Geographic Clustering Patterns in Mortality from Biliary Tract Cancer in Japan

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We calculated the standardized mortality ratios (SMRs) of biliary tract cancer (BTC) in Japan from 1981 to 1990 and statistically analyzed the results according to 333 Secondary Areas of Medical Care, as well as sex and subsite [gallbladder cancer (GBC) and extrahepatic bile duct cancer (BDC)], in order to examine geographic clustering patterns of BTC. In GBC in both sexes, the Secondary Areas of Medical Care with high SMRs were clustered in the eastern part of Japan. In BDC in both sexes, the Areas with high SMRs were clustered between the northern and eastern parts of Japan. In comparison with GBC, this clustering favored the northern part of Japan. In males, the clustering pattern in mortality from BTC was mainly due to the occurrence of BDC. In females, the clustering pattern in mortality from BTC reflected that of GBC. The clustering of BTC, especially GBC, seems to be related to the distribution of plains, basins, and rivers.

Key words: Biliary tract cancer — Gallbladder cancer — Extrahepatic bile duct cancer — Standardized mortality ratio — Geographic clustering pattern

According to the Vital Statistics of Japan, the top cause of death in Japan in 1991 was malignant neoplasm, the total number of deaths being 223,727 (a crude mortality rate of 181.7 per 100,000).1) The proportional mortality ratio of biliary tract cancer (BTC), including gallbladder cancer (GBC) and extrahepatic bile duct cancer (BDC), was 5.6% (number of deaths, 25,768; mortality rate, 10.2).1) However, studies on risk factors for BTC are important because the mortality from BTC is very high in comparison with other countries.2, 3)

Some studies indicate that the geographic distribution of mortality rates from BTC in Japan shows characteristic clustering patterns. Tominaga4) and Yamamoto et al.5, 6) reported that prefectures with high standardized mortality ratios (SMRs) of BTC were clustered in the eastern part of Japan, and the prefecture with the highest SMR was Niigata. Kato et al.7) indicated that clusters of prefectures with high age-adjusted mortality rates (AAMRs) for GBC were observed in the mid-northern part of Japan, and a clear cluster of prefectures with high AAMRs was observed in the northern part of Japan for BDC. Endoh et al.8) mapped the distribution of the SMRs by city and country areas for BTC in Niigata, which was the prefecture with the highest SMR in Japan, and showed that the regions with high SMRs clustered on the Niigata plains, and, even in Niigata, there were some regions with low SMRs. Kato and Akai9) suggested that the high mortality rate from BTC around Niigata city was due to GBC.

Because there are few reports describing national geographical clustering patterns of BTC,5, 10) we have examined in detail the geographical clustering pattern of BTC in Japan, one of the countries with the highest mortality rate from BTC in the world. Here, we present a statistical analysis of the geographical clustering characteristics of mortality from GBC and BDC among 333 Secondary Areas of Medical Care in Japan, as well as according to sex and subsite of the cancer.

MATERIALS AND METHODS

In the ninth revision of the International Classification of Diseases (ICD-9), BTC (ICD-9 156) is divided broadly into GBC (ICD-9 156.0) and BDC (ICD-9 156.1–156.9). Therefore, we calculated SMRs for BTC, GBC and BDC. For the separation of areas, we used the Secondary Areas of Medical Care (341 Areas) in Japan in 1992. The population range with median was between 100,000 and 200,000 in 1991.11) The Areas are defined as groups of cities and towns for efficiently covering inpatient medical needs on the basis of the Medical Service Law. Prefectural government offices selected the Areas on the basis that people in each Area were within the same cultural and daily milieu. In the present study, however, we used 333 Areas because we combined some wards and cities divided by ordinance. We calculated SMRs by Secondary Area of Medical Care although cities and towns were more regular and smaller divisions than prefectures. However, the mortality from BTC was small in individual cities or towns, so division by city or town was unsuitable for the calculation of SMRs.

The mortality rates of BTC, GBC, and BDC by sex and Secondary Area of Medical Care (1981–1990), and the numbers of deaths by sex and age-group in Japan (1981–1990) were provided by the Ministry of Health and Welfare, permission having been obtained from the Agency of General Affairs. The total population in Japan by sex and age-group, and the population by sex, age-group, and Secondary Area of Medical Care were obtained from the National Census in 1985. The age-groups of both numbers of deaths and population were divided into 17 categories: 0–4, 5–9, 10–14, 15–19, 20–24, 25–29, 30–34, 35–39, 40–44,
We calculated the SMRs by sex, subsite (ICD-9 156, 156.0, 156.1–156.9), and Secondary Area of Medical Care as follows:

$$\text{SMR} = \left[ \frac{d}{\sum (ni \times Di) \times 100} \right],$$

in which $d$ = the total numbers of deaths (1981–1990), $ni$ = the population by age-group (1985), and $Di$ = the mortality rate by age-group in Japan, i.e., the total numbers of deaths by age-group (1981–1990)/the total population by age-group (1985).

Then we divided all 333 Secondary Areas of Medical Care using the $\chi^2$ test into three groups in which SMR was significantly higher than the mean ($P<0.05$), not significantly different from the mean and significantly lower than the mean ($P<0.05$). We referred to these three groups as high, medium and low SMR Areas respectively. Finally we mapped the results.

RESULTS

**Biliary tract cancer (ICD-9 156)** For males, 49 Secondary Areas of Medical Care (14.7%) were evaluated as high SMR Areas, 239 (71.1%) as medium SMR Areas, and 45 (13.5%) as low SMR Areas. High SMR Areas were clustered in the eastern part of Japan. On the other hand, low SMR Areas were in the western part (Fig. 1).

For females, 69 Secondary Areas of Medical Care (20.7%) were evaluated as high SMR Areas, 191 (57.4%) as medium SMR Areas, and 73 (21.9%) as low SMR Areas. Although, in comparison with males, there were a few low SMR Areas in the eastern part, the clustered high SMR Areas were the same as those for males in the eastern part of Japan. Again, the clustered low SMR Areas were in the western part (Fig. 2).

**Gallbladder cancer (ICD-9 156.0)** For males, 26 Secondary Areas of Medical Care (7.8%) were evaluated as high SMR Areas, 275 (82.6%) as medium SMR Areas, and 32 (9.6%) as low SMR Areas. High SMR Areas were clustered in the eastern part of Japan, especially along the Japan Sea and the Pacific coast. Low SMR Areas were mainly in the western part, but several low SMR Areas were scattered in the eastern part (Fig. 3).

For females, 54 Secondary Areas of Medical Care (16.2%) were evaluated as high SMR Areas, 214 (64.3%) as medium SMR Areas, and 65 (19.5%) as low SMR Areas. The clustered high SMR Areas were observed in the eastern part, especially in the central region of Japan. This clustering pattern was observed more clearly than in males. On the other hand, low SMR Areas were clustered in the western part of Japan. However, there were clustered high SMR Areas in the southwestern part (Fig. 4).
Fig. 3. Male standardized mortality ratios (SMRs) of gallbladder cancer (ICD-9* 156.0) by Secondary Area of Medical Care during 1981–1990. ■ High SMR Areas; □ Low SMR Areas. *Same as Fig.1.

Fig. 4. Female standardized mortality ratios (SMRs) of gallbladder cancer (ICD-9* 156.0) by Secondary Area of Medical Care during 1981–1990. ■ High SMR Areas; □ Low SMR Areas. *Same as Fig.1.

Fig. 5. Male standardized mortality ratios (SMRs) of extrahepatic bile duct cancer (ICD-9* 156.1–9) by Secondary Area of Medical Care during 1981–1990. ■ High SMR Areas; □ Low SMR Areas. *Same as Fig.1.

Fig. 6. Female standardized mortality ratios (SMRs) of extrahepatic bile duct cancer (ICD-9* 156.1–9) by Secondary Area of Medical Care during 1981–1990. ■ High SMR Areas; □ Low SMR Areas. *Same as Fig.1.
Extrahepatic bile duct cancer (ICD-9 156.1–9) For males, 60 Secondary Areas of Medical Care (18.0%) were evaluated as high SMR Areas, 240 (72.1%) as medium SMR Areas, and 33 (9.9%) as low SMR Areas. High SMR Areas were clustered between the northern and eastern parts of Japan. Low SMR Areas were observed in the western part. In comparison with GBC, the cluster of high SMR Areas was found to be more toward the northern part of Japan than that of GBC, in the same way as in males. On the other hand, low SMR Areas were observed in the western part. However, in comparison with males, more high SMR Areas were dotted in the western part. Although there were some scattered low SMR Areas in the northern part in the case of GBC, such a pattern was not observed in the case of BDC (Fig. 5).

Geographical features Fig. 7 shows the distribution of large plains, basins, and rivers in Japan.

For females, 56 Secondary Areas of Medical Care (16.8%) were evaluated as high SMR Areas, 244 (73.3%) as medium SMR Areas, and 33 (9.9%) as low SMR Areas. The clustering of high SMR Areas was found to be more toward the northern part of Japan than that of GBC, in the same way as in males. On the other hand, low SMR Areas were observed in the western part. However, in comparison with males, more high SMR Areas were dotted in the western part. Although there were some scattered low SMR Areas in the northern part in the case of GBC, such a pattern was not observed in the case of BDC (Fig. 6).
and/or basins was higher in high SMR Areas, the difference was not statistically significant.

In GBC in females, 45 (83.3%) Secondary Areas of Medical Care among 54 high SMR Areas contained plains and/or basins, and almost all of them had large rivers too. On the other hand, 35 (53.8%) Areas among 65 low SMR Areas had plains and/or basins. The ratio with plains and/or basins was significantly higher in high SMR areas (P < 0.05).

In the case of BDC in both males and females, no statistically significant differences were observed.

**DISCUSSION**

Previous reports have described the geographical clustering characteristics of mortality from BTC in Japan, and we examined these clustering patterns in detail. Endoh et al. suggested that the clustering pattern in mortality from BTC in Niigata more closely reflected that of GBC than that of BDC. Kato and Akai also demonstrated that the clustering pattern of BTC in Niigata was mainly due to the occurrence of GBC, not BDC.

In the present study, the clustering pattern of mortality from BTC in females reflected more closely that of GBC than that of BDC. Among 69 high SMR Areas for BTC, 30 were high SMR Areas for GBC alone; on the other hand, 19 were for BDC alone. In males, however, the clustering pattern of mortality from BTC was mainly due to the occurrence of BDC. Among 49 high SMR Areas for BTC, only seven were high SMR Areas for GBC alone, while 29 were for BDC alone. Overall, GBC amounted to 60% of BTC in females, and BDC to 60% of BTC in males. Therefore, it is necessary to discuss separately the clustering patterns of GBC and BDC.

Regarding the causes of these geographical clustering patterns, there are several known risk factors of BTC, such as ethnic groups, some diseases, including cholelithiasis (especially in GBC), anomalous arrangement of the pancreaticobiliary tract, cholecystitis or cholangitis caused by typhoid fever, and clonorchiasis (especially in BDC), and the variability of diagnoses. Frequent ingestion of animal proteins and fats is a low risk factor of GBC. Although a single predominant factor may not exist, studies of regional difference are of interest because most people are of the same ethnic group in Japan, there is no correlation between mortality from BTC by prefecture and prevalence of cholelithiasis by prefecture in Japan, the regional difference in mortality from BTC is observed even after allowing for the effects of the variability of diagnoses, and the consumption of animal proteins and fats has been increasing throughout Japan.

Yamamoto et al. reported that some phenoxy and diphenylether herbicides were found to be frequently associated with SMRs for BTC. It was reported that the levels of pollution with some diphenylether herbicides in faucet water were well correlated with SMRs of BTC in the Niigata plains. We found that the clustering of GBC, especially in females, is related to the distribution of plains, basins, and rivers. We now need to study the relevance of various factors related to plains, basins, or rivers, e.g., water quality or agricultural chemicals. At the same time, we need to discuss why there are both high and low SMR Areas together in the same plains, such as in the Kanto plains. Yamamoto et al. are studying the hypothesis that regions in Niigata with high and low SMRs of BTC are supplied with water from different sources.

At present, we cannot obtain BTC mortality data for smaller areas than the Secondary Areas of Medical Care, so the results in the present study should be useful in generating and testing hypotheses about the epidemiology of BTC, especially GBC.

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