Background: Although experimental studies have shown that gamma-glutamyltransferase (GGT) has a role in tumor progression, epidemiologic evidence for a relationship between GGT and cancer incidence is limited. The present study investigated the association between GGT and cancer incidence and assessed the role of alcohol consumption in this association.

Methods: We examined a cohort of 15,031 Japanese adults aged 40 to 79 years who attended a health checkup in 1995 and were free of cancer at that time. GGT was measured using the Szasz method. The participants were then followed from 1 January 1996 until 31 December 2005, and cancer incidence was recorded by using the Miyagi Regional Cancer Registry. Hazard ratios (HRs) and 95% confidence intervals (CIs) were computed for each quartile of GGT and compared. The lowest quartile (GGT < 13.0 IU/ml) was used as the reference category.

Results: We documented 1,505 cancers. Among participants in the highest quartile (GGT ≥ 31.0 IU/ml), the multivariate HR for any cancer was 1.28 (95% CI, 1.08–1.53; P for trend, <0.001), the HR for colorectal cancer was significantly greater than unity, and the HRs for esophageal, pancreatic, and breast cancers were greater than unity but not significantly so. This positive trend was observed only in current drinkers.

Conclusions: Our findings suggest that there is a positive relationship between GGT and cancer incidence only for alcohol-related cancers in current drinkers and that the positive association of GGT with cancer incidence largely reflects alcohol consumption.

Key words: gamma-glutamyltransferase; cancer incidence; population-based; prospective study; Ohsaki Study
METHODS

Study cohort
We conducted this population-based cohort study by using data from the Ohsaki National Health Insurance (NHI) Cohort. The details of the Ohsaki National Health Insurance (NHI) Cohort have been previously published.\textsuperscript{16-19} In brief, between October and December 1994, we delivered a self-reported questionnaire to all individuals aged 40 to 79 years who were enrolled in the NHI and lived in the district covered by the Ohsaki Public Health Center, Miyagi Prefecture, in northeastern Japan. The Ohsaki Public Health Center is a local government agency that provides preventive health services for residents of 14 municipalities in northern Miyagi Prefecture. Of 54,996 eligible individuals, 52,029 (95\%) responded. We started prospective collection of the NHI files on withdrawal history on 1 January 1995 to ascertain the dates of and reasons for withdrawal from the NHI. We excluded 776 participants who had withdrawn from the NHI before the baseline questionnaire survey. Thus, 51,253 participants (24,573 men and 26,680 women) were entered into the present study as our cohort participants. The ethics committee of the Tohoku University School of Medicine reviewed and approved the study protocol. The return of self-administered questionnaires signed by the participants was regarded as consent to take part in the study.

For the present analysis, we excluded 3,170 participants (1,571 men and 1,599 women) who had received a diagnosis of cancer before the baseline survey was conducted, as determined by self-report or the Miyagi Prefectural Cancer Registry (described below), which resulted in a total of 48,083 participants, of whom 15,031 attended the annual health checkup in 1995. In Japan, the Health and Medical Service Law for the Aged requires all municipalities to provide annual health checkups for all residents aged 40 years or older. The checkup consists of an interview, measurement of weight, height, and blood pressure, a physical examination, and blood sampling. Nonfasting blood samples were obtained from all 15,031 participants. We combined these health checkup data within a period of 1 year and subsequently responded to the questionnaire. The return of self-administered questionnaires signed by the participants was regarded as consent to take part in the study.

Follow-up and ascertainment of cancer incidence
We followed the participants from 1 January 1996 to 31 December 2005. The end point was diagnosis of cancer, end of follow-up, death, emigration, or loss of NHI qualification, whichever occurred first. Using the NHI files on withdrawal history, we collected data on withdrawals from the NHI that occurred due to death, emigration, or loss of NHI qualification. We ascertained cancer incidence by computer linkage with the Miyagi Prefectural Cancer Registry, which covers the study area. The Miyagi Prefectural Cancer Registry is the oldest and most accurate population-based cancer registry in Japan.\textsuperscript{20} The percentage of cancer at any site, as recorded on death certificates, was 11.3\% for men and 13.0\% for women.\textsuperscript{20} Cancers were coded according to the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) as esophageal cancer (C15.0–C15.9), gastric cancer (C16.0–C16.9), colorectal cancer (C18.0–C20.9), liver cancer (C22.0–C22.1), pancreatic cancer (C25.0–C25.9), malignant neoplasms of the respiratory system and intrathoracic organs (C33.0–C39.8), breast cancer (C50.0–C50.9), prostate cancer (C61.9), malignant neoplasms of urinary organs (C64.9–C68.9), all cancers (C00.0–C80.9), and non-liver cancers (C00.0–C21.8 or C23.9–C80.9).

Variables
GGT was measured by the Szasz method under nonfasting conditions.\textsuperscript{21,22} The participants were divided by GGT level into 4 quartiles: GGT <13 IU/ml, 13.0 to 17.9 IU/ml, 18.0 to 29.9 IU/ml, and 30.0 IU/ml or higher. The details of the survey of cancer risk factors have been described elsewhere.\textsuperscript{18,23} At the baseline survey in 1994, we used a self-reported questionnaire to collect information on personal and family history of disease, smoking habits, job status, level of education, body weight, height, participation in sports or exercise, and time spent walking per day. We also asked about drinking habits, including frequency of alcohol consumption, and the quantity and type of alcoholic beverages consumed. We then classified alcohol consumption status into 4 categories: never drinkers, former drinkers, light current drinkers (<45.6 g ethanol/day on average), and heavy current drinkers (≥45.6 g ethanol/day on average). We conducted a validation study in which 113 participants provided four 3-day dietary records (including details of alcoholic beverages) within a period of 1 year and subsequently responded to the questionnaire. The Spearman’s rank correlation coefficient between the amount of alcohol consumed according to the questionnaire and the amount consumed according to the dietary records was 0.70 for men and 0.60 for women; the correlation between consumption levels measured by the 2 questionnaires administered 1 year apart was 0.76 for men and 0.66 for women.\textsuperscript{23}

Statistical analysis
The Cox proportional hazards regression model was used to estimate hazard ratios (HRs) and 95\% confidence intervals (CIs) for cancer incidence according to GGT quartile and to adjust for potential confounding variables. SAS version 9.2 (SAS Institute, Inc., Cary, NC, USA) statistical software was used for the analysis. An HR was computed for each GGT value less than 0.05 were considered statistically significant. Because the distribution of GGT was
skewed to the right, a test for trend was computed using log-transformed GGT as a continuous value. All HRs were also calculated in an age- and sex-adjusted model (model 1) and in a multivariate-adjusted model (model 2). In the multivariate model, we considered the following variables to be potential confounders: age (continuous variable, years), sex, drinking habit (never drinker, former drinker, light current drinker, heavy current drinker), self-reported history of liver disease, smoking habit (never smoker, former smoker, current smoker), body mass index ($\leq 18.5\text{ kg/m}^2$, $18.5–25.0\text{ kg/m}^2$, $\geq 25\text{ kg/m}^2$), education (less than high school, high school or higher), time spent walking ($\leq 30\text{ min/day}$, $\geq 30\text{ min/day}$) and time spent on sports (exercise $\leq 1$ hour/week, exercise $\geq 1$ hour/week). To eliminate reverse causation, we repeated all analyses after excluding participants who suffered from cancers in the first 3 years of follow-up (model 3). The multivariate HRs and 95% CIs for non-liver cancer and for individual sites were also calculated. We also conducted stratified analyses by drinking habit (never drinker, former drinker, current drinker), smoking habit (never smoker, former smoker, current smoker), and sex. We stratified the data by drinking habit because chronic and excessive alcohol consumption increases GGT and is associated with an increased risk of some cancers, especially those of the esophagus, liver, pancreas, colorectum, and breast.12–15 We stratified the data by smoking habit because there was a higher prevalence of smokers in the highest GGT quartile (Table 1). We stratified the data by sex because GGT distribution in men was different from that in women. In addition, we examined the statistical significance of interaction terms, namely, the products of GGT quartile and drinking habit, GGT quartile and smoking habit, and GGT quartile and sex.

RESULTS

After a total of 130,649 person-years of follow-up, we documented 1505 cancers (947 in men, 558 in women). Of the study subjects, 9.4% were lost to follow-up. Table 1 shows the baseline characteristics of the study participants according to GGT quartile. In comparison with participants in the lowest GGT quartile (Q1), those in the highest quartile (Q4) were younger and more likely to be male, a smoker, an alcohol drinker, less active (in terms of walking time), and to have liver disease. There was also a higher percentage of heavy current drinkers in the highest quartile.

Table 2 shows the HRs for any cancer and for cancers at major sites by GGT quartile. The multivariate HRs (95% CI) for any cancer were 1.03 (0.74–1.43) in never drinkers and 1.30 (0.96–1.75) in current drinkers. A significant trend was observed in current drinkers but not in never drinkers. When stratified by smoking habit, the multivariate HRs for non-liver cancers in Q4 were 1.10 (0.82–1.46) in never smokers and 1.63 (1.12–2.37) in current smokers. A significant trend was observed in current smokers but not in never smokers. When stratified, the multivariate HR was 1.16 in men and 1.22 in women. Thus, there was no apparent sex difference in the association between GGT level and cancer incidence, even though the distribution of GGT differs between men and women. We added the various interaction terms to our multivariate model, ie, the products of GGT quartile and drinking habit, GGT quartile and smoking habit, GGT quartile and sex.

Because of the clinically obvious positive association between GGT and liver cancer, we repeatedly examined the association of GGT level with liver cancer and non-liver cancer. The multivariate HR (95% CI) in Q4 for liver cancer was 6.57 (2.48–17.41). That for non-liver cancers was attenuated to 1.19 (1.00–1.42) but was nevertheless significantly elevated. Regarding the analysis of selected cancer sites, the multivariate HR for colorectal cancer was significantly elevated: 1.57 (1.06–2.32; $P$ for trend, 0.02). The HRs for esophageal, pancreatic, and breast cancer were also elevated (1.53, 1.89, and 1.39, respectively) but not significantly so. All these cancers (colorectal, esophageal, pancreatic, and breast cancers) are alcohol-related.12–15 In contrast, the risks of other, non–alcohol-related cancers, ie, stomach, respiratory and intrathoracic, kidney and urinary, and prostate cancers, were not increased.

Stratified analysis

We examined the multivariate HRs for non-liver cancers using stratified analysis (Table 3). When stratified by drinking habit, the multivariate HRs (95% CI) for non-liver cancers in Q4 were 1.03 (0.74–1.43) in never drinkers and 1.30 (0.96–1.75) in current drinkers. A significant trend was observed in current drinkers but not in never drinkers. When stratified by smoking habit, the multivariate HRs for non-liver cancers in Q4 were 1.10 (0.82–1.46) in never smokers and 1.63 (1.12–2.37) in current smokers. A significant trend was observed in current smokers but not in never smokers. When stratified, the multivariate HR was 1.16 in men and 1.22 in women. Thus, there was no apparent sex difference in the association between GGT level and cancer incidence, even though the distribution of GGT differs between men and women. We added the various interaction terms to our multivariate model, ie, the products of GGT quartile and drinking habit, GGT quartile and smoking habit, GGT quartile and sex.

Table 1. Characteristics of study population by quartile of serum gamma-glutamyltransferase (GGT) level

| Quartile of GGT (IU/L) | Q1 | Q2 | Q3 | Q4 |
|-----------------------|----|----|----|----|
| GGT <13 (SD)          | 9.8 (2.7) | 14.8 (2.7) | 22.6 (3.6) | 69.6 (74.0) |
| Women (%)             | 85.7 | 70.9 | 50.0 | 27.8 |
| Mean age, years       | 80.6 | 61.7 | 61.4 | 59.1 |
| (SD)                  | 10.0 (9.1) | (8.5) | 9.4 |
| Mean BMI, kg/m²       | 22.9 (2.8) | 23.4 (2.9) | 23.9 (3.1) | 24.3 |
| (SD)                  | (2.8) | (2.9) | (3.1) | (3.0) |
| Self-reported history of liver disease (%) | 2.6 | 2.9 | 4.6 | 9.2 |
| Current smoker (%)    | 10.5 | 17.1 | 27.8 | 43.7 |
| Current drinker (%)   | 22.7 | 34.8 | 51.6 | 75.4 |
| <45.6 g/day (%)       | 19.7 | 28.8 | 36.2 | 37.6 |
| >45.6 g/day (%)       | 3.0 | 6.0 | 15.4 | 37.8 |
| Walking ≥30 minutes/day (%) | 49.7 | 46.7 | 44.6 | 43.8 |
| Sports ≥1 hour/week (%) | 29.3 | 32.3 | 34.8 | 31.9 |
| Education (high school or more) (%) | 45.6 | 42.4 | 41.1 | 44.6 |
### Table 2. Hazard ratios (95% CI) for any cancer and cancers at selected sites by quartile of serum gamma-glutamyltransferase (GGT) level

| Quartile of GGT (IU/L) | Q1 <13 | Q2 13.0–17.9 | Q3 18.0–30.9 | Q4 ≥31.0 | P for trend |
|------------------------|--------|--------------|--------------|---------|------------|
| No. at risk            | 3471   | 3547         | 4240         | 3773    |            |
| All cancers            |        |              |              |         |            |
| person-years           | 30,216 | 31,060       | 36,950       | 32,423  |            |
| No. of cases           | 252    | 314          | 447          | 492     |            |
| crude                  | 1.00   | 1.21 (1.03–1.43) | 1.45 (1.25–1.70) | 1.82 (1.57–2.12) |            |
| model 1                | 1.00   | 1.03 (0.87–1.22) | 1.08 (0.92–1.26) | 1.32 (1.12–1.56) |            |
| model 2                | 1.00   | 1.03 (0.87–1.22) | 1.09 (0.92–1.28) | 1.28 (1.08–1.53) | 0.0008     |
| model 3                | 1.00   | 0.98 (0.81–1.18) | 1.09 (0.91–1.30) | 1.28 (1.06–1.55) | 0.0007     |
| Liver cancer           |        |              |              |         |            |
| person-years           | 31,015 | 32,071       | 38,230       | 33,772  |            |
| No. of cases           | 5      | 8            | 16           | 46      |            |
| crude                  | 1.00   | 1.55 (0.51–4.73) | 2.59 (0.95–7.08) | 8.44 (3.35–21.24) |            |
| model 1                | 1.00   | 1.39 (0.45–4.26) | 2.23 (0.80–6.21) | 8.00 (3.05–21.03) | <0.0001    |
| model 2                | 1.00   | 1.40 (0.46–4.31) | 1.99 (0.72–5.56) | 6.57 (2.48–17.41) |            |
| Non-liver cancer       |        |              |              |         |            |
| person-years           | 30,227 | 31,082       | 36,986       | 32,495  |            |
| No. of cases           | 247    | 306          | 431          | 451     |            |
| crude                  | 1.00   | 1.21 (1.02–1.43) | 1.43 (1.22–1.67) | 1.70 (1.46–1.99) |            |
| model 1                | 1.00   | 1.02 (0.86–1.21) | 1.05 (0.89–1.24) | 1.21 (1.02–1.44) |            |
| model 2                | 1.00   | 1.02 (0.86–1.21) | 1.06 (0.90–1.25) | 1.19 (1.00–1.42) | 0.04       |
| Esophageal cancer      |        |              |              |         |            |
| person-years           | 31,008 | 32,073       | 38,242       | 33,764  |            |
| No. of cases           | 6      | 9            | 15           | 31      |            |
| model 2                | 1.00   | 0.93 (0.33–2.65) | 0.91 (0.34–2.44) | 1.53 (0.58–4.03) | 0.2        |
| Stomach cancer         |        |              |              |         |            |
| person-years           | 30,812 | 31,794       | 37,971       | 33,533  |            |
| No. of cases           | 55     | 88           | 99           | 100     |            |
| Respiratory/intrathoracic cancer | 1.00 | 1.26 (0.89–1.77) | 0.96 (0.69–1.36) | 1.00 (0.69–1.45) | 0.6        |
| person-years           | 30,977 | 32,010       | 38,073       | 33,733  |            |
| No. of cases           | 31     | 45           | 79           | 61      |            |
| model 2                | 1.00   | 1.10 (0.69–1.74) | 1.36 (0.88–2.10) | 1.13 (0.69–1.82) | 0.4        |
| Pancreatic cancer      |        |              |              |         |            |
| person-year            | 31,014 | 32,088       | 38,241       | 33,838  |            |
| No. of cases           | 10     | 12           | 25           | 20      |            |
| model 2                | 1.00   | 1.08 (0.46–2.51) | 1.81 (0.84–3.90) | 1.89 (0.81–4.38) | 0.2        |
| Colorectal cancer      |        |              |              |         |            |
| person-years           | 30,859 | 31,823       | 37,949       | 33,427  |            |
| No. of cases           | 45     | 58           | 83           | 114     |            |
| model 2                | 1.00   | 1.07 (0.73–1.59) | 1.12 (0.77–1.64) | 1.57 (1.06–2.32) | 0.02       |
| Kidney and urinary cancer | 30,977 | 32,022       | 38,178       | 33,779  |            |
| No. of cases           | 14     | 21           | 28           | 20      |            |
| model 2                | 1.00   | 1.29 (0.65–2.55) | 1.34 (0.69–2.63) | 1.10 (0.51–2.36) | 0.7        |
| Prostate cancer        |        |              |              |         |            |
| No. at risk            | 497    | 1031         | 2119         | 2725    |            |
| person-years           | 4327   | 9114         | 18,949       | 24,399  |            |
| No. of cases           | 18     | 32           | 55           | 45      |            |
| model 2                | 1.00   | 0.95 (0.53–1.70) | 0.92 (0.53–1.58) | 0.75 (0.42–1.34) | 0.1        |
| Breast cancer          |        |              |              |         |            |
| No. at risk            | 2974   | 2516         | 2121         | 1048    |            |
| person-years           | 26,547 | 22,785       | 19,096       | 9306    |            |
| No. of cases           | 24     | 20           | 16           | 11      |            |
| model 2                | 1.00   | 1.03 (0.56–1.87) | 0.98 (0.52–1.87) | 1.39 (0.67–2.92) | 0.8        |

model 1: adjusted for sex and age (continuous variable, years).
model 2: model 1 + alcohol consumption (never, former, currently <45.6 g/day, currently >45.6 g/day ethanol), self-reported history of liver disease, cigarette smoking (never, former, current), body mass index (<18.5, 18.5 to <25.0, ≥25.0 kg/m²), education (junior high school, high school or more), walking (<30 minutes/day, >30 minutes/day) and sports (rarely, >1 hour/week).
model 3: excluded participants who developed cancers in the first 3 years of follow-up in model 2.

P for trend was computed with log-transformed GGT as a continuous value in the multivariate model.
However, none of these interaction terms were statistically significant: the interaction $P$ values were 0.19, 0.43, and 0.44, respectively.

**DISCUSSION**

In this prospective population-based cohort of adults living in Japan, we found a significant relationship between GGT level and cancer incidence—after adjusting for a number of confounders—during a follow-up period of 10 years. A positive trend was observed in current drinkers ($P_{\text{for trend}} = 0.02$) but not in never drinkers.

Experimental data show that GGT level reflects the degree of oxidative stress, a key factor in tumor progression. Thus, it could be hypothesized that the association between GGT and carcinogenesis is not specific to liver cancer but rather is generalizable to all cancers. However, the present results do not support this hypothesis.

The only published epidemiologic study on the association of GGT with cancer incidence, which was conducted in Austria, reported a positive association of GGT level with cancer risk. That study documented an increased risk of cancer in digestive organs, respiratory system/intrathoracic organs, urinary organs (in men), breast and female genital organs (in women), and lymphoid and hematopoietic cancers.
Smokers (Table 3). The increased HR remained significant only in current smokers but not in never smokers. By alcohol. Furthermore, the positive association was observed only in current drinkers, among whom residual confounding by alcohol is plausible. This further supports our hypothesis that the positive associations were due to residual confounding by alcohol.

Unexpectedly, a positive association of GGT with cancer incidence was observed in current smokers but not in never smokers (Table 3). The increased HR remained significant even after further adjustment for pack-years smoked (packs per day × years smoked; data not shown). This increment might be due the fact that the HR for esophageal cancer in Q4 tended to be higher (1.72 [0.46–6.44]), whereas those for other alcohol-related cancers did not. In addition, the increment may also be due to alcohol consumption. When we examined participants who currently smoked and drank (n = 2483), the multivariate HR in Q4 was 1.87 (1.09–3.20). By contrast, when we examined participants who currently drank and never smoked (n = 519), the multivariate HR in Q4 was 1.05 (0.41–2.70). These results suggest that the increased HR in Q4 among current smokers largely reflected the effect of alcohol consumption.

Strengths and limitations
We investigated the effect of alcohol consumption on the association between GGT level and cancer incidence. Our questionnaire on alcohol consumption was well validated. We conducted a validation study in which 113 participants provided four 3-day dietary records. The Spearman correlation coefficient between the amount of alcohol consumed according to the questionnaire and the amount consumed according to the dietary records was 0.70 for men and 0.60 for women; the correlation between consumption measured by the 2 questionnaires administered 1 year apart was 0.76 for men and 0.66 for women.23

This study did have some limitations. First, we used part of a cohort, ie, those who attended an annual health checkup in 1995. However, we compared cancer incidence between those who did and did not attend this health checkup and found that the rate did not differ between groups: the multivariate HR (95% CI) for any cancer in subjects who attended the 1995 checkup was 0.98 (0.92–1.04) relative to those who did not. This suggests that the present results are generalizable to our original population. A second limitation is that information on whether participants had liver disease was determined from a self-reported questionnaire. We did not collect any information on hepatitis B/C virus infection, nor did we perform abdominal ultrasonography. However, these factors would affect only liver cancer and not non-liver cancers. Finally, 9.4% of the total participants were lost to follow-up. This proportion did not vary largely across the GGT quartiles; the proportions were 11.3%, 9.6%, 8.8%, and 8.1% of participants in the lowest to the highest GGT quartiles, respectively. Therefore, we consider it unlikely that the association between GGT and cancer incidence was substantially distorted because of loss to follow-up.

Recent experimental evidence has indicated that GGT is a sensitive and reliable marker of oxidative stress,1–5 a key factor involved in tumor pathogenesis via glutathione metabolism.7–9 On the basis of experimental studies, a general causative of GGT with carcinogenesis has been reported, but associations have not been reported for specific sites. However, the present results do not support the hypothesis that GGT is related to cancer in general. A positive association was observed only for specific cancers that are related to alcohol consumption. In addition, this positive association was observed only in current drinkers.

In conclusion, our results suggest that the positive association of GGT with cancer incidence largely reflects alcohol consumption. Our findings confirm the importance of considering alcohol consumption when attempting to interpret the association of GGT with cancers and show that GGT could be a marker of alcohol-related cancers, which indicates that individuals who have a high level of GGT should be assessed for alcohol-related cancers, such as those of the esophagus, liver, pancreas, colorectum, liver, and breast.

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REFERENCES
1. Lee DH, Ha MH, Kam S, Chun B, Lee J, Song K, et al. A strong secular trend in serum gamma-glutamyltransferase from 1996 to
2003 among South Korean men. *Am J Epidemiol.* 2006;163:57–65.

2. Pompella A, Emdin M, Passino C, Paolicchi A. The significance of serum gamma-glutamyltransferase in cardiovascular diseases. *Clin Chem Lab Med.* 2004;42:1085–91.

3. Lee DH, Blomhoff R, Jacobs DR Jr. Is serum gamma glutamyltransferase a marker of oxidative stress? *Free Rad Res.* 2004;38:535–9.

4. Dröge W. Free radicals in the physiological control of cell function. *Physiol Rev.* 2002;82:47–95.

5. Ross JS, Stagliano NE, Donovan MJ, Breithart RE, Ginsburg GS. Atherosclerosis and cancer: common molecular pathways of disease development and progression. *Ann N Y Acad Sci.* 2001;947:271–92.

6. Hochwald SN, Harrison LE, Rose DM, Anderson M, Burt ME. Gamma-glutamyl transpeptidase mediation of tumor glutathione utilization in vivo. *J Natl Cancer Inst.* 1996;88:193–7.

7. Franzini M, Corti A, Lorenzini E, Paolicchi A, Pompella A, De Cesare M, et al. Modulation of cell growth and cisplatin sensitivity by membrane gamma-glutamyltransferase in melanoma cells. *Eur J Cancer.* 2006;42:2623–30.

8. Pompella A, Corti A, Paolicchi A, Giommarelli C, Zunino F. Gamma-glutamyltransferase, redox regulation and cancer drug resistance. *Curr Opin Pharmacol.* 2007;7:360–6.

9. Pompella A, De Tata V, Paolicchi A, Zunino F. Expression of gamma-glutamyltransferase in cancer cells and its significance in drug resistance. *Biochem Pharmacol.* 2006;71:231–8.

10. Strasak AM, Pfeiffer RM, Klenk J, Hilbe W, Oberaigner W, Gregory M, et al. Prospective study of the association of gamma-glutamyltransferase with cancer incidence in women. *Int J Cancer.* 2008;123:1902–6.

11. Strasak AM, Rapp K, Brant LJ, Hilbe W, Gregory M, Oberaigner W, et al. Association of gamma-glutamyltransferase and risk of cancer incidence in men: a prospective study. *Cancer Res.* 2008;68:3970–7.

12. Allen NE, Beral V, Casabonne D, Kan SW, Reeves GK, Brown A, et al. Moderate alcohol intake and cancer incidence in women. *J Natl Cancer Inst.* 2009;101:296–305.

13. Genkinger JM, Spiegelman D, Anderson KE, Bergkvist L, Bernstein L, van den Brandt PA, et al. Alcohol intake and pancreatic cancer risk: a pooled analysis of fourteen cohort studies. *Cancer Epidemiol Biomarkers Prev.* 2009;18:765–76.

14. Li CI, Chlebowski RT, Freiberg M, Johnson KC, Kuller L, Lane D, et al. Alcohol consumption and risk of postmenopausal breast cancer by subtype: the women’s health initiative observational study. *J Natl Cancer Inst.* 2010;102:1422–31.

15. Tramacere I, Scotti L, Jenab M, Bagnardi V, Bellocco R, Rota M, et al. Alcohol drinking and pancreatic cancer risk: a meta-analysis of the dose-risk relation. *Int J Cancer.* 2010;126:1474–86.

16. Tsuji I, Nishino Y, Ohkubo T, Kuwahara A, Ogawa K, Watanabe Y, et al. A prospective cohort study on National Health Insurance beneficiaries in Ohsaki, Miyagi Prefecture, Japan: study design, profiles of the subjects and medical cost during the first year. *J Epidemiol.* 1998;8:258–63.

17. Tsuji I, Kuwahara A, Nishino Y, Ohkubo T, Sasaki A, Hisamichi S. Medical cost for disability: a longitudinal observation of national health insurance beneficiaries in Japan. *J Am Geriatr Soc.* 1999;47:470–6.

18. Kuriyama S, Shimazu T, Ohmori K, Kikuchi N, Nakaya N, Nishino Y, et al. Green tea consumption and mortality due to cardiovascular disease, cancer, and all causes in Japan: the Ohsaki study. *JAMA.* 2006;296:1255–65.

19. Naganuma T, Kuriyama S, Kakizaki M, Sone T, Nakaya N, Ohmori-Matsuda K, et al. Green tea consumption and hematologic malignancies in Japan: the Ohsaki study. *Am J Epidemiol.* 2009;170:730–8.

20. North, AB, South, CD. Cancer Incidence in Antarctica, 1998–2002. In: Curado MP, Edwards B, Shin HR, Storm H, Ferlay J, Heanue M, et al, editors. Cancer Incidence in Five Continents Vol. IX. IARC Scientific Publications No. 160. Lyon: IARC; 2007.

21. Szasz G. Methods of Enzymatic Analysis. 2nd ed. English ed. New York: Academic Press, Inc.; 1974. p. 717.

22. Szasz G. Reaction-rate method for gamma-glutamyltransferase activity in serum. *Clin Chem.* 1976;22:2051–5.

23. Ogawa K, Tsuibo Y, Nishino Y, Watanabe Y, Ohkubo T, Watanabe T, et al. Validation of a food-frequency questionnaire for cohort studies in rural Japan. *Public Health Nutr.* 2003;6:147–57.