3. 細胞診の精度管理（1/2）

解説：(5) ~ (9) 及び (12) が自施設以外で行われる場合は、実施している施設での状況を確認する。医師会など、検査を委託している機関から得られる情報による確認も可とする。

	①実施している	②実施していない	③わからない	④回答できない
(1) 細胞診は直視下に子宮頸部及び腟部表面の全面擦過により細胞を採取し、迅速に処理（固定など）しているか。	○	○	○	○
(2) 各検診機関、医療機関で採取された細胞診検体が適切な細胞診標本に作製されているかどうか確認しているか。	○	○	○	○
(3) 細胞診の方法（従来法 / 液状検体法、採取器具）を、都道府県（あるいは市町村、医師会）等の求めに応じて報告できるか。	○	○	○	○
(4) 細胞診判定の委託機関（施設名）を仕様書に明記しているか 解説：自施設で実施している場合は「①実施している」とする。	○	○	○	○
(5) 公益社団法人日本臨床細胞学会の認定を受けた細胞診専門医と細胞検査士が連携して検査を行っているか※。 ※公益社団法人日本臨床細胞学会　細胞診精度管理ガイドライン参照	○	○	○	○
(6) 細胞診陰性と判断された検体は、その 10%以上について、再スクリーニングを行っているか※。または再スクリーニング施行率を報告できるか。 ※公益社団法人日本臨床細胞学会　細胞診精度管理ガイドライン参照 解説：10%以上であれば「①実施している」とし、10% 未満であれば「②実施していない」とする。また公益社団法人日本臨床細胞学会の認定施設においては、再スクリーニング率を学会に報告していれば「①実施している」とする。	○	○	○	○
(7) 細胞診の結果は、速やかに検査を依頼したものに通知しているか。 解説：依頼したものとは、市町村、細胞診委託元検診機関、受診者のいずれも可。	○	○	○	○
(8) 細胞診結果の報告には、ベセスダシステム※を用いているか。 ※ Bethesda System による分類：The Bethesda System for Reporting Cervical Cytology second edition およびベセスダシステム 2001 アトラス 参照	○	○	○	○
(9) 細胞診結果には、検体の状態に応じて「適正・不適正」（ベセスダシステムに基づく）を明記しているか。	○	○	○	○
(10) 検体が適正でなく、判定できないと判断された場合には、再検査を行っているか。	○	○	○	○
(11) 検体が適正でない場合はその原因等を検討し対策を構じているか。	○	○	○	○
(12) がん発見例は、過去の細胞所見の見直しを行っているか。	○	○	○	○

3. 細胞診の精度管理（2/2）

解説：（13）が自施設以外で行われる場合は、実施している施設での状況を確認する。医師会など、検査を委託している機関から得られる情報による確認も可とする。

	①実施している	②実施していない	③わからない	④回答できない
(13) 標本は少なくとも 3 年間は保存しているか。	○	○	○	○
(14) 検診結果は少なくとも 5 年間は保存しているか。	○	○	○	○

「④回答できない」と回答した場合は、その理由を具体的にお書きください。

4. システムとしての精度管理

	①実施している	②実施していない	③わからない	④回答できない
(1) 精密検査結果※及び治療結果の報告を、精密検査機関（あるいは市町村、医師会等）から受けているか。 ※病理組織診断、臨床進行期を指す。治療機関からの報告も含む。	O	O	O	O
(2) 受診者への通知・説明、またはそのための市町村への結果報告は、検診受診後 4 週間以内になされているか。	O	O	O	O
(3) 診断のための検討会や委員会（第三者の子宮頸がん専門家を交えた会）を設置しているか。 解説：所属する医師会あるいは市町村等による、診断・判定の精度向上のための症例検討会が定期的に開催され、そこに参加している場合は「①実施している」とする。	O	O	O	O
(4) チェックリストに基づく検討を実施しているか。 解説：チェックリストの項目（この調査票記載の項目のこと）の達成状況を確認し、改善に向けた検討を行なっているか。	O	O	O	O
(5) 市町村へのがん検診の集計・報告は、地域保健・健康増進事業報告に必要な項目で集計しているか。 解説：個人の受診結果報告書等をそのまま提出する場合は、市町村から求められた情報が報告書に全て含まれていること。	O	O	O	O
(6) 都道府県がプロセス指標（受診率、要精検率、精検受診率、がん発見率、陽性反応適中度）に基づく検討ができるようデータを提出しているか。 解説：個人の受診結果報告書等をそのまま提出する場合は、市町村から求められた情報が報告書に全て含まれていること。	O	O	O	O

「④回答できない」と回答した場合は、その理由を具体的にお書きください。

自治体名（市区町村名）	医療機関 / 検診機関名	メールアドレス
担当者名	TEL	FAX

質問は以上です。記入漏れがないかをご確認の上、
同封の返信用封筒に入れ、ポストに投函して下さい。
ご協力ありがとうございました。

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
Shoichiro Tsugane	Epidemiology of ESCC	Nobutoshi Ando	Esophageal Squamous Cell Carcinoma.	Springer Japan	Tokyo	2015	1-12
津金昌一郎	胃がんを遠ざける生活習慣	認定NPO法人日本胃がん予知・診断・治療研究機構	胃がんリスク検診（ABC検診）マニュアル（改訂2版）胃がんを予知して，予防するために	南山堂	東京	2014	159-161
笹月静、津金昌一郎	がん予防	丹羽利充	臨床栄養実践ガイド	中外医学社	東京	2014	236-240
斎藤　博、雑賀公実子、町井涼子.	自治体担当者のためのがん検診精度管理マニュアル	斎藤博、雑賀公実子、町井涼子.	自治体担当者のためのがん検診精度管理マニュアル	独立行政法人国立がん研究センターがん対策情報センター発行	東京	2014	

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Hidaka A, Sasazuki S, Matsuo K, Ito H, Sawada N, Shimazu T, Yamaji T, Iwasaki M, Inoue M, Tsugane S; JPHC Study Group.	Genetic polymorphisms of ADH1B, ADH1C and ALDH2, alcohol consumption, and the risk of gastric cancer: the Japan Public Health Center-based prospective study.	Carcinogenesis	36(2)	223-31	2015

Shimazu T, Wakai K, Tamakoshi A, Tsuji I, Tanaka K, Matsuo K, Nagata C, Mizoue T, Inoue M, Tsugane S, Sasazuki S; Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan.	Association of vegetable and fruit intake with gastric cancer risk among Japanese: a pooled analysis of four cohort studies.	Ann Oncol.	25(6)	1228-33	2014
Hidaka A, Sasazuki S, Goto A, Sawada N, Shimazu T, Yamaji T, Iwasaki M, Inoue M, Noda M, Tajiri H, Tsugane S, for the JPHC Study Group.	Plasma insulin, C-peptide, and blood glucose and risk of gastric cancer: The Japan Public Health Center-based Prospective Study.	Int J Cancer	136(6)	1402-10	2015
Tanaka K, Tsuji I, Tamakoshi A, Matsuo K, Wakai K, Nagata C, Mizoue T, Inoue M, Tsugane S, Sasazuki S; Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan.	Diabetes mellitus and liver cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population.	Jpn J Clin Oncol	44(10)	986-99	2014
Pham NM, Mizoue T, Tanaka K, Tsuji I, Tamakoshi A, Matsuo K, Wakai K, Nagata C, Inoue M, Tsugane S, Sasazuki S; Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan.	Meat consumption and colorectal cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population.	Jpn J Clin Oncol	44(7):	641-50	2014
Zheng W, McLerran DF, Rolland B, Fu Z, Boffetta P, He J, Gupta PC, Ramadas K, Tsugane S (9th/56), et al.	Burden of total and cause-specific mortality related to tobacco smoking among adults aged ≥ 45 years in Asia: a pooled analysis of 21 cohorts.	PloS Med	11(4)	e1001631.	2014

Kota Katanoda, Ken-ichi Kamo, Megumi Hori, and Shoichiro Tsugane	Estimated prevalence of thyroid cancer in Fukushima prior to the Fukushima Daiichi nuclear disaster.	BMJ	http://www.bmj.com/content/346/bmj.f1271/rr	(online rapid response)	
Sano H, Goto R, Hamashima C	What is the most effective strategy for improving the cancer screening rate in Japan?	Asian Pac J Cancer Prev.	15(6)	2607-2612	2014
岸知輝、濱島ちさと	高濃度バリウムによる胃X線検査偶発症推計方法の検討	日本消化器がん検診学会雑誌	52(4)	431-440	2014
Hamashima C	Current issues and future perspectives of gastric cancer screening.	World J Gastroenterol	20(38)	13767-13774	2014
Terasawa T, Nishida H, Kato K, Miyashiro I, Yoshikawa T, Takaku R, Hamashima C	Prediction of gastric cancer development by serum pepsinogen test and helicobacter pylori seropositivity in Eastern Asians: A systematic review and meta-analysis.	PLoS ONE	9(10)	e109783	2014
新井康平・謝花典子・後藤励・濱島ちさと	内視鏡胃がん検診プログラムへの参加要因	厚生の指標	62(2)	30-35	2015
Hamashima C, Ogoshi K, Narisawa R, Kishi T, Kato T, Fujita K, Sano M, Tsukioka S	Impact of endoscopic screening on mortality reduction from gastric cancer.	World J Gastroenterol	21(8)	2460-2466	2015
Goto R, Hamashima C, Sunghyun Mun, Won-Chul Lee	Why screening rates vary between Korea and Japan - Differences between two national healthcare systems.	Asian Pac. J. Cancer Prev.	16 (2)	395-400	2015
濱島ちさと	〔がん検診の最新事情〕40歳代の乳がん検診の可能性：日本と海外の比較	乳癌BOOK2014	12(8)	23-26	2014
濱島ちさと、斎藤博	内視鏡検診の可能性	Frontiers in Gastroenterology	19(3)	20-21	2014
Leja M, You W, Camargo M.C, Saito H.	Implementation of gastric cancer screening The global experience.	Best Practice & Research Clinical Gastroenterology	28	1093-1106	2014
斎藤　博.	大腸がん検診の実際と課題克服のための対策	消化器の臨床	17	289-295	2014

斎藤　博.	大腸がん検診：成果を上げるには	成人病と生活習慣病	44	647-651	2014
濱島ちさと、斎藤　博.	内視鏡検診の可能性	Frontiers in Gastroenterology	19	2014-2017	2014
Tanaka S, Saitoh Y, Matsuda T, Igarashi M, Matsumoto T, Iwao Y, Suzuki Y, Nishida H, Watanabe T, Tamotsu Sugai T, Sugihara K, Tsuruta O, Hirata I, Hiwatashi N, Saito H, Watanabe M, Sugano K, Shimosegawa T.	Evidence-based clinical practice guidelines for management of colorectal polyps.	The Japanese Society of Gastroenterology		DOI 10.1007/s00535-014-1021-4.	2015
斎藤　博	斎藤　博.大腸がん検診のあり方―最近のエビデンスを踏まえて	診療と治療	103	173-178	2015
Saika K, Machii R.	Five-year relative survival rate of uterus cancer in the USA, Europe and Japan.	Jpn J Clin Oncol.	44	513-4	2014
Saika K, Machii R.	Five-year relative survival rate of gallbladder cancer in the USA, Europe and Japan.	Jpn J Clin Oncol.	44	704	2014
Machii R, Saika K.	Five-year Relative Survival Rate of Larynx Cancer in the USA, Europe and Japan.	Jpn J Clin Oncol.	44	1015-6	2014

Carcinogenesis, 2015, Vol. 36, No. 2, 223–231

doi:10.1093/carcin/bgu244
Advance Access publication December 18, 2014
Original Manuscript

ORIGINAL MANUSCRIPT

Genetic polymorphisms of *ADH1B*, *ADH1C* and *ALDH2*, alcohol consumption, and the risk of gastric cancer: the Japan Public Health Center-based prospective study

Akihisa Hidaka[1], Shizuka Sasazuki[1,*], Keitaro Matsuo[2], Hidemi Ito[3], Norie Sawada[1], Taichi Shimazu[1], Taiki Yamaji[1], Motoki Iwasaki[1], Manami Inoue[1,4], Shoichiro Tsugane[1], and for the JPHC Study Group[†]

[1]Epidemiology and Prevention Group, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo 104-0045, Japan,
[2] Department of Preventive Medicine, Kyushu University Faculty of Medical Sciences, Fukuoka 812-8582, Japan, [3] Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute, Nagoya 464-8681, Japan, and [4] Graduate School of Medicine, The University of Tokyo, Tokyo 113-0033, Japan

*To whom correspondence should be addressed. Tel: +81 3 3542 2511; Fax: +81 3 3547 8578; Email: ssasazuk@ncc.go.jp

†The members of JPHC Study Group are listed under Appendix.

Abstract

The association between alcohol consumption, genetic polymorphisms of alcohol dehydrogenase (*ADH*) and aldehyde dehydrogenase (*ALDH*) and gastric cancer risk is not completely understood. We investigated the association between *ADH1B* (rs1229984), *ADH1C* (rs698) and *ALDH2* (rs671) polymorphisms, alcohol consumption and the risk of gastric cancer among Japanese subjects in a population-based, nested, case–control study (1990–2004). Among 36 745 subjects who answered the baseline questionnaire and provided blood samples, 457 new gastric cancer cases matched to 457 controls were used in the analysis. The odds ratios (OR) and corresponding 95% confidence intervals (CI) were calculated using logistic regression models. No association was observed between alcohol consumption, *ADH1B* (rs1229984), *ADH1C* (rs698) and *ALDH2* (rs671) polymorphisms and gastric cancer risk. However, considering gene–environmental interaction, *ADH1C* G allele carriers who drink ≥150 g/week of ethanol had a 2.5-fold increased risk of gastric cancer (OR = 2.54, 95% CI = 1.05–6.17) relative to AA genotype carriers who drink 0 to <150 g/week (*P* for interaction = 0.02). *ALDH2* A allele carriers who drink ≥150 g/week also had an increased risk (OR = 2.08, 95% CI = 1.05–4.12) relative to GG genotype carriers who drink 0 to < 150 g/week (*P* for interaction = 0.08). To find the relation between alcohol consumption and gastric cancer risk, it is important to consider both alcohol consumption level and *ADH1C* and *ALDH2* polymorphisms.

Introduction

Alcohol consumption is a strong risk factor for some cancers of the head and neck, liver, breast and colon and rectum (1). However, based on many epidemiological studies, the association between alcohol consumption and gastric cancer risk was reported as inconsistent by the World Cancer Research Fund/ American Institute for Cancer Research (2).

In general, the metabolism of ethanol (alcohol) by alcohol dehydrogenases (ADH) is converted into the generation of acetaldehyde, and acetaldehyde is oxidized into nontoxic acetate by aldehyde dehydrogenases (ALDH (3)). Among all classes of ADH and ALDH isoenzymes, ADH1B, ADH1C and ALDH2 are the main ethanol-metabolizing enzymes (4,5). It has been suggested that

Received: August 12, 2014; **Revised:** December 3, 2014; **Accepted:** December 13, 2014

Abbreviations

ADH	alcohol dehydrogenases
ALDH	aldehyde dehydrogenases
BMI	body mass index
CagA	cytotoxin-associated gene A
CI	confidence interval
DM	diabetes mellitus
DR	dietary records
FFQ	food frequency questionnaire
ICD-O	International Classification of Diseases for Oncology
JPHC study	Japan Public Health Center-based prospective study
OR	odds ratio
PHC	public health center.

the metabolism of ethanol leads to accumulation of acetaldehyde (acetaldehyde associated with alcoholic beverages) that is toxic and classified as a group 1 carcinogen in humans by the International Agency for Research on Cancer (IARC (6)). Accumulation of acetaldehyde differs according to functional enzymatic *ADH1B*, *ADH1C* and *ALDH2* genetic polymorphisms. In previous studies, active *ADH1B* allele metabolizes ethanol into acetaldehyde ~40 times more than inactive allele, and active *ADH1C* allele metabolizes ~2.5 times more than inactive allele (5). Furthermore, light drinkers with inactive homozygote *ALDH2* genotype and with heterozygote genotype have 18 times and 5 times higher, respectively, average peaks of acetaldehyde concentrations in blood than moderate drinkers with active homozygote genotypes (7). Therefore, it is important to consider alcohol consumption level and functional genetic polymorphisms of ethanol-metabolizing enzymes to clarify the association between alcohol consumption and gastric cancer risk.

The genotype frequencies of *ADH1B*, *ADH1C* and *ALDH2* polymorphisms differ according to race. The genotype frequencies of *ADH1B* and *ALDH2* polymorphisms are unevenly distributed in Caucasians, but not in Asians (8). Thus, we suggest that it is necessary to evaluate the association of *ADH1B* and *ALDH2* polymorphisms in Asians. In contrast, the genotype frequencies of the *ADH1C* polymorphism are unevenly distributed in Asians, but not in Caucasians (8). However, this polymorphism is also an important gene in alcohol metabolism, and there is no published study regarding the association between the *ADH1C* polymorphism and gastric cancer risk in Asians.

In our study, we selected genetic polymorphisms *ADH1B* (rs1229984), *ADH1C* (rs698) and *ALDH2* (rs671), which are functionally established single nucleotide polymorphisms, and aimed to clarify the association between these genetic polymorphisms, alcohol consumption and gastric cancer risk in a large-scale Japanese population-based study. Our hypothesis was that drinkers with inactive *ADH1B* and *ADH1C* G alleles would have an increased risk for gastric cancer compared with those with active A alleles. Because inactive allele carriers cannot metabolize ethanol into acetaldehyde, they are less prone to the effects of acetaldehyde such as nausea, increased heart rate and flushing (9). International Agency for Research on Cancer classifies ethanol in alcoholic beverages as a group 1 carcinogen in humans, the same classification as acetaldehyde (6). In addition, drinkers with inactive *ALDH2* A alleles would be at increased risk compared with those with active G alleles because inactive allele carriers cannot oxidize acetaldehyde.

Materials and methods

Study population

The Japan Public Health Center-based prospective study (JPHC study) was launched in 1990 for cohort I (subject age range, 40–59 years) and in 1993 for cohort II (subject age range, 40–69 years) and investigated cancer, cardiovascular disease and other lifestyle-related diseases (10). The JPHC study consisted of 11 public health centers (PHCs) throughout Japan with a total of 140 420 subjects (68 722 men and 71 698 women). Among study subjects, those who registered at two PHC areas (Tokyo and Osaka) were excluded from this study because data regarding cancer incidence was not available or selection of subjects was defined differently from that of other cohort subjects. A population-based cohort of 123 576 subjects (61 009 men and 62 567 women) was established. This study was approved by the Institutional Review Board of the National Cancer Center, Tokyo, Japan.

Baseline survey

In the baseline survey, the study subjects were asked to reply to a self-administered questionnaire about various lifestyle factors, such as sociodemographic characteristics, personal medical history, family history, smoking and drinking habits, dietary habits and physical activity. A total of 99 808 subjects (47 525 men and 52 283 women) responded, giving a response rate of 80.8%.

We excluded subjects who self-reported cancer at baseline (n = 2136), who were not Japanese (n = 18) and who did not live in the area at the baseline (n = 11), which left 97 644 eligible subjects (46 803 men and 50 841 women). One subject reported having cancer at baseline and was also not Japanese. Among the eligible subjects, 36 745 subjects (13 467 men and 23 278 women) provided a 10-ml blood sample at the time of the health check-up conducted by each PHC area. These blood samples were stored at −80°C until analysis. Blood samples were collected from 1990 to 1992 for cohort I and from 1993 to 1995 for cohort II. Following the standard protocol, subjects were asked to avoid having a meal after 21:00 hours on the day before the health check-up and they recorded the last time of caloric intake (including a meal and/or drinking).

Follow-up and cancer registry for JPHC Study

Subjects were observed until 31 December 2004. In Japan, residence and death registration are required by law, and residence status, survival and death were identified annually through residential registries in each area. Among the 36 745 subjects, 3.9% moved outside the study area, 4.4% died and 0.03% were lost to follow-up during the study period, which left 33 701 subjects.

Incidence data regarding gastric cancer cases were identified from two major sources: local major hospitals in the study area and population-based cancer registries. Death certificate information was also used as an information source. In our cancer registry system, 7.6% of gastric cancer cases were based on information first notified via death certificate and 2.1% were registered based on information from the death certificate alone.

Selection of cases and controls

The anatomic site of each case was coded according to the International Classification of Diseases for Oncology (ICD-O), 3rd edition, codes C16.0–16.9 (11). A tumor located in the upper third of the stomach was classified as proximal gastric cancer 'cardia site' (ICD-O code C16.0–16.1), and that in the lower position of the stomach was classified as distal gastric cancer 'noncardia site' (ICD-O code C16.2–16.7). The other cases were tumors that could not be classified because of overlapping lesions (ICD-O code C16.8) or no information (ICD-O code C16.9). The subdivisions by histological type were based on classification derived by Lauren (12). For each case, we selected one control subject who had no history of gastric cancer when the case was diagnosed. Each control was matched to the case for age (±3 years), sex, PHC area, fasting time at blood donation (±5 h) and blood donation date (±2 months). Among 1681 cases diagnosed histologically and registered in cohort I or cohort II (study period from 1990 to 2004), 512 cases replied to a self-administered questionnaire and provided blood. Furthermore, among the 512 new gastric cancer cases, one case was excluded because of a technical error in the measurement of *Helicobacter pylori* (*H.pylori*) and 45 cases for one PHC area in Osaka were excluded because buffy coat was not available. Another nine cases were excluded because of an inadequate concentration of buffy coat for DNA extraction. The final analysis included 457 matched sets of cases and controls. A flowchart of the study subjects is presented in Figure 1.

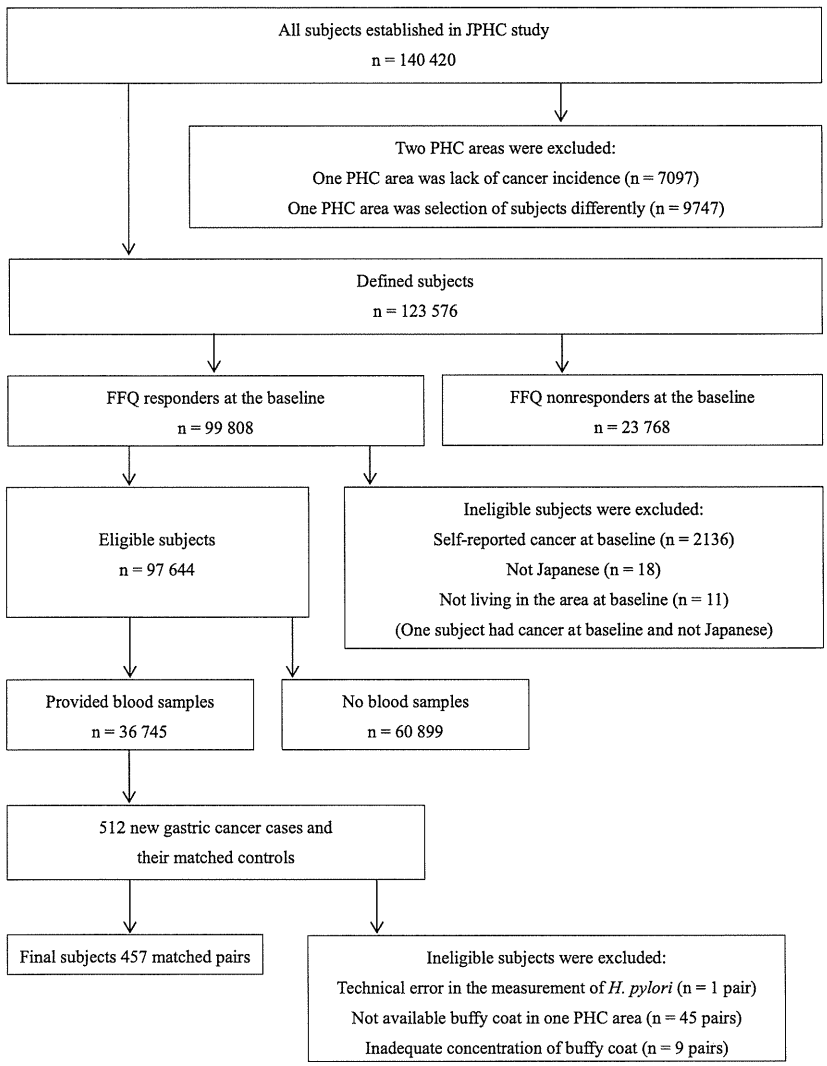

Figure 1. Flowchart of the study subjects.

Assessment of alcohol consumption

Information regarding alcohol consumption was assessed based on the frequency and amount using a validated self-administered food frequency questionnaire (FFQ). During the baseline survey, cohort I and cohort II used slightly different FFQ. In cohort I, the average frequency of alcohol consumption was reported in six categories (almost never, 1–3 days per month, 1–2 days per week, 3–4 days per week, 5–6 days per week and every day). Subjects who drank at least once per week were also asked about the average amount and types of drinks. In cohort II, alcohol consumption status (never, former and current drinkers) was asked first, and then former and current drinkers were asked for more information, similar to cohort I. We then assigned a score to each category of the average frequency of consumption as follows: 1.5 for 1–2 days per week, 3.5 for 3–4 days per week, 5.5 for 5–6 days per week and 7 for every day in cohort I; and 1.5 for 1–2 days per week, 3.5 for 3–4 days per week and 6 for almost every day in cohort II. The amount of alcohol consumption was quantified in grams of ethanol by each type of beverage as follows: 180 ml of sake classified as 23 g of ethanol, 180 ml of shochu or awamori classified as 36 g, 633 ml of beer classified as 23 g, 30 ml of whiskey or brandy classified as 10 g and 60 ml wine classified as 6 g. Finally, we calculated the weekly ethanol intake, which was estimated by multiplying the quantity by the score. In our study, alcohol consumption was classified into three groups: never or occasional drinker; ethanol <150 g per week and ethanol ≥150 g per week. Alcohol consumption levels were defined by the unit *go*, the standard measure of ethanol content of alcoholic beverages in Japan. This unit equals 23 g of alcohol, the amount contained in 180 ml of sake. If a subject drinks 1 *go* every day, he or she is consuming ~150 g of ethanol per week. Validity of this FFQ-based estimated alcohol consumption was evaluated in a subsample of the JPHC study subjects who completed 28-day dietary records (DR). In cohort I, Spearman rank correlation coefficients between the FFQ and DR were 0.79 (n = 94) for men and 0.44 (n = 107) for women, respectively (13). In cohort II, these results were 0.59 (n = 176) for men and 0.40 (n = 178) for women, respectively (14).

Assessment of other potential confounding factors

Smoking status was divided into four groups: never smoker, former smoker, current smoker using ≤20 cigarettes per day and current smoker using ≥21 cigarettes per day. Body mass index (BMI) status was divided into three groups: BMI <22 kg/m^2, 22 kg/m^2 ≤ BMI <25 kg/m^2 and BMI ≥25 kg/m^2. According to a previous prospective study of the association with gastric cancer risk in Japan (15), the classifications for smoking status and BMI are reasonable. Total calorie intake and salt intake were treated as continuous variables. Family history of gastric cancer was considered positive if at least one parent or sibling had gastric cancer. The *H.pylori* infection status was regarded as positive if subjects had either *H.pylori* antibody ≥10 U/ml or cytotoxin-associated gene A (CagA) antibody >10. Atrophy was regarded

as positive if pepsinogen I was ≤70 ng/ml and pepsinogen I:pepsinogen II ratio was ≤3 (16). History of diabetes mellitus (DM) was considered positive if subjects reported a history of DM and/or drug use for DM at baseline.

Genotyping of ADH1B, ADH1C and ALDH2 polymorphisms

DNA of each subject was extracted from white blood cells in the buffy coat using a FlexiGene DNA kit (Qiagen, Hilden, Germany). Genotyping of *ADH1B* (rs1229984), *ADH1C* (rs698) and *ALDH2* (rs671) polymorphisms was analyzed by using TaqMan single nucleotide polymorphism genotyping assays (Applied Biosystems Inc, Foster City, CA). In this assay, fluorescently labeled sequence-specific primers were used in polymerase chain reaction. These measurements were performed with blinding of case and control status. The genotype distributions of *ADH1B*, *ADH1C* and *ALDH2* polymorphisms among controls were all in agreement with Hardy–Weinberg equilibrium ($P > 0.05$).

Statistical analysis

The chi-square test was used to compare baseline characteristics between cases and controls. Matched odds ratios (OR) and their corresponding 95% confidence intervals (CIs) were calculated to indicate the association between alcohol consumption, *ADH1B*, *ADH1C* and *ALDH2* polymorphisms, and gastric cancer risk using conditional logistic regression models. OR1 was matched for age (±3 years), sex, PHC area, blood donation date (±2 months) and fasting time at blood donation (±5 h). OR2 was further adjusted for potential confounding factors such as smoking status, alcohol consumption, total calorie intake, salt intake, BMI, family history of gastric cancer, *H.pylori* infection status, atrophy and history of DM. Data for subjects who were missing values for BMI ($n = 8$), total calorie intake ($n = 1$) and salt intake ($n = 1$) were deleted from the study when adjusting for these confounding factors. When we calculated the effect modification of *ADH1B*, *ADH1C* and *ALDH2* polymorphisms on gastric cancer risk associated with alcohol consumption, and that of these polymorphisms combined, unconditional logistic regression models were used. We conducted the effect modification of *ADH1B*, *ADH1C* and *ALDH2* polymorphisms associated with alcohol consumption with further adjustment for these polymorphisms mutually. Reported *P* values were two-sided, and $P < 0.05$ was defined as statistically significant. All statistical analyses were performed with SAS software version 9.3 (SAS Institute, Cary, NC).

Results

Baseline characteristics of cases and controls are shown in Table 1. Higher BMI was more frequently distributed among controls than patients with gastric cancer. In contrast, history of DM, family history of gastric cancer, *H.pylori*, CagA positivity and atrophy were more frequently distributed among patients. These results generally agree with previous reports, including the JPHC study (15,17–19).

Table 2 presents the association between alcohol consumption, *ADH1B*, *ADH1C* and *ALDH2* polymorphisms and gastric cancer risk. Alcohol consumption was marginally associated with an increased risk of gastric cancer in the OR1 group compared with never to occasional drinkers; drinkers with ethanol <150 g/week had OR of 0.89 and with ≥150 g/week had OR of 1.29 (*P* for trend = 0.15). However, after further adjustment for potential confounding factors, the association became null (OR2 group). Compared with *ALDH2* GG genotype, GA and AA genotypes were marginally associated with an increased risk, with OR2 values of 1.09 (95% CI = 0.77–1.54) and 2.01 (95% CI = 0.91–4.48), respectively (*P* for trend = 0.18). However, *ALDH2* A allele carriers had no risk association compared with GG genotype carriers. We found no association between alcohol consumption and *ADH1B* and *ADH1C* polymorphisms. *ADH1C* GG genotype was rare in this Japanese population.

Table 3 shows the effect modification of *ADH1B*, *ADH1C* and *ALDH2* polymorphisms on gastric cancer risk associated with alcohol consumption (gene–environmental interaction). Compared with *ADH1C* AA genotype carriers who drink 0 to <150 g/week, G allele carriers who drink ≥150 g/week had an increased risk, with OR2 value of 2.54 (95% CI = 1.05–6.17); the interaction between alcohol consumption and G allele carriers was statistically significant (*P* for interaction = 0.02). *ALDH2* A allele carriers who drink ≥150 g/week had an increased risk compared with GG genotype carriers who drink 0 to <150 g/week, with OR2 value of 2.08 (95% CI = 1.05–4.12). A trend toward a positive interaction between alcohol consumption and A allele carrier status was shown (*P* for interaction = 0.08). No association was shown for *ADH1B* polymorphism and alcohol consumption.

We further examined the effect modification of the combination of *ADH1B*, *ADH1C* and *ALDH2* polymorphisms on gastric cancer risk associated with alcohol consumption (gene–gene–environmental interaction) in Table 4. Compared with the combination of *ADH1B* AA and *ALDH2* GG genotype carriers who drink 0 to <150 g/week, each combination of *ADH1B* AA genotype and *ALDH2* A allele, *ADH1B* G allele and *ALDH2* A allele carriers who drink ≥150 g/week showed a trend toward an increased risk for gastric cancer, with OR2 values of 2.16 (95% CI = 0.83–5.63) and 1.66 (95% CI = 0.66–4.16), respectively. However, the interaction between *ADH1B* G allele and *ALDH2* A allele and alcohol consumption was not statistically significant (*P* for interaction = 0.40). In addition, compared with the combination of *ADH1C* AA and *ALDH2* GG genotype carriers who drink 0 to <150 g/week, the combination of *ADH1C* G and *ALDH2* A alleles in carriers who drink 0 to <150 g/week showed a statistically significant decreased risk (OR = 0.43, 95% CI = 0.21–0.91). Each combination of *ADH1C* AA genotype and *ALDH2* A, *ADH1C* G and *ALDH2* A alleles in carriers who drink ≥150 g/week showed a marginally increased risk, with OR2 values 1.92 (95% CI = 0.95–3.87) and 8.95 (95% CI = 0.62–129.25), respectively. Moreover, the interaction between *ADH1C* G allele and *ALDH2* A allele and alcohol consumption seemed to be marginally statistically significant (*P* for interaction = 0.13).

We performed stratified analyses by sex regarding the association of each polymorphism with gastric cancer risk and observed no differences by stratification (data not shown). In addition, the gene–environmental interaction analysis was repeated with stratification by gastric atrophy. Among the subjects with gastric atrophy, *ALDH2* A allele carriers who drink ≥150 g/week had an increased risk of gastric cancer compared with those with GG genotype who drink 0 to <150 g/week (OR2 = 2.71, 95% CI = 1.18–6.27). An interaction between alcohol consumption and A allele was shown (*P* for interaction = 0.02). However, the subjects without gastric atrophy and *ALDH2* polymorphism did not show a positive association with risk. *ADH1B* and *ADH1C* polymorphisms also did not show any positive association with risk when stratified by atrophy. We also evaluated the combination effects of *ADH1B*, *ADH1C* and *ALDH2* polymorphisms on gastric cancer risk. Compared with *ADH1B* AA, *ADH1C* AA and *ALDH2* GG genotype carriers, OR2s were 1.15 (95% CI = 0.75–1.76) (*P* for interaction = 0.13) for *ADH1B* G and *ALDH2* A allele carriers and 0.59 (95% CI = 0.30–1.15) (*P* for interaction = 0.02) for *ADH1C* G and *ALDH2* A allele carriers. Although the interaction between *ADH1C* and *ALDH2* polymorphisms was statistically significant, a chance finding cannot be ruled out because *ADH1C* GG genotype was rare among our study subjects. Analyses considering anatomic site and histological type of gastric cancer were also performed. Cardia site ($n = 76$) was not robustly evaluated because of the small number of subjects. When limited to distal site and intestinal or diffuse type of gastric cancer, *ADH1C* G allele and *ALDH2* A allele carriers who drink ≥150 g/week showed a trend

Table 1. Baseline characteristics of cases and controls

Characteristics	Cases	Controls	*P* value[a]
n	457	457	
Age, mean (SD)	56.9 (7.10)	56.9 (7.12)	Matching value
Men (%)	307(67.2)	307 (67.2)	Matching value
Smoking status			
Never (%)	209 (45.7)	229 (50.1)	
Former (%)	81 (17.7)	88 (19.3)	
Current: ≤20 cigarettes/day (%)	130 (28.5)	101 (22.1)	
Current: ≥21 cigarettes/day (%)	37 (8.1)	39 (8.5)	0.18
Alcohol consumption			
Never to occasional (%)	222 (48.6)	228 (49.9)	
1+ per day and <150 g/week (%)	86 (18.8)	105 (23.0)	
1+ per day and ≥150 g/week (%)	149 (32.6)	124 (27.1)	0.12
BMI (kg/m^2)[b]			
BMI <22 (%)	168 (37.1)	141 (31.1)	
22≤ BMI <25 (%)	193 (42.6)	191 (42.2)	
25≤ BMI (%)	92 (20.3)	121 (26.8)	0.04
History of DM (%)	41 (9.0)	19 (4.2)	0.005
Family history of gastric cancer (%)	53 (11.6)	31 (6.8)	0.02
Helicobacter pylori-positive (%)[c]	428 (93.7)	341 (74.6)	<0.001
CagA-positive (%)	349 (76.4)	318 (69.6)	0.03
Atrophy (%)[d]	375 (82.1)	261 (57.1)	<0.001

[a]Based on chi-square test.
[b]Subject data without calculated BMI data because of missing values for height or weight in four cases and four controls were deleted.
[c]Based on immunoglobulin G antibody.
[d]Atrophy: positive if pepsinogen I ≤70 ng/ml and pepsinogen I:pepsinogen II ratio ≤3.

Table 2. Association between alcohol consumption, *ADH1B*, *ADH1C* and *ALDH2* polymorphisms, and gastric cancer risk

	Genotype frequency (%)[a]	Cases (*n*)/controls (*n*)	OR1 (95% CI)[b]	OR2 (95% CI)[c]
Alcohol consumption[d]				
Never to occasional		222/228	1.00 (reference)	1.00 (reference)
1+ per day and <150 g/week		86/105	0.89 (0.60–1.33)	0.73 (0.46–1.17)
1+ per day and ≥150 g/week		149/124	1.29 (0.88–1.89)	1.09 (0.68–1.74)
P for trend			0.15	0.64
ADH1B (rs1229984)				
AA	55.6	252/254	1.00 (reference)	1.00 (reference)
AG	36.8	173/168	1.03 (0.78–1.36)	0.93 (0.67–1.29)
GG	7.6	32/35	0.92 (0.56–1.51)	0.88 (0.50–1.54)
P for trend			0.92	0.56
AG+GG	44.4	205/203	1.01 (0.78–1.31)	0.91 (0.67–1.24)
ADH1C (rs698)				
AA	85.6	396/391	1.00 (reference)	1.00 (reference)
AG	14.2	60/65	0.91 (0.63–1.33)	0.79 (0.51–1.21)
GG	0.2	1/1	1.00 (0.06–15.99)	1.51 (0.02–97.99)
P for trend			0.65	0.26
AG+GG	14.4	61/66	0.90 (0.62–1.30)	0.79 (0.51–1.22)
ALDH2 (rs671)				
GG	63.9	287/292	1.00 (reference)	1.00 (reference)
GA	32.8	149/150	0.99 (0.74–1.32)	1.09 (0.77–1.54)
AA	3.3	21/15	1.33 (0.67–2.61)	2.01 (0.91–4.48)
P for trend			0.68	0.18
GA+AA	36.1	170/165	1.02 (0.77–1.34)	1.16 (0.83–1.62)

Based on conditional logistic regression model.
[a]Among controls.
[b]Matched for age (±3 years), sex, area, blood donation date (±2 months) and fasting time at blood donation (±5 h).
[c]Further adjusted for smoking status, alcohol consumption, body mass index, total calorie, salt intake, family history of gastric cancer, *Helicobacter pylori* infection status, atrophy and history of DM.
[d]Not adjusted for alcohol consumption.

toward having an increased risk relative to those who drink 0 to <150 g/week (data not shown). When we evaluated heavy drinkers who drink ≥300 or ≥450 g/week, similar associations were observed (data not shown).

Discussion

In our population-based, nested, case–control study, we observed no association between alcohol consumption, *ADH1B*

Table 3. Effect modification of *ADH1B*, *ADH1C* and *ALDH2* polymorphisms on gastric cancer risk associated with alcohol consumption

	ADH1B (rs1229984)						
	AA			AG+GG			
	Cases (*n*)/controls (*n*)	OR1 (95% CI)[a]	OR2 (95% CI)[b]	Cases (*n*)/controls (*n*)	OR1 (95% CI)[a]	OR2 (95% CI)[b]	P for interaction[b]
Alcohol consumption							
0 to <150 g/week	167/189	1.00 (reference)	1.00 (reference)	141/144	1.09 (0.79–1.49)	1.01 (0.72–1.42)	0.76
≥150 g /week	85/65	1.57 (1.04–2.38)	1.37 (0.86–2.19)	64/59	1.30 (0.84–2.02)	1.25 (0.77–2.05)	
	ADH1C (rs698)						
	AA			AG+GG			
	Cases (*n*)/controls (*n*)	OR1 (95% CI)[a]	OR2 (95% CI)[b]	Cases (*n*)/controls (*n*)	OR1 (95% CI)[a]	OR2 (95% CI)[b]	P for interaction[b]
Alcohol consumption							
0 to <150 g/week	270/277	1.00 (reference)	1.00 (reference)	38/56	0.68 (0.43–1.07)	0.66 (0.41–1.08)	0.02
≥150 g/week	126/114	1.23 (0.87–1.72)	1.16 (0.78–1.71)	23/10	2.49 (1.14–5.42)	2.54 (1.05–6.17)	
	ALDH2 (rs671)						
	GG			GA+AA			
	Cases (*n*)/controls (*n*)	OR1 (95% CI)[a]	OR2 (95% CI)[c]	Cases (*n*)/controls (*n*)	OR1 (95% CI)[a]	OR2 (95% CI)[c]	P for interaction[c]
Alcohol consumption							
0 to <150 g/week	177/185	1.00 (reference)	1.00 (reference)	131/148	0.93 (0.68–1.28)	0.98 (0.69–1.38)	0.08
≥150 g/week	110/107	1.16 (0.79–1.69)	1.09 (0.72–1.67)	39/17	2.51 (1.34–4.72)	2.08 (1.05–4.12)	

Based on unconditional logistic regression model.

[a]Adjusted for age (±3 years), sex, area, blood donation date (±2 months) and fasting time at blood donation (±5 h).

[b]Further adjusted for smoking status, BMI, total calorie, salt intake, family history of gastric cancer, *H.pylori* infection status, atrophy, history of DM and *ALDH2* polymorphism.

[c]Further adjusted for smoking status, BMI, total calorie, salt intake, family history of gastric cancer, *H.pylori* infection status, atrophy, history of DM and *ADH1B* and *ADH1C* polymorphisms.

Table 4. Effect modification of the combination of *ADH1B*, *ADH1C* and *ALDH2* polymorphisms on gastric cancer risk associated with alcohol consumption

		ALDH2 (rs671)						
		GG			GA+AA			
		Cases (*n*)/controls (*n*)	OR1 (95% CI)[a]	OR2 (95% CI)[b]	Cases (*n*)/controls (*n*)	OR1 (95% CI)[a]	OR2 (95% CI)[b]	P for interaction[b]
ADH1B (rs1229984)	Alcohol consumption							
AA	0 to <150 g/week	103/105	1.00 (reference)	1.00 (reference)	64/84	0.77 (0.50–1.19)	0.75 (0.47–1.19)	0.40
	≥150 g/week	64/58	1.20 (0.74–1.94)	0.99 (0.58–1.68)	21/7	3.09 (1.23–7.76)	2.16 (0.83–5.63)	
AG+GG	0 to <150 g/week	74/80	0.91 (0.60–1.39)	0.79 (0.50–1.24)	67/64	1.07 (0.68–1.66)	1.06 (0.65–1.71)	
	≥150 g/week	46/49	1.01 (0.60–1.69)	0.94 (0.53–1.65)	18/10	1.93 (0.83–4.46)	1.66 (0.66–4.16)	
ADH1C (rs698)	Alcohol consumption							
AA	0 to <150 g/week	152/161	1.00 (reference)	1.00 (reference)	118/116	1.07 (0.76–1.51)	1.13 (0.78–1.63)	0.13
	≥150 g/week	92/98	1.07 (0.72–1.59)	1.01 (0.65–1.57)	34/16	2.34 (1.21–4.51)	1.92 (0.95–3.87)	
AG+GG	0 to <150 g/week	25/24	1.03 (0.56–1.90)	1.03 (0.54–1.99)	13/32	0.44 (0.22–0.87)	0.43 (0.21–0.91)	
	≥150 g/week	18/9	2.20 (0.94–5.14)	2.14 (0.83–5.52)	5/1	5.63 (0.64–49.22)	8.95 (0.62–129.25)	

Based on unconditional logistic regression model.
[a]Adjusted for age (±3 years), sex, area, blood donation date (±2 months) and fasting time at blood donation (±5 h).
[b]Further adjusted for smoking status, BMI, total calorie, salt intake, family history of gastric cancer, *H.pylori* infection status, atrophy and history of DM.

(rs1229984), *ADH1C* (rs698) and *ALDH2* (rs671) polymorphisms and gastric cancer risk. However, statistically significant interactions between inactive *ADH1C* and alcohol consumption and nonsignificant interactions between inactive *ALDH2* alleles and alcohol consumption were shown for gastric cancer risk.

To date, one prospective study in Europe (20) and several case–control studies (21–25) have reported an association between alcohol consumption and *ADH1B* (rs1229984), *ADH1C* (rs698) and *ALDH2* (rs671) polymorphisms and gastric cancer risk. For *ADH1B* (rs1229984) and *ADH1C* (rs698) polymorphisms, two previous studies reported that the inactive *ADH1B* allele was not associated with gastric cancer risk among drinkers (20,23). In one case–control study performed in the United States, the active *ADH1C* genotype was associated with an increased risk among drinkers and nondrinkers (24). However, the sample size of this case–control study was small, and caution may be needed in interpreting the results. For the *ALDH2* (rs671) polymorphism, two recent, large, Japanese and Korean case–control studies reported that the interaction between the inactive *ALDH2* allele and alcohol consumption regarding gastric cancer risk was statistically significant (21,22). Another case–control study conducted in China also indicated that inactive *ALDH2* allele carriers with larger cumulative amount of alcohol consumption had a marginally increased risk of gastric cancer compared with active *ALDH2* allele carries with smaller cumulative amount of alcohol consumption (23).

As shown in our study (Tables 3 and 4), the association between alcohol consumption, *ADH1B* polymorphism and gastric cancer risk was similar to that in previous studies. In contrast, a positive association between inactive *ADH1C* G allele and alcohol consumption regarding gastric cancer risk was found, opposite to that found in previous studies (24). However, the number of study subjects in our population is small for some *ADH1C* genotypes because *ADH1C* GG genotype is rare in Asians (8). In addition, evidence is lacking on any difference between *ADH1B* and *ADH1C* polymorphisms in the ability to metabolize ethanol. Caution is necessary when interpreting the results for *ADH1C* polymorphisms in our study. Inactive *ALDH2* A allele carriers who drink ≥150 g/week have an increased risk of gastric cancer, similar to that in previous studies, which may be attributable to accumulation of acetaldehyde. When subjects with an inactive *ALDH2* allele did not drink alcohol, the risk of gastric cancer did not increase. We suggest that accumulation of acetaldehyde modified by *ALDH2* (rs671), rather than *ADH1B* (rs1229984) and *ADH1C* (rs698) polymorphisms, may play an important role in gastric carcinogenesis.

It has been reported that the carcinogenic mechanisms of acetaldehyde are complicated and are not completely understood. Acetaldehyde reacts with the exocyclic amino group of deoxyguanosine to form DNA adducts, called N (2)-ethylidenedeoxyguanosine [N (2)- ethylidene-dGuo]. The DNA adducts are involved in metagenesis (26,27). The other kinds of acetaldehyde-related adducts are the 1,N (2)-propano-2′-deoxyguanosine [1, N (2)-propanodGuo] and 1,N (2)-etheno-dGuo (27). Other candidate mechanisms may be DNA hypomethylation by DNA methyltransferase, direct adduction of histone, and inhibition of the activity of O6-methylguanine-DNA methyltranseferase (MGMT), which protect against alkylation of DNA (27).

In our study, we conducted a stratified analysis of gastric atrophy. Interestingly, among the subjects with gastric atrophy, *ALDH2* A allele carriers who drink ≥150 g/week had an increased risk of gastric cancer compared with GG genotype carriers who drink 0 to <150 g/week; statistically significant interaction was also found. This phenomenon was not found among the

subjects without gastric atrophy. Our result suggests that acetaldehyde may induce gastric carcinogenesis with gastric atrophy, which is caused by chronic inflammation with *H.pylori* infection. In a previous study, although statistical interaction was not significant, similar results were found (21). Further studies are needed to clarify the contribution of acetaldehyde to gastric carcinogenesis.

This study has several strengths. First, this is a population-based prospective study, which is more reliable than case–control studies. Detailed information regarding the potential confounding factors including alcohol consumption was recorded before diagnosis of gastric cancer, thus confirming our results. A validated FFQ was used. Also, we were able to control potential confounding factors, as compared with a previous European study that was only adjusted for age, sex and country (20).

Our study does have some weakness. First, among 97 644 eligible subjects of the JPHC study, only 36 745 (37.6%) subjects provided blood samples. The participants in the health check-up survey relative to nonparticipants had a favorable lifestyle with less smoking and alcohol consumption, as reported previously (28). Second, we were not able to assess the other genes of ethanol-metabolizing enzymes such as *CYP2E1*. Third, we analyzed the gastric cancer risk only using the lifestyle information at baseline. Lifestyle habits of study subjects might change during the follow-up period. However, this change may not be different between cases and controls and likely would have led to the underestimation of results. Finally, sample size was not necessarily enough for evaluating the association among some anatomic sites.

In conclusion, to find the relation between alcohol consumption and gastric cancer risk, it is important to consider both alcohol consumption level and *ADH1C* and *ALDH2* polymorphisms. However, caution is needed to interpret the results associated with the *ADH1C* polymorphism because some genotypes of the *ADH1C* polymorphism occurred in only a small number of subjects.

Funding

National Cancer Center Research and Development Fund (23-A31[toku] and 26-A-2; since 2011), a grant-in-aid for Cancer Research (1989 to 2010), and a grant-in-aid for the Third-Term Comprehensive Ten-Year Strategy for Cancer Control (H24-3jigan-ippan-002) from the Ministry of Health, Labor and Welfare of Japan.

Acknowledgements

We are indebted to the Aomori, Iwate, Ibaraki, Niigata, Osaka, Kochi, Nagasaki and Okinawa Cancer Registries for providing their incidence data. A.H. was awarded a Research Resident Fellowship from the Foundation for Promotion of Cancer Research (Japan) for the Third-Term Comprehensive 10-Year Strategy for Cancer Control.
Conflict of Interest Statement: None declared.

References

1. Boffetta, P. et al. (2006) Alcohol and cancer. Lancet Oncol., 7, 149–156.
2. WCRF/AICR (2007) Alcoholic drinks. In *Food, Nutrition, physical Activity, and the Prevention of Cancer: a Global Perspective*. American Institute for Cancer Research, Washington DC.
3. Klyosov, A.A. (1996) Kinetics and specificity of human liver aldehyde dehydrogenases toward aliphatic, aromatic, and fused polycyclic aldehydes. Biochemistry, 35, 4457–4467.
4. Ehrig, T. et al. (1990) Alcohol and aldehyde dehydrogenase. Alcohol Alcohol, 25, 105–116.
5. Bosron, W.F. et al. (1986) Genetic polymorphism of human liver alcohol and aldehyde dehydrogenases, and their relationship to alcohol metabolism and alcoholism. Hepatology, 6, 502–510.
6. IARC (2012) A Review of Human Carcinogens: Personal Habits and Indoor Combustions. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 100E. International Agency for Research on Cancer, Lyon.
7. Enomoto, N. et al. (1991) Acetaldehyde metabolism in different aldehyde dehydrogenase-2 genotypes. Alcohol. Clin. Exp. Res., 15, 141–144.
8. Brennan, P. et al. (2004) Pooled analysis of alcohol dehydrogenase genotypes and head and neck cancer: a HuGE review. Am. J. Epidemiol., 159, 1–16.
9. Crabb, D.W. et al. (1989) Genotypes for aldehyde dehydrogenase deficiency and alcohol sensitivity. The inactive ALDH2(2) allele is dominant. J. Clin. Invest., 83, 314–316.
10. Tsugane, S. et al. (2001) Baseline survey of JPHC study–design and participation rate. Japan Public Health Center-based Prospective Study on Cancer and Cardiovascular Diseases. J. Epidemiol., 11(6 suppl.), S24–S29.
11. WHO (2000) International Classification of Diseases for Oncology. World Health Organization, Geneva, Switzerland.
12. Lauren, P. (1965) The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. An attempt at a histo-clinical classification. Acta Pathol. Microbiol. Scand., 64, 31–49.
13. Tsubono, Y. et al. (2003) Validity and reproducibility of a self-administered food frequency questionnaire used in the baseline survey of the JPHC Study Cohort I. J. Epidemiol., 13(1 suppl.), S125–S133.
14. Otani, T. et al. (2003) Alcohol consumption, smoking, and subsequent risk of colorectal cancer in middle-aged and elderly Japanese men and women: Japan Public Health Center-based prospective study. Cancer Epidemiol. Biomarkers Prev., 12, 1492–1500.
15. Sasazuki, S. et al. (2002) Cigarette smoking, alcohol consumption and subsequent gastric cancer risk by subsite and histologic type. Int. J. Cancer, 101, 560–566.
16. Miki, K. et al. (2003) Usefulness of gastric cancer screening using the serum pepsinogen test method. Am. J. Gastroenterol., 98, 735–739.
17. Inoue, M. et al. (2006) Diabetes mellitus and the risk of cancer: results from a large-scale population-based cohort study in Japan. Arch. Intern. Med., 166, 1871–1877.
18. Inoue, M. et al. (2009) Impact of metabolic factors on subsequent cancer risk: results from a large-scale population-based cohort study in Japan. Eur. J. Cancer Prev., 18, 240–247.
19. Hidaka, A. et al. (2014) Plasma insulin, C-peptide and blood glucose and the risk of gastric cancer: The Japan Public Health Center-based prospective study. Int J Cancer.
20. Duell, E.J. et al. (2012) Genetic variation in alcohol dehydrogenase (ADH1A, ADH1B, ADH1C, ADH7) and aldehyde dehydrogenase (ALDH2), alcohol consumption and gastric cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. Carcinogenesis, 33, 361–367.
21. Matsuo, K. et al. (2013) The aldehyde dehydrogenase 2 (ALDH2) Glu504Lys polymorphism interacts with alcohol drinking in the risk of stomach cancer. Carcinogenesis, 34, 1510–1515.
22. Shin, C.M. et al. (2011) Association between alcohol intake and risk for gastric cancer with regard to ALDH2 genotype in the Korean population. Int. J. Epidemiol., 40, 1047–1055.
23. Cao, H.X. et al. (2010) Alcohol dehydrogenase-2 and aldehyde dehydrogenase-2 genotypes, alcohol drinking and the risk for stomach cancer in Chinese males. Asian Pac. J. Cancer Prev., 11, 1073–1077.
24. Terry, M.B. et al. (2007) Alcohol dehydrogenase 3 and risk of esophageal and gastric adenocarcinomas. Cancer Causes Control, 18, 1039–1046.
25. Yokoyama, A. et al. (2001) Alcohol and aldehyde dehydrogenase gene polymorphisms and oropharyngolaryngeal, esophageal and stomach cancers in Japanese alcoholics. Carcinogenesis, 22, 433–439.
26. Balbo, S. et al. (2012) Time course of DNA adduct formation in peripheral blood granulocytes and lymphocytes after drinking alcohol. Mutagenesis, 27, 485–490.
27. Brooks, P.J. et al. (2014) Acetaldehyde and the genome: beyond nuclear DNA adducts and carcinogenesis. Environ. Mol. Mutagen., 55, 77–91.
28. Iwasaki, M. et al. (2003) Background characteristics of basic health examination participants: the JPHC Study Baseline Survey. J. Epidemiol., 13, 216–225.

Appendix

Members of the Japan Public Health Center-based Prospective Study Group (JPHC Study, principal investigator: S. Tsugane) are as follows: S. Tsugane, N. Sawada, S. Sasazuki, M. Iwasaki, T. Shimazu, T. Yamaji and T. Hanaoka, National Cancer Center, Tokyo; J. Ogata, S. Baba, T. Mannami, A. Okayama and Y. Kokubo, National Cerebral and Cardiovascular Center, Osaka; K. Miyakawa, F. Saito, A. Koizumi, Y. Sano, I. Hashimoto, T. Ikuta, Y. Tanaba, H. Sato, Y. Roppongi and T. Takashima, Iwate Prefectural Ninohe Public Health Center, Iwate; Y. Miyajima, N. Suzuki, S. Nagasawa, Y. Furusugi, N. Nagai, Y. Ito, S. Komatsu and T. Minamizono, Akita Prefectural Yokote Public Health Center, Akita; H. Sanada, Y. Hatayama, F. Kobayashi, H. Uchino, Y. Shirai, T. Kondo, R. Sasaki, Y. Watanabe, Y. Miyagawa, Y. Kobayashi, M. Machida, K. Kobayashi and M. Tsukada, Nagano Prefectural Saku Public Health Center, Nagano; Y. Kishimoto, E. Takara, T. Fukuyama, M. Kinjo, M. Irei and H. Sakiyama, Okinawa Prefectural Chubu Public Health Center, Okinawa; K. Imoto, H. Yazawa, T. Seo, A. Seiko, F. Ito, F. Shoji and R. Saito, Katsushika Public Health Center, Tokyo; A. Murata, K. Minato, K. Motegi, T. Fujieda and S. Yamato, Ibaraki Prefectural Mito Public Health Center, Ibaraki; K. Matsui, T. Abe, M. Katagiri, M. Suzuki and K. Matsui, Niigata Prefectural Kashiwazaki and Nagaoka Public Health Center, Niigata; M. Doi, A. Terao, Y. Ishikawa and T. Tagami, Kochi Prefectural Chuo-higashi Public Health Center, Kochi; H. Sueta, H. Doi, M. Urata, N. Okamoto, F. Ide and H. Goto, Nagasaki Prefectural Kamigoto Public Health Center, Nagasaki; H. Sakiyama, N. Onga, H. Takaesu, M. Uehara, T. Nakasone and M. Yamakawa, Okinawa Prefectural Miyako Public Health Center, Okinawa; F. Horii, I. Asano, H. Yamaguchi, K. Aoki, S. Maruyama, M. Ichii and M. Takano, Osaka Prefectural Suita Public Health Center, Osaka; Y. Tsubono, Tohoku University, Miyagi; K. Suzuki, Research Institute for Brain and Blood Vessels Akita, Akita; Y. Honda, K. Yamagishi, S. Sakurai and N. Tsuchiya, University of Tsukuba, Ibaraki; M. Kabuto, National Institute for Environmental Studies, Ibaraki; M. Yamaguchi, Y. Matsumura, S. Sasaki and S. Watanabe, National Institute of Health and Nutrition, Tokyo; M. Akabane, Tokyo University of Agriculture, Tokyo; T. Kadowaki and M. Inoue, The University of Tokyo, Tokyo; M. Noda and T. Mizoue, National Center for Global Health and Medicine, Tokyo; Y. Kawaguchi, Tokyo Medical and Dental University, Tokyo; Y. Takashima and Y. Yoshida, Kyorin University, Tokyo; K. Nakamura and R. Takachi, Niigata University, Niigata; J. Ishihara, Sagami Women's University, Kanagawa; S. Matsushima and S. Natsukawa, Saku General Hospital, Nagano; H. Shimizu, Sakihae Institute, Gifu; H. Sugimura, Hamamatsu University School of Medicine, Shizuoka; S. Tominaga, Aichi Cancer Center, Aichi; N. Hamajima, Nagoya University, Aichi; H. Iso and T. Sobue, Osaka University, Osaka; M. Iida, W. Ajiki and A. Ioka, Osaka Medical Center for Cancer and Cardiovascular Disease, Osaka; S. Sato, Chiba Prefectural Institute of Public Health, Chiba; E. Maruyama, Kobe University, Hyogo; M. Konishi, K. Okada and I. Saito, Ehime University, Ehime; N. Yasuda, Kochi University, Kochi; S. Kono, Kyushu University, Fukuoka; S. Akiba, Kagoshima University, Kagoshima.

disclosure

The authors have declared no conflicts of interest.

references

1. Italiano A, Mathoulin-Pelissier S, Cesne AL et al. Trends in survival for patients with metastatic soft-tissue sarcoma. Cancer 2010; 117: 1049–1054.
2. Verweij J, Casali PG, Zalcberg J et al. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. Lancet 2004; 364: 1127–1134.
3. Butrynski JE, D'Adamo DR, Hornick JL et al. Crizotinib in ALK-rearranged inflammatory myofibroblastic tumor. N Engl J Med 2010; 363: 1727–1733.
4. Stacchiotti S, Tamborini E, Bertulli R et al. Response to sunitinib malate (SM) in alveolar soft part sarcoma (ASPS). J Clin Oncol (Meeting Abstracts) 2008; 26: 10592.
5. Rutkowski P, Van Glabbeke M, Rankin CJ et al. Imatinib mesylate in advanced dermatofibrosarcoma protuberans: pooled analysis of two phase II clinical trials. J Clin Oncol 2010; 28: 1772–1779.
6. Olmos D, A'hern RP, Marsoni S et al. Patient selection for oncology phase I trials: a multi-institutional study of prognostic factors. J Clin Oncol 2012; 30: 996–1004.
7. Arkenau HT, Barriuso J, Olmos D et al. Prospective validation of a prognostic score to improve patient selection for oncology phase I trials. J Clin Oncol 2009; 27: 2692–2696.
8. Horstmann E, McCabe MS, Grochow L et al. Risks and benefits of phase 1 oncology trials, 1991 through 2002. N Engl J Med 2005; 352: 895–904.
9. Van Glabbeke M, van Oosterom AT, Oosterhuis JW et al. Prognostic factors for the outcome of chemotherapy in advanced soft tissue sarcoma: an analysis of 2,185 patients treated with anthracycline-containing first-line regimens—a European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Study. J Clin Oncol 1999; 17: 150–157.
10. Daugherty C, Ratain MJ, Grochowski E et al. Perceptions of cancer patients and their physicians involved in phase I trials. J Clin Oncol 1995; 13: 1062–1072.
11. Nurgat ZA, Craig W, Campbell NC et al. Patient motivations surrounding participation in phase I and phase II clinical trials of cancer chemotherapy. Br J Cancer 2005; 92: 1001–1005.
12. Schuetze SM. Imaging and response in soft tissue sarcomas. Hematol Oncol Clin North Am 2005; 19: 471–487, vi.
13. Benjamin RS. SARC-CTOS imaging symposium: introduction to the problem from a clinical perspective. Oncologist 2008; 13(Suppl 2): 1–3.
14. Stacchiotti S, Verderio P, Messina A et al. Tumor response assessment by modified Choi criteria in localized high-risk soft tissue sarcoma treated with chemotherapy. Cancer 2012; 118: 5857–5866.
15. Van Glabbeke M, Verweij J, Judson I et al. Progression-free rate as the principal end-point for phase II trials in soft-tissue sarcomas. Eur J Cancer 2002; 38: 543–549.
16. Jones RL, Olmos D, Thway K et al. Clinical benefit of early phase clinical trial participation for advanced sarcoma patients. Cancer Chemother Pharmacol 2011; 68: 423–429.

Annals of Oncology 25: 1228–1233, 2014
doi:10.1093/annonc/mdu115
Published online 11 March 2014

Association of vegetable and fruit intake with gastric cancer risk among Japanese: a pooled analysis of four cohort studies

T. Shimazu[1]*, K. Wakai[2], A. Tamakoshi[3], I. Tsuji[4], K. Tanaka[5], K. Matsuo[6], C. Nagata[7], T. Mizoue[8], M. Inoue[1,9], S. Tsugane[1], & S. Sasazuki[1] & for the Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan†

[1]Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo; [2]Department of Preventive Medicine, Nagoya University Graduate School of Medicine, Nagoya; [3]Department of Public Health, Hokkaido University Graduate School of Medicine, Sapporo; [4]Division of Epidemiology, Department of Public Health and Forensic Medicine, Tohoku University Graduate School of Medicine, Sendai; [5]Department of Preventive Medicine, Faculty of Medicine, Saga University, Saga; [6]Department of Preventive Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka; [7]Department of Epidemiology and Preventive Medicine, Gifu University Graduate School of Medicine, Gifu; [8]Department of Epidemiology and Prevention, Clinical Research Center, National Center for Global Health and Medicine, Tokyo; [9]Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

Received 31 August 2013; revised 4 February 2014; accepted 2 March 2014

Background: Prospective evidence is inconsistent regarding the association between vegetable/fruit intake and the risk of gastric cancer.

Methods: In an analysis of original data from four population-based prospective cohort studies encompassing 191 232 participants, we used Cox proportional hazards regression to estimate hazard ratios (HRs) and 95% confidence intervals

*Correspondence to: Dr Taichi Shimazu, Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. Tel: +81-3-3542-2511; Fax: +81-3-3547-8578; E-mail: tshimazu@ncc.go.jp

†See acknowledgement for the Research group members.

(CIs) of gastric cancer incidence according to vegetable and fruit intake and conducted a meta-analysis of HRs derived from each study.

Results: During 2 094 428 person-years of follow-up, 2995 gastric cancer cases were identified. After adjustment for potential confounders, we found a marginally significant decrease in gastric cancer risk in relation to total vegetable intake but not total fruit intake: the multivariate-adjusted HR (95% CI; *P* for trend) for the highest versus the lowest quintile of total vegetable intake was 0.89 (0.77–1.03; *P* for trend = 0.13) among men and 0.83 (0.67–1.03; *P* for trend = 0.40) among women. For distal gastric cancer, the multivariate HR for the highest quintile of total vegetable intake was 0.78 (0.63–0.97; *P* for trend = 0.02) among men.

Conclusion(s): This pooled analysis of data from large prospective studies in Japan suggests that vegetable intake reduces gastric cancer risk, especially the risk of distal gastric cancer among men.

Key words: vegetables, fruit, stomach neoplasms, prospective studies, pooled analysis, epidemiology

introduction

Although the incidence of gastric cancer is declining, it remains the second most common cause of cancer death worldwide [1]. Epidemiologic studies have extensively investigated dietary variables as preventive factors in gastric cancer. In particular, vegetables and fruit rich in a large number of phytochemical antioxidants have been comprehensively studied [2]. In 2007, the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) concluded that non-starchy vegetables and fruits probably protect against gastric cancer, largely on the basis of results from case–control studies, which have consistently shown protective associations [3]. In addition, a meta-analysis of case–control studies found that risk was decreased regardless of subsite or histologic subtype [4]. Although five prospective cohort studies of the association of vegetable and fruit intake with gastric cancer risk have been published since then, the findings, including results from subsite-specific analyses, remain inconsistent [5–9]. Furthermore, there are few prospective data regarding the associations of vegetable/fruit intake with gastric cancer classified by histologic subtype (intestinal and diffuse) [5, 10, 11] or sex [7, 8, 12].

To clarify these issues, we conducted a pooled analysis of data from four large-scale cohort studies carried out in Japan. In addition, we investigated the association of vegetable/fruit intake with gastric cancer risk by subsite and histologic type.

methods

study population

The following a priori inclusion criteria were established for the present analysis: population-based cohort studies conducted in Japan, study initiation between the mid-1980s and mid-1990s, inclusion of more than 30 000 participants, use of a validated questionnaire or similar method for baseline collection of information on vegetable and fruit intake (g/day), and collection of incidence data for gastric cancer during the follow-up period. We identified three ongoing studies that met these criteria: (i) The Japan Public Health Center-based prospective Study (JPHC) [13], (ii) The Japan Collaborative Cohort Study (JACC) [14], and (iii) The Miyagi Cohort Study (MIYAGI) [15]. The geographic areas examined in these studies did not overlap. Due to its use of differing dietary questionnaires (available at http://epi.ncc.go.jp/en/questionnaire/index.html), the JPHC was treated as two independent studies (JPHC I and JPHC II). Thus, data from a total of four studies were analyzed. We excluded participants with extreme energy intakes (>3 standard deviations from the mean log-transformed energy intake in each study by sex) or a history of cancer at baseline. In the JACC, information on cancer diagnosis was not collected in 23 of 45 study areas. Therefore, participants in those areas were excluded. Selected characteristics of these studies are summarized in supplementary Table S1, available at *Annals of Oncology* online.

Findings regarding the association of vegetable and fruit intake with gastric cancer risk in the JPHC I and JACC have been previously reported [10, 16]. In the present analysis, we used updated datasets, with longer follow-up periods, for the JPHC. For the JACC, we updated the datasets using incidence data for gastric cancer because previous reports on the current topic analyzed only gastric cancer mortality [16]. Each study obtained approval from the relevant institutional ethical review boards.

exposure assessment

In each study, dietary intake was assessed by using self-administered food-frequency questionnaires (FFQs) on diet and various health habits (including personal medical history, smoking history, and other lifestyle factors) at baseline. Although the wording of the questions varied among studies, each study calculated dietary intake (in grams per day) on the basis of frequency. Daily intake of each food item was calculated by multiplying its frequency by portion size, after which the amounts of total vegetable, green–yellow vegetable, total fruit, and total vegetable/fruit intake (g/day) were calculated. To calculate the amount of green–yellow vegetable intake, we used two items in the JPHC I questionnaire (green vegetables and yellow vegetables), three items in the JPHC II questionnaire (green vegetables, carrots, and tomatoes), and three items in the MIYAGI and JACC questionnaires (green leafy vegetables, carrots and pumpkins, and tomatoes). Intakes of food and nutrients were log-transformed and adjusted for total energy intake, using the residual model [17]. Detailed information on the FFQs is included in the supplementary data, available at *Annals of Oncology* online.

case ascertainment

Participants were followed from the baseline survey (JPHC I: 1990, JPHC II: 1993–1994, JACC: 1988–1990, MIYAGI: 1990) until the final date of follow-up for incidence in each study (JPHC I: 2004, JPHC II: 2004, JACC: 1999, MIYAGI: 2001). In each study, residence status, including vital status, was confirmed by examining the residential registry. Information on cancer diagnosis was collected for the entire population included in the analysis; cases were identified by active patient notification from major local hospitals and/or examination of population-based cancer registries. Cases were coded using the International Classification of Diseases for Oncology, Third Edition [18]. Each study also collected information from death certificates on cause of death and coded it according to the International Statistical Classification of Diseases, 10th Revision [19], which was used to complement hospital and registry data on cancer diagnosis. If detailed information

on the date of gastric cancer diagnosis was not available for gastric cancer cases confirmed by death certificate, we used the date of death from gastric cancer as the date of diagnosis. The quality and completeness of case ascertainment are described in detail elsewhere [20]. The study outcome was defined as incidence of gastric cancer (C16.0–16.9) during the follow-up period of each study.

The inclusion of information on gastric cancer subsite and histology in the JPHC-I, JPHC-II, and MIYAGI allowed for additional analysis. For subsite-specific analysis, we classified the gastric cancer subsite as upper third (C16.0–C16.1) or distal (C16.2–C16.6). For the analysis of risk in relation to histologic type, we used a classification system derived from Lauren [21], i.e. differentiated cancer (corresponding to the intestinal types in Lauren's classification) and undifferentiated cancer (corresponding to the diffuse types in Lauren's classification).

statistical analysis

Person-years of follow-up were calculated from the date of the baseline survey for each study until either the date of a gastric cancer diagnosis, migration from the study area, death, or end of follow-up, whichever occurred first. Each study used Cox proportional hazards models to estimate sex-specific hazard ratios (HRs) and their 95% confidence intervals (CIs) for gastric cancer, according to quintiles of each intake, with the lowest quintile of intake as the reference category. The multivariate models are described in detail in Tables. SAS Version 9.1 (SAS Institute, Inc., Cary, NC) was used for these calculations. A random-effects model, which considers both within-study and between-study variation [22], was used to obtain a single pooled estimate of the HRs from the individual studies for each category. Study-specific HRs were weighted by the inverse of the sum of their variance and the estimated between-studies variance component. The trend association was assessed in a similar manner: investigators from each study calculated the regression coefficient and its standard error of linear trend for intake category treated as an ordinal variable. Then, these values from individual studies were combined using a random-effects model. We used Q statistics to test for heterogeneity among studies [22]. Stata Version 11.2 (Stata Corporation, College Station, TX) statistical software was used for the meta-analysis. All reported *P*-values are two tailed.

results

The present study included 191 232 participants (87 771 men and 103 461 women) and 2995 gastric cancer cases (2104 men and 891 women) during 2 094 428 person-years of follow-up (supplementary Table S1, available at *Annals of Oncology* online).

Supplementary Table S2, available at *Annals of Oncology* online shows the association of total vegetable, green–yellow vegetable, total fruit, and total vegetable/fruit intake with gastric cancer risk among men and women. After adjustment for potential confounders, we found a marginally significant reduction in gastric cancer risk in relation to total vegetable intake but not total fruit intake among men and women. For total vegetable/fruit intake, we also found a marginally significant reduction in gastric cancer risk among men (P for trend = 0.08) but not among women. The results for green–yellow vegetables were similar to those for total vegetable intake.

Table 1 shows the association with gastric cancer incidence according to quintile of vegetable and fruit intake among men, by gastric cancer subsite and histologic type, using data from the JPHC I, JPHC II, and MIYAGI (i.e. the studies that included the relevant information). Analysis by gastric cancer subsite showed that the risk of distal gastric cancer was inversely associated with total vegetable, green–yellow vegetable, and total vegetable/fruit intakes among men; however, no such associations were found for gastric cancer in the upper third of the stomach. We found no significant association of any category of vegetable or fruit intake with gastric cancer histology.

As for women (supplementary Table S3, available at *Annals of Oncology* online), we found no association of any category of vegetable and fruit intake with gastric cancer incidence by subsite. In the analysis by histologic type, we observed that the risk of differentiated gastric cancer significantly decreased with increasing quintile of total fruit intake (P for trend = 0.03). None of the P values for heterogeneity across quintiles of intakes were statistically significant. In addition, the results were essentially unchanged when cases diagnosed during the first 3 years of follow-up were excluded. The results of sensitivity analysis are included in the supplementary data, available at *Annals of Oncology* online.

discussion

In this pooled analysis of major population-based cohort studies in Japan, which included data on 2995 gastric cancer cases, we found a marginally significant reduction in gastric cancer risk in relation to total vegetable and green–yellow vegetable intakes but not total fruit intake among men and women. For total vegetable intake, the multivariate-adjusted HR (95% CI; P for trend) for gastric cancer in the highest versus the lowest quintile of intake was 0.89 (0.77–1.03; P for trend = 0.13) among men and 0.83 (0.67–1.03; P for trend = 0.40) among women. In subsite-specific analyses, men in the highest quintiles of total vegetable, green–yellow vegetable, and total vegetable/fruit intakes had an ~20% decrease in distal gastric cancer risk. Among women, we found no significant association of any category of vegetable or fruit intake with gastric cancer incidence by subsite. However, there was an inverse association of total fruit intake with risk of differentiated gastric cancer (P for trend = 0.03). To our knowledge, the present pooled analysis included the largest number of gastric cancer cases to date. Moreover, it revealed associations in analysis stratified by sex, subsite, and histologic type.

In the last WCRF/AICR report, in 2007, a meta-analysis of cohort data showed that green–yellow vegetable intake was associated with a reduction in gastric cancer risk (19% per 50-g intake/day); however, intakes of non-starchy vegetables and fruit were not associated with gastric cancer risk [3]. After that report, five prospective cohort studies found associations of vegetable and fruit intake with gastric cancer risk [5–9], but the results were inconsistent. A Swedish study reported that total vegetable, green leafy vegetable, and root vegetable intakes were significantly associated with decreased risk of total gastric cancer [9]. In contrast, three other studies reported a significant inverse association of fruit intake with gastric cancer. A study conducted in Shanghai showed reduced risk of non-cardia gastric cancer among men [7], and updated results from the EPIC-EURGAST study [5] and the Netherlands Cohort Study [6] showed that citrus fruit intake was inversely associated only with the risk of gastric cardia cancer.

Table 1. Hazard ratios and 95% confidence intervals for gastric cancer incidence by quintile of vegetable and fruit intake in men, by cancer subsite and histology

Variables	Quintile of intake (g/day)					*P* for Trend	*P* for between-study heterogeneity
	1 (low)	2	3	4	5 (high)		
Total vegetable intake							
Distal							
No. of cases	199	196	220	216	197		
Model 1[a]	1	0.90 (0.74–1.11)	0.94 (0.77–1.15)	0.86 (0.70–1.05)	0.78 (0.63–0.97)	0.02	0.65
Upper third							
No. of cases	29	38	41	49	50		
Model 1[a]	1	1.30 (0.79–2.14)	1.30 (0.79–2.13)	1.43 (0.87–2.33)	1.48 (0.89–2.46)	0.13	0.72
Differentiated							
No. of cases	177	184	204	196	198		
Model 1[a]	1	1.00 (0.81–1.23)	1.03 (0.83–1.27)	0.92 (0.74–1.14)	0.92 (0.73–1.14)	0.26	0.45
Undifferentiated							
No. of cases	90	94	84	106	95		
Model 1[a]	1	1.01 (0.75–1.36)	0.89 (0.65–1.21)	1.07 (0.79–1.44)	1.02 (0.74–1.40)	0.80	0.66
Green–yellow vegetable intake							
Distal							
No. of cases	220	206	198	214	190		
Model 1[a]	1	0.96 (0.79–1.16)	0.88 (0.69–1.12)	0.91 (0.75–1.11)	0.81 (0.66–0.996)	0.049	0.67
Upper third							
No. of cases	37	36	52	50	32		
Model 1[a]	1	1.05 (0.66–1.69)	1.43 (0.93–2.21)	1.30 (0.67–2.52)	0.83 (0.50–1.36)	0.27	0.85
Differentiated							
No. of cases	192	174	205	198	190		
Model 1[a]	1	0.96 (0.78–1.18)	1.08 (0.88–1.32)	1.00 (0.81–1.22)	0.93 (0.76–1.15)	0.67	0.91
Undifferentiated							
No. of cases	105	95	81	106	82		
Model 1[a]	1	0.93 (0.70–1.23)	0.79 (0.55–1.13)	1.02 (0.73–1.42)	0.82 (0.55–1.23)	0.57	0.18
Total fruit intake							
Distal							
No. of cases	211	209	215	189	204		
Model 1[a]	1	1.03 (0.85–1.26)	1.02 (0.83–1.25)	0.86 (0.65–1.15)	0.90 (0.67–1.22)	0.23	0.12
Upper third							
No. of cases	35	49	31	48	44		
Model 1[a]	1	1.52 (0.97–2.38)	0.94 (0.57–1.54)	1.39 (0.89–2.19)	1.23 (0.70–2.17)	0.55	0.25
Differentiated							
No. of cases	179	196	203	181	200		
Model 1[a]	1	1.17 (0.95–1.43)	1.16 (0.93–1.43)	0.98 (0.79–1.21)	1.06 (0.77–1.46)	0.86	0.11
Undifferentiated							
No. of cases	112	90	85	86	96		
Model 1[a]	1	0.82 (0.62–1.09)	0.76 (0.56–1.04)	0.76 (0.57–1.02)	0.88 (0.63–1.23)	0.38	0.27
Total vegetable/fruit intake							
Distal							
No. of cases	195	205	229	208	191		
Model 1[a]	1	0.98 (0.72–1.34)	1.01 (0.83–1.23)	0.88 (0.69–1.13)	0.79 (0.59–1.06)	0.03	0.28
Upper third							
No. of cases	29	38	42	53	45		
Model 1[a]	1	1.31 (0.79–2.16)	1.32 (0.81–2.18)	1.67 (1.03–2.70)	1.38 (0.82–2.31)	0.20	0.27
Differentiated							
No. of cases	165	198	202	208	186		
Model 1[a]	1	1.15 (0.86–1.54)	1.09 (0.88–1.35)	1.08 (0.83–1.42)	0.94 (0.73–1.22)	0.46	0.24
Undifferentiated							
No. of cases	103	76	103	89	98		
Model 1[a]	1	0.72 (0.53–0.98)	0.94 (0.70–1.27)	0.81 (0.60–1.09)	0.93 (0.64–1.33)	0.84	0.31

[a]Model 1 was adjusted for age (in years), location within the study area (for Japan Public Health Center-based prospective Study [JPHC] I and JPHC II), smoking status (never, former, currently smoking <20 cigarettes/day, and currently smoking ≥20 cigarettes/day), sodium intake (continuous), and total energy intake (continuous).