Jpn. J. Cancer Res. 80, 932–938, October 1989

A Case-Control Study of Biliary Tract Cancer in Niigata Prefecture, Japan

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A case-control study of biliary tract cancer was conducted in Niigata prefecture where the mortality of the cancer is the highest in Japan. The cases were 109 patients with gallbladder cancer and 84 with bile duct cancer, and the controls were 386 sex- and age-matched neighborhood controls. For gallbladder cancer, a past history of biliary tract disease, a positive family history of cholelithiasis and a taste for oily foods were high risk factors. Intakes of animal proteins and fats such as fish, eggs, meat, etc., ingestion of vegetables and fruits, and taking snacks were low risk factors for gallbladder cancer. For bile duct cancer, a past history of biliary tract disease, a family history of cerebral vascular accident, a thin constitution and taking a small amount of foods were high risk factors, and a family history of heart disease, obesity, intakes of alcohol, animal proteins and fats, or frequent intakes of vegetables and fruits were low risk factors.

Key words: Biliary tract cancer — Gallbladder cancer — Bile duct cancer — Risk factors — Case-control study

Biliary tract cancer is still a relatively rare cancer in Japan, but the Japanese, especially Japanese males, show the highest mortality of this cancer in 31 countries.[1] The relatively high mortality of biliary tract cancer in Japan was confirmed by recent vital statistics.[2] Previously, we suggested that the age-adjusted mortality rates for both gallbladder cancer and bile duct cancer were increasing in Japan, but the rate for gallbladder cancer was higher in females than in males and the rate for bile duct cancer was higher in males than in females.[1] Furthermore, the gallbladder and the bile duct have different physiologic functions in bile metabolism and flow. Therefore, it is likely that etiological factors are partly different between these two cancers.

Little has been reported about the etiology of biliary tract cancer,[3–5] except a close association with gallstones.[3, 7–12] Some other factors such as obesity,[12, 13] pregnancy,[13–17] female sex hormones,[18–23] workers in rubber and some other chemical industries[24–26] and genetic factors[4–6, 27–30] have been suspected to be associated with gallbladder cancer directly or indirectly through cholelithiasis.

Although the role of diet in the pathogenesis of biliary tract cancer still remains unclear, we speculate that dietary habits which influence bile metabolism and flow may be related to the risk of this disease. From a correlation analysis conducted in Japan it was suggested that larger consumptions of dried noodles and pork were positively associated with biliary tract cancer, and fat and protein-rich western-type foods were negatively associated with this cancer.[1] These possible associations needed further clarification by analytical epidemiology. Thus, in order to study more precisely the relationship between various environmental factors, especially dietary habits, and biliary tract cancer, i.e., gallbladder cancer and bile duct cancer, we conducted a case-control study of biliary tract cancer in Niigata prefecture where the mortality of this cancer was the highest within Japan.[1] Major results of this study are reported and discussed in this communication.

MATERIALS AND METHODS

The cases were 109 patients with gallbladder cancer (35 males and 74 females) and 84 patients with bile duct cancer (46 males and 38 females) who were surgically treated in 39 medical institutes of Niigata prefecture from 1982 to 1986. One hundred and four of 109 cases with gallbladder cancer and 74 of 84 cases with bile duct cancer were histologically confirmed. Thirty-eight cases were collected at the Niigata Cancer Center Hospital and the other 155 cases were collected from Niigata University School of Medicine and other medical institutes.

For each case, two sex-, age (within two years)- and residence (the same area of the municipality)-matched controls were randomly selected from the resident registry list of each municipality using a random number table.

Surveys were conducted by using a self-administered questionnaire. For cases, a questionnaire was distributed and collected by physicians in the year following surgical treatment. The response rate was 84.3%. For controls, a questionnaire was distributed and collected by public health nurses of each public health center in this prefecture. The response rate was virtually 100%. Incompleteness of answers for cases was checked by one of the

Table I. Items Included in the Questionnaire

1) Age, sex and address
2) Height, body weight and grade of obesity (Broca index)
3) Past history, family history (parents and siblings), occupation, occupation of head of household
4) Marital status, age of menarche and menopause, regularity of menstruation, numbers of pregnancies, births and children breast-fed, use of hormonal preparations and oral contraceptives
5) Intake of alcoholic beverages, use of tobacco, the drinking of coffee, black tea, and milk
6) Drinking water now and in about 1945 (tap, well, river)
7) Taste in food: oily food, less greasy food, sweet food, salty food, spices
8) Type of breakfast, rice, bean paste soup, snack, quantity of meals, regularity of meals, river fish (former intake)
9) Frequency of ingestion: boiled rice, bread,[a] noodles, instant Chinese noodles, bean paste soup, pickles, fresh fish, salted fish, dried fish, cod roe,[a] cuttlefish,[a] octopus,[a] lobster, shellfish,[a] river fish, minced fish,[a] minced fish roll,[a] fishcake, fried minced fish,[a] pork,[b] beef,[b] chicken,[b] liver,[a] viscera,[a] ham, sausage, bacon,[a] roast pork,[a] eggs, milk,[a] cheese,[a] fermented soybeans,[a] boiled beans,[a] bean-curd,[a] fried bean-curd,[a] potatoes,[a] green-yellow vegetables, other vegetables,[a] wild plants,[a] quantity of wild plants eaten at a time,[a] lettuce, cabbage, mushrooms,[a] seaweed,[a] fruit, fried food,[a] butter, mayonnaise,[a] dressing[a]
10) Method of cooking: broiled fish, boiled fish,[a] sliced raw fish,[a] fried foods,[a] salad,[a] boiled vegetables,[a] vinegary foods,[a] grated radish,[a] vegetables cooked with oil,[a] kimpira-burdock,[a] Japanese hot-pot,[a] bean-curd,[a] Japanese salad (Aemono),[a] Japanese chowder,[a] broiled beef, pork cutlette,[a] sukiyaki,[a] hamburgers[a] croquettes,[a] curry,[a] stew,[a] boiled vegetables,[a] omelets,[a] fresh eggs,[a] laver,[a] raw vegetables,[a] steamed food[a]

a) Items newly added during the study.
b) Items deleted in the revised questionnaire.

Table II. Sex and Age Distribution of Cases and Controls

Age	Gallbladder cancer						Bile duct cancer					
	Cases			Controls			Cases			Controls		
	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total
40–44	1	2	3	2	2	4	1	1	2	2	2	4
45–49	1	2	3	1	6	7	2	2	4	4	4	8
50–54	2	7	9	5	13	18	2	2	4	4	4	8
55–59	7	2	9	11	7	18	4	7	11	9	14	23
60–64	5	8	13	12	19	31	12	6	18	25	16	41
65–69	8	18	26	18	34	52	10	9	19	18	14	32
70–74	8	22	30	15	40	55	8	6	14	18	13	31
75–79	3	10	13	6	22	28	7	5	12	12	9	21
80–84	0	3	3	0	5	5	0	0	0	0	0	0
Total	35	74	109	70	148	218	46	38	84	92	76	168

authors and incompleteness of answers for controls was checked by one of the authors as well as the public health nurses in charge and a medical doctor of the Department of Health and Environment, Niigata prefecture.

Items investigated in this case-control study are listed in Table I. Considering the results of the other nutritional survey conducted in this prefecture, we modified the questionnaire once during the study period by adding several new items, which are marked with *a*) in Table I. The frequencies of foods intake were classified into five groups from almost none to more than once daily.

It is likely that the time of occurrence of cancer would have been some decades before the survey. However, it is difficult to identify the time of occurrence and it is difficult for study subjects to recall precisely dietary habits some decades ago. Therefore, the dietary habits before surgical treatment were obtained and studied assuming that the changes in dietary habits during past decades were similar between cases and controls.

An odds ratio (OR) based on the unmatched method and its 95% confidence interval (CI) were calculated for each item investigated. A multiple conditional logistic

model[31] was used to calculate a relative risk adjusted for other risk factors (aRR).

Sex and age distributions of cases and controls are shown in Table II. The mean ages of cases and controls were almost the same in both groups and the mean age of cases with gallbladder cancer was a little older (65.9) than that of cases with bile duct cancer (64.6). The number of female cases was over twice that of male cases in gallbladder cancer, while the proportion of males cases was a little higher than that of female cases in bile duct cancer.

RESULTS

We have summarized the items for which odds ratios were statistically significantly increased from unity as high risk factors in Tables III and IV and the items for which odds ratios were statistically significantly decreased from unity as low risk factors in Tables V and VI. The cut-point of exposure category was set on the point which showed the greatest difference between cases and controls.

High risk factors among dietary habits were a taste for oily foods, wild plants, river fish, liver and viscera, kimpira (oil-frizzled) burdock, Japanese salad (Aemono), laver, steamed foods, sliced raw fish and croquettes for gallbladder cancer and taking a small amount of foods and sliced raw fish for bile duct cancer (Table III).

High risk factors other than dietary habits were histories of cholelithiasis and cholecystitis and a family history of cholelithiasis for gallbladder cancer and a history of cholelithiasis, cholecystitis and liver diseases, a family history of cerebral vascular accident and a thin

Table III. High Risk Factors of Biliary Tract Cancer among Dietary Habits

Factor	Gallbladder cancer				Bile duct cancer			
	Item	No. of pairs	Odds ratio	95% CI	Item	No. of pairs	Odds ratio	95% CI
Taste in food	Oily taste	100	2.82	1.68–4.72				
Quantity of meals					Small	57	2.73	1.36–5.45
Frequency of ingestion	Wild plants[a]	53	5.22	1.29–21.11				
	River fish[b]	101	2.96	1.15–7.62				
	Liver viscera[b]	49	2.26	1.06–4.85				
Method of cooking	Kimpira-burdock[b]	53	2.54	1.28–5.04	Sliced raw fish[a]	26	4.42	1.16–16.87
	Japanese salad (Aemono)[b]	48	2.54	1.18–5.47				
	Laver[b]	53	2.95	1.14–7.64				
	Steamed foods[b]	50	2.56	1.27–5.16				
	Sliced raw fish[b]	49	2.18	1.05–4.49				
	Croquettes[b]	46	2.07	1.00–4.26				

a) Three times or more/week.
b) Once or more/week.

Table IV. High Risk Factors of Biliary Tract Cancer among Factors Other than Dietary Habits

Factor	Gallbladder cancer				Bile duct cancer			
	Item	No. of pairs	Odds ratio	95% CI	Item	No. of pairs	Odds ratio	95% CI
Past history	Cholelithiasis	109	—[a]	—	Cholelithiasis	72	—[a]	—
	Cholecystitis	109	34.36	4.51–265.96	Cholecystitis	73	12.77	2.75–59.34
					Liver diseases	73	27.17	6.14–120.23
Family history	Cholelithiasis	109	2.96	1.34–6.50	Vascular accident	83	2.23	1.30–3.82
Obesity					Thin	73	5.13	2.25–11.68

a) Odds ratio could not be calculated because none of the controls had a past history of cholelithiasis.

Table V. Low Risk Factors of Biliary Tract Cancer on Dietary Habits

Factor	Gallbladder cancer				Bile duct cancer			
	Item	No. of pairs	Odds ratio	95% CI	Item	No. of pairs	Odds ratio	95% CI
Beverage and snacks	Taking snacks[a]	62	0.23	0.11–0.48	Alcohol[c]	80	0.46	0.26–0.81
	Coffee[a]	97	0.35	0.16–0.77				
	Milk[a]	48	0.45	0.21–1.00				
Frequency of ingestion	Noodles[c]	105	0.41	0.25–0.68	Instant noodles[c]	81	0.40	0.19–0.85
	Fresh fish[a]	105	0.36	0.18–0.73	Noodles[c]	84	0.48	0.28–0.82
	Salted fish[c]	105	0.43	0.24–0.77	Fresh fish[c]	81	0.14	0.06–0.32
	Egg[c]	103	0.21	0.10–0.45	Salted fish[c]	81	0.43	0.24–0.76
	Pork, beef, chicken[b]	54	0.38	0.18–0.77	Egg[c]	80	0.38	0.17–0.87
					Fruits[a]	83	0.48	0.28–0.81
	Fruits[a]	107	0.30	0.19–0.49	Pickles[a]	75	0.49	0.26–0.92
	Pickles[a]	103	0.54	0.31–0.94	Potato[b]	28	0.33	0.13–0.84
	Potato[b]	49	0.30	0.12–0.78	Lettuce, cabbage[c]	54	0.33	0.16–0.67
	Lettuce, cabbage[c]	60	0.39	0.20–0.78	Green-yellow vegetables[c]	50	0.35	0.15–0.81
	Seaweed[a]	50	0.13	0.02–0.98				
	Mushroom[b]	50	0.33	0.12–0.93	Other vegetables[a]	28	0.30	0.09–0.99
	Fried food[b]	50	0.43	0.20–0.90				
					Bean paste soup[a]	55	0.29	0.10–0.88
					Butter[c]	80	0.51	0.26–1.00
Method of cooking	Broiled fish[b]	108	0.28	0.16–0.49	Broiled fish[b]	83	0.29	0.16–0.52
	Boiled vegetables[b]	52	0.37	0.19–0.75	Sukiyaki[c]	26	0.28	0.10–0.80
	Grated radish[b]	51	0.45	0.22–0.92				
	Salad[b]	48	0.45	0.21–1.00				
	Omelet[b]	51	0.47	0.22–0.99				

a) Daily.
b) Three times or more/week.
c) Once or more/week.

Table VI. Low Risk Factors of Biliary Tract Cancer among Factors Other than Dietary Habits

Factor	Gallbladder cancer				Bile duct cancer			
	Item	No. of pairs	Odds ratio	95% CI	Item	No. of pairs	Odds ratio	95% CI
Past history	Diseases[a]	109	0.34	0.18–0.65	Diseases[a]	64	0.24	0.09–0.66
Family history					Heart diseases	83	0.39	0.16–0.92
Obesity					Obesity	73	0.23	0.11–0.49

a) Diseases other than gastrointestinal diseases, liver diseases, cholelithiasis, cholecystitis, diabetes mellitus, parasitic diseases and infectious diseases.

constitution (Broca index <0.8) for bile duct cancer (Table IV).

Unfortunately, we could not perform further analysis on past histories of cholelithiasis and cholecystitis, because we did not obtain sufficiently detailed information on these diseases such as date of episode, nature of stone and diagnostic methods.

Low risk factors among dietary habits were noodles, fresh fish, salted fish, eggs, meats, fruits, pickles, potatoes, lettuce and cabbage, seaweeds, mushrooms, and fried foods, taking snacks, drinking coffee, milk, broiled fish, boiled vegetables, grated radish, salad and omelet for gallbladder cancer and alcohol drinking, noodles including instant noodles, fresh fish, salted fish,

Table VII. Adjusted Relative Risks Calculated by Using a Conditional Logistic Model for 1:2 Matched Pairs

Factor	Definition	Control %	Adjusted relative risk	95% CI	*t*-value
Gallbladder cancer					
Oily foods	(like)	38.6	3.29[a]	1.68–6.43	3.48
Taking snacks	(every day)	39.9	0.26[b]	0.09–0.72	−2.59
Fruit	(every day)	71.1	0.26[a]	0.13–0.50	−4.00
Coffee	(every day)	21.2	0.25[a]	0.09–0.68	−2.74
Broiled fish	(3 times-/week)	45.0	0.33[a]	0.15–0.71	−2.84
Bile duct cancer					
Quantity of ingestion	(small)	23.2	3.26[d]	1.32–8.03	2.57
Sliced raw fish	(3 times-/week)	7.3	20.60[e]	1.98–214.11	2.53
Alcohol	(occasionally-every day)	51.2	0.46[c]	0.23–0.93	−2.18
Broiled fish	(3 times-/week)	55.4	0.39[c]	0.20–0.75	−2.80

a) Adjusted for marital status and intakes of pickles, fresh fish, salted fish, river fish and egg in addition to intakes of fruit, coffee and broiled fish and preference of oily foods, but excluding the factor to be adjusted (n=109 pairs).
b) Adjusted for an intake of snacks and regularity of meals in addition to the variables in *a*), but excluding the factor to be adjusted (n=53 pairs).
c) Adjusted for intakes of pickles, fresh fish, fruit and butter and preference of oily foods in addition to intakes of alcohol and broiled fish, but excluding the factor to be adjusted (n=84 pairs).
d) Adjusted for quantity of ingestion and an intake of miso soup in addition to the variables in *c*), but excluding the factor to be adjusted (n=57 pairs).
e) Adjusted for intakes of potatoes, sukiyaki and sliced raw fish in addition to the variables in *c*), but excluding the factor to be adjusted (n=28 pairs).

eggs, fruits, pickles, potatoes, lettuce, cabbage, green-yellow vegetables, other vegetables, bean paste soup, butter, broiled fish, and sukiyaki for bile duct cancer (Table V).

Low risk factors other than dietary habits were a past history of diseases other than gastrointestinal diseases, liver diseases, cholelithiasis, cholecystitis, diabetes mellitus, parasitic infection and infectious diseases for both gallbladder and bile duct cancers and a family history of heart diseases and obesity (Broca index >1.0) for bile duct cancer (Table VI).

Including items showing significant results in the univariate analyses except disease history (since the frequency of cholelithiasis in controls was 0) and obesity, a multivariate analysis was carried out using a conditional logistic model for 1:2 matched pairs (Table VII).

For gallbladder cancer, a taste for oily food was a high risk factor, and taking snacks, fruits, coffee and broiled fish were low risk factors, while, for bile duct cancer, taking a small amount of foods and sliced raw fish were high risk factors, and alcohol and broiled fish were low risk factors.

DISCUSSION

To our knowledge this is the first case-control study conducted in Japan on the relationship between detailed dietary habits and biliary tract cancer. A sufficient number of cases and their neighborhood controls were collected in cooperation with 39 medical institutes and the Department of Health and Environment, Niigata prefecture. The comparability of cases and controls was relatively good with regard to sex, age and residence distribution at entry, but the reliability of answers on the questionnaire, which was self-recorded, could not be ascertained in this study. Some kinds of biases which may accompany the use of neighborhood controls, such as recall and rumination biases, should be considered especially for some food items, such as river fish and wild plants, which are not frequently consumed. However, since intakes of main foods were generally higher in controls, the effect of these biases was considered unlikely to be large.

The present study confirmed a close association between cholelithiasis and biliary tract cancer as shown in the previous studies.[3, 7–12] Although the date of episode of this disease was not covered in the questionnaire, there is

a possibility that the episode of the disease may have changed the patients' dietary habits. However, the comparison between cases with a history of cholelithiasis and/or cholecystitis and cases without showed no significant differences in intakes of several food items which showed significant differences between cases and controls. Therefore, the episode of these diseases is considered to have little effect on the results of the present study.

For both gallbladder and bile duct cancers, several high and low risk factors related to dietary habits were identified in the present study. The results for bile duct cancer were opposite to what we expected. Although the biological mechanism involved is unclear, frequent intakes of several foods, such as animal proteins and fats, which were identified as low risk factors of gallbladder cancer may have increased bile metabolism or flow and may have lowered the risk of gallbladder cancer.

Gallbladder cancer has a close association with gallstones. Especially, cholesterol stones are frequently found within the gallbladder in this disease (in the present study 68.9% of gallstones of cases with this disease were cholesterol stones), and the participation of abnormal bile composition and bile metabolism was suspected. In this study, a taste for oily foods was noted as a high risk factor, but, on the other hand, frequent ingestion of animal proteins and fats, such as meats and eggs, was a low risk factor. Furthermore, the intake of fried foods (oil-frizzled and deep-fried foods), which were mainly cooked with vegetable oil, was less in cases than in controls. Therefore, a taste for oily foods may not reflect the amount of ingestion of vegetable oil and animal fat. Some unresolved problems on nutrition and food intakes remain for future studies. It seems also interesting and necessary to compare our results with those in other areas/countries with high and low incidences of biliary tract cancers.

ACKNOWLEDGMENTS

This work was supported by Grants-in-Aid for Cancer Research (58-1) and for the Comprehensive 10-Year Strategy for Cancer Control, Japan, from the Ministry of Health and Welfare. We are indebted to surgeons of medical institutes and hospitals, and the staff of public health centers in Niigata prefecture for their cooperation in the registry of surgical cases with biliary tract cancer and their controls. We wish to thank Dr. K. Kamimura and Dr. S. Toyama for useful discussions, and Mrs. M. Naito and Mrs. M. Aoyama for excellent secretarial assistance.

(Received March 18, 1989/Accepted August 3, 1989)

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