ORIGINAL CONTRIBUTION

Cross-sectional Epidemiologic Study for Assessing Cancer Risks at the Population Level

I. Study Design and Participation Rate

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A cross-sectional study to assess the associations between lifestyle factors and cancer risk was conducted in five areas of Japan (Ninohe in Iwate, Yokote in Akita, Katsushika-kita in Tokyo, Saku in Nagano and Ishikawa in Okinawa) with different cancer mortality patterns. The subjects were randomly selected men aged 40 to 49 years and their spouses, and they all volunteered to participate in this study. The study included a questionnaire on lifestyle performed by interview, a health check-up and sampling of blood and urine. Furthermore, a 24-hour urine collection and 3-day nutritional survey were added as supplementary items. The overall participation rate was 72% (634/880): 77% in Ninohe, 78% in Yokote, 61% in Katsushika-kita, 71% in Saku, and 76% in Ishikawa. The wives of 59% (373/634) of the male participants also entered the study. A 24-hour urine collection and 3-day nutritional survey were also conducted in about one third of the participants. Profiles of participants revealed significant differences among each study area, such as length of residence, marital status, and occupation. J Epidemiol, 1992; 2: 75-81.

cross-sectional study, correlation study, cancer, biologic markers, lifestyle

Geographic variation in the cancer mortality are present even among the relatively homogeneous population of Japan11. For example, stomach cancer mortality shows an almost three-fold difference between the areas with the highest and lowest age-adjusted mortality rates1. Such a large difference suggests that the risk factors for stomach cancer may be related to lifestyle, especially to local dietary habits. Such distinct differences are also recognized for cancer of the esophagus, liver, and hematopoietic system as well as for other cancers in Japan1.

The purpose of this study was to clarify the prevalence and the level of possible risk factors for several types of cancer in five different areas of Japan and to find the factors which could explain cancer mortality at the population level. The measurements of several biologic markers was performed in addition to a questionnaire given by interview.
Although a large number of cross-sectional study was conducted for the participants of health check-up in Japan, little has been published using a strict random sampling method in the subject selection. This paper describes the design of our cross-sectional study, and provides the participation rates and participant profile. The basic findings about health-related factors are shown in the part II.

STUDY DESIGN

Study areas and their mortality statistics

Each study area had a population of approximately 100,000 people, and was covered by a single health center which supervised the health administration of the several cities, towns, and villages in the area. Four areas of Japan were selected for this study on the basis of the age-adjusted mortality rates for male stomach cancer: Yokote (consisting of 1 city, 5 towns, and 2 villages) in Akita prefecture has one of the highest rates in Japan, Saku (1 city, 3 towns, and 5 villages) in Nagano prefecture has an intermediate rate, Ninohe (1 city, 3 towns, and 1 village) in Iwate prefecture has a low rate, and Ishikawa (2 cities, 2 towns, and 3 villages) in Okinawa prefecture has one of the lowest rate. Because these areas are relatively rural, Katsushika-kita (a part of Katsushika-ward) in the Tokyo metropolitan was included as a representative urbanized areas. The

| ICD 9 | All causes 140-208 | Cancer 410-414 | Ischemic heart disease 410-414 | Other heart disease 420-429 | Cerebrovascular disease 430-438 |
|-------|------------------|---------------|------------------|-----------------|------------------|
| **Males** | | | | | |
| Ninohe | 630.39+ | 127.11- | 34.07 | 94.99+ | 100.51+ |
| Yokote | 544.29 | 154.66 | 24.28- | 62.77 | 91.97+ |
| Katsushika-kita | 579.53+ | 169.44+ | 54.90+ | 32.97- | 78.85 |
| Saku | 475.35- | 130.90- | 16.65- | 55.72 | 69.99 |
| Ishikawa | 458.17- | 115.89- | 23.63- | 43.36- | 35.29- |
| Japan 1987 | 527.74 | 150.84 | 31.75 | 58.10 | 72.20 |
| **Females** | | | | | |
| Ninohe | 336.34+ | 68.38- | 12.82- | 52.66+ | 70.33+ |
| Yokote | 329.99+ | 78.20 | 14.89 | 41.83 | 67.75+ |
| Katsushika-Kita | 358.27+ | 88.37+ | 28.36+ | 30.65- | 64.76+ |
| Saku | 274.94- | 68.13- | 12.82- | 29.18 | 50.37 |
| Ishikawa | 225.29- | 56.05- | 13.17- | 20.51- | 21.10- |
| Japan 1987 | 304.28 | 77.82 | 17.44 | 42.17 | 51.32 |

+ : significantly high rate (p<0.05) when compared with all Japan in 1987
- : significantly low rate (p<0.05) when compared with all Japan in 1987
geographic location, the population in 1987, and size of the land area are shown in Fig. 1.

Age-adjusted mortality rates (adjusted to the World population) during the five years from 1985 to 1989 are shown in Table 1 for the major causes of deaths and in Table 2a for various type of cancer. The cumulative mortality rates, 0-74 years (%), for each cancer were also shown in Table 2b. The rates for Katsushika-Kita in Table 1 are only calculated during the three years from 1987 to 1989, except for cancer mortality, because of the lack of data for 1985 and 1986. Statistical differences from the national rates of Japan in 1987 were assessed by 95% confidence intervals calculated from the standard errors of each rate.

The male mortality rates from all causes were higher in Ninohe and Katsushika-Kita, and lower in Saku and Ishikawa, when compared with the rate for Japan as a whole. Ninohe had the highest total mortality rate and this was mainly due to having the highest rate of death due to cerebrovascular disease (CVD) and other heart disease. Ishikawa had the lowest total, CVD, and cancer mortality rates. The high mortality rate

### Table 2a. Age-adjusted mortality rates for various types of cancer in 1985-1989 per 100,000 population.

| Type of Cancer | Ninohe | Yokote | Katsushika-Kita | Saku | Ishikawa |
|----------------|--------|--------|----------------|------|---------|
| Esophagus | 150 | 151 | 153 | 154 | 155 |
| Stomach | 151 | 152 | 153 | 154 | 155 |
| Colon | 153 | 154 | 155 | 156 | 157 |
| Rectum | 154 | 155 | 156 | 157 | 158 |
| Liver | 155 | 156 | 157 | 158 | 159 |
| Pancreas | 157 | 158 | 159 | 160 | 161 |
| Lung | 156 | 157 | 158 | 159 | 160 |
| Breast | 158 | 159 | 160 | 161 | 162 |
| Uterus | 159 | 160 | 161 | 162 | 163 |
| Prostate | 160 | 161 | 162 | 163 | 164 |
| Lymphoma | 162 | 163 | 164 | 165 | 166 |
| Leukemia | 164 | 165 | 166 | 167 | 168 |

| Gender | Males | Females |
|--------|--------|----------|
| Ninohe | 4.50+ | 7.09- |
| Yokote | 12.26+ | 0.83- |
| Katsushika-Kita | 11.43+ | 0.64- |
| Saku | 8.37 | 0.41- |
| Ishikawa | 12.00+ | 1.18- |
| Japan 1987 | 7.09 | 1.00- |

*+ : significantly high rate (p<0.05) when compared with all Japan in 1987
- : significantly low rate (p<0.05) when compared with all Japan in 1987

### Table 2b. Cumulative mortality rates, 0-74 years (%), from selected cancer sites in 1985-1989.

| Type of Cancer | Ninohe | Yokote | Katsushika-Kita | Saku | Ishikawa |
|----------------|--------|--------|----------------|------|---------|
| Esophagus | 150 | 151 | 153 | 154 | 155 |
| Stomach | 151 | 152 | 153 | 154 | 155 |
| Colon | 153 | 154 | 155 | 156 | 157 |
| Rectum | 154 | 155 | 156 | 157 | 158 |
| Liver | 155 | 156 | 157 | 158 | 159 |
| Pancreas | 157 | 158 | 159 | 160 | 161 |
| Lung | 156 | 157 | 158 | 159 | 160 |
| Breast | 158 | 159 | 160 | 161 | 162 |
| Uterus | 159 | 160 | 161 | 162 | 163 |
| Prostate | 160 | 161 | 162 | 163 | 164 |
| Lymphoma | 162 | 163 | 164 | 165 | 166 |
| Leukemia | 164 | 165 | 166 | 167 | 168 |

| Gender | Males | Females |
|--------|--------|----------|
| Ninohe | 0.58 | 0.00- |
| Yokote | 1.46+ | 0.08- |
| Katsushika-Kita | 1.33+ | 0.05- |
| Saku | 0.84 | 0.00- |
| Ishikawa | 1.58+ | 0.14- |
| Japan 1987 | 0.86 | 0.11- |

*+ : statistically significant (p<0.05) high rates when compared with those in Japan 1987
- : statistically significant (p<0.05) low rates when compared with those in Japan 1987
due to ischemic heart disease (IHD) in Katsushika-kita was noteworthy in both males and females.

The age-adjusted mortality rate from stomach cancer showed a three-fold difference between the highest rate in Yokote (49 in males and 21 in females) or Katsushika-kita (49 and 21) and the lowest rate in Ishikawa (17 and 6), both for males and for females. Esophageal cancer mortality was high for males in Yokote, Katsushika-kita and Ishikawa, while lymphoma in males and leukemia in both sexes showed significantly higher mortality rates in Ishikawa. The cumulative mortality rates reflected the age-adjusted rates, although some discordances in the rank were recognized.

Selection and recruitment of subjects

One-hundred seventy men aged 40 to 49 years old were selected from each area by a random sampling method using the resident registration list. This number of 170 was decided with the intention of getting at least 100 participants from projected response rate of 60%. One-hundred ninety-five men were selected in Katsushika-kita, because the response rate had been predicted to be lower than in the other areas.

The selected individuals were approached by a letter, accompanied by a prepaid postcard for reply, explaining the purpose of this study and requesting voluntary participation. The spouses of the participating men were also invited to participate in the study. In order to obtain a sufficient response rate, an additional letter, telephone call and home visiting were used to encourage the participation.

Survey items

The participating men and their spouses were requested to attend the places of examination in each district. The examinations for eight individuals (4 in Ishikawa and 4 in Katsushikakita) were done at home for their convenience. The following items were studied in each person.

1. Questionnaire by interview
   The participants were interviewed by trained public health nurses or nutritionists using a questionnaire to assess their lifestyle. The questionnaire explored the personal history, medical history, family history, smoking and drinking history, dietary patterns, physical activity, stress history, personality, and other features. The gynecological and reproductive history were added for women.

2. Health check-up
   A health check-up was performed with anthropometric measurements such as height, weight, and upper arm circumference, and the measurement of blood pressure using an automated manometer.

3. Blood/urine collection and items analyzed
   A total of 25 ml (14 ml for women) of blood was collected by venipuncture using a 30 ml syringe with a 19 gauge butterfly needle for males and a 21 gauge needle for females. Fasting for at least 5 hours was requested before blood collection. The blood was divided into three tubes; an 11-ml heparinized tube (only for men), 2-ml heparinized tube and a 12-ml tube without anticoagulant. The 11-ml heparinized tube was immediately centrifuged for 10 min at 2,500-3,000 rpm to obtain plasma and a buffy coat layer. The 2-ml tube was used for blood cell counts and hemoglobin measurement. The 12-ml tube was left for an hour at room temperature to facilitate clotting and the serum was then separated by centrifugation.

   The plasma, buffy layer, and serum were divided into several tubes and stored frozen in an ice box with sufficient dry ice at the examination sites until they were sent to the laboratories where they were stored at −80°C until analysis. The time from blood collection until freezing was strictly kept within 30 min for plasma samples.

   The serum and plasma samples were sent to several laboratories for analysis. The following parameters were measured from serum and plasma samples: biochemical analysis such as cholesterols and liver function test, vitamins and antioxidants such as β-carotene, lycopene, α-tocopherol, retinol, ascorbic acid, hormones such as sex hormones and steroid hormones, trace elements such as selenium, copper and zinc, viral and bacterial marker such as hepatitis B, hepatitis C, HTLV-1 and Helicobacter Pylori. The buffy coat layer was processed for the detection of DNA adducts such as O6-methyl- and N7-methyldeoxyguanosine adducts, and for the identification of genetic polymorphisms such as the P-450 isozyme pattern or polymorphisms of proto-oncogene loci. These results will be published separately.

   The measurement of vitamins and antioxidant compounds was conducted as a part of “The Optional Study on Antioxidant Vitamins and Polyunsaturated Fatty Acids, WHO/MONICA Project”, which was organized by one of the authors [F.G.].

   Casual urine samples (5 ml) were also frozen for future analysis after checking protein, glucose, and occult blood using test paper (Miles-Sankyo, Hema-Combistix No. 2876).

Supplementary studies

In addition to the above-mentioned items, the collection of 24-hour urine and 3-day nutritional survey were
done for volunteers among the participants.

1. Twenty-four-hour urine sampling

Twenty-four-hour urine samples were collected voluntarily from participants in the main study on any day except Saturday, Sunday, and holidays. We planned for approximately 30 men and 30 women in each area to participate in the 24-h urine collection. A simple portable device (Urine Mate P, Sumitomo Bakelite, Tokyo) was used for the collection of urine. After measuring the total urine volume, samples were stored in frozen at -80°C until analysis for sodium, potassium, creatinine, nitrate, and N-nitroso compounds.

2. Three-day nutritional survey

A nutritional survey was done in volunteer couples over three consecutive weekdays using the same method as the National Nutritional Survey in order to obtain more precise and quantitative information about dietary habits. We planned for approximately 30 households in each area to provide nutritional data.

In addition, five participants in the nutritional survey in each area were requested to submit the same meals consumed in a day. These meals were homogenized by mixer and the nutritional components were measured.

Survey period

The surveys were done in the winter season from February to March in 1989 for Ninohe and Ishikawa, in 1990 for Yokote and Saku, and in 1991 for Katsushika-kita.

RESULTS

Participation rate and interview time

Participants in the main and supplementary studies are shown in Table 3. A total of 634 men participated in the main study from the original 880 randomly selected men. The overall participation rate was 72%, ranging from 61% in Katsushika-kita to 78% in Yokote. Fifty-nine per cent (373/634) of the wives of the participating men entered the study, ranging from 43% in Katsushika-kita to 72% in Ishikawa. A total of 197 men and 167 wives participated in the optional 24-hour urine collection, and 208 men and 176 wives in the 3-day nutrition survey (Table 3).

The average interview time was 26.0 min (standard deviation: 9.1 min, range: 11-154 min) for males and 25.8 min (7.1 min, 11-78 min) for females. The average time was longer in Ishikawa (33.3±13.1 min in males and 31.6±8.6 min in females) than in the other four areas (Ninohe: 22.2±8.2 and 22.4±4.8 min, Yokote: 25.1±5.8 and 23.2±4.7 min, Katsushika-kita: 25.5±5.4 and 25.2±5.8 min, Saku: 23.9±5.9 and 24.9±5.6 min).

Profile of the participants

A profile of the participants is shown in Table 4. The male participants were oldest in Katsushika-kita, and age was inversely correlated with the participation rate in each area; even in the narrow age range from 40 to 49 years. The ages of the women depended on the corresponding ages of the men, since they were all the wives of participating men. Over 90% of the men and women had been born in the same prefecture in the Ninohe and Yokote, whereas in the case of Katsushika-kita less than half of them were born in the Tokyo area. The same trend was also found for the duration of living in the study area for both sexes. The percentage of married men was a little lower in Ishikawa and Katsushika-kita.

The numbers of siblings and children were highest in Ishikawa and lowest in Katsushika-kita. The percentage of subjects with a high school or better education was the highest in Saku, especially among women. The distribution of male job categories varied slightly between the areas. The most frequent occupation was in the category of “Craftsman, process worker, or labor” in the four rural areas, except for Ninohe where agriculture occupied one third. The percentage of women without a job was the highest in Katsushika-kita.

Table 3. Number of participants in the main study, and in the supplementary 24-hour urine collection and 3-day nutritional survey.

| Area      | Main study | 24-hour urine collection | 3-day nutritional survey |
|-----------|------------|--------------------------|--------------------------|
|           | Selected   | Participated (%) | Spouses | Participated | Spouses | Participated | Spouses |
| Ninohe    | 175        | 134 (76.6) | 70     | 33          | 33     | 26          | 26      |
| Yokote    | 170        | 133 (78.2) | 80     | 43          | 30     | 50          | 41      |
| Katsushika-Kita | 195 | 118 (60.5) | 51     | 36          | 30     | 63          | 35      |
| Saku      | 170        | 120 (70.6) | 79     | 48          | 39     | 41          | 46      |
| Ishikawa  | 170        | 129 (75.9) | 93     | 32          | 32     | 27          | 28      |
The enrollment of representative subjects is essential for a correlation study testing the association between mortality due to specific diseases and their possible determinants among a population. For this reason, our subjects were selected by random sampling and efforts were made to achieve a high response rate by telephone follow-up and home visiting when necessary. Since the response rate remained between 60% and 80%, the participants may have been biased to some degree. However, the comparability of the groups was expected to be good, even when the small numbers in the 24-hour urine collection and 3-day nutritional survey are considered.

Although the subjects were selected randomly from men aged 40 to 49 years, the average ages were significantly different in the five study areas. The average age of the male participants was negatively correlated with the participation rate in each area and the r-square value was 0.95. Older people were more likely to participate in the study even in the narrow age range of 40-49 years. However, the difference of average ages between the oldest (Katsushika-kita) and the youngest (Yokote) areas was only 1.5 years, so adjustment for age would not be necessary in the future analysis.

More than 90% of the participants were born in the same prefecture in the Ninohe and Yokote areas and the rate was almost 80% in Saku and Ishikawa. Thus, most of the individuals in these four areas had spent all of their life in the same region. In contrast, half of the inhabitants in Katsushika-kita were born outside Tokyo and they may have changed their lifestyles after coming to metropolitan Tokyo. Accordingly, the data from Katsushika-kita should be carefully treated in the correlation analysis. The low participation rate of 61% and the low percentage of married men in Katsushika-kita are other differences that require consideration.

A different distribution of job categories was noted between the five study areas. Since occupation is closely related to lifestyle and disease occurrence, adjustment will be required in future analysis.

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