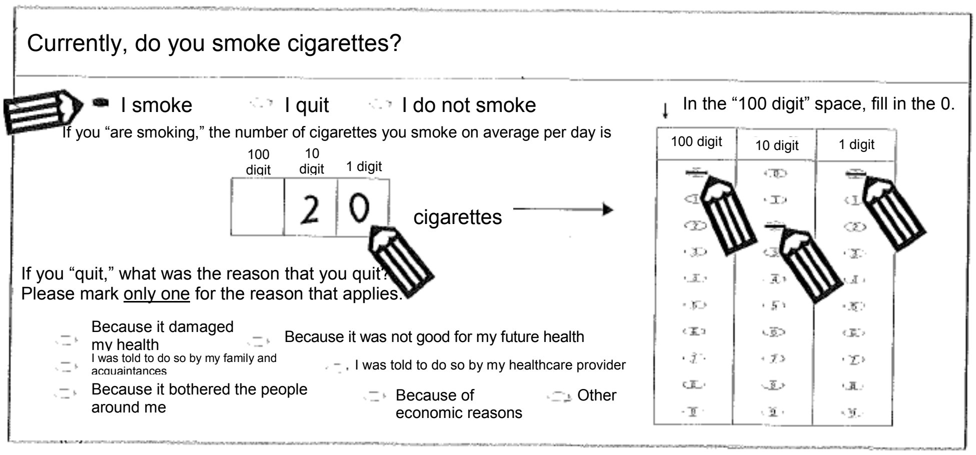
If you are willing to participate this time, please read the "Instructions on How to Filli in the Questionnaire" below and answer the questions beginning on the following page.

Instructions on How to Fill in the Questionnaire

1. As much as possible, please fill in this questionnaire by yourself.
2. Please fill in the given space (the oval circles) that apply with a black pencil, or enter a number of letter in the box. If you choose "Other" in the multiple choice selections, please fill in specific details in the parentheses.
3. Please use an <u>HB, B or H</u> graphite pencil.
4. <u>Please do not use a fountain pen or ballpoint pen.</u>
5. If you have any corrections, please erase <u>them entirely with an eraser</u>.
6. Please do not fill in anything in the blank spaces.

   (example for filling in the mark)

For example, please fill it in as shown below if you currently smoke cigarettes, and you smoke 20 cigarettes on average per day.



What month is it today?					
○ January	○ February	○ March	○ April	○ May	○ June
○ July	○ August	○ September	○ October	○ November	○ December

What is your gender?	○ Male	○ Female

About how tall are you currently?	About how much do you weigh currently?
100 digit / 10 digit / 1 digit: [ ][ ][ ] cm (round off the fractions)	100 digit / 10 digit / 1 digit: [ ][ ][ ] kg (round off the fractions)
100 digit / 10 digit / 1 digit	100 digit / 10 digit / 1 digit

We are going to ask you about "rice (cooked rice)."

About what size rice bowl do you eat with?
○ Small rice bowl ○ Normal rice bowl ○ Donburi large rice bowl

About how many bowls do you eat in 1 day, combining breakfast, lunch and dinner?
○ Less than 1 bowl ○ 1 bowl ○ 2 bowls ○ 3 bowls 4 bowls
○ 5 bowls ○ 6 bowls ○ 7 - 9 bowls ○ 10 bowls or more

Do you eat vitamin-enriched rice?
○ No ○ Yes

Do you mix in wheat or millet or Japanese hie?
○ I do notmix it in ○ I sometimes mix it in ○ I always mix it in

We are going to ask you about "miso soup."

About how frequently do you eat it?
○ I hardly ever eat it ○ 1 - 3 days a month ○ 1 - 2 days a week ○ 3 - 4 days a week
○ 5 - 6 days a week ○ I eat it every day

About how many cups do you eat in 1 day, combining breakfast, lunch and dinner?
○ Less than 1 cup ○ 1 cup ○ 2 cups ○ 3 cups ○ 4 cups
○ 5 cups ○ 6 cups ○ 7 - 9 cups ○ 10 cups or more

How do you season it?
○ Fairly diluted ○ Normal ○ Fairly thick

Do not fill in

Currently, do you smoke cigarettes?
I smoke / I quit / I do not smoke

If you "are smoking," the number of cigarettes you smoke on average per day is

100 digit | 10 digit | 1 digit — cigarettes

100 digit	10 digit	1 digit

If you "quit," what was the reason that you quit?
Please mark only one for the reason that applies.

- Because it damaged my health
- Because it was not good for my future health
- I was told to do so by my family and acquaintances
- I was told to do so by my healthcare provider
- Because it bothered the people around me
- Because of economic reasons
- Other

How frequently do you drink?		
I hardly ever drink	1 - 3 days a month	1 - 2 days a week
3 - 4 days a week	5 - 6 days a week	I drink every day

Please choose the most usual combination that you drink in one day.

(Example) If normally after drinking one large bottle of beer you drink 2 go of Japanese sake, in the "Beer" area fill in "1 bottle" and in the "Japanese Sake" area fill in "2 go," and in the "Shochu or Awamori," "Whiskey," and "Wine" areas, fill in "I do not drink."

Japanese Sake 1 go (180ml)	I do not drink	less than 0.5 go	1 go	2 go	3 go	4 go	5 - 6 go	7 go or more
Shochu or Awamori 1 go (180ml)	I do not drink	less than 0.5 go	1 go	2 go	3 go	4 go	5 - 6 go	7 go or more
*Beer Large bottle (633ml)	I do not drink	less than 0.5 bottle	1 bottle	2 bottles	3 bottles	4 bottles	5 - 6 bottles	7 bottles or more
Whiskey Single (30ml)	I do not drink	less than 0.5 glass	1 glass	2 glasses	3 glasses	4 glasses	5 - 6 glasses	7 bottles or more
Wine Glass (100ml)	I do not drink	less than 0.5 glass	1 glass	2 glasses	3 glasses	4 glasses	5 - 6 glasses	7 bottles or more

*Please make the conversion at medium bottle or 500ml can, 0.8 of a bottle; small bottle or 350ml can, 0.6 of a bottle

Currently, is there a medicine that is prescribed by your healthcare provider and that you take periodically?

- Yes
- No

If "Yes," please mark all that apply.

- High Blood Pressure Medicine
- Medicine to Lower Cholesterol
- Diabetes Medicine
- Gout Medicine
- Other

Mark Not Necessary

Are there any vitamins that you take once or more per week?

Yes No

If answered “yes” above, please fill in the product name, and mark the type of vitamin, frequency that you take it, and time period.
(Example) If you have been taking 1 tablet of the vitamin C agent called “Hi-C S” every day for 8 years, please fill it in as follows.

Vitamin C
Product Name
Hi-C S
Mark Not Necessary

Type and Product Name	Frequency: 1 - 2 tablets a week	3 - 4 tablets a week	5 - 6 tablets a week	1 tablet daily	2 - 3 tablets daily	4 - 6 tablets daily	7 tablets or more daily		Time Period: Less than 1 year	1 - 2 years	3 - 4 years	5 - 9 years	10 - 19 years	20 years or more
Multivitamin														
Product Name:														
No Mark Necessary														
Beta Carotene														
Product Name:														
No Mark Necessary														
Vitamin C														
Product Name:														
No Mark Necessary														
Vitamin E														
Product Name:														
No Mark Necessary														
Other														
Product Name:														
No Mark Necessary														

In the past 5 years (from January 1, 1990 to present), have you been told by your healthcare provider that you have the following illness(es), and you had the following surgery(ies)? Please mark all that apply.

Disease

Stroke	Myocardial Infarction	Angina Pectoris	Diabetes	
Gout	Cataracts	Gall Stones	Urethral Stones or Kidney Stones	
Stomach Ulcers	Duodenal Ulcers	Stomach Polyps	Colon Polyps	Chronic Hepatitis or Cirrhosis of the Liver
Stomach Cancer	Colon Cancer	Liver Cancer	Lung Cancer	
Breast Cancer	Uterine Cancer	Other Cancer → Site ____ (Mark Not Necessary)		

Surgery

Stomach	Colon	Gall Stones	
Ovaries	Lung	Mammary glands	other → Site ____ (Mark Not Necessary)

Do not fill in

Questions about Your Dietary Life

Now some questions about your diet will follow.

Recalling your diet over the past one year, please answer with average frequencies and amounts.

If you answer all the items, a detailed nutritional calculation of your normal dietary life can be made, so we will be able to report to each of you individually at a later date whether you have a nutritional balance, or whether your vitamins are enough, etc.

There are a lot of questions, and it this may be difficult for you, but we ask you to please complete it to the end.

Example

If you eat beef steak about 2 times a month, and the amount you eat per time is about half a steak, then fill it in as follows.

	Name of Food Item	I do not eat it	1 - 3 times a month	1 - 2 times a week	3 - 4 times a week	5 - 6 times a week	Once daily	2 - 3 times daily	4 - 6 times daily	7 times or more daily	Estimated Amount Per Time	Estimated Amount Per Time: Less (half or less) than the estimated amount	Same as the estimated amount	More (1.5 time or more) than the estimated amount
Beef	Steak		—								1 steak slice (about 150g)	—		
	Grilled (grilled meat, etc.)										5 thin slices (about 100g)			

If you hardly ever eat beef steak (less than once a month), fill it in as follows.

	Name of Food Item	I do not eat it	1 - 3 times a month	1 - 2 times a week	3 - 4 times a week	5 - 6 times a week	Once daily	2 - 3 times daily	4 - 6 times daily	7 times or more daily	Estimated Amount Per Time	Estimated Amount Per Time: Less (half or less) than the estimated amount	Same as the estimated amount	More (1.5 time or more) than the estimated amount
Beef	Steak	—									1 steak slice (about 150g)			
	Grilled (grilled meat, etc.)										5 thin slices (about 100g)			

Do not fill in anything in the estimated amount. ↑

Recalling your diet over the past one year, please fill in average frequencies and amounts.

Name of Food Item		I do not eat it	1 – 3 times a month	1 – 2 times a week	3 – 4 times a week	5 – 6 times a week	Once daily	2 – 3 times daily	4 – 6 times daily	Estimated Amount Per Time	Estimated Amount Per Time: Less (half or less) than the estimated amount	Same as the estimated amount	More (1.5 time or more) than the estimated amount
Beef	Steak									1 steak slice (about 150g)			
	Grilled (grilled meat, etc.)									5 thin slices (about 100g)			
	Stewed (curry or stew, etc.)									3 pieces 2 - 3cm-diced (about 50g)			
Pork	Stir-Fried (vegetable stir-fry, etc.)									3 thin slices (about 60g)			
	Fried (port cutlet, etc.)									1 pork cutlet (about 100g)			
	Stewed (curry or stew, etc.)									3 pieces 2 - 3cm-diced (about 50g)			
	Boiled (boiled kakuni or Okinawan name: rafty, etc.)									2 slices (about 60g)			
	Soups (pork soup or Okinawan name: chumi soup, etc.)									2 thin slices (about 40g)			
	Pork liver (Nirareba stir-fry, etc.)									2 slices (about 40g)			
Chicken	Grilled (yakitori, etc.)									2 skewers of yakitori (about 70g)			
	Fried (karaage, etc.)									3 pieces (about 50g)			
	Chicken liver (yakitori, etc.)									1 skewer of yakitori (about 30g)			
Roast Ham										1 normal slice (about 15g)			
Wieners and Sausages										2 pieces (about 30g)			
Bacon										1 strip (about 20g)			
Canned Luncheon Meet										1/8 can (about 40g)			
Milk										1 200cc-glass			
Eggs										1 medium (about 50g)			
Cheese										1 slice of sliced cheese (about 20g)			
Yogurt										1 container (about 120g)			

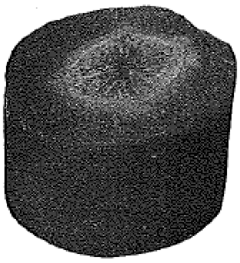
Salted cod, salted mackerel, salted salmon									1 slice of fish meat (about 70g)			
Dried fish (open dried flavor)									1 piece (about 50g)			

Do not fill in

Estimated Amount of Vegetables (full size)

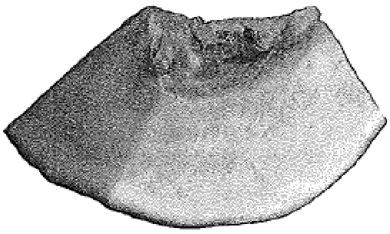
If the amount you eat per time is about the same as in the photograph, please fill in "Same." If it is more than what is in the photograph (1.5 times or more), please fill in "More," and if less (less than half), please fill in "Less."

(a) Carrot, 1/4 carrot
(about 50g)



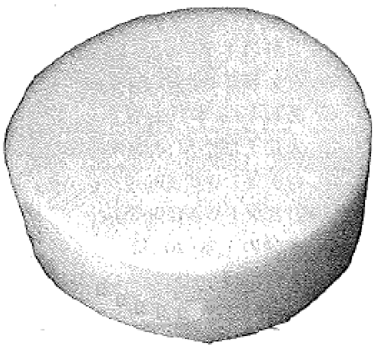
(b) Spinach, 2 bunches
(about 50g)

(c) Pumpkin, one 4 - 5cm cube
(about 40g)



(d) Cabbage, 1/2 medium-sized leaf
(about 30g)

(e) Radish, one 2-cm-thick round slice
(about 80g)



Recalling your diet over the past one year, please fill in average frequencies and amounts.

Name of Food Item	I do not eat it	1 – 3 times a month	1 – 2 times a week	3 – 4 times a week	5 – 6 times a week	Once daily	2 – 3 times daily	4 – 6 times daily	Estimated Amount Per Time	Estimated Amount Per Time: Less (half or less) than the estimated amount	Same as the estimated amount	More (1.5 time or more) than the estimated amount
Canned tuna (sea chicken flakes)									1/4 can (about 20g)			
Salmon or trout									1 slice of fish meat (about 70g)			
Bonito or tuna									4 raw slices (about 60g)			
Cod or flounder									1/2 slice (about 40g)			
Bream (Red Sea bream, Okinawan name: gurkun, Okinawan name: machi, etc.)									1 slice (about 70g)			
Horse mackerel or sardines									1 fish (about 80g)			
Pike or mackerel									1 fish (about 80g)			
Dried whitebait									2 tablespoonfuls (about 10g)			
Cod roe or salmon roe									1/4 sac (about 20g)			
Eel									1/2 fish (about 50g)			
Squid									3 raw slices (about 50g)			
Octopus									1/3 tentacle (about 50g)			
Shrimp									2 Taisho shrimp (about 40g)			
Clams or freshwater clams									10 shucked pieces of meat (about 20g)			
Snails									10 shucked pieces of meat (about 20g)			
Fish cake									1/6 tube (about 20g)			
Fish paste									2 slices (about 20g)			

For the following vegetables, please refer to the photographs on the page on the left, and fill in the frequency or amount you eat in the season when they appear on the market.

Carrot									Refer to photograph (a)			
Spinach									Refer to photograph (b)			
Pumpkin									Refer to photograph (c)			
Cabbage									Refer to photograph (d)			
Radish									Refer to photograph (e)			

Do not fill in

For the following vegetables and fruits, please fill in the frequency or amount you eat in the season when they are available on the market.

Name of Food Item		I do not eat it	1 – 3 times a month	1 – 2 times a week	3 – 4 times a week	5 – 6 times a week	Once daily	2 – 3 times daily	4 – 6 times daily	Estimated Amount Per Time	Estimated Amount Per Time: Less (half or less) than the estimated amount	Same as the estimated amount	More (1.5 time or more) than the estimated amount
Tsukemono Pickles	Takuwan									3 slices (about 30g)			
	Green-leafed tsukemono (Nozawana, leaf mustard)									1 small tsukemono plate (about 30g)			
	Dried plums									1 medium plum (about 8g)			
	Chinese cabbage									1 small tsukemono plate (about 30g)			
	Cucumbers									1 small tsukemono plate (about 30g)			
	Eggplant									1 small tsukemono plate (about 30g)			
Green peppers										1 pepper (about 30g)			
Tomatoes										¼ tomato (about 50g)			
Leeks										2 leeks (about 20g)			
Edible chrysanthemums										1/3 bunch (about 30g)			
Rape										1 stalk (about 20g)			
Broccoli										3 stalks (about 30g)			
Onions										¼ onion (about 50g)			
Cucumbers										1/3 cucumber (about 30g)			
Chinese cabbage										1/3 medium leaf (about 30g)			
Bean sprouts										¼ bag (about 25g)			
Haricot verts										6 beans (about 30g)			
Lettuces										1 medium leaf (about 10g)			
Chingensai (Okinawan name: pak-choi)										1 stalk (about 70g)			
Leaf mustard (Okinawan name: shimana)										2 stalks (about 70g)			
Bitter melon (Okinawan name: goya)										1/2 melon (about 100g)			
Swiss chard (Okinawan name: nsubana)										2 stalks (about 100g)			
Sponge gourd (Okinawan name: nabera)										1 gourd (about 100g)			
Mugwort (Okinawan name: fuchiba)										1 head (about 10g)			

For the following vegetables and fruits, please fill in the frequency or amount you eat in the season when they are available on the market.

Name of Food Item	I do not eat it	1 – 3 times a month	1 – 2 times a week	3 – 4 times a week	5 – 6 times a week	Once daily	2 – 3 times daily	4 – 6 times edaily	Estimated Amount Per Time	Estimated Amount Per Time		
										Less (half or less) than the estimated amount	Same as the estimated amount	More (1.5 time or more) than the estimated amount
Papaya									1/4 papaya (about 50g)			
Mandarin oranges									2 oranges (about 140g)			
Other citrus types (Hasssaku oranges, iyokan, oranges)									1/2 of one (about 75g)			
Apples									1/2 apple (about 85g)			
Persimmons									1/2 persimmon (about 80g)			
Strawberries									5 berries (about 75g)			
Grapes									10 large grapes (about 100g)			
Melons									1/4 prince melon (about 60g)			
Watermelon									1/8 melon (about 1200g)			
Peaches									1/2 peach (about 65g)			
Nashi pears									1/2 pear (about 80g)			
Kiwi fruit									1/2 kiwi (about 50g)			
Pineapple									1/8 pineapple (about 130g)			
Banana									1 banana (about 75g)			

Recalling your diet over the past one year, please fill in average frequencies and amounts.

Bread types (including pastries also)									1 piece of 6 slices (about 60g)			
Udon									1 donburi bowlful (about 250g)			
Soba									1 donburi bowlful (about 200g)			
Okinawa soba									1 donburi bowlful (about 200g)			
Ramen									1 donburi bowlful (about 220g)			
Mochi cakes									1 commercially marketed cake (about 50g)			
Japanese confections (Daifuku, manju)									1 confection (about 70g)			
Cakes									1 slice small cake (about 70g)			

Do not fill in

Recalling your diet over the past one year, please fill in average frequencies and amounts.

Name of Food Item	I do not eat it	1 – 3 times a month	1 – 2 times a week	3 – 4 times a week	5 – 6 times a week	Once daily	2 – 3 times daily	4 – 6 times daily	Estimated Amount Per Time	Estimated Amount Per Time: Less (half or less) than the estimated amount	Same as the estimated amount	More (1.5 time or more) than the estimated amount
Biscuits and Cookies									2 cookies (about 25g)			
Chocolate									1/2 chocolate bar (about 25g)			
Peanuts									20 peanuts (about 20g)			
Tofu (ingredient of miso soup)									5 cubes (about 20g)			
Tofu (fried tofu, or cold or cut into cubes)									1/4 tofu cake (about 75g)			
Yushi dofu									1 soup bowlful (about 150g)			
Freeze-dried Takano tofu or shimi tofu									1/2 slice (about 60g)			
Fried auburaage tofu									1 miso soup bowlful (about 2g)			
Natto									1 small cup (about 50g)			
Satsuma sweet potatoes									1/6 potato (about 40g)			
Potatoes									1/3 potato (about 50g)			
Taro									1 taro (about 30g)			
Shiitake mushrooms									1 mushroom (about 20g)			
Enoki mushrooms/Shimeji mushrooms									1/4 mushroom (about 20g)			
Wakame seaweed or kelp									1 small bowlful (about 20g)			
Hijiki sea vegetable									1 small bowlful (about 20g)			
Nori dried seaweed (roasted seaweed or flavored seaweed)									5 sheets of flavored nori (about 2g)			

Please answer with average frequencies and amounts of what you use at the dining table.

Butter to put on bread									amount to spread on 1 piece of bread (about 8g)			
Margarine to put on bread									amount to spread on 1 piece of bread (about 8g)			
Dressing									1 tablespoonful (about 10g)			
Mayonnaise									1/2 tablespoonful (about 7g)			
Sauce									1 teaspoonful (5g)			
Ketchup									1 teaspoonful (6g)			

How frequently do you drink the following beverages?

Beverage Name	I do not eat it	1 - 2 times a week	3 - 4 times a week	5 - 6 times a week	A cup or glass daily	2 - 3 cups or glasses daily	4 - 6 cups or glasses daily	7 - 9 cups or glasses daily	10 cups or glasses or more daily
Soybean milk									
Japanese tea (green sencha tea)									
Japanese tea (coarse bancha tea or brown-rice genmaicha tea)									
Oolong tea									
Western black tea									
Coffee (other than canned coffee)									
Canned coffee									
Soup									
Lactic acid beverages (Yakult, etc.)									
100% fruit-juice orange juice									
100% fruit-juice apple juice									
Tomato juice									
Soft drinks (colas, etc.)									
Drink tonics (Lipovitan D, etc.)									
Drinking water (tap water or well water)									
Drinking water (marketed or water purifier)									

For people who drink black tea or coffee, do you add sugar or milk?

		I do not add them	Half spoonful	1 spoonful	2 spoonfuls	3 or more spoonfuls
Black tea	Sugar Milk					
Coffee	Sugar Milk					

Do not fill in

Appendix 5. Further acknowledgements

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