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Epidemiology of Biliary Tract Cancer in Japan: Descriptive Studies

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Summary. **Descriptive studies on Biliary Tract Cancer (BTC) were reviewed from viewpoints of distribution by space, time and person. Standardized Mortality Ratios (SMRs) for BTC in Japan ranked second in males and fifth in females among 39 countries. SMRs for both sexes in Niigata Prefecture was the highest among 47 prefectures in Japan. Increasing rates of SMRs for BTC were the highest among 9 sites of cancer in males and 11 sites in females. By using birth cohort analysis, BTC showed both 'Age Effect' and 'Cohort Effect'. As personal factors, the role of gender, gallstone and food consumption was taken into consideration on the onset of BTC.**

INTRODUCTION

Descriptive epidemiology is assigned the fundamental role of data aggregation and analysis, according to the schema for an epidemiological study cycle as shown in Fig. 1.[1] Although it is difficult for an investigator to pursue the ultimate cause or causes of a disease only through descriptive data, the results derived from the data lead investigator to the next phase of model-building and formation of hypotheses. After analytical studies are carried out, additional descriptive studies are sometimes necessary to produce new hypotheses, as is shown in the fourth phase of the schema. The cycle of study resembles the feedback systems in a human body. The main task of descriptive epidemiology is to elucidate the distribution of a disease by space, time and person.

Epidemiological studies of biliary tract cancer (BTC) have been conducted in our laboratory over the past decade. The trigger which evoked our studies is the fact that Niigata Prefecture, where we live, has the highest mortality rate for BTC among 47 prefectures in Japan.[2] We believe that it is our priority to decribe the distribution of BTC and then to specify a determinant or determinants of the higher occurrence

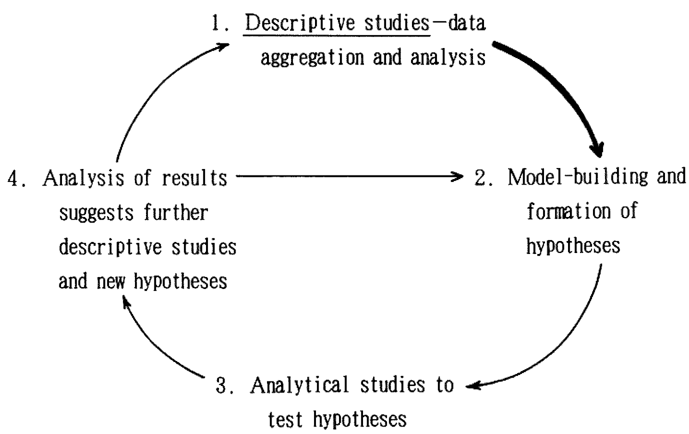

Fig. 1. Schema for an epidemiological study cycle (from Mausner, J. S. and Kramer, S., 1985)

of BTC in our prefecture.

BTC, including gallbladder cancer (GBC) and extrahepatic bile duct cancer (BDC), still draws less attention than other sites of cancer in epidemiological studies in Japan, probably because of its low proportional mortality ratio (5.46% in 1990). Nevertheless, from an epidemiological viewpoint, BTC seems to be an intriguing field for investigation based on the flow of an epidemiological study cycle, since its geographic distribution of death rates shows quite a characteristic clustering pattern.

It is our main purpose in the present paper to digest the results accumulated in our previous epidemiological studies. First of all, we focus on the distribution of deaths from BTC in the world, Japan and Niigata Prefecture in particular using demographic data. Secondly, trends for mortality rates for BTC are presented by using a birth cohort analysis. Thirdly, personal factors are mentioned with the results of data analyses. Details of analytical studies after model-building and formation of hypotheses have been reviewed by Yamamoto et al.[3] elsewhere.

DISTRIBUTION BY SPACE

1. Standardized mortality ratios (SMRs) in the world

The demographic data on BTC in 39 countries were offered from WHO. The study period was from 1981 through 1986. We compensated for the lack of reported data by estimations based on the assumption that the supplied data may reveal the average from 1981 to 1986.[4] The world population by sex and age in each year of the period was then obtained from the Demographic Yearbook.[5] The indirect method was applied for age-adjustment to calculate SMRs. The male- and female-specific standard populations and corresponding standard death numbers were obtained by adding up sex- and age-specific populations and respective death numbers in 39 countries. Because some of the countries reported only the numbers of BTC (International Classification of Diseases; ICD 156) to WHO, it was not possible to compute SMRs for GBC (ICD 156.0) and BDC (ICD 156.1-9) separately.

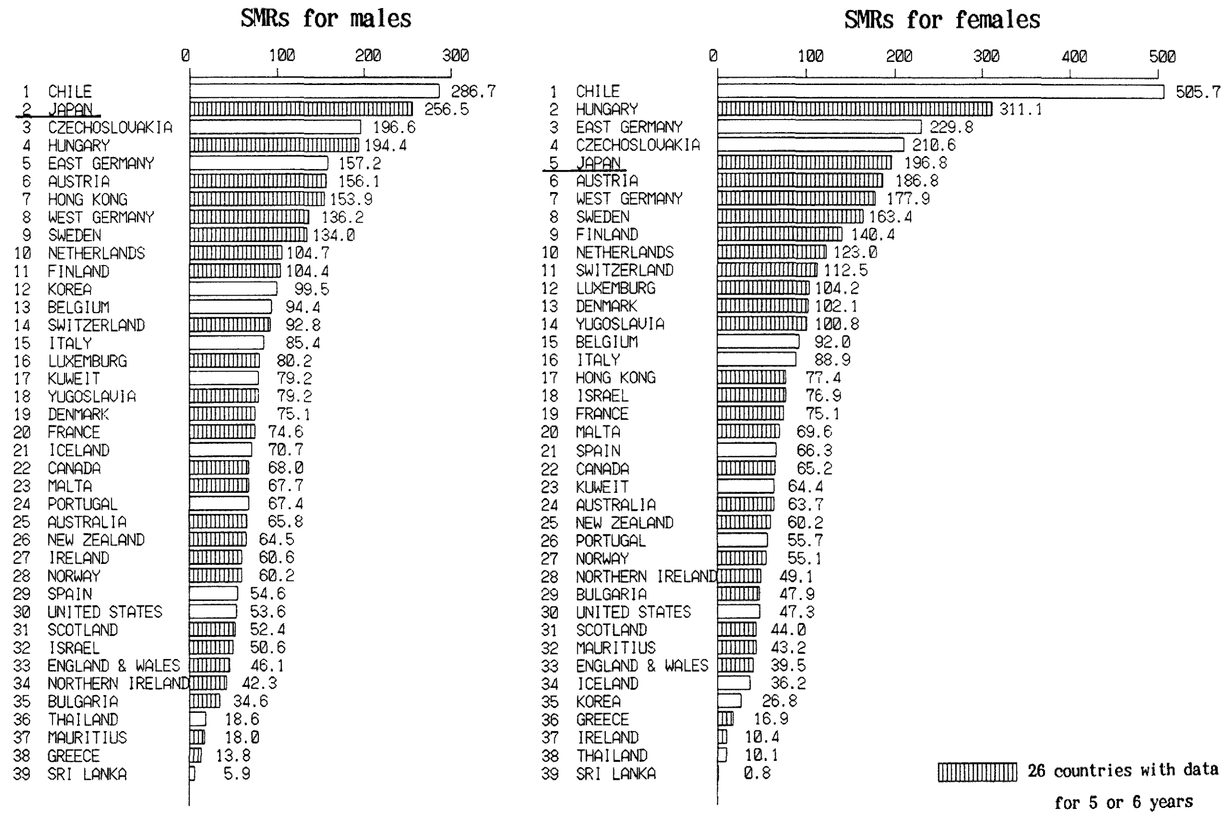

Fig. 2. Standardized mortality ratios (SMRs) of biliary tract cancer for both sexes among 39 countries during 1981-1986.

The results of SMRs for BTC are shown in Fig. 2. In males, the five countries with the highest SMRs are Chile (286.7), Japan (256.5), the former Czechoslovakia (196.6), Hungary (194.4) and former East Germany (157.2). In females, they are Chile (505.7), Hungary (311.1), East Germany (229.8), Czechoslovakia (210.6) and Japan (196.8). The SMRs of Japan corresponded to the second and fifth places in the world for males and females, respectively.

There were 14 countries with complete mortality data on BTC during 1981-1986 and 12 with those for 5 years during the period. A total of 26 countries, whose reporting of death certificates can be considered to be relatively well-documented, are shown with hatched bars in Fig. 2. Among those countries, Japan occupies the first and second places for males and females, respectively.

By using Pearson's Product Moment Method, the correlation coefficients of SMRs between males and females were computed at 0.885 (Fig. 3) and 0.843 among the 39 and 26 countries respectively. Because both of the coefficients are evaluated with high statistical significance ($p < 0.001$), common factors independent of sex have the highest priority as risk factors of BTC.

2. SMRs in Japan

The mortality data on BTC (1981-1986) was obtained

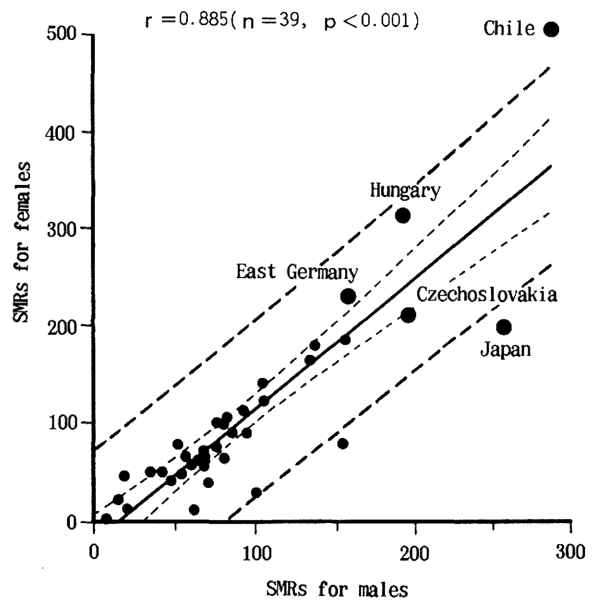

Fig. 3. Correlation of standardized mortality ratios (SMRs) of biliary tract cancer between males (X-axis) and females (Y-axis).

from the Vital Statistics of Japan,[6,7] and the total populations of Japan in 1980 and 1985 were from the National Census. The standard population by sex and age each year was estimated by an extrapolating method from the census population. The indirect method was then applied to calculate SMRs for each of the 47 prefectures.

Fig. 4 shows the distribution of SMRs for BTC by prefecture in Japan. The top five prefectures with high SMRs in males are Niigata (131.8), Yamagata (126.3), Aomori (123.6), Akita (121.5) and Nagasaki (119.6). In females, they are Niigata (143.1), Aomori (130.4), Yamagata (129.7), Fukushima (127.1) and Yamanashi (124.9).

In general, SMRs for both sexes showed a similar pattern of geographic distribution with a few exception. A clustering of prefectures with high SMRs was observed in the northeastern part of Japan. Among those prefectures, SMRs for both sexes in Niigata were the highest. These findings correspond to the previous study by Tominaga.[8]

Correlation coefficient of SMRs between males and females among the 47 prefectures in Japan was computed at 0.820 with high statistical significance ($p < 0.001$).

3. SMRs in Niigata

Mortality data on BTC (1981-1990) in Niigata Prefecture were collected from the death certificates for vital statistics. Although they were listed separately as GBC, BDC and BTC in 112 cities, towns and villages, they were combined as BTC in 36 cities and counties which are comprised of towns and villages, because of the paucity of deaths. The census population of Japan in 1985 was used as a standard to calculate SMRs by applying the indirect method.

Fig. 5 shows the geographic variation of SMRs for both sexes. Despite few exceptions, Arai City and Sado County in males, clustered areas with high SMRs were observed on the Niigata plains, an area famous for rice production. The hypothesis proposed by Yamamoto et al.[9] was derived from that pattern, as mentioned in detail elsewhere.[3] The Niigata plains may be particularly worthy of attention, because there is no other area reported in the world to show a clustering of BTC mortality.[10]

The clustering pattern was more distinct in females than in males and in GBC than in BDC.[11] Kato et al.[12] also demonstrated that the clustering pattern of BTC was mainly due to the occurrence of GBC instead of BDC, by means of the analysis of the registered clinical cases. It should be pointed out that,

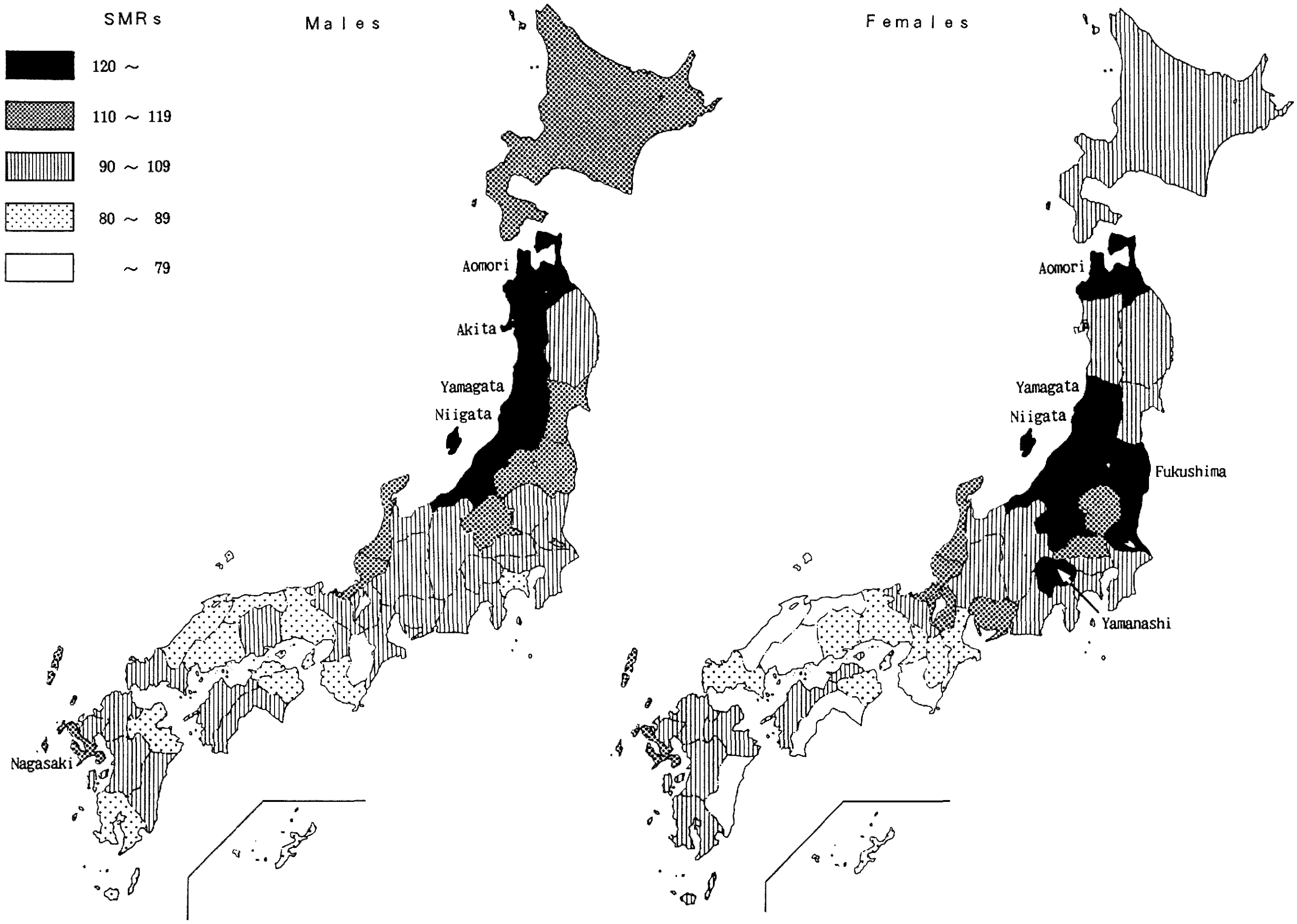

Fig. 4. Standardized mortality ratios (SMRs) of biliary tract cancer for both sexes by prefecture in Japan during 1981-1986.

even on the Niigata plains, there are some cities —Murakami, Gosen and Kamo—with relatively low SMRs. This may give us a clue for clarifying the causes of BTC to investigate the difference between cities and counties with high SMRs and those with relatively low SMRs in Niigata Prefecture.

DISTRIBUTION BY TIME

1. Trends of cancer mortality in Japan

The trends of mortality from major sites of cancer during 1955-1990 are shown in Fig. 6. Data were extracted from Vital Statistics.[13] The direct method was applied to calculate the age-adjusted mortality rates for excluding the influence of an aging population. There were no data on BTC deaths until 1958, when the 8th revision of ICD was adopted and BTC was recorded apart from liver cancer.

The adjusted mortality rates of BTC for both sexes have increased year by year. In 1990, BTC occupied the 8th and 5th places in males and females, respectively.

2. Trends of SMRs by cancer site

Because the starting year for the calculation of BTC mortality rate differs from other cancer sites, its increase is not so impressive in comparison with that of lung cancer. Using the census population in 1960 as a standard, SMR for each cancer was calculated again every 5 years during the study period to avoid the influence of fluctuations of cancer deaths by year. The middle year of the 5-year period is designated to represent its period (e.g. in 1960 instead of during 1958-1962). The SMR for each site in 1960 was fixed to 100. SMRs of every period (1965, 1970, 1975, 1980 and 1985) indicate the increasing tendency of cancer

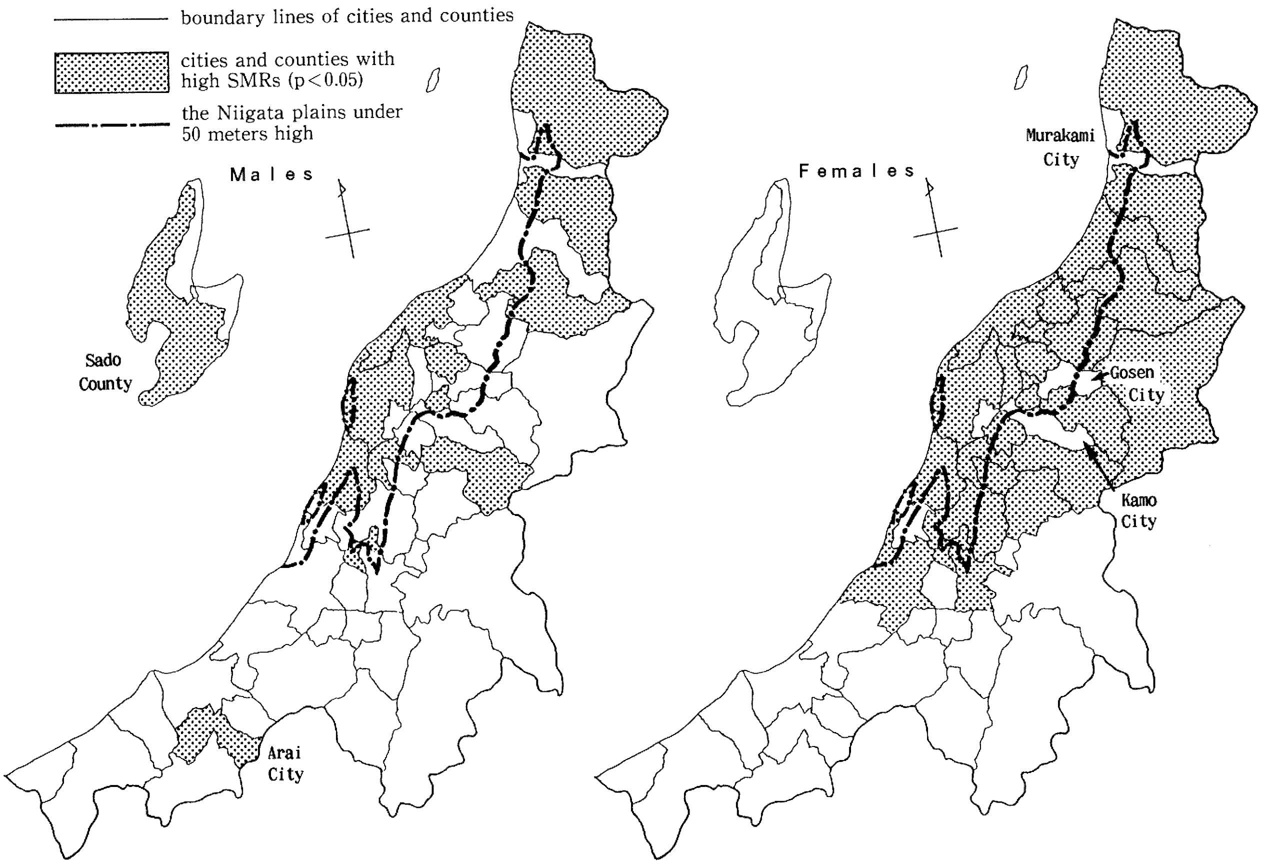

Fig. 5. Standardized mortality ratios (SMRs) of biliary tract cancer for both sexes by city and county in Niigata Prefecture during 1981-1990.

mortality.[14]

Those in males are shown in Fig. 7. The SMR of BTC in 1985 was 358.9, the highest among 9 sites of cancer studied, indicating that BTC mortality has risen about 3.6 times over the past 25 years. Although the adjusted mortality rate of BTC in 1990 (Fig. 6) was not very high, its increasing rate exceeded those of lung, pancreas, and colon cancer. SMR of BTC in females (Fig. 8) was 395.0 in 1985, also the highest among 11 sites of cancer, followed by the pancreas, lung and colon.

3. Trends of SMRs from BTC by prefecture

The procedure mentioned above was applied to calculate SMRs by prefecture.[14] The SMRs of all Japan in males (Table 1) were 100, 149.9, 191.2, 236.1, 292.3, 358.9 in every 5-year period, respectively. The top five prefectures with high SMR in 1960 were Miyagi, Akita, Niigata, Aomori and Iwate; in 1985, their SMRs increased to 378.8 (20th place), 437.8 (2nd), 460.5 (1st), 432.3 (4th) and 410.7 (7th), respectively. The prefectures which entered within the top five for the first time in 1985 are Nagasaki (17th to 3rd) and Fukushima (8th to 5th). Niigata Prefecture overtook Miyagi Prefecture in 1975 and has since been in the 1st place.

The SMRs of all Japan in females (Table 2) were 100, 157.0, 207.3, 259.7, 323.8 and 395.0. The prefectures with high SMR in 1960 were Miyagi, Niigata, Gunma, Fukushima and Aomori, and their SMRs increased to 378.8 (20th place), 437.8 (2nd), 460.5 (1st), 432.3 (4th), 410.7 (7th), respectively in 1985. Yamagata Prefecture rose from the 6th place to 3rd. Niigata Prefecture has also claimed the 1st place since 1970.

The increasing rate of SMR for BTC in Niigata Prefecture from 1960 to 1985 is computed to be 245.6% for males and 284.1% for females, with both rates lower than those for all of Japan. The range of SMRs (Maximum-Minimum) becomes smaller; however, SMRs for both sexes are still the highest in Niigata Prefecture.

Because the prefectures with high SMRs are located in the northeastern part of Japan (except for

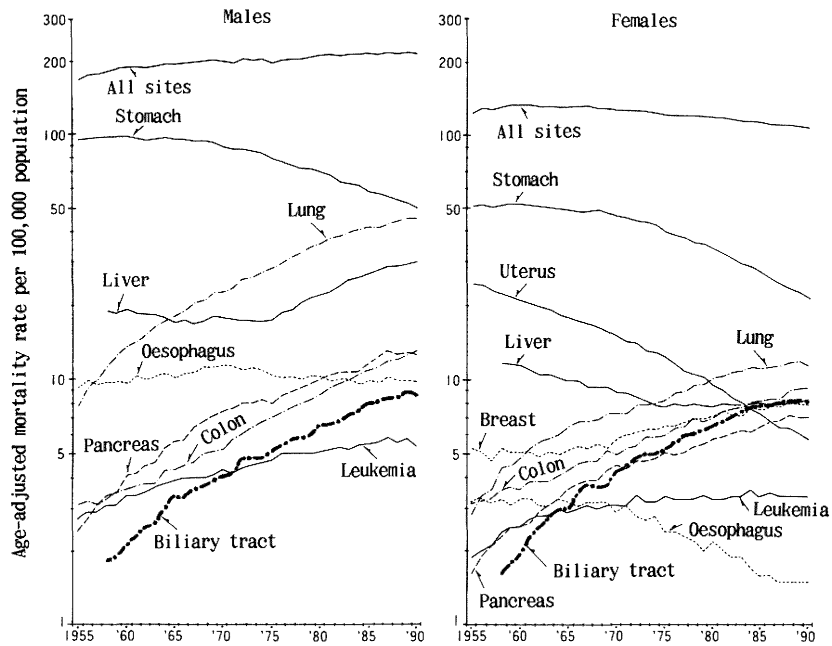

Fig. 6. Trends of age-adjusted mortality rates by cancer site in Japan. (from Ministry of Health & Welfare, 1992).

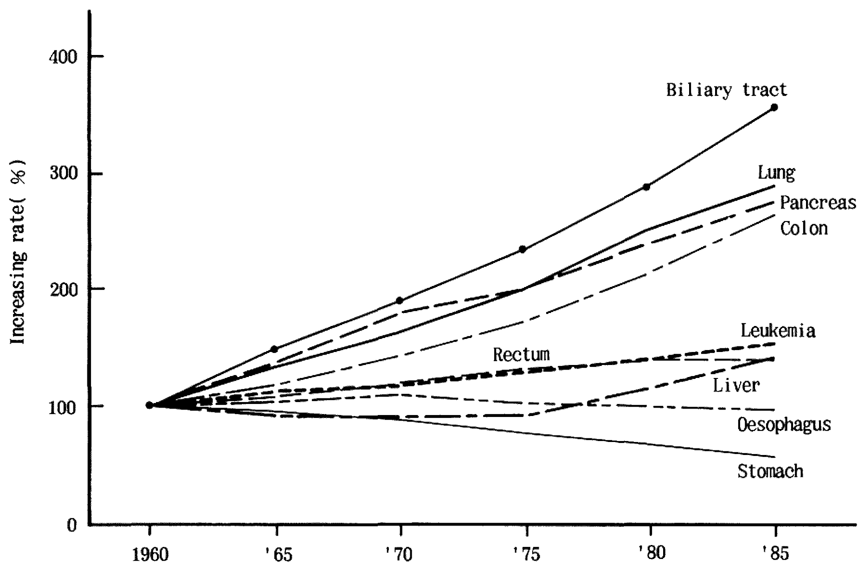

Fig. 7. Increasing rates (%) of cancer mortality by site in males. Note: The middle year of the 5-year period is designated to represent its period, e.g. 1960 instead of during 1958-1962.

Table 1. Trends and increasing rates (%) of standardized mortality ratios (SMRs) for biliary tract cancer in leading prefectures for males.

Prefecture	Trends of SMRs (rank among 47 prefectures)						Increasing Rate (%)[b] of SMRs
	1960[a]	1965	1970	1975	1980	1985	
All Japan	100.0	149.9	191.2	236.1	292.3	358.9	358.9
Miyagi	254.8(1)	307.7(2)	341.4(1)	350.4(2)	342.1(8)	378.8(20)	148.7
Akita	204.6(2)	218.9(3)	287.1(3)	306.7(5)	355.3(6)	347.8(6)	214.0
Niigata	187.5(3)	311.5(1)	331.0(2)	373.5(1)	408.7(1)	460.5(1)	245.6
Aomori	150.6(4)	212.3(4)	269.2(4)	347.1(3)	377.3(3)	432.3(4)	287.1
Iwate	142.8(5)	150.0(19)	252.8(5)	266.0(12)	334.2(9)	410.7(7)	287.6
Fukushima	134.2(8)	185.1(8)	244.4(8)	281.2(8)	316.9(16)	414.5(5)	308.9
Nagasaki	99.3(17)	147.3(20)	161.2(34)	223.3(27)	358.1(5)	436.8(3)	439.9

[a] The middle year of the 5-year period is designated to represent its period. (e.g. 1960 instead of during 1958-62)
[b] Rate of increase was calculated by dividing SMR value in 1985 by that in 1960.

Table 2. Trends and increasing rates (%) of standardized mortality ratios (SMRs) from biliary tract cancer in leading prefectures for females.

Prefecture	Trends of SMRs (order among 47 prefectures)						Increasing Rate (%)[b] of SMRs
	1960[a]	1965	1970	1975	1980	1985	
All Japan	100.0	157.0	207.3	259.7	323.8	395.0	395.0
Miyagi	223.6(1)	299.8(1)	305.6(3)	321.7(5)	351.5(18)	383.5(26)	171.5
Niigata	195.1(2)	288.4(3)	347.8(1)	474.9(1)	518.4(1)	554.3(1)	284.1
Gunma	169.3(3)	294.6(2)	325.5(2)	379.2(3)	416.6(5)	491.1(5)	251.7
Fukushima	151.6(4)	242.9(5)	303.9(5)	404.4(2)	449.4(2)	491.9(4)	324.5
Aomori	144.0(5)	202.2(8)	305.4(4)	351.7(4)	395.4(8)	509.1(2)	353.5
Yamagata	139.6(6)	201.8(9)	219.1(14)	259.8(23)	410.8(6)	506.3(3)	362.7

[a] The middle year of the 5-year period is designated to represent its period. (e.g. 1960 instead of during 1958-62)
[b] Rate of increase was calculated by dividing SMR value in 1985 by that in 1960.

Nagasaki Prefecture) and there was almost no change in this pattern between in 1960 and 1985, the possible causes of BTC should be investigated among factors which existed at least 25 years ago.

4. Analysis of birth cohort

On the basis of demographic data taken from 1958 to 1987, the age-specific death rates for BTC were computed for every 5-year period by using age-specific populations of the census (1960, 1965, 1970, 1975, 1980 and 1985). The numbers of BTC deaths were divided into 10 age-groups: under 40, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84, and 85 years and over.[14] Age-specific mortality rates in males are shown with solid lines in Fig. 9. Age-groups with the highest rates elevated gradually, from 70-74 years of age in 1960, 75-79 in 1965, 1970, 80-84 in 1975, 1980 to 85 years and over in 1985.[15]

A person who was born in 1896-1900 would advance in age to 60-64 in 1960, and then 65-69, 70-74, 75-79, 80-84 and 85 years and over in 1965, 1970, 1975, 1980 and 1985, respectively. A method to pursue the trend of mortality rates of an age-group born during a particular time period (calendar years) is called the Birth-Cohort Analysis,[16] and the results of the analysis in this study are shown with broken lines in Fig. 9. If the mortality rates of a birth-cohort group increase according to the rise in age, i.e. the broken lines show an upward tendency, and 'Age Effect' is regarded to be positive from an epidemiological viewpoint. On the other hand, if they are higher than those of the cohorts born earlier from all age-groups, i.e. the broken lines become steeper, the 'Cohort Effect' can be said to be positive.

The mortality rates also in females revealed both a

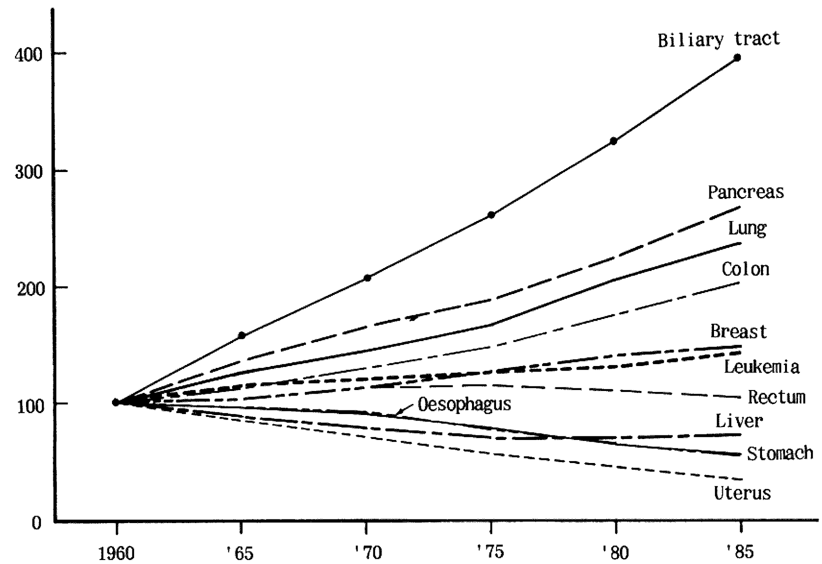

Fig. 8. Increasing rates (%) of cancer mortality by site in females. Note: The middle year of the 5-year period is designated to represent its period, e.g. 1960 instead of during 1958-1962.

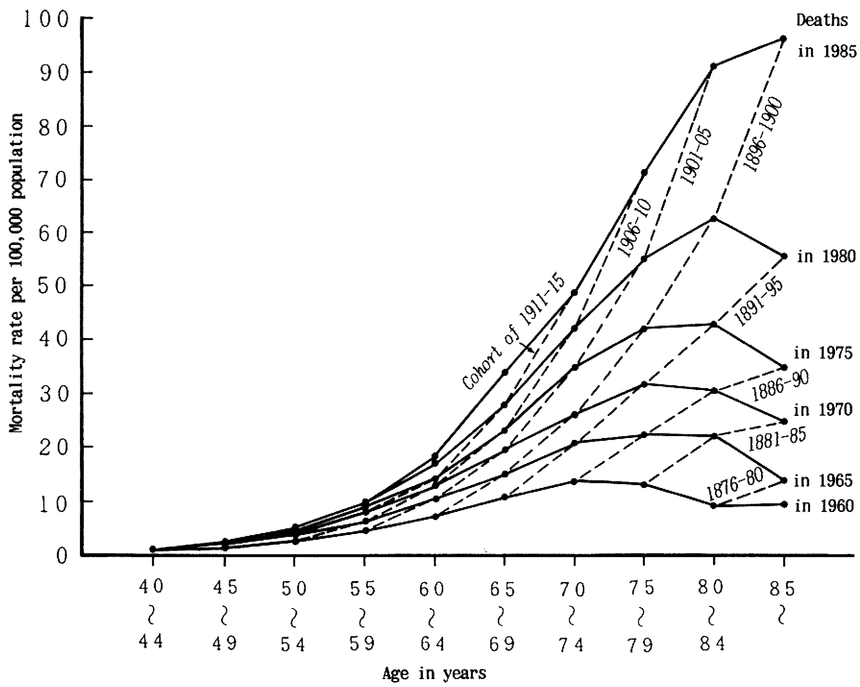

Fig. 9. Birth cohort analysis of biliary tract cancer in males.

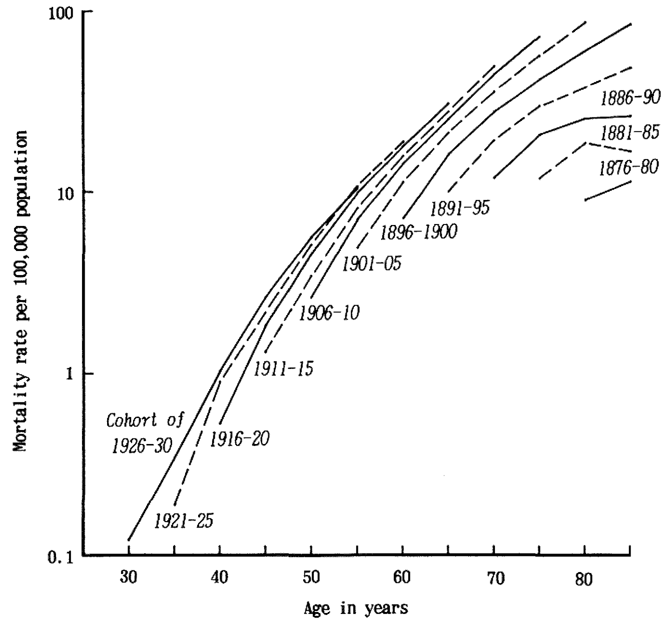

Fig. 10. Birth cohort analysis of biliary tract cancer in females by using logarithmic scale on the Y-axis.

positive 'Age Effect' and 'Cohort Effect' (data not shown). The results in females is illustrated in Fig. 10 to clarify the trends of the birth-cohort groups by using a logarithmic scale on the Y-axis. The solid line of the current cohort born in 1926-1930 is almost overlapped with the broken line of the cohort in 1921-1925. Though the age-adjusted mortality from BTC may decrease in the near future, the real number of BTC cases may increase according to the aging of the Japanese population. It should be pointed out that the effectiveness of a birth cohort analysis is limited because the rates of the current cohort cannot be tracked to the end of the life span.[16]

DISTRIBUTION BY PERSON

1. Sex

GBC was designated as one of the few cancers in which women are at greater risk than men, with the risk to men being two to six times greater.[17] BTC mortality rates (1981-1990) by sex and site in Japan are shown in Fig. 11. Mortality rates from GBC in females with solid circles (●)are higher in all age-groups than those in males with open circles (○). In contrast, those from BDC in males (△) are higher than those in females (▲). The sex ratio of BTC in total is almost 1 : 1 in Japan.

This predominance of GBC in females was explained by the fact that the prevalence of gallstone in females is higher than that in males.[18]

2. Gallstone

Controversial results have been reported on the association between gallstones and BTC. On the basis of autopsy records in Japan, the proportional rate with gallstone among BTC cases was three to eight times as high as that of other cases; however, there was no positive correlation between the rates of gallstone and BTC mortality by prefecture.[8]

Fig. 12 shows the trend of the estimated rates of patients with biliary tract diseases and with cholelithiasis and cholecystitis.[19] The straight lines of the rates on the figure do not demonstrate an upward tendency in recent years, and the broken line of the percentage stays at almost a constant level. As the result of the birth cohort analysis of gallstone in females, Fig. 13 shows the negative cohort-effect in all ages, in contrast to the positive age-effect in some birth-cohorts. Because the risk of gallstone mortality in Japan has not increased by calendar year, there is no evidence that cholelithiasis works as a direct factor at the onset of BTC.

3. Food consumption

On the basis of the National Survey of Family In-

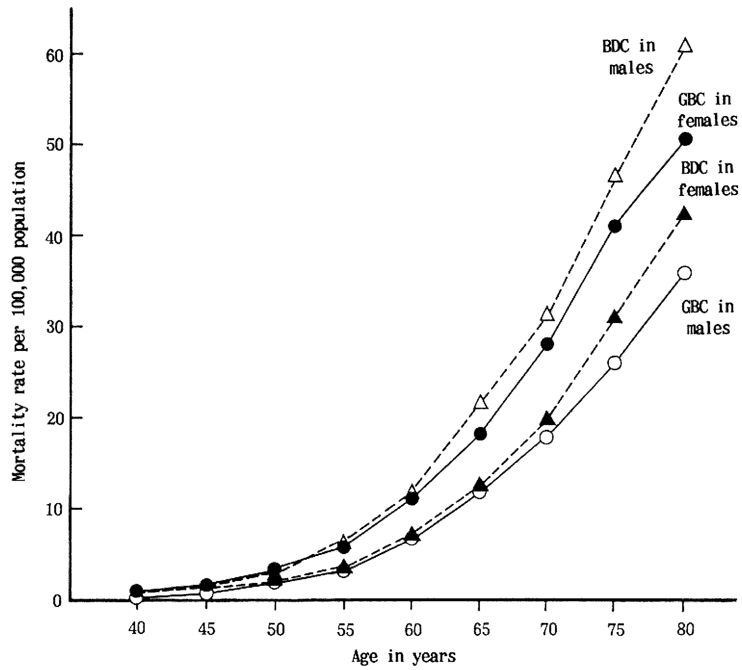

Fig. 11. Age-specific mortality rates for biliary tract cancer (BTC) by sex and site in Japan during 1981-1990. GBC; Gallbladder cancer, BDC; Bile duct cancer.

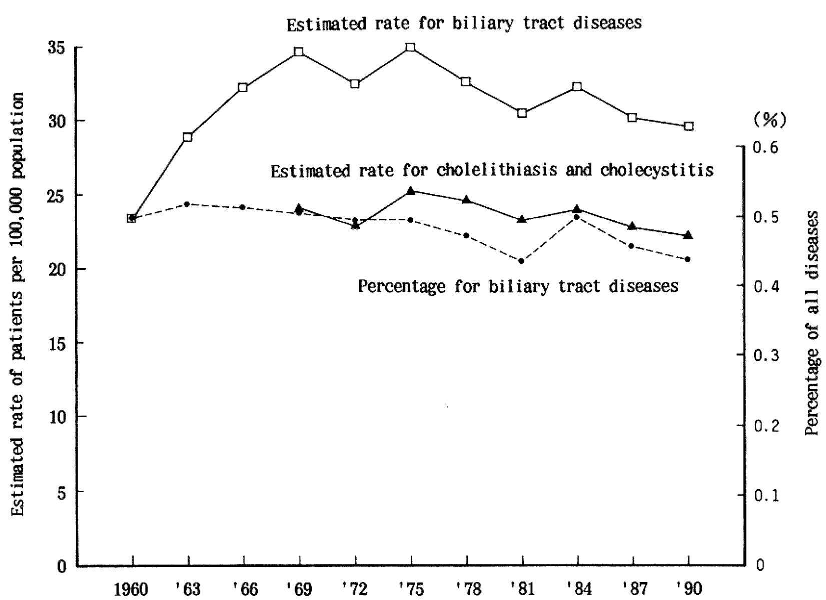

Fig. 12. Trends in the estimated rates of patients and the percentage of all diseases for biliary tract diseases during 1960-1990. Note: Three-year moving averages were calculated during 1959-1982. The survey has been carried out every 3 years since 1984.

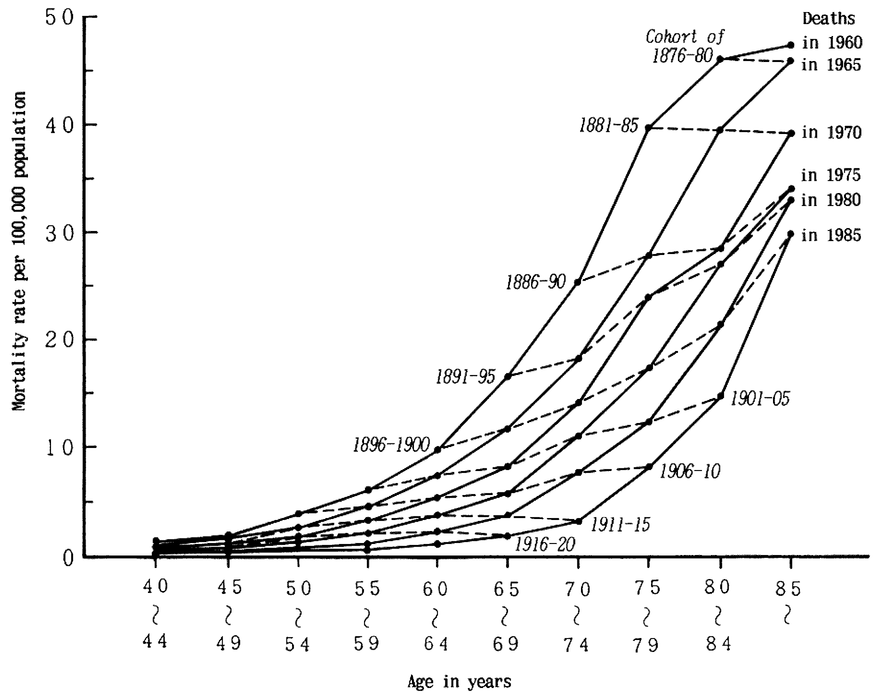

Fig. 13. Birth cohort analysis of gallstone in females.

Table 3. Correlation coefficients between SMRs[a] for BTC[b] in 1985 and food indicators amomg 46 (in 1969) or 47 (in 1974) prefectures.

Food indicators	in 1969 (n=46)		in 1974 (n=47)	
	Males	Females	Males	Females
Rice	0.130	0.245	0.214	0.196
Bread	−0.421−**[c]	−0.325−*	−0.484−***	−0.378−**
Boiled noodles	−0.212	−0.066	−0.201	−0.176
Dried noodles	0.430 **	0.539 **	0.270	0.437 **
Fresh fish	−0.073	−0.156	−0.190	0.068
Beef	−0.600−***	−0.507−***	−0.564−***	−0.508−***
Pork	0.280	0.409 **	0.094	0.253
Ham	−0.390−**	−0.106	−0.313−*	−0.132
Eggs	−0.517−***	−0.482−***	−0.550−***	−0.542−***
Fresh vegetables	0.123	0.308 *	0.073	0.187
Salt	0.654 ***	0.512 ***	0.538 ***	0.459 **
Sugar	0.025	−0.239	−0.016	−0.367−*
Dairy products	−0.501−***	−0.242	−0.372−*	−0.168
Cod roe	0.555 ***	0.622 ***	0.581 ***	0.627 ***
Alcoholic beverages	0.285	0.273	0.419 **	0.315 *

[a] SMRs; standardized mortality ratios, [b] BTC; biliary tract cancer
[c] statistical significance: *$p<0.05$, **$p<0.01$, ***$p<0.001$

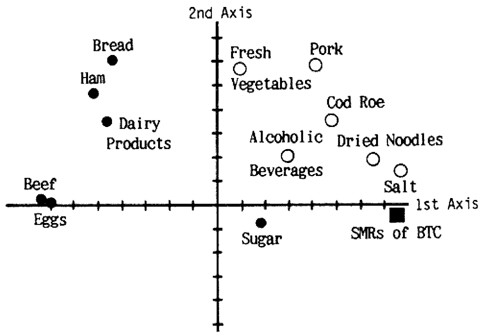

Fig. 14. Association between food indicators in 1969 and male standardized mortality ratios (SMRs) of biliary tract cancer (BTC) in 1985 by using principal coordinating analysis.

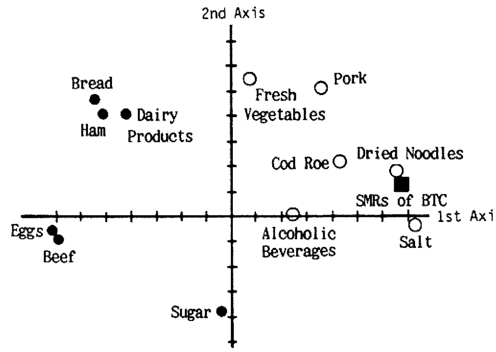

Fig. 15. Association between food indicators in 1974 and female standardized mortality ratios (SMRs) of biliary tract cancer (BTC) in 1985 by using principal coordinating analysis.

come and Expenditures in 1969 and 1974,[20] indicators of food consumption were obtained to calculate the correlation coefficients between those of 46 (in 1969) or 47 (in 1974) prefectures and their SMRs for BTC in 1985. An indicator was presented as the average of the expenditure or quantity of food per household per month. Among the total 15 types of indicators, 12 with significant correlation coefficients were selected as explanatory variables for Principle Coordinating Analysis.[21]

The kinds of foods which had a positive correlation with SMRs for BTC are dried noodles, pork, fresh fish, salt, cod roe and alcoholic beverages, and those which had a negative correlation are bread, boiled noodles, beef, ham, eggs and dairy products (Table 3). The analysis is designed to display the relationship between the explanatory variables (food consumption) and a criterion variable (SMRs of BTC) in the two-dimensional space; a factor with a close relation to another factor is displayed at a closer distance. According to the results of the analysis in this study, Figs. 14 and 15 reveal that SMRs in both sexes are more closely related to salty foods such as cod roe and salt itself, and are not so closely related to bread, beef, ham, eggs and dairy products.

Tominaga[8] suggested that the northeastern part of Japan where mortality from BTC is high adopted Westernized eating habits at a later date. Further findings from a case-control study on this matter were presented by Kato et al.[22]

4. Other factors

There might be a limitation clarifying the causes of BTC only by the descriptive epidemiology mainly based on demographic data, because there are many factors which are considered to have close associations with the etiology of BTC such as occupation,[23] female sex hormones,[24] bacterial infection,[25] agricultural chemicals[26] and a genetic factor.[27] The positive causal factors of BTC have been reviewed and examined by Yamamoto et al. elsewhere[3] from a viewpoint of analytical epidemiology.

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