EARLY GASTRIC CANCER

JAPANESE CANCER ASSOCIATION

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EARLY GASTRIC CANCER

Japanese Cancer Association

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Tomizo Yoshida, M. D.

PREFACE

This volume was produced with two main purposes: to clarify the term, "Early Gastric Cancer" (EGC), and to discuss the techniques developed in Japan for diagnosing EGC.

Rapid improvement in diagnostic techniques was stimulated partly by the desire to arrest, and possibly prevent gastric cancer—the most widespread disease of this country. Progress was also hastened by the simultaneous development of three techniques in cancer in ten years, between 1950 and 1960. These were the pathological analysis of EGC, and the gastrocamera and double contrast methods of stomach X-ray examination. In 1962, the Japan Society for Gastroenterological Endoscopy defined and classified EGC. The diagnostics of EGC have been further completed by effective use of mass survey for gastric cancer and the use of the gastroduodenoscope which was originally devised by Hirschowitz, and improved in Japan for use in visible biopsy and cytology. These five techniques are closely related and complement each other; for example, minute cancer foci even within 1 cm in diameter in any region of the gastric mucosa can be detected when radiologists, endoscopists, cytologists and pathologists work in cooperation with one another. It has become common in Japan for every gastroenterologist to be trained in both stomach X-ray examination and endoscopy.

The reports in this volume were written by pioneers in their fields during the past twenty years. Most of them give guidance in new diagnostic techniques, while the remaining papers introduce new problems on more highly specialized aspects of gastric carcinoma.

The frequency of EGC in resected specimens with gastric cancer has increased, reaching an average of nearly 20% in most clinics in Japan, and up to 30% in clinics which have good gastroenterological departments. If the frequency reaches 50%, we will feel that our efforts have been successful.

The epidemiology suggests that the mortality rate of gastric cancer in Japan has decreased during the past few years, but it is not yet known if the decrease is a natural one or if it is the result of the early detection of gastric carcinoma. We endeavor to ascertain with certainty the source of the lower mortality rate from gastric cancer in Japan when the frequency of EGC in the resected gastric carcinoma reaches 50%

It is the hope of the authors of this book that the contents will help worldwide efforts towards early detection and prevention of gastric carcinoma, thus contributing ultimately to a lower mortality rate of this disease everywhere.

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Takeshi HIRAYAMA

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The purpose of this paper is to outline the results of an epidemiological study of stomach cancer in Japan.

Size of the Problem Descriptive Epidemiology

1. Classification

Although this paper deals mainly with the epidemiology of cancer of the "stomach," more detailed studies in future will require classification of such cancers according to the various anatomical sites of the stomach. Preliminary results from such studies have already indicated that the epidemiological pattern in cancer of the cardia of the stomach appears to be somewhat different from that of the pylorus, risk factors of the former being closer to the pattern found in cancer of the lower third of the esophagus.

Classification by histological type is equally important (*9*, *11*). Apparently cancer of the stomach can be divided into two main types diffuse or undifferentiated and intestinal or differentiated as first described by Lauren. The latter usually arises from mucosa with intestinal metaplasia while the former stems from proper gastric mucosa. These two types show distinct epidemiological features and are sharply contrasted. With the help of Dr. Haruo Sugano, 10,494 autopsy records dating from 1958 to 1967 were reviewed and classified into these two types. They were found to show quite different distribution in terms of sex, age, occupation and geography. The undifferentiated type is more predominant in females, 42.3% of 3,618 cases, than in males, 29.1% of 6,876 cases. It is also more frequent in younger age groups: under age 39, 51.8% of 1,535 cases, age 40–59, 35.6% of 4,336 cases and over age 60, 25.8% of 4,623 cases. It is also more predominant in certain occupations and prefectures. The ratio of undifferentiated type to differentiated type by occupation was as follows: 0.77 for miners, 0.54 for professional, 0.53 for transport, 0.48 for farmers, 0.45 for clerical, 0.44 for sales, 0.42 for administrative, 0.39 for industry and 0.36 for service workers.

A significant positive partial correlation coefficient was obtained in the standardized death rate from stomach cancer by prefectures between males and females in each histological type: +0.385 for the undifferentiated type and +0.394 for the differentiated type. On the other hand a significant negative correlation coefficient was obtained between different histological types: −0.432 for males and −0.579 for females. In the future, epidemiological studies of stomach cancer

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should be planned and implemented by classifying the disease according to histological type as stressed by Muñoz and Correa. This was also strongly recommended by WHO in the guide lines of the International Clinical Reference Center on Stomach Cancer at the start of its activities in Tokyo in 1970.

2. Measurement of the frequency

According to the National Vital Statistics* for 1970, 29,634 men and 19,164 women died from stomach cancer, the mortality rate per 100,000 population being 58.4 and 36.5, respectively. The corresponding rates for U.S. whites (1966) are 10.2 and 6.5, and for England and Wales (1967) are 31.6 and 22.1, respectively. The relative frequency or the percentage of stomach cancer to total sites of cancer is 44.2 for males and 36.3 for females. The corresponding ratio for U.S. whites is 5.8 and 4.5, and for England and Wales, 12.5 and 10.9 respectively. In 1960, a cancer morbidity survey was conducted by the Ministry of Health and Welfare in four prefectures (Miyagi, Ishikawa, Yamaguchi and Kumamoto).** The total number of cancer patients visiting all the medical institutions in these districts during the previous year was studied. According to this survey, the annual incidence rate per 100,000 population was calculated as 86.6 for males and 47.7 for females. The relative frequency was 52.8 and 25.7%, respectively.

The results of cancer registry in Miyagi (1962–64) and in Osaka (1965–66) and of a cancer morbidity survey in Okayama (1966) and in Okinawa (1968) revealed that the standardized incidence rates (standardized to the 1950 world population) of stomach cancer per 100,000 population were 95.1, 102.9, 92.9 and 50.5 for males, and 44.7, 48.4, 45.4 and 22.8 for females. These rates in Okinawa resemble to those for Japanese in Hawaii (1960–64), 47.6 for males and 26.9 for females. The relative frequency to total cancer in Miyagi, Osaka, Okayama and Okinawa was 49.0, 49.0, 49.7 and 28.3 for males, and 31.7, 32.1, 31.7 and 15.7 for females. Out of 16,363 male and 13,523 female autopsied cancer cases in the period from 1958 to 1963 in Japan, cancer of the stomach was found in 25.1% of males and 16.2% of females. Out of 27,797 male and 18,421 female autopsied cancer cases in the period from 1964 to 1968 cancer of the stomach was noted in 22.3% of males and 17.6% of females. In 1969, 1,852,220 adults were examined by mass stomach X-rays in Japan. Out of these, 2,361 or 0.12% were found to have cancer in the stomach; 4,150 cases of gastric polyp and 29,374 cases of gastric ulcer were also found in this mass examination, 0.22% and 1.59% of the screened population respectively.

In summary, it should be understood that the high frequency of cancer of the stomach shown by mortality, morbidity, autopsy and mass-screening figures makes this type of cancer of particular importance in Japan.

Epidemiological Phenomena

1. Time trend

The number of deaths from cancer of the stomach is still on the increase

* Vital Statistics, 1950–1964, Japan, Ministry of Health and Welfare, Tokyo.

** Cancer Morbidity Survey, 1960, Ministry of Health and Welfare, Tokyo.

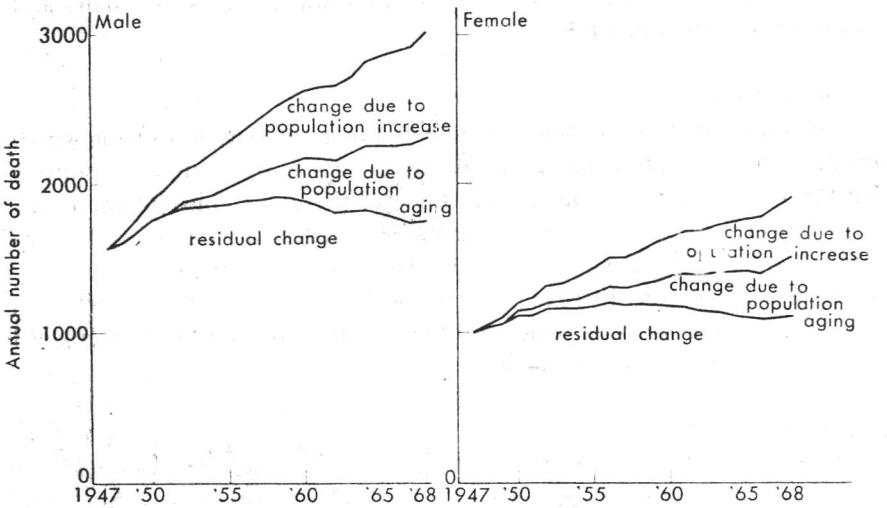

FIG. 1. Number of deaths from cancer of the stomach in Japan (1947–68).

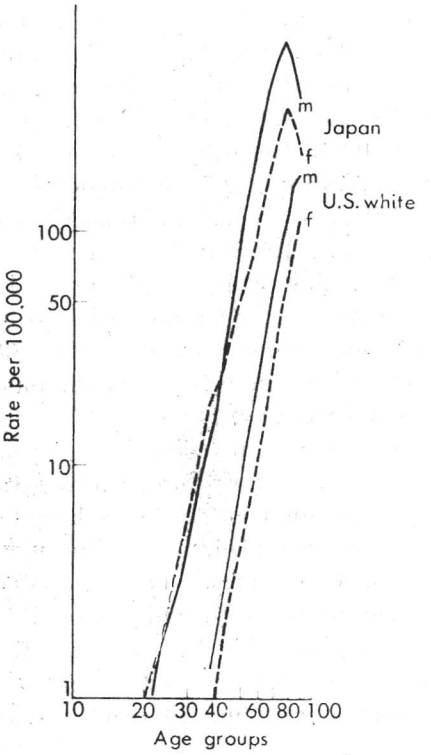

FIG. 2. Age-specific death rate for stomach cancer in Japan and in U.S. whites (1964–65).

in Japan. Most of the increase, however, was found to be due to the increase in population itself. When the change in age structure of the population was taken into account, the disease was noted to be on the downward trend since 1958

(Fig. 1). The death rate for age 45–49 in 1970 was 29% less for males and 14% less for females than in 1955.

2. Age and sex

The rates for stomach cancer were noted to go up with advancing age in both mortality and morbidity statistics. If these age-specific rates are plotted on a logarithmic scale both for deaths and for age, there is a constant increase in the rate of cancer incidence. This is true for both males and females. The rate was slightly higher for females up to age 39. However, a striking male preponderance was observed after age 40 (Fig. 2). In log-log scale graphs in which linear increases were noted for both males and females, the slope for the former was found to be much steeper than for the latter.

3. Regional differences

The age standardized death rate for this type of cancer in Japan (*15*) reached as high as 68.57 for men and 35.31 for women in 1964–65, in Chile 58.43 and 39.02, in Poland 44.18 and 21.17, in Hungary 42.74 and 23.18, in Czechoslovakia 42.74 and 22.59, in Austria 42.11 and 23.62, in Bulgaria 40.56 and 26.67, in Finland 39.66 and 20.38, in Germany 37.05 and 20.69, in Italy 33.61 and 17.81, in Portugal 32.95 and 19.65, in Venezuela 30.08 and 21.77, in the Netherlands 28.26 and 15.18, in Belgium 27.13 and 15.27, in Puerto Rico 27.12 and 13.20, in Switzerland 26.04 and 14.90, in Norway 26.01 and 14.63, in Scotland 25.47 and 14.50, in South Africa 25.27 and 13.00, in Ireland 23.88 and 15.94, in England and Wales 23.42 and 11.46, in Taiwan 22.45 and 12.77, in Sweden 22.04 and 12.03, in Northern Ireland 21.87 and 13.59, in Denmark 21.76 and 13.39, in France 21.44 and 10.63, in Hong Kong 21.33 and 12.27, in Yugoslavia 21.10 and 11.95, in Israel 18.20 and 12.58, in the U.S. (non-white) 17.99 and 8.12, in Canada 17.56 and 8.13, in New Zealand 16.54 and 8.33, in Greece 16.49 and 10.04, in Australia 15.48 and 7.95, in Panama 13.45 and 8.83, in Mexico 9.67 and 8.89, in the U.S. (white) 9.42 and 4.72, in El Salvador 7.68 and 6.76, in the Philippines 6.18 and 4.64, and in Thailand 1.82 and 0.83 respectively (Segi).

It should be noted that the rate in Japan is over seven times higher than for U.S. whites. Similarity in rates in East European countries is impressive. The death rate for stomach cancer for men reaches a height of 50 per 100,000 at age 45–49 in Japan, age 55–59 in Finland and in England and Wales, age 60–64 in Australia and age 65–69 in U.S. whites. The corresponding figures for women are age 55–59 in Japan, age 60–64 in Finland, age 65–69 in England and Wales, age 70–74 in Australia and age 75–79 in U.S. whites. In other words Japanese people tend to die from stomach cancer about 20 years earlier than U.S. whites. It was also noted that men were dying 10 years earlier than women in each country.

The map of age-adjusted death rates for stomach cancer by prefectures in Japan clearly indicates that the disease is endemic in Hokuriku, Southern Kanto and Kinki, and relatively less endemic in Southern Kyushu. More or less the same tendency is noted for both sexes and also for different age groups. A similar regional variation in the frequency of the disease can also be observed in autopsy

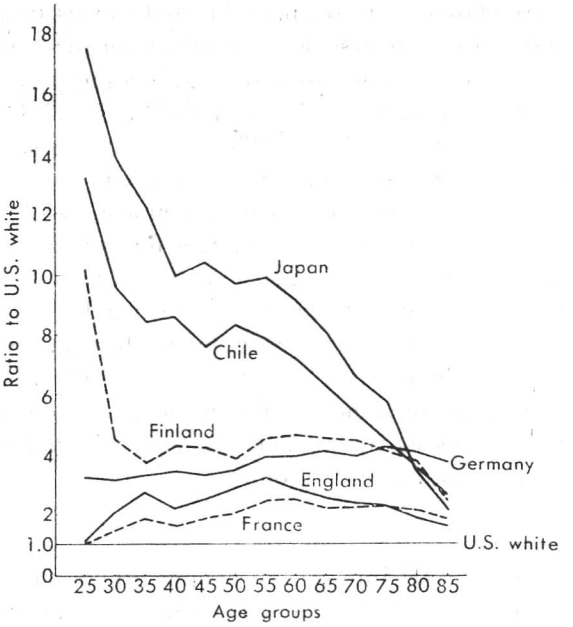

FIG. 3. Stomach cancer death rates in selected countries (ratio to U.S. whites).

and morbidity statistics as well as mortality statistics. Therefore diagnostic accuracy or completeness of reporting does not seem to be the main reason of this geographical fluctuation. A similar tendency has been also observed in the recent population study. It is of interest to note that people born in endemic areas tend to die from stomach cancer with a higher frequency than people born in less endemic areas even when they move to Tokyo and die there, the relative frequency for those born in Hokuriku district and Southern Kyushu district ($\chi^2=9.5$, $p<0.01$), being 55.8% and 39.6%, indicating that the causative factors of stomach cancer probably lie in special host or environmental conditions operative before the change of residence or in factors which continue to exist even after the change of residence.

4. Ratio by age groups

Although the frequency of stomach cancer in Japan was noted to be one of the highest in the world, the ratio based on the comparison of the age-specific rates for Japan and U.S. whites was found to be quite different in each age group (Fig. 3). In younger age groups such as 25–29, the stomach cancer death rate was noted to be almost 18 times higher than the corresponding rate for U.S. whites, while in older age groups the difference in rates in the two countries was calculated to be not more than 2 to 3-fold. A similar tendency was observed in Chile but not in Germany or France. In the latter countries the ratio was almost constant throughout the different age groups.

5. Ethnic differences

The variation in incidence among different ethnic groups in the same country

is also of interest. In Hawaii, both the mortality and morbidity rates for this type of cancer are highest among Japanese, lower among Caucasians and lowest among Chinese (*12*). Quite similar variations according to ethnic groups were noted in our study. In Japan there were 93,147,200 Japanese, 516,211 Koreans, 40,084 Chinese and 20,910 Caucasians in 1960. The death rate for stomach cancer per 100,000 in 1958–67 in Japan was calculated highest among Japanese and Koreans, 57.3 for men and 34.6 for women, and 73.3 for men and 33.5 for women respectively. The rates were low among Chinese, 32.4 for men and 33.8 for women, and lowest among Caucasians, 16.7 for men and 16.0 for women. The death rate for other sites of cancer was calculated as 53.7 for men and 55.6 for women among Japanese, 76.3 for men and 48.5 for women among Koreans, 80.7 for men and 66.9 for women among Chinese, and 38.3 for men and 35.5 for women among Caucasians. Such marked differences in the incidence of stomach cancer among various ethnic groups suggests the possible influence of different environmental and host factors characteristic to each group.

6. Socio-economic status

In classifying cancer cases into socio-economic groups the following criteria are conventionally applied: i) skill required in each occupation; ii) average length of schooling in each occupation; iii) average income of each occupation; iv) type of residential area.

The average length of schooling in each occupation was found to be a practical and useful criterion in converting figures by occupation into those by socio-economic classes as the information is readily available from census reports.

Since the fall of 1965, a prospective population study (cohort study) covering 265,118 adults over 40 (91–99% of all the inhabitants of that age in each district) has been in progress in 29 Health Center Districts in 6 prefectures in Japan. Occupational mortality figures in this study were arranged according to the average length of schooling for each occupation group. The result of 3 years' follow-up shows clearly that the standardized death rate for stomach cancer is highest among the lower socio-economic classes, and lowest among the higher socio-economic classes. The standardized stomach cancer death rate was calculated as 92.4 for classes I and II, 113.3 for class III, 118.7 for class IV and 121.0 for class V, the ratio being 1.00, 1.23, 1.28 and 1.31 respectively.

Similar results were obtained by using morbidity data (*6*). In 1958 a cancer morbidity survey was conducted on a nation-wide scale covering 98.8% of all the general hospitals in Japan; 4,187 male cancer cases were tabulated according to occupation for each site of cancer. For cancer of the stomach, the ratio of the number of actual cases to that of expected cases was highest in the lowest socio-economic strata, and lowest in the highest socio-economic strata. For class I the actual number of cases was 91 when 106.4 cases were expected, for class II 157 *vs.* 173.6, for class III 657 *vs.* 697.1, for class IV 352 *vs.* 356.9 and for class V 1,007 *vs.* 932 [illegible] ratio being 1.00, 1.05, 1.09, 1.15 and 1.26 respectively. These data are quite similar to those observed in England and Wales, the U.S. and Denmark (*2, 3, 13*). The fact that the incidence of stomach cancer increases with the decrease of socio-economic conditions indicates the importance of the role of

nutrition or diet closely related to lower socio-economic conditions as a key factor influencing the occurrence of cancer of the stomach.

7. Occupation

The distribution by occupation of 34,742 stomach cancer deaths in 1958 and 1959 was analyzed. An age standardized comparison of actual deaths and expected deaths revealed that cancer of the stomach had a tendency to occur with a significantly higher frequency in agricultural workers (with a mortality ratio of 1.09),** workers in mining and quarrying (1.29),** metal industry workers (1.11),** transportation equipment repair and assembly workers (1.36),** silk reel and textile workers (1.30),** printing and book-binding workers (1.31),** ceramic, clay and stone product workers (1.23),** construction workers (1.23)** and clerical and related workers (1.20).** The disease was found to occur with a significantly lower frequency in technicians and engineers (0.83),* medical and public health technicians (0.73),** managers and officials (0.74),** sales workers (0.96),* wood, bamboo, grass and vine products workers (0.90)** and service workers (0.79).**

The prospective population study described above also showed a significant rise in the standardized mortality rate from stomach cancer among mining workers. The highest rate was noted in workers in mining and quarrying occupations (341.9 per 100,000), the next highest in workers in transport and communications (140.5), in service workers (124.6), and in clerical workers (123.8). The rates for farmers, lumbermen and fishermen (118.2) and craftsmen, production process workers and laborers (116.4) were noted to be higher than those for professional and technical workers (105.2), sales workers (96.1) and managers and officials (65.4).

8. Marital status

The standardized death rate per 100,000 for stomach cancer based on the result of 3 years' follow-up in our study was calculated as 75.1 in single men (observed person-years were 3,262), 116.4 in married men (312,416), 273.6 in separated men (2,386) and 376.3 in widowed men (14,082). Corresponding figures for women were: 0 in single (5,944), 48.6 in married (316,900), 75.3 in separated (8,549) and 88.4 in widowed (84,031).

In summary, the observed epidemiological phenomena provide us with many important clues for the etiological study of this disease. It should be emphasized that these epidemiological characteristics should provide a solid base for formulating an etiological hypothesis of cancer of the stomach. These characteristics should also be used in testing any "existing hypothesis" of the disease.

Analytic Epidemiology

1. Correlation study

a) Diet factors and regional variation—The influence of various foods and drinks on the incidence of stomach cancer can be observed by calculating the

*, ** Significant at the 5% and 1% level, respectively.