Original Article

Fruit and vegetable intake and the risk of overall cancer in Japanese: A pooled analysis of population-based cohort studies

Ribeka Takachi a, Manami Inoue b,*, Yumi Sugawara c, Ichiro Tsuji c, Shoichiro Tsugane d, Hidemi Ito e, Keitaro Matsuo f, Keitaro Tanaka g, Akiko Tamakoshi h, Tetsuya Mizoue i, Kenji Wakai j, Chisato Nagata k, Shizuka Sasazuki l, for the Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan

a Department of Food Science and Nutrition, Nara Women’s University Graduate School of of Humanities and Sciences, Nara, Japan
b AXA Department of Health and Human Security, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
c Division of Epidemiology, Department of Public Health and Forensic Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan
d Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan
e Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute, Nagoya, Japan
f Division of Molecular Medicine, Aichi Cancer Center Research Institute, Nagoya, Japan
g Department of Preventive Medicine, Saga Medical School, Faculty of Medicine, Saga University, Saga, Japan
h Division of Epidemiology and Prevention, Aichi Cancer Center, Nagoya, Japan
i Department of Public Health, Hokkaido University Graduate School of Medicine, Sapporo, Japan
j Department of Epidemiology and International Health, International Clinical Research Center, National Center for Global Health and Medicine, Tokyo, Japan
k Department of Preventive Medicine, Nagoya University Graduate School of Medicine, Nagoya, Japan
l Division of Molecular Medicine and Preventive Medicine, Gifu University Graduate School of Medicine, Gifu, Japan
m Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan

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A B S T R A C T

Background: A series of recent reports from large-scale cohort studies involving more than 100,000 subjects reported no or only very small inverse associations between fruit and vegetable intake and overall cancer incidence, despite having sufficient power to do so. To date, however, no such data have been reported for Asian populations.

Objective: To provide some indication of the net impact of fruit and vegetable consumption on overall cancer prevention, we examined these associations in a pooled analysis of large-scale cohort studies in Japanese populations.

Methods: We analyzed original data from four cohort studies that measured fruit and vegetable consumption using validated questionnaires at baseline. Hazard ratios (HRs) in the individual studies were calculated, with adjustment for a common set of variables, and combined using a random-effects model.

Results: During 2,318,927 person-years of follow-up for a total of 191,519 subjects, 17,681 cases of overall cancers were identified. Consumption of fruit or vegetables was not associated with decreased risk of overall cancers: corresponding HRs for the highest versus lowest quartiles of intake for men and women were 1.03 (95% CI, 0.97–1.10; trend p = 1.00) and 1.03 (95% CI, 0.95–1.11; trend p = 0.97), respectively, for fruit and 1.07 (95% CI, 1.01–1.14; trend p = 0.18) and 0.98 (95% CI, 0.91–1.06; trend p = 0.99), respectively, for vegetables, even in analyses stratified by smoking status and alcohol drinking.

Conclusions: The results of this pooled analysis do not support inverse associations of fruit and vegetable consumption with overall cancers in the Japanese population.

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Introduction

Cancer is the leading cause of death in many parts of the world. Fruit and vegetable consumption has long been considered to
protect against a number of respiratory and digestive cancers. However, associations with overall cancers in previous prospective cohort studies of fruit and vegetable consumption in relation to the risk of overall cancer and cardiovascular disease (CVD) simultaneously in the same population were controversial, despite comparatively clear associations for CVD. We cannot rule out, however, the possibility that these studies might have been unable to detect smaller protective effects of fruit and vegetable intake against the risk of overall cancers: four of the seven studies included fewer than 10,000 subjects, resulting in relatively few cases of overall cancers (200–300 cases) and the other three included more than 70,000 subjects and showed significant inverse associations between the consumption of fruit and vegetables and risk of CVD only, and not for the risk of overall cancers.

One approach to determining the net impact of fruit and vegetable consumption on cancer prevention is to examine associations between consumption and the risk of overall cancer incidence in larger scale (e.g., more than 100,000 people, with more than 10,000 cases) cohort studies. To our knowledge, three such prospective cohort studies have been reported, and all found no or only very small inverse associations. However, these studies were all conducted in Western populations (in the United States and Europe), and no data have been reported for Asian populations. Asian populations tend to differ from Western populations with respect to the distribution of exposure (higher vegetable consumption and lower fruit consumption), outcome (higher incidence of infection-related cancers and lower incidence of hormone-related cancers), and covariates (higher prevalence of smoking and lower prevalence of obesity and low fat intake). Similar studies in Asian populations will aid characterization of the overall impact of fruit and vegetable consumption against the global burden of cancer.

In this study, we conducted a pooled analysis of larger-scale population-based cohort studies that investigated the associations of fruit and vegetable consumption with the risk of overall cancers in Japan.

Methods

Study population

In 2006, the Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan initiated a pooling project using original data from major cohort studies to evaluate the association between lifestyle and major forms of cancer among Japanese. To maintain the quality and comparability of data, we set inclusion criteria for the present purpose a priori. These included population-based cohort studies conducted in Japan; commencement in the mid-1980s to mid-1990s; more than 30,000 participants; baseline information on diet, including fruit and vegetable consumption, using a validated questionnaire; and incidence data for overall cancers during the follow-up period. We identified four studies that met these criteria: (1) the Japan Public Health Center-based Prospective Study (JPHC)-II; (2) the JPHC-II; (3) the Miyagi Cohort Study (MIYAGI); and (4) the Ohsaki Cohort Study (OHSAKI). These studies included information on energy-adjusted consumption, which was incorporated into the main pooled analysis of the present study (based on quintiles of energy-adjusted intake). For sub-analyses based on intake frequency, two additional studies were included; (5) the Three Prefecture Study - Miyagi portion (3-pref MIYAGI) and (6) the Three Prefectures Study - Aichi portion (3-pref AICHI). All studies had been approved by the relevant institutional review board. Results on the associations of fruit or vegetable intake with overall cancer risk in these cohorts have been reported. For the present analysis, we used updated data sets with extended follow-up periods.

We excluded participants with a history of cancer at baseline or missing information on all fruit and vegetable items, or with extreme energy intake (>3 standard deviations from the mean log-transformed energy intake in each study by sex, for the main analysis based on energy-adjusted quintiles). Selected characteristics of these studies are summarized in Table 1.

Follow-up

Subjects were followed from the baseline survey (JPHC-I, 1990; JPHC-II, 1993–1994; MIYAGI, 1990; OHSAKI, 1994) to the date of last follow-up for the incidence of overall cancer in each study (JPHC-I, 2006; JPHC-II, 2006; MIYAGI, 2003; OHSAKI, 2005). Residence status in each study, including survival, was confirmed through the residential registry.

Case ascertainment

In all cohorts, cancer diagnoses were identified through population-based cancer registries and active patient notification from major local hospitals. Cases were coded using the International Classification of Disease, Tenth Revision or the International Classification of Diseases for Oncology, Third Edition. Additional analyses restricted to smoking-related cancers as outcome were also conducted, namely for cancer of the lip, oral cavity, and pharynx; esophagus; stomach; colorectum; liver; pancreas; nasal cavity and paranasal sinus; larynx; lung; uterine cervix; ovary; kidney and renal pelvis; ureter; and bladder cancer.

Exposure assessment

In each study, dietary intake was assessed 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 FFQ items, number, and categories of frequency differed by study (2 or 3 items for fruit and 5 or 6 items for vegetables), each study was able to estimate consumption in grams per day for the following food groups on the basis of frequency: fruit and vegetables, vegetables excluding pickled vegetables, green-yellow vegetables, fruit, and fruit excluding juices. Standard portion sizes were specified for each cohort on the basis of median values observed in dietary records obtained from subsamples. The frequency of vegetable and fruit intake was classified using four categories: almost never (JPHC-I), almost never/seldom (JPHC-II), or almost never/1–2 days/month (MIYAGI, OHSAKI, 3-pref MIYAGI, and 3-pref AICHI), 1–2 days/week, 3–4 days/week, and almost daily. For analyses based on frequency, the self-administered questionnaires of 3-pref MIYAGI and 3-pref AICHI included three vegetable and one fruit items.

Daily intake of each food item was calculated via multiplying frequency by portion size, after which intakes were calculated in g/day for total vegetables, vegetables excluding pickles, green-yellow vegetables, total fruit, and total vegetable/fruit intake. These intakes were log-transformed and adjusted for total energy intake using the residual method. In contrast, for sub-analysis based on frequency, the intake frequency of each item was summed to provide a daily value and re-categorized as almost never: 1–2 days/week; 3–4 days/week, and almost daily.

Correlation coefficients (age-adjusted and de-attenuated for MIYAGI) between energy-adjusted total fruit and total vegetable intakes estimated from the FFQ and those from 12- or 28-day dietary records (DRs) were 0.55 and 0.27 among men and 0.35 and
Table 1
Characteristics of the four cohort studies included in a pooled analysis of fruits and vegetables and the risk of overall cancer incidence.

| Study       | Population Description                                                                 | Age (years) at baseline survey | Population size | Rate of response to baseline questionnaire (%) | For the present pooled analysis |
|-------------|---------------------------------------------------------------------------------------|-------------------------------|----------------|---------------------------------|----------------------------------|
|             |                                                                                       |                               |                |                                 | Age, years | Last follow-up time | Mean duration of follow-up, years | Size of cohort | Number of overall cancer incidence |
| JPHC-I      | Japanese residents of 5 public health center areas in Japan                           | 40–59                         | 61,595         | 82%                             | 40–59      | 2006               | 15.2                          | Men: 20,152  | Women: 21,581                       |
|             |                                                                                       |                               |                |                                 |            |                   |                              | Men: 20,298  | Women: 21,807                       |
| JPHC-II     | Japanese residents of 6 public health center areas in Japan                           | 40–69                         | 78,825         | 80%                             | 40–69      | 2006               | 12.0                          | Men: 28,933  | Women: 30,031                       |
|             |                                                                                       |                               |                |                                 |            |                   |                              | Men: 29,224  | Women: 30,439                       |
| MIYAGI      | Residents of 14 municipalities in Miyagi Prefecture, Japan                            | 40–64                         | 47,605         | 92%                             | 40–64      | 2003               | 12.5                          | Men: 20,911  | Women: 22,449                       |
|             |                                                                                       |                               |                |                                 |            |                   |                              | Men: 21,042  | Women: 22,709                       |
| OHSAKI      | Beneficiaries of National Health Insurance among residents of 14 municipalities in Miyagi Prefecture, Japan | 40–79                         | 54,996         | 95%                             | 40–79      | 2005               | 9.0                           | Men: 21,777  | Women: 23,667                       |
|             |                                                                                       |                               |                |                                 |            |                   |                              | Men: 21,980  | Women: 23,976                       |
| 3-pref MIYAGI | Residents of 3 municipalities in Miyagi Prefecture, Japan                             | 40–98                         | 31,345         | 94%                             | 40–98      | 1992               | 7.5                           | Men: 13,080  | Women: 15,377                       |
|             |                                                                                       |                               |                |                                 |            |                   |                              | Men: 15,778  | Women: 18,780                       |
| 3-pref AICHI | Residents of 2 municipalities in Aichi Prefecture, Japan                              | 40–103                        | 33,529         | 90%                             | 40–103     | 2000               | 11.3                          | Men: 15,340  | Women: 17,042                       |
|             |                                                                                       |                               |                |                                 |            |                   |                              | Men: 17,042  | Women: 15,877                       |
| Total       |                                                                                       | 40–79                         | 243,021        | 80–95                           | 40–79      | 2003–06            | 9.0–15.2                      | Men: 91,779  | Women: 99,740                       |
|             |                                                                                       |                               |                |                                 |            |                   |                              | Men: 120,964 | Women: 133,350                      |

JPHC, Japan Public Health Center-based Prospective Study; MIYAGI, The Miyagi Cohort Study; OHSAKI: The Ohsaki National Health Insurance Cohort Study 3-pref MIYAGI, The Three Prefectures Study - Miyagi portion; 3-pref AICHI, The Three Prefectures Study - Aichi portion. Sub-analysis based on frequencies of fruit and vegetable intake was independently conducted (Table 5-1 and 5-2): two cohort studies (3-pref MIYAGI and 3-pref AICHI) which were not suited for the analysis based on energy-adjusted intake because total energy intake could not be calculated from their FFQ were also included. Thus, exclusion criteria (extreme consumption according to total energy intake) in the analysis based on the frequency differed from those based on quintiles of energy-adjusted fruit and vegetable intake.
0.31 among women for the JPHC and 0.76 and 0.60 among men and 0.70 and 0.45 among women for MIYAGI. OHSASKI, for which information on the validation of fruit and vegetable consumption was not available (but whose population had similar cultural characteristics), utilized the same questionnaire as MIYAGI.

Statistical analysis

Person-years of follow-up were calculated from the date of the baseline survey in each study to the date of diagnosis of any cancer, migration from the study area, death, or the end of follow-up, whichever came first. In each individual study, age- (continuous) and area- (JPHC-I, JPHC-II) adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for overall cancer were estimated for the categories of energy-adjusted fruit and vegetable consumption in quintiles among men and women separately, with the lowest consumption category as the reference, using a Cox proportional hazards model. Further, linear associations were assessed using the ordinal (0–4) values for each quintile.

Further multivariate adjustments were made by including covariates in the model which were either known or suspected risk factors for cancer or had previously been found to be associated with the risk of major cancers. In the multivariate model, we further adjusted for smoking status (using sex-specific covariates; as 40 cigarettes/day for men), alcohol consumption (non, occasional, or ≥45 g ethanol/day), body mass index in kg/m²), history of diabetes mellitus (yes or no), and screening examination (yes or no; any kind of the following cancer screening for JPHC-I: chest X-ray, sputum test, photofluorography, gastrointestinal endoscopy, fecal occult blood test, barium enema, or colonoscopy; any kind of screening examination for JPHC-II; and chest X-ray, gastric cancer examination, Pap smear, mammography, or complete medical checkup for MIYAGI and OHSASKI). HR3 excluded diagnosed or deceased cases of any cancers during the first 3 years of follow-up. Linear trends across quintiles of fruit and vegetable intake were tested using 0 to 4 for each quintile.

Table 2-1

|                     | Lowest              | Second              | Third               | Fourth              | Highest             |
|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| **Fruits**          |                     |                     |                     |                     |                     |
| Number of subjects  | 18,354              | 18,354              | 18,355              | 18,355              | 18,354              |
| Person-years        | 217,070             | 218,667             | 218,957             | 217,783             | 214,059             |
| Number of cases     | 2081                | 2091                | 2152                | 2228                | 2348                |
| HR (95% CI)         | 1.0 (Ref.)          | 0.96 (0.92, 1.04)   | 0.95 (0.88, 1.03)   | 0.95 (0.90, 1.01)   | 0.95 (0.89, 1.01)   |
| ASR (per 100,000)   | 1.01 (1.01, 1.04)   | 1.00 (0.93, 1.07)   | 1.03 (0.96, 1.09)   | 1.04 (0.97, 1.11)   | 0.97 (0.91, 1.11)   |
| **Fruits, excluding juice** |                     |                     |                     |                     |                     |
| Number of subjects  | 18,354              | 18,354              | 18,355              | 18,355              | 18,354              |
| Person-years        | 217,028             | 217,845             | 218,569             | 218,887             | 214,208             |
| Number of cases     | 2141                | 2156                | 2130                | 2130                | 2131                |
| HR (95% CI)         | 1.01 (0.95, 1.07)   | 1.00 (0.94, 1.08)   | 0.96 (0.90, 1.02)   | 0.96 (0.89, 1.04)   | 0.96 (0.89, 1.04)   |
| ASR (per 100,000)   | 1.00 (0.93, 1.07)   | 0.99 (0.90, 1.03)   | 0.98 (0.92, 1.04)   | 1.00 (0.93, 1.07)   | 1.00 (0.93, 1.07)   |
| **Vegetables**      |                     |                     |                     |                     |                     |
| Number of subjects  | 18,354              | 18,354              | 18,355              | 18,355              | 18,354              |
| Person-years        | 217,320             | 217,056             | 218,766             | 218,274             | 215,726             |
| Number of cases     | 2126                | 2127                | 2043                | 2244                | 2330                |
| HR (95% CI)         | 1.01 (0.95, 1.07)   | 1.00 (0.94, 1.08)   | 0.96 (0.90, 1.03)   | 0.98 (0.92, 1.05)   | 1.00 (0.93, 1.07)   |
| ASR (per 100,000)   | 1.00 (0.93, 1.07)   | 0.99 (0.92, 1.05)   | 0.98 (0.92, 1.05)   | 1.00 (0.93, 1.07)   | 0.90 (0.95, 1.02)   |
| **Vegetables, excluding pickles** |                     |                     |                     |                     |                     |
| Number of subjects  | 18,354              | 18,354              | 18,355              | 18,355              | 18,354              |
| Person-years        | 217,262             | 218,471             | 218,766             | 218,076             | 215,041             |
| Number of cases     | 2056                | 2091                | 2228                | 2230                | 2423                |
| HR (95% CI)         | 1.00 (0.94, 1.07)   | 1.04 (0.98, 1.11)   | 1.03 (0.96, 1.10)   | 1.06 (0.98, 1.11)   | 0.18 (0.01, 0.15)   |
| ASR (per 100,000)   | 1.00 (0.93, 1.06)   | 1.03 (0.96, 1.10)   | 1.03 (0.96, 1.10)   | 1.08 (1.01, 1.15)   | 0.18 (0.02, 0.16)   |
| **Green and yellow vegetables** |                     |                     |                     |                     |                     |
| Number of subjects  | 18,354              | 18,354              | 18,355              | 18,355              | 18,354              |
| Person-years        | 216,692             | 218,428             | 218,289             | 217,287             | 215,844             |
| Number of cases     | 2083                | 2001                | 2157                | 2311                | 2408                |
| HR (95% CI)         | 1.00 (0.94, 1.07)   | 1.04 (0.98, 1.11)   | 1.00 (0.94, 1.07)   | 1.00 (0.94, 1.07)   | 0.71 (0.86, 0.85)   |
| ASR (per 100,000)   | 1.00 (0.94, 1.07)   | 1.04 (0.98, 1.11)   | 1.00 (0.94, 1.07)   | 1.00 (0.94, 1.07)   | 0.71 (0.86, 0.85)   |

ASR, age-standardized rate; CI, confidence interval; HR, hazard ratio.

HR1 was adjusted for age (continuous), area (for JPHC-I, JPHC-II only); HR2 and 3: further adjusted for total energy intake (quintile); smoking status (never, past, <19, 19–39, or ≥40 cigarettes/day for men), alcohol consumption (non, occasional, <23, 23–45, or ≥46 g ethanol/day), body mass index in kg/m² (14–18.9, 19–20.9, 21–22.9, 23–24.9, 25–26.9, 27–29.9, or 30–40 kg/m²), history of diabetes mellitus (yes or no), and screening examination (yes or no; any kind of the following cancer screening for JPHC-I: chest X-ray, sputum test, photofluorography, gastrointestinal endoscopy, fecal occult blood test, barium enema, or colonoscopy; any kind of screening examination for JPHC-II; and chest X-ray, gastric cancer examination, Pap smear, mammography, or complete medical checkup for MIYAGI and OHSASKI). HR3 excluded diagnosed or deceased cases of any cancers during the first 3 years of follow-up. Linear trends across quintiles of fruit and vegetable intake were tested using 0 to 4 for each quintile as an ordinal variable.
 screening examination within the preceding year for JPHC-II; ≥1 or ≥5 examinations of chest X-ray, gastric cancer examination, Pap smear, mammography, or complete medical checkup within the preceding 1 year or 5 years, respectively, for MIYAGI and OHSAKI). Leisure time sport (almost daily or <3–4 times/w for JPHC-I and II, ≥5 h/w or <3–4 h/w for MIYAGI and OHSAKI) was also included in the model as a sensitivity analysis. To minimize the effects of malignancy itself, the first 3 years from baseline were excluded from the risk period. An indicator term for missing data was created for each covariate. Further, we also conducted stratified analysis by smoking or drinking status among never smokers and among ever smokers, as well as among never or occasional drinkers and among

| Table 2-2 | Pooled analysis of overall cancer incidence according to quintile of fruit and vegetable consumption in Japanese women, 1990–2006. |
|-----------|-----------------------------------------------------------------------------------------------------|
|           | Lowest HR (95% CI) | Second HR (95% CI) | Third HR (95% CI) | Fourth HR (95% CI) | Highest HR (95% CI) | p for trend | p for heterogeneity for the highest category | For trend category |
| Total fruit and vegetables | | | | | | | |
| Number of subjects | 19,946 | 19,949 | 19,949 | 19,949 | 19,947 | | |
| Person-years | 245,257 | 246,517 | 248,367 | 246,836 | 245,414 | | |
| Number of cases | 1331 | 1269 | 1313 | 1382 | 1426 | | |
| ASR (per 100,000) | 579 | 544 | 552 | 573 | 583 | | |
| HR1 (1.0 Ref) | 0.98 (0.87, 1.07) | 1.00 (0.91, 1.10) | 1.03 (0.95, 1.12) | 1.05 (0.96, 1.14) | 0.55 | 0.41 | 0.52 |
| Fruits | | | | | | | |
| Number of subjects | 19,946 | 19,949 | 19,949 | 19,947 | 19,947 | | |
| Person-years | 244,973 | 246,783 | 247,730 | 247,730 | 248,730 | | |
| Number of cases | 1375 | 1278 | 1311 | 1310 | 1446 | | |
| ASR (per 100,000) | 588 | 554 | 539 | 598 | 604 | | |
| HR1 (1.0 Ref) | 0.98 (0.87, 1.07) | 0.99 (0.89, 1.10) | 1.03 (0.85, 1.03) | 1.05 (0.97, 1.14) | 0.86 | 0.59 | 0.46 |
| Fruits, excluding juice | | | | | | | |
| Number of subjects | 19,946 | 19,949 | 19,949 | 19,947 | 19,947 | | |
| Person-years | 244,709 | 245,699 | 247,885 | 247,934 | 246,163 | | |
| Number of cases | 1374 | 1262 | 1313 | 1301 | 1446 | | |
| ASR (per 100,000) | 589 | 546 | 563 | 542 | 592 | | |
| HR1 (1.0 Ref) | 0.98 (0.86, 1.01) | 0.97 (0.87, 1.03) | 0.93 (0.86, 1.00) | 0.91 (0.89, 1.00) | 0.72 | 0.46 | 0.68 |
| Vegetables | | | | | | | |
| Number of subjects | 19,946 | 19,949 | 19,949 | 19,947 | 19,947 | | |
| Person-years | 245,417 | 246,791 | 247,663 | 246,524 | 245,995 | | |
| Number of cases | 1327 | 1328 | 1374 | 1402 | 1390 | | |
| ASR (per 100,000) | 576 | 572 | 539 | 584 | 563 | | |
| HR1 (1.0 Ref) | 0.98 (0.86, 1.01) | 0.97 (0.86, 1.02) | 0.93 (0.86, 1.01) | 0.91 (0.89, 1.00) | 0.59 | 0.46 | 0.85 |
| Vegetable, excluding pickles | | | | | | | |
| Number of subjects | 19,946 | 19,949 | 19,949 | 19,947 | 19,947 | | |
| Person-years | 245,703 | 246,306 | 247,225 | 246,562 | 245,594 | | |
| Number of cases | 1329 | 1313 | 1363 | 1317 | 1399 | | |
| ASR (per 100,000) | 585 | 582 | 577 | 559 | 560 | | |
| HR1 (1.0 Ref) | 1.00 (0.90, 1.10) | 1.02 (0.94, 1.10) | 0.97 (0.89, 1.03) | 1.00 (0.92, 1.08) | 0.97 | 0.57 | 0.57 |
| Green and yellow vegetables | | | | | | | |
| Number of subjects | 19,946 | 19,949 | 19,949 | 19,947 | 19,947 | | |
| Person-years | 246,769 | 246,500 | 246,852 | 247,565 | 246,705 | | |
| Number of cases | 1305 | 1286 | 1325 | 1354 | 1391 | | |
| ASR (per 100,000) | 595 | 558 | 566 | 561 | 557 | | |
| HR1 (1.0 Ref) | 0.98 (0.87, 1.03) | 0.98 (0.87, 1.03) | 0.96 (0.89, 1.05) | 0.95 (0.88, 1.04) | 0.96 | 0.98 | 0.96 |

ASR, age-standardized rate; CI, confidence interval; HR, hazard ratio.

HR1 was adjusted for age (continuous), area (for JPHC-I, JPHC-II only); HR2 and 3: further adjusted for total energy intake (quintile), smoking status (never, past, or current); alcohol consumption (non, occasional, <23, 23–45, ≤46 g ethanol/day), body mass index (BMI) in kg/m² (14–18.9, 19–20.9, 21–22.9, 23–24.9, 25–26.9, 27–29.9, or ≥30–40 kg/m²), quintile of total energy intake (for analysis based on quintiles), history of diabetes mellitus (yes/no), and cancer screening examination (yes/no, study-specific question as follows: ≥1 examination of chest X-ray, sputum test, photofluorography, gastrointestinal endoscopy, fecal occult blood test, barium enema, or colonoscopy within the preceding year for JPHC-I; ≥1 of any kind of screening examination within the preceding year for JPHC-II; ≥1 or ≥5 examinations of chest X-ray, gastric cancer examination, Pap smear, mammography, or complete medical checkup within the preceding 1 year or 5 years, respectively, for MIYAGI and OHSAKI). Leisure time sport (almost daily or <3–4 times/w for JPHC-I and II, ≥5 h/w or <3–4 h/w for MIYAGI and OHSAKI) was also included in the model as a sensitivity analysis. To minimize the effects of malignancy itself, the first 3 years from baseline were excluded from the risk period. An indicator term for missing data was created for each covariate. Further, we also conducted stratified analysis by smoking or drinking status among never smokers and among ever smokers, as well as among never or occasional drinkers and among

Table 2-2
Pooled analysis of overall cancer incidence according to quintile of fruit and vegetable consumption in Japanese women, 1990–2006.
regular drinkers. These analyses were repeated for cancers associated with tobacco smoking.

A random-effects model was used to obtain a single pooled estimate of the HRs from the individual studies for each category. The study-specific HRs were weighted by the inverse of the sum of their variance and the estimated between-studies variance component. A study that had no cases for a category was not included in the pooled estimate for that category. 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 fruit/vegetable consumption category treated as an ordinal variable. These values from the individual studies were then combined using a random-effects model. We tested for and quantified the heterogeneity of the HRs for the highest category and the trend association of fruit/vegetables consumption among studies using the $I^2$ statistic.

All statistical analyses were conducted using SAS (Version 9.1.3, 2006, SAS Institute Inc., Cary, NC, USA) statistical software.

## Results

The present study included 191,519 subjects (91,779 men and 99,740 women) and 17,681 cases of overall cancer (10,960 men and 99,740 women) accumulated during 2,318,927 person-years of follow-up from four large-scale cohorts (Table 1). With regard to the variation of intakes by quintiles, cut-offs of the fourth/highest quintile of fruit or vegetable consumption were three- to five-fold or more and two- to three-fold, respectively, of those for the lowest/second quintile for each cohort. In the study-specific analysis, no associations were found between fruit or vegetable consumption and the risk of overall cancer in either gender or specific cohorts in the multivariate analysis, although a significant inverse association was found for fruit consumption in JPHC-I and OHSAKI men in the age- and area-adjusted analysis (data not shown).

Among both men and women, no significant inverse associations were found between fruit or vegetable intake and the risk of overall cancer, whether combined or separated (see HR1 and HR2 in Table 2-1 and Table 2-2) (multivariate HR of highest quintiles of total fruit and vegetables vs. the lowest: 1.04; 95% CI, 0.98–1.11; trend $p = 0.54$ for men; and 1.02; 95% CI, 0.94–1.10; trend $p = 0.81$ for women). Rather, a statistically significant positive HR was found for the highest quintile of total vegetable consumption, after adjustment for potential confounders (HR2) among men (multivariate HR of highest quintile of vegetables vs. the lowest: 1.07; 95% CI, 1.01–1.14) without any significant trend association (trend $p = 0.18$). Fruit intake showed a small significant inverse association in age- and area-adjusted HRs among men (HR1 of highest quintile vs. the lowest: 0.92; 95% CI, 0.86–0.97; trend $p < 0.01$); however, the association did not remain statistically significant when adjusted for further variables (highest quintile vs. the lowest: 1.03; 95% CI, 0.97–1.10; trend $p = 1.00$). No specific fruit or vegetable showed significant inverse association with the risk of overall cancer. The results were not materially different in the analyses that

### Table 3

Pooled analysis of overall cancer incidence according to quintile of fruit and vegetable consumption, stratified by smoking status, in Japanese men and women.

|                      | Lowest HR (95% CI) | Second HR (95% CI) | Third HR (95% CI) | Fourth HR (95% CI) | Highest HR (95% CI) | p for trend | p for heterogeneity |
|----------------------|--------------------|--------------------|-------------------|-------------------|---------------------|-------------|---------------------|
| **Fruits**           |                    |                    |                   |                   |                     |             |                     |
| **Men (19,299 never smokers and 70,924 ever smokers)** |                    |                    |                   |                   |                     |             |                     |
| Never smokers        |                    |                    |                   |                   |                     |             |                     |
| HR2                  | 1.0 (Ref.)         | 1.11 (0.94, 1.3)   | 0.92 (0.77, 1.1)  | 1.06 (0.92, 1.28) | 1.10 (0.93, 1.29)  | 0.86        | 0.88                |
| Ever smokers         |                    |                    |                   |                   |                     |             |                     |
| Number of cases      | 1825               | 1736               | 1820              | 1761              | 1957                |             |                     |
| HR2                  | 1.0 (Ref.)         | 1.09 (0.92, 1.05)  | 1.01 (0.93, 1.1)  | 0.95 (0.89, 1.01) | 1.01 (0.95, 1.08)  | 1.00        | 0.56                | 0.39 |
| **Vegetables**       |                    |                    |                   |                   |                     |             |                     |
| Never smokers        |                    |                    |                   |                   |                     |             |                     |
| HR2                  | 1.0 (Ref.)         | 0.91 (0.77, 1.07)  | 0.96 (0.82, 1.12) | 1.09 (0.93, 1.27) | 1.06 (0.91, 1.24)  | 0.37        | 0.49                | 0.79 |
| Ever smokers         |                    |                    |                   |                   |                     |             |                     |
| Number of cases      | 1650               | 1706               | 1828              | 1883              | 2032                |             |                     |
| HR2                  | 1.0 (Ref.)         | 1.02 (0.95, 1.09)  | 1.05 (0.98, 1.12) | 1.02 (0.96, 1.09) | 1.07 (1.00, 1.15)  | 0.31        | 0.81                | 0.78 |
| **Women (80,600 never smokers and 8300 ever smokers)** |                    |                    |                   |                   |                     |             |                     |
| Never smokers        |                    |                    |                   |                   |                     |             |                     |
| HR2                  | 1.0 (Ref.)         | 1.09 (0.89, 1.06)  | 1.04 (0.89, 1.06) | 1.06 (0.88, 1.04) | 1.04 (0.95, 1.13)  | 0.96        | 0.54                | 0.51 |
| Ever smokers         |                    |                    |                   |                   |                     |             |                     |
| Number of cases      | 134                | 119                | 105               | 122               | 119                 |             |                     |
| HR                   | 1.0 (Ref.)         | 0.86 (0.67, 1.11)  | 0.86 (0.66, 1.11) | 0.92 (0.69, 1.22) | 0.90 (0.70, 1.15)  | 0.85        | 0.74                | 0.78 |
| **Vegetables**       |                    |                    |                   |                   |                     |             |                     |
| Never smokers        |                    |                    |                   |                   |                     |             |                     |
| HR2                  | 1.0 (Ref.)         | 1.05 (0.90, 1.1)   | 1.04 (0.86, 1.03) | 1.15 (0.95, 1.12) | 1.09 (0.87, 1.05)  | 0.98        | 0.35                | 0.91 |
| Ever smokers         |                    |                    |                   |                   |                     |             |                     |
| Number of cases      | 1058               | 1053               | 1031              | 1099              |                     |             |                     |
| HR                   | 1.0 (Ref.)         | 1.05 (0.90, 1.1)   | 1.04 (0.86, 1.03) | 1.15 (0.95, 1.12) | 1.09 (0.87, 1.05)  | 0.98        | 0.35                | 0.91 |
| HR (95% CI)          | 1.00               | 1.00               | 1.00             | 1.00              |                     |             |                     |

Hazard ratios were adjusted for age (continuous), area (for JPHC-I, JPHC-II only), total energy intake (quintile), smoking status (never, past, $<19$, 19–39, or $\geq 40$ cigarette/day for men; never, past, or current for women), alcohol consumption (non, occasional, $<23, 23$–45, or $\geq 46$ g ethanol/day), body mass index in kg/m$^2$ (14–18.9, 19–20.9, 21–22.9, 23–24.9, 25–26.9, 27–29.9, or $30–40$ kg/m$^2$), history of diabetes mellitus (yes or no), and screening examination (yes or no; any kind of the following cancer screening for JPHC-I: chest X-ray, sputum test, photofluorography, gastrointestinal endoscopy, fecal occult blood test, barium enema, or colonoscopy; any kind of screening examination for JPHC-II; and chest X-ray, gastric cancer examination, Pap smear, mammography, or complete medical checkup for MIYAGI and OHSAKI). Linear trends across quintiles of fruit and vegetable intake were tested using 0 to 4 for each quintile as an ordinal variable.
further adjusted for leisure time sport (data not shown), excluded cancer screening examinations from adjustment factors (data not shown), or excluded cases of cancer diagnosed during the first 3 years of follow-up (HR3).

Further, these results did substantially change in analyses that used sub-tetiles of the lowest quintile of total fruit and vegetable consumption and highest quintile as reference category: the multivariate HR for the lowest sub-tetile of the lowest quintile versus the highest quintile of consumption for men and women was 0.89 (95% CI, 0.77–1.02; trend $p = 0.35$) and 1.01 (95% CI, 0.92–1.10; trend $p = 0.95$), respectively.

In stratified analysis by smoking status or alcohol drinking, no significant inverse association was found between fruit or vegetable intake and the risk of overall cancer, whether combined or separated both among men and women (Table 3 and Table 4). A significant positive HR was found for the highest quintile of vegetables (1.07; 95% CI, 1.00–1.15), without a significant trend association (trend $p = 0.31$) among male smokers. However, no associations were found between fruit or vegetable consumption and smoking-related cancers in either gender: multivariate HRs of the highest quintile of fruit or vegetable intake versus the lowest were 1.02 (95% CI, 0.95–1.09) and 1.05 (95% CI, 0.98–1.12), respectively, among men (trend $p = 1.00$ and 0.56, respectively) and 1.0 (95% CI, 0.91–1.10) and 0.98 (95% CI, 0.85–1.12), respectively, among women (trend $p = 1.00$ for both).

In a sub-analysis based on intake frequency, which included the two added cohort studies, with a total of 254,314 subjects (120,964 men and 133,350 women) and 22,442 cases of overall cancer (13,729 men and 8713 women), no association was again found between fruit or vegetable consumption and overall cancer risk among either gender (Table 5-1 and Table 5-2): corresponding multivariate HRs of almost daily versus almost never were 1.02 (95% CI, 0.86–1.08) and 0.99 (95% CI, 0.89–1.11), respectively, for men (trend $p = 1.00$ and 0.95, respectively), and 0.95 (95% CI, 0.88–1.02) and 0.92 (95% CI, 0.72–1.18), respectively, for women (trend $p = 1.00$ for both). Further, no specific fruit or vegetable showed a significant inverse association with the risk of overall cancer. Moreover, no significant inverse association was found between fruit or vegetable intake and the risk of smoking-related cancer for either gender (data not shown).

### Discussion

This pooled analysis of major population-based cohort studies in Japan, which included data on 17,681 cancer cases, revealed no significant inverse associations of fruit or vegetable consumption with the risk of overall cancer, whether combined or separated by specific groups. Further, these results did not substantially change in stratified analyses by smoking status or alcohol drinking. Moreover, no significant inverse associations were shown when outcomes were confined to smoking-related cancers. To our knowledge, this pooled analysis included the largest number of overall cancer cases in an Asian population to date.

| Table 4 | Pooled analysis of overall cancer incidence according to quintile of fruit and vegetable consumption, stratified by alcohol drinking, in Japanese men and women. |
|---|---|
| | Men (29,057 non-drinkers or occasional drinkers and 59,737 drinkers) |
| | Fruits |
| | Non-drinkers or occasional drinkers |
| | Number of cases | HR (95% CI) |
| | HR2 Drunkers | 693 | 1.0 (Ref.) |
| | 1.02 (0.77, 1.16) | 634 | 0.95 (0.77, 1.16) |
| | 0.95 (0.79, 1.13) | 665 | 0.95 (0.79, 1.13) |
| | 0.98 (0.88, 1.09) | 702 | 0.98 (0.88, 1.09) |
| | 1.06 (0.95, 1.17) | 790 | 1.06 (0.95, 1.17) |
| | p for trend | 0.51 | 0.51 |
| | p for heterogeneity | 0.88 | 0.88 |
| | for the highest category | 0.86 | 0.86 |
| | Women (79,057 nondrinkers or occasional drinkers and 11,369 drinkers) |
| | Fruits |
| | Non-drinkers or occasional drinkers |
| | Number of cases | HR (95% CI) |
| | HR2 Drunkers | 1301 | 1.0 (Ref.) |
| | 1.07 (0.90, 1.05) | 639 | 1.07 (0.90, 1.05) |
| | 1.03 (0.92, 1.15) | 687 | 1.03 (0.92, 1.15) |
| | 1.00 (0.90, 1.12) | 726 | 1.00 (0.90, 1.12) |
| | 1.11 (0.998, 1.23) | 794 | 1.11 (0.998, 1.23) |
| | p for trend | 0.39 | 0.39 |
| | p for heterogeneity | 0.55 | 0.55 |
| | for the highest category | 0.73 | 0.73 |
| || Vegetables |
| | Non-drinkers or occasional drinkers |
| | Number of cases | HR (95% CI) |
| | HR2 Drunkers | 1301 | 1.0 (Ref.) |
| | 1.07 (0.90, 1.05) | 639 | 1.07 (0.90, 1.05) |
| | 1.03 (0.92, 1.15) | 687 | 1.03 (0.92, 1.15) |
| | 1.00 (0.90, 1.12) | 726 | 1.00 (0.90, 1.12) |
| | 1.11 (0.998, 1.23) | 794 | 1.11 (0.998, 1.23) |
| | p for trend | 0.39 | 0.39 |
| | p for heterogeneity | 0.55 | 0.55 |
| | for the highest category | 0.73 | 0.73 |

Hazard ratios were adjusted for age (continuous), area (for JPHC-I; JPHC-II only), total energy intake (quintile), smoking status (never, past, <19, 19–39, or ≥40 cigarette/day for men; never, past, or current for women), alcohol consumption (non, occasional, <23, 23–45, or ≥46 g ethanol/day), body mass index in kg/m² (>18.9, 19–20.9, 21–22.9, 23–24.9, 25–26.9, 27–29.9, or 30–40 kg/m²), history of diabetes mellitus (yes or no), and screening examination (yes or no; any kind of the following cancer screening for JPHC-I: chest X-ray, sputum test, photofluorography, gastrointestinal endoscopy, fecal occult blood test, barium enema, or colonoscopy; any kind of screening examination for JPHC-II; and chest X-ray, gastric cancer examination, Pap smear, mammography, or complete medical checkup for MIVAGI and OHSAKI). Linear trends across quintiles of fruit and vegetable intake were tested using 0 to 4 for each quintile as an ordinal variable.
Three very large-scale (including over 100,000 subjects) prospective cohort studies reported to date have found a very small inverse or no association between vegetables and overall cancers\(^6,9\) and no association for fruit, with consistency among the studies.\(^9\) The pooled analysis of the Health Professionals' Follow-up Study and Nurses' Health Study in 109,635 subjects (9261 cancer cases) reported relative risks for the incident of overall cancer of 1.01 (95% CI, 0.95–1.06) for fruit and 0.99 (95% CI, 0.95–1.04) for vegetables by continuous measure for increments of three servings.\(^9\) The European Prospective Investigation Into Cancer and Nutrition Study in 478,478 subjects (30,604 cancer cases) reported a very small inverse association for vegetables only (HR by increments of 100 g/day, 0.98; 95% CI, 0.97–0.99) but not for fruit (HR 0.99; 95% CI, 0.98–1.00).\(^9\) Finally, the National Institutes of Health-American Association of Retired Persons Diet and Health Study reported relative risks for the highest quintiles of fruit or vegetables of 0.98 (95% CI, 0.95–0.98) but not for fruit and 0.99 (95% CI, 0.98–1.00) for vegetables.\(^9\) Studies conducted in Western populations (in the United States\(^6,9\) and Europe\(^10\)), and no such large-scale data from Asian populations have been reported to date.
Among studies in Asia reported to date, a relatively small-scale male cohort study (14,198 subject) in Korea reported an inverse association between vegetable intake and total cancer incidence (HR for ≥300 g/day vs. <50 g/day of vegetables: 0.72; 95% CI, 0.58–0.90; trend p = 0.02) but not for fruit (HR 1.04; 95% CI, 0.87–1.25; trend p = 0.56).25 Also, a large-scale (134,796 subject) cohort study in China (Shanghai Women's and Men's Health Study), which treated mortality as the primary outcome, reported no association of fruit and vegetable intakes with cancer but an inverse association with CVD: corresponding HRs for the highest versus lowest quintile of intake were 0.96 (95% CI, 0.83–1.10) and 1.05 (95% CI, 0.90–1.21), respectively, for cancer (trend p = 0.25 and 0.58, respectively) versus 0.72 (95% CI, 0.59–0.87) and 0.74 (95% CI, 0.57–0.96), respectively, for CVD (trend p = 0.02 for both).8 A previous Japanese study (the JPHC Study, with 77,891 subjects) reported that higher fruit intake was significantly associated with a lower risk of CVD incidence (HR for the highest vs. lowest quartile of intake: 0.81; 95% CI, 0.67–0.97; trend p = 0.01), although neither fruit nor vegetable intakes were associated with decreased risk of overall cancer incidence, with corresponding hazard ratios of 1.02 (95% CI, 0.90–1.14; trend p = 0.95) for fruit and 0.94 (95% CI, 0.84–1.05; trend p = 0.16) for vegetables.7

In the present study, adjustment for a common set of variables, such as smoking status, would bias the associations toward an

### Table 5-2

Pooled analysis of total cancer incidence according to frequency of fruit and vegetable intake among 133,350 Japanese women, 1990–2006.

| Category                        | HR (95% CI) | HR (95% CI) | HR (95% CI) | HR (95% CI) | p for trend | p for heterogeneity |
|---------------------------------|-------------|-------------|-------------|-------------|-------------|-------------------|
| **Total fruit and vegetables**  |             |             |             |             |             |                   |
| Number of subjects              | 1035        | 1347        | 1944        | 127,745     |             |                   |
| Person-years                    | 10,492      | 15,843      | 22,634      | 1,498,738   |             |                   |
| Number of cases                 | 79          | 79          | 134         | 8324        |             |                   |
| ASR (per 100,000)               | 676         | 459         | 645         | 585         |             |                   |
| HR1                             | 1.0 (Ref.)  | 0.69 (0.5, 0.97) | 0.97 (0.66, 1.44) | 0.87 (0.67, 1.14) | 1.00         | 0.28              | 0.69              |
| HR2                             | 1.0 (Ref.)  | 0.69 (0.49, 0.97) | 0.96 (0.60, 1.4) | 0.88 (0.67, 1.15) | 1.00         | 0.27              | 0.55              |
| HR3                             | 1.0 (Ref.)  | 0.67 (0.45, 1)  | 0.97 (0.6, 1.57) | 0.90 (0.64, 1.27) | 1.00         | 0.20              | 0.20              |
| **Fruits**                      |             |             |             |             |             |                   |
| Number of subjects              | 12,464      | 13,402      | 22,478      | 84,523      |             |                   |
| Person-years                    | 143,440     | 162,964     | 271,785     | 978,385     |             |                   |
| Number of cases                 | 871         | 880         | 1354        | 5568        |             |                   |
| ASR (per 100,000)               | 610         | 599         | 548         | 588         |             |                   |
| HR1                             | 1.0 (Ref.)  | 0.94 (0.85, 1.04) | 0.89 (0.82, 0.98) | 0.93 (0.87, 1.00) | 1.00         | 0.93              | 0.88              |
| HR2                             | 1.0 (Ref.)  | 0.95 (0.86, 1.05) | 0.90 (0.82, 0.99) | 0.95 (0.88, 1.02) | 1.00         | 0.93              | 0.74              |
| HR3                             | 1.0 (Ref.)  | 0.92 (0.82, 1.03) | 0.90 (0.81, 1.00) | 0.95 (0.87, 1.03) | 1.00         | 1.00              | 0.93              |
| **Vegetables**                  |             |             |             |             |             |                   |
| Number of subjects              | 1874        | 2305        | 4164        | 123,992     |             |                   |
| Person-years                    | 20,199      | 27,103      | 49,354      | 1,454,268   |             |                   |
| Number of cases                 | 138         | 137         | 296         | 8068        |             |                   |
| ASR (per 100,000)               | 598         | 577         | 646         | 584         |             |                   |
| HR1                             | 1.0 (Ref.)  | 0.84 (0.66, 1.07) | 1.09 (0.77, 1.56) | 0.91 (0.73, 1.15) | 0.98         | 0.21              | 0.73              |
| HR2                             | 1.0 (Ref.)  | 0.84 (0.66, 1.07) | 1.09 (0.77, 1.54) | 0.92 (0.72, 1.18) | 1.00         | 0.17              | 0.51              |
| HR3                             | 1.0 (Ref.)  | 0.92 (0.68, 1.23) | 1.08 (0.8, 1.46) | 1.01 (0.74, 1.37) | 1.00         | 0.14              | 0.29              |
| **Vegetables, excluding pickles** |             |             |             |             |             |                   |
| Number of subjects              | 3953        | 3416        | 11,615      | 113,897     |             |                   |
| Person-years                    | 44,361      | 39,777      | 138,591     | 1,334,133   |             |                   |
| Number of cases                 | 281         | 240         | 763         | 7397        |             |                   |
| ASR (per 100,000)               | 591         | 653         | 595         | 581         |             |                   |
| HR1                             | 1.0 (Ref.)  | 1.08 (0.76, 1.54) | 0.94 (0.74, 1.2) | 0.91 (0.75, 1.12) | 0.59         | 0.10              | 0.69              |
| HR2                             | 1.0 (Ref.)  | 1.09 (0.77, 1.53) | 0.94 (0.73, 1.21) | 0.92 (0.74, 1.15) | 0.88         | 0.07              | 0.61              |
| HR3                             | 1.0 (Ref.)  | 1.15 (0.79, 1.68) | 0.99 (0.78, 1.26) | 0.94 (0.73, 1.22) | 0.90         | 0.05              | 0.33              |
| **Green and yellow vegetables** |             |             |             |             |             |                   |
| Number of subjects              | 7217        | 10,283      | 24,528      | 91,010      |             |                   |
| Person-years                    | 78,742      | 112,495     | 278,824     | 1,088,495   |             |                   |
| Number of cases                 | 503         | 644         | 1556        | 5988        |             |                   |
| ASR (per 100,000)               | 606         | 570         | 596         | 581         |             |                   |
| HR1                             | 1.0 (Ref.)  | 0.93 (0.82, 1.05) | 0.96 (0.87, 1.07) | 0.93 (0.85, 1.02) | 0.64         | 0.63              | 0.49              |
| HR2                             | 1.0 (Ref.)  | 0.93 (0.80, 1.07) | 0.97 (0.88, 1.08) | 0.95 (0.86, 1.04) | 0.94         | 0.50              | 0.58              |
| HR3                             | 1.0 (Ref.)  | 0.90 (0.75, 1.08) | 0.96 (0.85, 1.08) | 0.94 (0.84, 1.04) | 0.94         | 0.46              | 0.52              |
increased risk. In the age- and area-adjusted HRs for fruit and vegetables, for example, our finding of an inverse and no association changed to no and a positive association, respectively, after adjustment for smoking status. A lower prevalence of ever smokers or heavy drinkers with higher fruit and vegetable consumption in the present cohorts would result in an increased risk after adjustment for these confounding factors. These results were notable among men, who had a higher prevalence of smoking than women. An association with vegetable intake was not seen when the multivariable-adjusted analysis was confined to never-smokers, but a marginally increased risk was seen when it was confined to smokers. In a similar pooled analysis of Japanese cohort studies, Wakai et al. also reported a positive association between vegetable consumption and lung cancer incidence in the multivariate-adjusted analysis only (especially among ever smokers). However, in contrast to these results, no association with either fruit or vegetable intakes was shown when the analysis treated smoking-related cancers as the outcome of interest. These findings suggest substantial residual confounding by tobacco smoking.

The variation in fruit and vegetable consumption among subjects in this study is likely to be sufficiently large: cut-offs of the fourth and fifth quintiles of vegetable consumption were 2- to 3-fold higher than those for the first and second quintile in each cohort. This is similar to previous studies that found very small inverse associations between vegetable intake and overall cancer (2.5- and 3-fold difference between these cut-offs for vegetables). Also, a similar previous pooled analysis in Japan showed an inverse association between vegetable (but not fruit) intake and distal gastric cancer. Further, fruit consumption did not show any inverse association in multivariate analysis, despite having consistently larger variation than vegetable intakes in the present and these previous studies (2- to 4-fold for vegetables, 3.2- to 6.5 fold for fruit). These facts argue against the possibility that the observed absence of any inverse association with cancer incidence is attributable to insufficient variation in fruit and vegetable consumption.

Our study has several potential limitations. First, the validity of the FFQ for fruit and vegetable intake was moderate at best ( r = 0.3 to 0.7). Measurement error in the FFQ would have biased the association of fruit or vegetable intakes with overall cancer toward the null, and the observed associations would have thereby underestimated the true magnitude of a small protective association. Second, the difference in true absolute intake among the cohorts cannot be calibrated. Although sub-analyses using frequency categories and a larger number of subjects and cancer cases (6 cohorts) than in the present study did not differ from the present main analysis by quintiles of energy-adjusted intake, we cannot entirely rule out the possibility of misclassification among the cohort caused by the different number of items from the different FFQs. Third, we used and adjusted for a study-specific question on cancer screening examination (varieties and time span). Although detection bias resulting from health conscious behaviors, such as participation in cancer screening examination and higher fruit and vegetable consumption, likely accounted for the positive association on assessment using cancer incidence as outcomes, our results did not substantially change before and after adjustment for cancer screening in the present study. Although we have adjusted for possible confounding variables in common categories as much as possible, the effects of residual confounding by unmeasured or unstandardized variables cannot be totally discarded.

Although the impact for overall cancer prevention was undetectable, the results do not contradict the possibly small but protective effect of fruit and vegetable intakes for site-specific cancers, such as stomach cancer, lung cancer, or breast cancer by hormone receptor status. It is possible that the aggregation of cancer sites in the analysis might dilute the impact of association. Therefore, in accordance with the biological plausibility, the recommendation that “higher consumption of several plant foods probably protects against cancers of various sites” may still be applicable in Japan.

In conclusion, the results of this pooled analysis of large-scale population-based prospective cohort studies in Japan do not provide evidence for inverse associations of fruit or vegetable consumption with risk of overall cancer incidence.

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**Research group members**

Shizuka Sasazuki [principal investigator], Shoichiro Tsugane, Manami Inoue, Motoki Iwasaki, Tetsuya Otani [until 2006], Norie Sawada [since 2007], Taichi Shimazu [since 2007], Taiki Yamaji [since 2007] (National Cancer Center, Tokyo); Ichiro Tsuji [from 2004 until 2015], Yoshitaka Tsubono [in 2003] (Tohoku University, Sendai); Yoshikazu Nishino [until 2006] (Miyagi Cancer Research Institute, Natori); Akiko Tamakoshi [since 2010] (Hokkaido University, Sapporo); Keitaro Matsuo [until 2010, since 2012], Hitoshi Ito [from 2010 until 2011, since 2015] (Aichi Cancer Center, Nagoya); Kenji Wakai (Nagoya University, Nagoya); Chisato Nagata (Gifu University, Gifu); Tetsuya Mizoue (National Center for Global Health and Medicine, Tokyo); Keitaro Tanaka (Saga University, Saga), Tomio Nakayama [since 2015] (Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka); Atsuko Sadakane [since 2015] (Radiation Effects Research Foundation, Hiroshima).

**Conflicts of interest**

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