The worldwide death rate from esophageal cancer, according to World Health Organization statistics from the year 2000, for men was 226,000, the fifth leading cause of death for that group, behind lung, gastric, liver, and colon cancers. For women, the number of deaths totaled 110,000, the 7th leading cause of death behind breast, lung, gastric, colon, uterine, and ovarian cancers.1 In Japan, according to estimates from the 2001 vital statistics, 9026 men and 1651 women died of the disease, a continued increase in terms of number of deaths but unchanged in terms of age-adjusted mortality rate.2 According to results from the National Cancer Center's Central Hospital, the five-year survival rate from 1992 through 1996 for esophageal cancer for men was 40%, indicating that this malignant neoplasm has poorer prognosis than the 72% for both gastric and colon cancers, and near the rate of 35% for lung cancer.3

Smoking and alcohol drinking as risk factors for esophageal cancer have been clarified by many case-control studies4-9 and three cohort studies.10-12 In all such studies, a consistent associa-
tion was observed with smoking and alcohol intake both in Japan and in other countries, and therefore, that contribution is thought to be real. However, though there have been case-control studies on how smoking and alcohol intake interact to contribute to esophageal cancer, no detailed cohort-study analysis has been conducted. One reason for this is the need for a long-term follow-up of an extensive cohort. This study's objective was to elucidate which characteristics of smoking and alcohol intake contribute to esophageal cancer mortality, using data from the Japan Collaborative Cohort Study (JACC Study) for Evaluation of Cancer Risk sponsored by the Ministry of Education, Science, Sports and Culture of Japan (Monbusho). Another purpose was to clarify the joint effects of smoking and alcohol intake.

Study Population
Details of the cohort and follow-up procedures have been described elsewhere. In brief, a baseline survey was conducted in 45 areas throughout Japan from 1988 through 1990 by investigators from 24 centers. At the end of 1990, a total of 125,760 inhabitants were enrolled in this cohort. Among them, 110,792 subjects (46,465 men and 64,327 women; aged between 40 and 79 years at baseline) were followed up through the end of 1999. Because women who had smoked or drunk alcohol were insufficient in number, we excluded women from the analysis. For this study, 308 men were eliminated because they had a history of cancer; 3579 men were excluded because they did not give information about their smoking or drinking status. The 42,578 men remaining were available for analysis. The research protocol was approved by the Ethical Boards of Nagoya University School of Medicine and Wakayama Medical University.

Baseline Data Collection
The baseline data were collected utilizing a self-administered questionnaire, which included details about alcohol consumption, smoking history, dietary habits, health conditions, healthy habits, exercise, occupation, educational background, and subjective view of life. Smoking habit was established by asking the subjects whether they were a non-, ex-, or current smoker. Those who were current smokers were asked about the amount of cigarettes consumed per day and age at which smoking started. Packs were calculated by the number of cigarettes smoked divided by 20, and pack-years were calculated as the product of packs per day and the duration of smoking. Alcohol intake was based on the usual yearly intake of sake (Japanese rice wine), shochu (Japanese spirits), beer, whisky, and wine among current drinkers. The daily amount of alcohol consumption was assessed in terms of the conventional alcohol unit (go) of Japanese sake, one unit of which is equivalent to about 22 grams of alcohol.

Follow-up Procedure
The date and cause of death were annually or biannually confirmed, with the permission of the director-general of the Prime Minister's Office (Ministry of Public Management, Home Affairs, Post and Telecommunications). The date of move-out from the study area was also annually verified by the investigator in each area by reviewing population-register sheets of the cohort members. For deceased subjects, the causes of death were identified with underlying causes of death by reviewing all death certificates in each area once a year with permission from the Director-General of the Prime Minister's Office. The underlying causes of death were coded according to the International Statistical Classification of Diseases, Injuries, and Causes of Death, Ninth Revision (ICD-9), from baseline through 1994, and the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10), in and after 1995. Death from esophageal cancer was determined by the coding 150.0 through 150.9 for ICD-9 and C15.0 through C15.9 for ICD-10.

Statistical Analysis
Cox proportional hazards model was used to estimate the relative risk due to cigarette smoking or alcohol intake adjusted by age and study centers. To test significance, the two-sided Wald's test was used. All calculations were performed with Statistical Analysis System® (SAS) software.

### Table 1. Baseline characteristics of study participants (men).

| Factors            | Categories | No. | (%) |
|--------------------|------------|-----|-----|
| Total              |            | 42,578 | 100.0 |
| Age at baseline (year) | 40-49     | 11,265 | 26.5 |
|                    | 50-59      | 12,941 | 30.4 |
|                    | 60-69      | 12,605 | 29.6 |
|                    | 70-79      | 5,767 | 13.5 |
| Tobacco            | Non-smokers | 8,743  | 20.5 |
|                    | Ex-smokers | 11,155 | 26.2 |
|                    | Smokers    | 22,680 | 53.3 |
| Alcohol            | Non-drinkers | 8,010  | 18.8 |
|                    | Ex-drinkers | 2,629  | 6.2 |
|                    | Drinkers   | 31,939 | 75.0 |
Characteristics of the smokers are shown in Table 2. With respect to age at the start of smoking, those starting between the ages of 20 to 24 years comprised about 60% of the total, while those 25 years of age or older and those between the ages of 10 and 19 made up slightly less than 20%, each. As for number of cigarettes smoked daily, those smoking from 11 to 20 comprised 56% of the total, those smoking 21 to 30 cigarettes made up 17%, and those smoking from 1 to 10 comprised 16%. Subjects smoking 31 or more cigarettes per day comprised only 9% of the total. With respect to number of smoking years, the largest category comprised those who smoked from 35.1 to 45.0 years (32% of the total). By pack-years, the category of 40 or more comprised 33% of the total, 30 to 39 made up 23%, and 20 to 29 comprised 24%.

Characteristics of the drinkers are shown in Table 3. In terms of amount of alcohol consumed per day, those drinking 1.0 to 1.9 units comprised the largest group (32% of the total), with those drinking 2.0 to 2.9 units making up the next largest group (27%). Those who drank 3.0 units or more made up 13% of the total, and those drinking less than 1.0 unit only comprised 7% of the total. As for years of alcohol intake, the largest group was those drinking 25 years or less (35% of the total), followed by those drinking alcohol 25.1 to 35.0 years (21%), and those drinking 35.1 to 45.0 years (15%). By unit-year, 40 or more was the largest group (37% of the total), followed by the group of less than 30 (23%). In terms of type of alcohol, those drinking sake comprised the largest group (56% of the total), followed by those drinking beer (40%), and then shochu (15%), and then whiskey (14%). Wine drinkers comprised only 5% of the total.

Hazard ratio of esophageal cancer by smoking status is shown in Table 4, after adjusting for age and study center. Using non-smokers as the standard, current smokers and ex-smokers had a significantly higher mortality risk (4.36 and 2.71, respectively). Considering age when smokers started smoking, in all categories, the risk rose three to five times, but no dose-response association was observed. This was also the case when looking at the data by

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**Table 2. Characteristics of current smokers (men).**

| Categories                  | No.   | (%)  |
|-----------------------------|-------|------|
| Total                       | 22,680| 100.0|
| Age at baseline (year)      |       |      |
| 25+                         | 3,768 | 16.6 |
| 20-24                       | 13,503| 59.5 |
| 10-19                       | 4,254 | 18.8 |
| Unknown                     | 1,155 | 5.1  |
| Cigarettes smoked per day   |       |      |
| 1-10 cigarettes/day         | 3,618 | 16.0 |
| 11-20                       | 12,674| 55.9 |
| 21-30                       | 3,944 | 17.4 |
| 31+                         | 2,141 | 9.4  |
| Unknown                     | 303   | 1.3  |
| Duration of smoking (year)  |       |      |
| -25                         | 4,851 | 21.4 |
| 25.1-35.0                   | 6,232 | 27.5 |
| 35.1-45.0                   | 7,286 | 32.1 |
| 45.1+                       | 3,170 | 14.0 |
| Unknown                     | 1,141 | 5.0  |
| Cumulative amount of smoking|       |      |
| 1-19.9 pack-years           | 3,234 | 14.3 |
| 20.0-29.9                   | 5,404 | 23.8 |
| 30.0-39.9                   | 5,196 | 22.9 |
| 40.0+                       | 7,567 | 33.4 |
| Unknown                     | 1,279 | 5.6  |

**Table 3. Characteristics of alcohol drinkers (men).**

| Categories                  | No.   | (%)  |
|-----------------------------|-------|------|
| Total                       | 31,939| 100.0|
| Alcohol units’ consumed per day|       |      |
| <1.0 units/day              | 2,273 | 7.1  |
| 1.0-1.9                     | 10,346| 32.4 |
| 2.0-2.9                     | 8,587 | 26.9 |
| 3.0+                        | 4,049 | 12.7 |
| Unknown                     | 6,684 | 20.9 |
| Duration of alcohol drinking (year) |       |      |
| -25                         | 11,298| 35.4 |
| 25.1-35.0                   | 6,780 | 21.2 |
| 35.1-45.0                   | 4,683 | 14.7 |
| 45.1+                       | 1,836 | 5.8  |
| Unknown                     | 7,342 | 23.0 |
| Cumulative amount of alcohol intake (unit-year) |       |      |
| 1-29.9                      | 7,493 | 23.5 |
| 30.0-39.9                   | 3,007 | 9.4  |
| 40.0+                       | 11,970| 37.5 |
| Unknown                     | 9,469 | 29.7 |
| Type of alcohol (multiple answer) |       |      |
| Sake                        | 17,868| 55.9 |
| Shochu                      | 4,895 | 15.3 |
| Beer                        | 12,927| 40.5 |
| Whisky                      | 4,518 | 14.1 |
| Wine                        | 1,491 | 4.7  |

*: One unit contains about 22g of alcohol.
□: Japanese spirits.
number of cigarettes smoked per day. With respect to number of smoking years, a higher risk trend was observed as number of smoking years increased. With regard to investigation of pack-year, however, no dose-response relationship was observed.

Hazard ratio of esophageal cancer based on drinking status is shown in Table 5. Current drinkers had a significantly increased risk (2.40) compared with non-drinkers. Ex-drinkers had a 2.43 times higher risk, but the risk was not considered significant. By amount of alcohol consumed per day, esophageal cancer risk increased with increased alcohol intake. As for number of years of alcohol intake, no dose-response relationship was observed. By unit-year, the group of subjects with 40 unit-years or greater had the highest risk, but that risk was insignificant in a test of linear trend at a p value of 0.05. Looking at the data by type of alcohol consumed, the highest risk was with wine (6.24), followed by shochu (3.40), and sake (2.72). For beer and whiskey no significant increase in risk was observed.

Results of investigation into the joint effects of smoking and drinking are shown in Table 6. Dividing smokers into the categories non-smoker, ex-smoker, and smoker, and drinkers into non-drinker, ex-drinker, and drinker, smokers and drinkers were compared with non-smokers and non-drinkers. The comparison showed that the hazard ratio by point estimate for the former group increased to 2.37, not significant at a p-value of 0.05. In terms of joint effects based on number of cigarettes and amount of alcohol consumed per day, comparing the non-smokers and non-drinkers or those drinking less than one unit per day with those smoking less than 20 cigarettes per day and drinking one or more units of alcohol but less than three, the hazard ratio was 3.88, which increased to 6.30 for those smoking 21 cigarettes or more and drinking three units or more per day. These results indicated a synergistic increase in risk for combined smoking and drinking. However, for non-smokers even with increased alcohol consumption, and for non-drinkers and those drinking less than one unit with increased cigarette intake, no increase in risk was observed. Looking at the cumulative effects of smoking and

| Table 4. Hazard Ratio (HR) of death from esophageal cancer according to smoking status at baseline (men). |
|-------------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Variables                                       | Person-years   | No. of deaths  | HR (95% confidence interval) | P for trend |
| Non-smokers                                     | 86,446         | 7              | 1.00 (reference)             |              |
| Ex-smokers                                      | 107,708        | 25             | 2.71 (1.16-6.36)             |              |
| Smokers                                         | 220,492        | 68             | 4.36 (2.00-9.52)             |              |
| Age at start of smoking                         |                |                |                              |              |
| Non-smokers 25+                                 | 86,446         | 7              | 1.00 (reference)             |              |
| 20-24                                           | 36,321         | 13             | 3.85 (1.54-9.64)             |              |
| 10-19                                           | 130,874        | 38             | 4.89 (1.98-12.07)            |              |
| Cigarettes smoked per day                       |                |                |                              |              |
| Non-smokers 1-10 cigarettes/day                 | 86,446         | 7              | 1.00 (reference)             |              |
| 11-20                                           | 123,009        | 39             | 4.42 (1.97-9.92)             |              |
| 21-30                                           | 39,206         | 8              | 3.19 (1.11-9.19)             |              |
| 31+                                             | 21,177         | 5              | 4.33 (1.25-14.99)            | 0.391        |
| Years of smoking                                |                |                |                              |              |
| Non-smokers -25.0                               | 86,446         | 7              | 1.00 (reference)             |              |
| 25.1-35.0                                       | 49,108         | 4              | 2.05 (0.42-9.98)             |              |
| 35.1-45.0                                       | 62,652         | 13             | 3.54 (1.27-9.89)             |              |
| 45.1+                                           | 26,774         | 15             | 4.85 (1.62-14.53)            | 0.014        |
| Cumulative amount of smoking                    |                |                |                              |              |
| Non-smokers 1-19.9 pack-years                   | 86,446         | 7              | 1.00 (reference)             |              |
| 20.0-29.9                                       | 31,784         | 6              | 3.24 (1.06-9.89)             |              |
| 30.0-39.9                                       | 53,136         | 16             | 4.89 (1.98-12.07)            |              |
| 40.0+                                           | 51,039         | 14             | 3.85 (1.54-9.64)             |              |
| 40.0+                                           | 71,896         | 28             | 4.86 (2.11-11.21)            | 0.086        |

*Hazard ratio adjusted for age and centers.
| Variables                  | Person-years | No. of deaths | HR * (95% confidence interval) | P for trend |
|---------------------------|--------------|---------------|--------------------------------|-------------|
| Non-drinkers              | 76,521       | 9             | 1.00 (reference)               |             |
| Ex-drinkers               | 22,754       | 8             | 2.43 (0.91-6.47)               |             |
| Drinkers                  | 315,370      | 83            | 2.40 (1.20-4.80)               |             |

### Alcohol units consumed per day

| Alcohol units consumed per day | Person-years | No. of deaths | HR * (95% confidence interval) | P for trend |
|-------------------------------|--------------|---------------|--------------------------------|-------------|
| Non-drinkers                  | 76,521       | 9             | 1.00 (reference)               |             |
| <1.0 units/day                | 21,532       | 2             | 1.47 (0.28-7.68)               |             |
| 1.0-1.9                       | 99,786       | 16            | 1.58 (0.65-3.86)               |             |
| 2.0-2.9                       | 83,124       | 31            | 3.74 (1.62-8.66)               |             |
| 3.0+                          | 39,027       | 18            | 6.39 (2.54-16.12)              | 0.028       |

### Years of alcohol drinking

| Years of alcohol drinking | Person-years | No. of deaths | HR * (95% confidence interval) | P for trend |
|---------------------------|--------------|---------------|--------------------------------|-------------|
| Non-drinkers              | 76,521       | 9             | 1.00 (reference)               |             |
| -25.0                     | 111,842      | 14            | 1.71 (0.64-4.60)               |             |
| 25.1-35.0                 | 66,150       | 19            | 3.23 (1.32-7.92)               |             |
| 35.1-45.0                 | 43,855       | 18            | 3.23 (1.33-7.81)               |             |
| 45.1+                     | 15,706       | 7             | 2.77 (0.85-9.03)               | 0.100       |

### Cumulative amount of alcohol intake

| Cumulative amount of alcohol intake | Person-years | No. of deaths | HR * (95% confidence interval) | P for trend |
|------------------------------------|--------------|---------------|--------------------------------|-------------|
| Non-drinkers                       | 76,521       | 9             | 1.00 (reference)               |             |
| 1-29.9 unit-years                  | 73,262       | 4             | 0.68 (0.19-2.42)               |             |
| 30.0-39.9                          | 29,201       | 6             | 2.31 (0.75-7.06)               |             |
| 40.0+                              | 113,822      | 46            | 3.80 (1.70-8.46)               | 0.089       |

### Type of alcohol

| Type of alcohol | Person-years | No. of deaths | HR * (95% confidence interval) | P for trend |
|-----------------|--------------|---------------|--------------------------------|-------------|
| Non-drinkers    | 76,521       | 9             | 1.00 (reference)               |             |
| Sake            | 172,587      | 48            | 2.72 (1.22-6.08)               |             |
| Shochu*         | 47,499       | 15            | 3.40 (1.33-8.68)               |             |
| Beer            | 125,265      | 17            | 1.43 (0.58-3.52)               |             |
| Whisky          | 44,414       | 9             | 2.60 (0.91-7.41)               |             |
| Wine            | 14,956       | 6             | 6.24 (1.53-25.37)              |             |

* : Hazard ratio adjusted for age and centers.

* : One unit contains about 22g of alcohol.

* : Japanese spirits.
Table 6. Joint effects of smoking and alcohol consumption on risk of esophageal cancer death (men).

| Tobacco | Alcohol | No. of deaths | HR (95% confidence interval) |
|---------|---------|---------------|-----------------------------|
| By smoking and drinking status |
| Non-smokers | Non-drinkers | 4 | 1.00 (reference) |
| Non-smokers | Ex-drinkers | 1 | 1.10 (0.12-10.24) |
| Non-smokers | Drinkers | 2 | 0.18 (0.03-1.02) |
| Ex-smokers | Non-drinkers | 1 | 0.34 (0.04-3.12) |
| Ex-smokers | Ex-drinkers | 3 | 1.47 (0.31-7.08) |
| Ex-smokers | Drinkers | 21 | 1.39 (0.47-4.10) |
| Smokers | Non-drinkers | 4 | 0.74 (0.18-3.02) |
| Smokers | Ex-drinkers | 4 | 2.19 (0.51-9.40) |
| Smokers | Drinkers | 60 | 2.37 (0.85-6.58) |
| By smoked cigarettes and consumed alcohol in units\(\text{c}^5\) per day |
| Non-smokers | Non- or <1.0 units/day drinkers | 4 | 1.00 (reference) |
| Non-smokers | 1.0-2.9 | 0 | - |
| Non-smokers | 3.0+ | 0 | - |
| 1-20 cigarettes/day | Non- or <1.0 | 3 | 0.81 (0.18-3.73) |
| 1-20 | 1.0-2.9 | 35 | 3.88 (1.19-12.69) |
| 1-20 | 3.0+ | 6 | 4.01 (0.93-17.31) |
| 21+ | Non- or <1.0 | 0 | - |
| 21+ | 1.0-2.9 | 4 | 1.80 (0.37-8.78) |
| 21+ | 3.0+ | 6 | 6.30 (1.33-29.76) |
| By cumulative amount of smoking and alcohol intake |
| Non-smokers | Non- or <30.0 unit-year drinkers | 4 | 1.00 (reference) |
| Non-smokers | 30.0-39.9 | 0 | - |
| Non-smokers | 40.0+ | 0 | - |
| 1-39.9 pack-years | Non- or <30.0 | 2 | 0.65 (0.12-3.70) |
| 1-39.9 | 30.0-39.9 | 3 | 4.56 (0.88-23.64) |
| 1-39.9 | 40.0+ | 21 | 5.78 (1.71-19.55) |
| 40.0+ | Non- or <30.0 | 2 | 0.89 (0.16-4.96) |
| 40.0+ | 30.0-39.9 | 2 | 12.33 (1.86-81.64) |
| 40.0+ | 40.0+ | 15 | 7.01 (2.01-24.45) |

\(\text{c}^5\): One unit contains about 22g of alcohol.
* : Hazard ratio adjusted for age and centers.
drinking using as a standard the group of non-smokers and non-drinkers or those with 30 unit-years, the hazard ratio was 5.78 for smokers with less than 40 pack-years and for drinkers with 40 unit-years or more. For smokers with 40 pack-years or more and alcohol drinkers with 40 unit-years or more, an increased risk of 7.01 was observed. In non-smokers, however, even with increased cumulative alcohol intake, and in non-drinkers or in those with less than 30.0 unit-years even with increased cumulative cigarettes smoked, no increased esophageal cancer mortality risk was observed.

For the 42,578 males, a follow-up was conducted over a period of about 10 years, analyzing the joint effects of smoking and drinking on esophageal cancer mortality. It was found from the follow-up that combined smoking and drinking, established previously as risk factors for esophageal cancer, were also clearly shown to contribute to the mortality in this cohort. In this study with regard to smoking, a trend of greater esophageal cancer mortality risk was observed the longer the duration of smoking, but no dose-response was observed for age at start of smoking, number of cigarettes smoked daily, or cumulative amount of cigarettes smoked. For alcohol intake, a dose-response association was observed for amount of alcohol consumed per day, but for number of drinking years or cumulative amount of alcohol intake, no dose-response association was observed. In a previous case-control study, for smoking, length of smoking period was most strongly associated, whereas for alcohol intake, average amount of alcohol consumption was most strongly associated, information that conform with the results obtained in this study. However, this study did not observe any association with cumulative amount of cigarette consumption or cumulative alcohol intake. The reason for this disparity is possibly because, compared with France, alcohol consumed in Japan is largely beer, which has low alcohol content, with a low level of wine intake. Regarding cumulative amount of smoking, relatively low consumption of high alcohol content drinks may have made any significant association hard to detect.

By type of alcohol, Japan is characterized by widespread consumption of sake, an alcohol unique to Japan. In terms of esophageal cancer, no association was observed with low alcohol content beer, but the risk rose with wine, shochu, sake, and whiskey, in that order. Wine had the strongest association. However, whether this was because wine drinkers were more likely to contract esophageal cancer than sake drinkers, or whether the risk increased not because wine drinkers drank wine but because they consumed more per day is an issue that requires future investigation. The limitation of this study is high percentage of unknown categories among drinkers. This might cause an information bias.

With respect to the interaction of smoking and drinking, a synergistic effect was proven in case-control studies conducted to date, but such effect has not yet been proven in a cohort study. Through analysis of the relationship, we investigated whether smoking or alcohol intake contributed to the onset of esophageal cancer independently or whether they are a risk only when present simultaneously. For non-smokers, no esophageal cancer mortality risk was observed even in the smokers who consumed the largest amount of alcohol. Among non-drinkers and those who consumed less than one unit of alcohol per day, no increased risk was observed even when daily tobacco consumption increased from 20 cigarettes or less to 21 cigarettes or more. As for cumulative effects among non-drinkers and drinkers with less than 30 unit-years, no increased risk was observed even when cumulative pack-years of less than 40 increased to 40 or more. A synergistic effect was observed in both analyses by amount per day and cumulative amount, but not in the analysis by smoking and drinking status. These findings imply that amounts of smoking and drinking are important to increased esophageal cancer.
7. Yokoyama A, Ohmori T, Makuuchi H, Maruyama K, Okuyama K, Takahashi H, et al. Successful screening for early esophageal cancer in alcoholics using endoscopy and mucosa iodine staining. Cancer 1995; 76: 928-34.

8. Zambon P, Talamini R, La Vecchia C, Dal Maso L, Negri E, Tognazzo S, et al. Smoking type of alcoholic beverage and squamous-cell oesophageal cancer in northern Italy. Int J Cancer 2000; 86: 144-9.

9. Znaor A, Brennan P, Gajalakshmi V, Mathew A, Shanta V, Varghese C, et al. Independent and combined effects of tobacco smoking, chewing and alcohol drinking on the risk of oral, pharyngeal and esophageal cancers in Indian men. Int J Cancer 2003; 105: 681-6.

10. Kono S, Ikeda M, Tokudome S, Nishizumi M, Kuratsune M. Cigarette smoking, alcohol and Cancer mortality: a cohort study of male Japanese physicians. Jpn J Cancer Res 1987; 78: 1323-8.

11. Hirayama T. Life-Style and Mortality: A Large-scale census-based cohort study in Japan. In: Heidelberg JW ed. Contributions to epidemiology and biostatistics. Vol. 6. Basel: Karger, 1990.

12. Akiba S. Analysis of cancer risk related to longitudinal information on smoking habits. Environ Health Perspect 1994; 102(Suppl.8): 15-9.

13. Aoki K. Report by the Research Committee of the Ministry of Education, Science, Sports and Culture on Evaluation of Risk Factors for Cancer. J Epidemiol 1996; 6: S107-S113.

14. Ohno Y, Tamakoshi A, JACC Study Group. Japan Collaborative Cohort Study for Evaluation of Cancer Risk Sponsored by Monbusho (JACC Study). J Epidemiol 2001; 11: 144-50.

15. World Health Organization. Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death, Based on the Recommendations of the Ninth Revision Conference, 1975. World Health Organization: Geneva, 1977.

16. World Health Organization. International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Volume 1. World Health Organization: Geneva, 1992.

17. Cox DR. Regression models and life tables (with discussion). J R Stat Soc Appl Stat Sect (B) 1972; 34: 187-220.

18. SAS Institute. SAS/STAT User's Guide, Version 6, Fourth Edition. SAS Institute Inc: Cary, 1990.

19. Launoy G, Milan CH, Faivre J, Pienkowski P, Milan Cl, Gignoux M. Alcohol, tobacco and oesophageal cancer: effects of the duration of consumption, mean intake and current and former consumption. Br J Cancer 1997; 75: 1389-96.