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Jiangsu Four Cancers Study: a large case-control study of lung, liver, stomach and esophageal cancers in Jiangsu Province, China

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Abstract

Objective: Cancer is a major public health burden both globally and in China. The most common cancer-related deaths in China are attributable to cancers of the lung, liver, stomach, and esophagus. Previous epidemiologic studies on cancer in China have often been limited by small sample sizes, inconsistent measurements, and lack of precise and accurate data. The Jiangsu Four Cancers (JFC) Study is a population-based case-control study conducted in an effort to obtain consistent and high quality data to investigate the life style, behavioral, environmental, and genetic factors associated with the four major cancers in China. The objective of this paper is to describe the overall design of the JFC Study and report selected findings on the major risk factors of cancers.

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CONFLICTS OF INTEREST
None declared.

Methods: Epidemiologic data were collected from 2003 to 2010 through in-person interviews using a structured questionnaire, and blood samples were drawn. Unconditional logistic regression was used to estimate the associations of putative risk factors with risks of cancers of the lung, liver, stomach, and esophagus.

Results: The Study included 2,871 lung cancer cases, 2,018 liver cancer cases, 2,969 esophageal cancer cases, 2,216 stomach cancer cases, and 8,019 community controls. Low educational level, low income level, tobacco smoking, alcohol drinking, and family history of cancer were confirmed as risk factors of these major cancers.

Conclusions: The JFC Study is one of the largest case-control studies of cancers in the Chinese population and will serve as a rich resource for future research on the four major cancers in China.

Keywords

Lung cancer; liver cancer; esophageal cancer; stomach cancer; case-control study; China

INTRODUCTION

Cancer is one of the leading causes of death worldwide. In 2012, there were 14.1 million adults newly diagnosed with cancer and 8.2 million deaths due to cancer (Ferlay *et al.*, 2013). Of these, 21.8% of all new cancer diagnoses and 26.9% of all cancer deaths occurred in China (Stewart *et al.*, 2014). It is expected that the number of worldwide annual cancer cases will increase to 22 million in the next two decades, a large proportion of which will occur in China (Stewart *et al.*, 2014). Cancers of the lung, liver, stomach, and esophagus are the four most common causes of cancer-related deaths in China, with annual age-standardized mortality rates of 32.5, 21.4, 17.9, and 10.9 per 100,000 persons, respectively (Ferlay *et al.*, 2013). They are also among the top ten cancers in the world in terms of both incidence and mortality (Ferlay *et al.*, 2013).

Identifying risk and protective factors for cancer is a critical step in the public health effort to reduce cancer incidence. Established risk factors for cancer include genetic susceptibility; lifestyle factors such as tobacco use and excessive alcohol consumption; infections such as those of HPV, HBV, HCV, and *H. pylori*; and exposures to various environmental and occupational carcinogens. Protective factors include physical activity, consumption of fruits and vegetables, and sunscreen use. However, there are many other factors for which either the available data are limited or studies have reported inconsistent results. For example, genetic polymorphisms found to be associated with cancer risk in some studies are often observed to have no association in other studies. A number of dietary factors, such as green tea (Yuan *et al.*, 2013), red meat (Bouvard *et al.*, 2015), and soy (Chen *et al.*, 2014), have also shown inconsistent relationships with cancer risk. Common methodological limitations, such as small sample sizes, inconsistent and imprecise measurements, and poor quality control, are partially accountable for such inconsistencies.

The Jiangsu Four Cancers (JFC) Study was conducted in an effort to collect consistent, high-quality data to minimize the effect of methodological limitations in the analysis. The JFC Study is a large scale, community-based case-control study of the cancers of the lung, liver, stomach, and esophagus in a Chinese population. Jiangsu Province, located in South-Eastern China, is an ideal location for conducting such a study due to its well-established cancer registry and high incidence of cancer. In 2010, the estimated age-adjusted mortality rates in Jiangsu Province were 26.1, 21.3, 24.5, and 20.2 per 100,000 for cancers of the lung, liver, stomach, and esophagus, respectively (Zhou *et al.*, 2012). The objectives of the JFC Study are 1) to evaluate the effects of established and putative risk and protective factors of cancers; 2) to test new hypotheses regarding genetic susceptibility; and 3) to examine potential gene-environment interactions for the most common causes of cancer deaths in China. In this paper, we describe the overall study design of the JFC Study and report the associations of putative risk factors with risks of the four cancers.

MATERIALS AND METHODS

Study Population

The JFC Study was funded by the government of Jiangsu Province and approved by the Human Subject Protection Committees of the Jiangsu Provincial Center for Disease Control (CDC) and the University of California at Los Angeles (UCLA). All participants provided informed consent prior to entering the study. Study participants were recruited from four counties in Jiangsu Province—Chuzhou, Dafeng, Ganyu and Tongshan—covering a population of approximately 4.3 million. The highest and the lowest cancer incidence and mortality in the province are observed in Dafeng and Tongshan, respectively. We chose to include these areas in order to contrast them in terms of their distributions of risk and protective factors of cancers.

Eligible cases were patients with a pathologically or clinically confirmed diagnosis of primary cancer of the lung, liver, stomach, or esophagus reported to the population-based cancer registry of one of the four counties between January 1, 2003 and December 31, 2010. All cancer cases were classified according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) and the International Classification of Diseases for Oncology, 2nd edition (ICD-O-2) and. Cases were identified through a rapid reporting system in which all regional hospitals were required by the local health authorities to report new cancer patients within a month after diagnosis. As the cancer registry departments are housed within the local CDC, investigators from the local CDC were able to identify and interview cases promptly after their diagnosis. Cases were required to be at least 18 years old, residents of the respective county for at least five years, and in stable medical condition as determined by their physician. Second primary and recurrent cancer cases were excluded. Data regarding the stage and histological type of cancer were not collected by the cancer registries and, therefore, are not available for analysis.

Potential controls were identified through the demographic database of each county. For each cancer case, a control was randomly selected from a list of residents living in the same county and within the same sex and age group (±5 years). Controls were required to be at least 18 years old, had lived in the respective county for at least five years, without any history of cancer, and in stable medical condition (i.e., apparently healthy individuals, not otherwise submitted to any screening). When individuals did not meet the eligibility criteria or refused to participate in the study, their basic demographic data were recorded and the same selection process was used to identify another potential control. Based on estimated power calculations for examining various exposure-cancer associations and gene-environment interactions, the original plan was to conduct a 1:1 matched study with 600 cases and 600 healthy controls for each cancer site in each county, for a total of 2,400 cases and 2,400 controls for each cancer site. However, we subsequently decided to pool together all controls in order to increase the statistical power of the study.

Data collection

Trained interviewers conducted in-person interviews using a standardized questionnaire which had been field tested in a previous study (Mu *et al.*, 2005). A summary of the structure of the questionnaire is provided in Table 1. The questionnaire included 1) demographic and socioeconomic factors; 2) residential environment; 3) health behaviors, including dietary practices (using a standardized food frequency questionnaire covering 30 dietary indicators and 86 food items), tobacco smoking, alcohol drinking, tea drinking, and physical activity; 4) medical history; 5) occupational history and related exposures; 6) family history of cancer; and 7) reproductive history among female participants. The interviews took an average of 45 minutes, during which measurements of the participant's height, weight, and blood pressure were also taken. Cases were interviewed either in the hospitals or their homes, while controls were interviewed in their homes. The interviews of cases took place as soon as new cancers were reported and registered in the county's cancer registry system. If a case was too ill to be interviewed, a family member served as a proxy respondent. The interviews of controls took place twice a year.

Strict quality control measures were in place for data collection and management. Staff of the Jiangsu CDC and the county CDCs monitored the interviews. Prior to the commencement of the Study, two-day intensive training sessions and field practices were provided to all interviewers by the Jiangsu CDC and UCLA staff for each of the four counties separately. Any new interviewers were trained and supervised by an experienced interviewer, and all interviewers received refresher training during annual reviews. Ten percent of the participants were randomly selected and re-interviewed, and results indicated an overall accuracy of 96% for cases and 97% for controls. The data were doubly entered into a database using EpiData (Odense, Denmark) and reviewed by research staff at the respective county CDC, then cleaned and combined by an epidemiologist at the Jiangsu CDC.

Approximately 5–8 mL of non-fasting peripheral blood samples were collected from the study participants after their interviews. Blood specimens were collected into EDTA- or heraprin-coated tubes and assigned an identification number. They were then separated into serum, red blood cells, and white blood cells and stored below −20°C at the local CDCs, after which they were transported to the Jiangsu CDC, where they are currently stored below −70°C.

Statistical analysis

We compared the distributions of socio-demographic factors and putative risk factors of cancer between cases and controls using the χ^2 test and estimated the associations between these factors and risk of cancer using unconditional logistic regression. Socio-demographic characteristics included sex, age, educational level, and income 10 years ago (calculated as total household income divided by the number of household members). For putative risk factors of cancer, we examined tobacco smoking status, pack-years of tobacco smoking, frequency of alcohol consumption, amount of alcohol consumption in the 1990s, and family history of cancer. Ever smokers were defined as individuals who had smoked at least 100 cigarettes in their lifetimes. The amount of alcohol intake was calculated based on the reported average frequency and number of drinks consumed in the 1990s and known ethanol concentrations of the six most popular alcoholic beverages in China (i.e., high-degree liquor, low-degree liquor, beer, wheat liquor, rice liquor, and wine). Adjusted odds ratios (aOR) and 95% confidence intervals (CI) were obtained by controlling for county of residence (Dafeng, Ganyu, Chuzhou, and Tongshan), age (<50, 50–59, 60–69, and ≥70 years old), sex, educational level (illiterate, primary school, middle school, and high school or above), income 10 years ago (<1,000, 1,000–1,499, 1,500–2,499, and ≥2,500 Yuan/year), pack-years of tobacco smoking (none, 1–20, 20–39, and ≥40), amount of alcohol consumption in the 1990s (none, 1–49, and ≥50 grams of ethanol per day), and family history of any cancer. All analyses were conducted using SAS v9.4 (SAS Institute; Cary, NC).

RESULTS

Basic information about the JFC study data, including numbers of reported cases, numbers of samples collected from each county, and methods of cancer diagnoses, are summarized in Table 2. During 2003–2010, the total numbers of new cancer cases reported in Jiangsu Province were 14,770 for esophageal cancer, 8,763 for stomach cancer, 9,152 for lung cancer, and 6,815 for liver cancer. Tongshan County did not have a cancer registry system in place until 2004. Hence, the numbers of cases for Tongshan County in 2003 were not counted. We collected questionnaire data from 8,019 controls, 2,969 esophageal cancer cases, 2,216 stomach cancer cases, 2,871 lung cancer cases, and 2,018 liver cancer cases. Proxy interviews were conducted for 28% of the esophageal cancer cases, 32% of the stomach cancer cases, 38% of the lung cancer cases, and 39% of the liver cancer cases. The participation rates were 87% among controls, 30% among esophageal cancer cases, 40% among stomach cancer cases, 43% among lung cancer cases, and 37% among liver cancer cases. The proportions of cases and controls recruited from each county ranged from 14.5% (esophageal cancer cases from Tongshan) to 34.3% (liver cancer cases from Tongshan). Blood samples are available for 83% of the controls, 83% of the esophageal cancer cases, 77% of the stomach cancer cases, 63% of the lung cancer cases, and 59% of the liver cancer cases. Overall, most of the questionnaire data elements contain complete or nearly complete (> 90%) data. The cancer registry data included information on methods of diagnosis, the distributions of which varied widely across cancer sites. For each caner site, over 90% of the cases had been diagnosed using either medical imaging, pathology, endoscopy, or biochemistry.

The distributions and associations of socio-demographic characteristics with risks of cancer are shown in Table 3. Approximately 70% of the study participants were male. The mean age among controls was 64 years old and between 59 (liver cancer) and 66 (esophageal cancer) years old among cases. Because the cases and controls were originally matched on sex and age, we did not estimate odd ratios for those two variables. Large proportions of both cases and controls were poorly educated, with illiteracy rates ranging from 38.0% among liver cancer cases to 57.9% among esophageal cancer cases. Educational level was inversely associated with risks of esophageal, stomach, and liver cancers (High school or above vs. illiterate, aOR=0.54, 95% CI 0.39–0.76 for esophageal cancer, aOR=0.60, 95% CI=0.44–0.83 for stomach cancer, and aOR=0.71, 95% CI 0.54–0.93 for liver cancer). Income level was inversely associated with risks of esophageal and stomach cancers (≥2,500 vs. <1,000 Yuan/year, aOR=0.53, 95% CI 0.46–0.60 for esophageal cancer and aOR=0.77, 95% CI 0.67–0.89 for stomach cancer).

The distributions and adjusted odds ratios of major risk factors of cancer are presented in Table 4. Tobacco smoking was positively associated with all four cancer sites (aOR=1.68, 95% CI 1.50–1.87 for esophageal cancer, aOR=1.61, 95% CI 1.43–1.81 for stomach cancer, aOR=2.86, 95% CI 2.55–3.21 for lung cancer, and aOR=1.27, 95% CI 1.12–1.43 for liver cancer). We observed dose-response relationships between pack-years of smoking and risks of cancer, with *P* for trend of less than 0.001 for esophageal, stomach, and lung cancers, and P=0.011 for liver cancer. Cases were more likely than controls to drink alcohol across all four cancer sites. Alcohol drinking frequency was positively associated with risks of esophageal and liver cancers, with *P* for trend of less than 0.001. Similarly, dose-response relationships were observed between amount of alcohol consumption in the 1990s and risks of esophageal and liver cancers (P<0.001 for both). Those who had consumed an average of at least 50 grams of ethanol per day in the 1990s were also at an increased risk for stomach cancer (aOR=1.18, 95% CI 1.02–1.36). Family history of cancer was associated with increased risks of cancers of the esophagus (aOR=1.63, 95% CI 1.45–1.83), stomach (aOR=1.48, 95% CI 1.30–2.68), and liver (aOR=1.62, 95% CI 1.41–1.85).

DISCUSSION

The JFC Study, one of the largest case-control studies of cancer among Chinese populations, offers extensive data collected through strict quality assurance procedures. The results of our preliminary analyses confirm the known effects of educational level, income level, tobacco smoking, alcohol drinking, and family history of cancer on cancer risk. These findings are consistent with the results of many previous studies, which support the validity of our data. Earlier analyses of this study based on data from two counties (Dafeng and Ganyu) have suggested several risk and protective factors (Wu *et al.*, 2009, 2011a,b, 2013; Jin *et al.*, 2013, 2014), and these research findings have been translated into the implementation of county-level cancer prevention efforts in both Dafeng and Ganyu.

Comparable past studies which have also examined the epidemiology of the leading causes of cancer-related deaths in Chinese populations using large sample sizes include those reported by Ji *et al.* (1996; 1,124 stomach cancer cases), Gao *et al.* (1994; 734 esophageal cancer cases), Lo *et al.* (2013; 1,540 lung cancer cases), and Yu *et al.* (2003; 577 liver cancer cases). A recent cohort study of note is the China Kadoorie Biobank (CKB) which includes 500,000 adults in 10 different parts of China (Chen *et al.*, 2005, 2011). Since the CKB also offers large, extensive data on both genetic and environmental factors which may be associated with various types of cancers, it would be interesting to compare the results from the CKB with those from the JFC Study.

Despite being a well-designed study, the JFC Study has several limitations. Many potential cases refused to participate, which may have resulted in selection bias if those who agreed to participate were systematically different from those who refused in terms of their exposure distributions. However, the distributions of key socioeconomic and behavioral factors (e.g., tobacco smoking and alcohol drinking) observed among the participants closely agree with known patterns in the study area. Diagnostic information came from local cancer registries, which lacked data on cancer stage and histology. Because this was a retrospective case-control study, the self-reported questionnaire data might be affected by recall bias, had there been differences in the ways in which cases and controls reported their exposure histories. Lastly, some of the information provided by proxy respondents may not be accurate. Therefore, future analyses using the JFC Study data should be supplemented with bias and sensitivity analyses to the extent possible.

In addition to the preliminary descriptive analyses presented here, there are many further analyses to be carried out using the data from the JFC Study. These include investigations of the roles of various lifestyle factors such as dietary habits and physical activity, environmental factors such as exposure to indoor and outdoor air pollution, genetic factors related to cancer susceptibility, and infections by HPV, HBV, HCV, and *H. pylori*. Furthermore, various gene-environment interactions will also be examined using the data from this study. Therefore, we expect the JFC Study to serve as a rich resource for many future epidemiologic studies of the four major cancers in China.

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Table 1.

Summary of questionnaire data collected in the Jiangsu Four Cancers Study, 2003–2010

1. Demographic and socioeconomic data
Age
Sex
Place of birth
Place of residence
Household composition
Education
Income
2. Residential environment
Nearby sources of environmental pollution
Type and size of residence
Household ventilation
Type of fuel used for heating and cooking
3. Health behaviors
Diet (food frequency questionnaire)
Tobacco smoking and passive smoking
Alcohol
Tea drinking
Physical activity
4. Medical history
5. Occupational history and related exposures
Exposure to pesticide
6. Family history of cancer
7. Reproductive history among women
Age at menarche
Age at menopause
History of pregnancy
Breast feeding practices
Contraception
Hormone replacement therapy

Table 2.

Population and sample sizes of the Jiangsu Four Cancers Study, 2003–2010

Four Study Sites in Jiangsu Province					
Total population in 2010		Cancer cases reported in 2003–2010[a]			
		Esophageal cancer	Stomach cancer	Lung cancer	Liver cancer
4,275,385		14,770	8,763	9,152	6,815
Jiangsu Four Cancers Study					
	Controls, N (%)	Cases, N (%)			
		Esophageal cancer	Stomach cancer	Lung cancer	Liver cancer
Questionnaire data collected	8,019 (100)	2,969 (100)	2,216 (100)	2,871 (100)	2,018 (100)
Proxy interviews	0 (0)	822 (27.7)	712 (32.1)	1,097 (38.2)	793 (39.3)
Blood samples collected	6,650 (82.9)	2,459 (82.8)	1,710 (77.2)	1,799 (62.7)	1,190 (59.0)
County of residence					
Dafeng	2,536 (31.6)	639 (21.5)	644 (29.1)	624 (21.7)	632 (31.3)
Ganyu	2,010 (25.1)	931 (31.4)	570 (25.7)	799 (27.8)	390 (19.3)
Chuzhou	1,180 (14.7)	968 (32.6)	470 (21.2)	514 (17.9)	303 (15.0)
Tongshan	2,293 (28.6)	431 (14.5)	532 (24.0)	934 (32.5)	693 (34.3)
Method of cancer diagnosis					
Medical imaging[b]		639 (21.5)	422 (19.0)	2,065 (71.9)	1,593 (78.9)
Pathology		1,240 (41.8)	1,035 (46.7)	508 (17.7)	237 (11.7)
Endoscopy		898 (30.2)	644 (29.1)	89 (3.1)	12 (0.6)
Biochemistry[c]		34 (1.1)	32 (1.4)	48 (1.7)	85 (4.2)
Clinical diagnosis		158 (5.3)	83 (3.7)	161 (5.6)	91 (4.5)

[a]Does not include the number of cases from Tongshan in 2003.

[b]Includes computer tomography (CT), X-ray, ultrasound, and magnetic resonance imaging (MRI).

[c]Includes biochemistry, immunology, cytology, and alpha-fetroprotein (AFP) tests.

Table 3.

Associations between sociodemographic characteristics and risks of cancer in the Jiangsu Four Cancers Study, 2003–2010

Sociodemographic characteristics	Controls	Esophageal cancer		Stomach cancer		Lung cancer		Liver cancer	
	N (%)	N (%)	aOR (95% CI)[a]	N (%)	aOR (95% CI)[a]	N (%)	aOR (95% CI)[a]	N (%)	aOR (95% CI)[a]
Sex									
Male	5,767 (71.9)	2,103 (70.8)		1,632 (73.6)		1,984 (69.1)		1,538 (76.2)	
Female	2,252 (28.1)	866 (29.2)		584 (26.4)		887 (30.9)		480 (23.8)	
Age (years)									
<50	884 (11.0)	138 (4.6)		237 (10.7)		304 (10.6)		474 (23.5)	
50–59	1,794 (22.4)	668 (22.5)		473 (21.3)		635 (22.1)		606 (30.0)	
60–69	2,565 (32.0)	1,095 (36.9)		745 (33.6)		931 (32.4)		515 (25.5)	
≥70	2,776 (34.6)	1,068 (35.97)		761 (34.3)		1,001 (34.9)		423 (21.0)	
Mean (SD)	63.9 (11.4)	65.6 (9.5)		63.8 (11.2)		63.9 (11.3)		58.7 (12.2)	
Education									
Illiterate	3,831 (47.8)	1,718 (57.9)	1.00 (reference)	1,096 (49.5)	1.00 (reference)	1,384 (48.2)	1.00 (reference)	766 (38.0)	1.00 (reference)
Primary school	2,515 (31.4)	898 (30.2)	0.87 (0.77–0.98)	773 (34.9)	1.06 (0.94–1.20)	976 (34.0)	1.15 (1.03–1.30)	664 (33.1)	0.89 (0.77–1.02)
Middle school	1,320 (16.5)	289 (9.7)	0.65 (0.55–0.77)	279 (12.6)	0.72 (0.60–0.86)	402 (14.0)	0.90 (0.76–1.06)	464 (23.0)	0.89 (0.75–1.05)
High school or above	335 (4.2)	57 (1.9)	0.54 (0.39–0.76)	62 (2.8)	0.60 (0.44–0.83)	95 (3.3)	0.96 (0.73–1.27)	113 (5.6)	0.71 (0.54–0.93)
Missing	18 (0.2)	7 (0.2)		6 (0.3)		14 (0.5)		11 (0.5)	
P for trend			<0.001		<0.001		0.562		0.020
Income 10 years ago (Yuan/year)									
<1,000	1,710 (21.3)	883 (29.7)	1.00 (reference)	525 (23.7)	1.00 (reference)	606 (21.1)	1.00 (reference)	404 (20.0)	1.00 (reference)
1,000–1,499	1,530 (19.1)	625 (21.1)	0.84 (0.73–0.97)	437 (19.7)	0.92 (0.79–1.08)	560 (19.5)	1.05 (0.90–1.22)	405 (20.1)	1.00 (0.85–1.19)
1,500–2,499	2,074 (25.9)	746 (25.1)	0.74 (0.65–0.84)	563 (25.4)	0.85 (0.73–0.98)	698 (24.3)	1.02 (0.89–1.17)	487 (24.1)	0.84 (0.71–0.99)
≥2,500	2,572 (32.1)	635 (21.4)	0.53 (0.46–0.60)	630 (28.4)	0.77 (0.67–0.89)	918 (32.0)	1.12 (0.98–1.28)	683 (33.8)	0.93 (0.79–1.08)
Missing	133 (1.7)	80 (2.7)		61 (2.8)		89 (3.1)		39 (1.9)	
P for trend			<0.001		<0.001		0.136		0.161

aOR, adjusted odds ratio; CI, confidence interval; SD, standard deviation

[a] Odds ratios were adjusted for county of residence, pack-years of tobacco smoking, alcohol drinking amount in the 1990s, family history of cancer, and mutually adjusted for all the other variables in this table. Odds ratios for sex and age are not reported because the cases and controls were originally matched on sex and age.

Table 4.

Associations between putative risk factors of cancer and risk of cancer in the Jiangsu Four Cancers Study, 2003–2010

Risk factors	Controls	Esophageal cancer		Stomach cancer		Lung cancer		Liver cancer	
	N (%)	N (%)	aOR (95% CI)[a]	N (%)	aOR (95% CI)[a]	N (%)	aOR (95% CI)[a]	N (%)	aOR (95% CI)[a]
Tobacco smoking									
Never	4,292 (53.5)	1,159 (39.0)	1.00 (reference)	923 (41.7)	1.00 (reference)	1,078 (37.5)	1.00 (reference)	976 (48.4)	1.00 (reference)
Ever	3,727 (46.5)	1,810 (61.0)	1.68 (1.50–1.87)	1,293 (58.3)	1.61 (1.43–1.81)	1,793 (62.5)	2.86 (2.55–3.21)	1,042 (51.6)	1.27 (1.12–1.43)
Pack-years of tobacco smoking									
0	4,292 (53.5)	1,159 (39.0)	1.00 (reference)	923 (41.7)	1.00 (reference)	1,078 (37.5)	1.00 (reference)	976 (48.4)	1.00 (reference)
1–20	840 (10.5)	297 (10.0)	1.38 (1.16–1.63)	264 (11.9)	1.49 (1.25–1.76)	258 (9.0)	1.86 (1.56–2.21)	284 (14.1)	1.33 (1.12–1.58)
20–39	1,163 (14.5)	556 (18.7)	1.71 (1.48–1.97)	346 (15.6)	1.37 (1.17–1.61)	449 (15.6)	2.44 (2.10–2.84)	320 (15.9)	1.18 (1.00–1.39)
≥40	1,227 (15.3)	695 (23.4)	2.00 (1.74–2.31)	512 (23.1)	1.95 (1.68–2.27)	800 (27.9)	4.43 (3.83–5.12)	278 (13.8)	1.24 (1.04–1.48)
Missing	497 (6.2)	262 (8.8)		171 (7.7)		286 (10.0)		160 (7.9)	
P for trend			<0.001		<0.001		<0.001		0.011
Alcohol drinking frequency									
Never	4,303 (53.7)	1,372 (46.2)	1.00 (reference)	1,073 (48.4)	1.00 (reference)	1,463 (51.0)	1.00 (reference)	891 (44.1)	1.00 (reference)
Occasionally	1,472 (18.4)	546 (18.4)	1.20 (1.04–1.39)	412 (18.6)	1.04 (0.90–1.21)	546 (19.0)	1.04 (0.90–1.20)	408 (20.2)	1.35 (1.15–1.57)
Often	2,244 (28.0)	1,051 (35.4)	1.40 (1.23–1.60)	731 (33.0)	1.10 (0.96–1.26)	862 (30.0)	0.98 (0.86–1.11)	719 (35.6)	1.55 (1.34–1.79)
P for trend			<0.001		0.177		0.740		<0.001
Alcohol drinking amount in the 1990s (grams of pure ethanol per day)									
0	5,018 (62.6)	1,627 (54.8)	1.00 (reference)	1,281 (57.8)	1.00 (reference)	1,743 (60.7)	1.00 (reference)	1,128 (55.9)	1.00 (reference)
1–49	1,359 (16.9)	509 (17.1)	1.14 (0.99–1.31)	381 (17.2)	0.98 (0.84–1.14)	451 (15.7)	0.90 (0.77–1.03)	341 (16.9)	1.11 (0.94–1.30)
≥ 50	1,492 (18.6)	773 (26.0)	1.46 (1.28–1.67)	523 (23.6)	1.18 (1.02–1.36)	617 (21.5)	1.07 (0.93–1.23)	505 (25.0)	1.50 (1.29–1.75)
Missing	150 (1.9)	60 (2.0)		31 (1.4)		60 (2.1)		44 (2.2)	
P for trend			<0.001		0.037		0.466		<0.001
Family history of any cancer									
No	6,443 (80.3)	2,097 (70.6)	1.00 (reference)	1,611 (72.7)	1.00 (reference)	2,315 (80.6)	1.00 (reference)	1,459 (72.3)	1.00 (reference)
Yes	1,576 (19.7)	872 (29.4)	1.63 (1.45–1.83)	605 (27.3)	1.48 (1.30–1.68)	556 (19.4)	1.09 (0.96–1.24)	559 (27.7)	1.62 (1.41–1.85)

aOR, adjusted odds ratio; CI, confidence interval

[a]Odds ratios were adjusted for county of residence, age, sex, education, income 10 years ago, pack-years of smoking (except when analyzing smoking), alcohol drinking amount in the 1990s (except when analyzing alcohol drinking), and family history of cancer (except when analyzing family history of cancer).