Bowel movement frequency, medical history and the risk of gallbladder cancer death: A cohort study in Japan

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Few risk factors for gallbladder cancer have been identified with sufficient statistical power, because this cancer is rare. The present study was conducted to evaluate the association of bowel movement frequency and medical history with the risk of death from gallbladder cancer using the data set from a large-scale cohort study. A total of 113,394 participants (42.0% males), aged 40 to 89 years, were followed up for 11 years. Information on the medical history of selected diseases, history of blood transfusions, frequency of stools, and tendency toward diarrhea at baseline was collected through a self-administered questionnaire. The Cox proportional hazard model was used to estimate the hazard ratio (HR). During the follow-up period, a total of 116 deaths (46 males, 70 females) from gallbladder cancer were identified. After adjustments for age and gender, history of hepatic disease (HR: 2.28; 95% confidence intervals (95% CI): 1.24–4.21), frequency of stool, and tendency toward diarrhea (HR: 0.26; 95% CI: 0.08–0.83) were found to be significantly associated with the risk of death from gallbladder cancer. Compared with those who had a stool at least once a day, the HR was 2.06 (95% CI: 0.82–5.18) for those who had a stool less than once in 6 days (*P* for trend=0.050). In this prospective study, constipation and a history of hepatic disease were found to elevate the risk of gallbladder cancer death, whereas a tendency toward diarrhea diminished it. (Cancer Sci 2004; 95: 674–678)

Gallbladder cancer has a poor prognosis, and its incidence increases with age.[1–3] Moreover, there are geographic and gender variations in both prevalence and mortality.[4–6] The mortality rate is relatively high in Japan,[7–10] and the incidence is increasing.[11–13] Although several risk factors for gallbladder cancer have been suggested, such as obesity,[14] history of gallstones[1, 15, 16, 23–29] or cholecystitis,[20, 22–30] history of typhoid infection,[14, 15, 21, 31–34] and life style-related factors,[17–23] the etiology of gallbladder cancer is poorly understood. However, because of the rarity of gallbladder cancer, most previous research has involved a case-control study of small numbers of patients. Therefore, they lacked sufficient statistical power to identify risk factors for this cancer. The results have been inconsistent regarding the association between bowel movement frequency and the risk of gallbladder cancer. A case-control study[20] indicated that loose stools were associated with an increased risk of gallbladder cancer, while constipation was found to be related to risk of gallbladder cancer in another case-control study.[35]

Using the data set from a large-scale prospective cohort study with approximately 11 years of follow-up, we assessed the association of the medical history of selected diseases and condition of bowel movement frequency with the risk of death from gallbladder cancer.

Subjects and Methods

JACC study (study cohorts). The Japan Collaborative Cohort Study for Evaluation of Cancer Risk sponsored by the Ministry of Education, Culture, Sports, Science and Technology of Japan (JACC Study) is a prospective cohort study conducted to evaluate risk factors for a variety of cancers. Details concerning the design and conduct of the JACC Study have been described elsewhere.[36] In brief, the study was conducted from 1988 through 1990, during which period 125,000 healthy individuals aged 40–89 years from 45 areas throughout Japan were enrolled as a basic cohort population. In the majority of study areas, individuals were enrolled by signing the cover page of a questionnaire, while in some areas, enrollment occurred at the group level by explaining the aim of the study and confidentiality of the data to a leader of the community. The participants were asked to complete a questionnaire including information on demographic characteristics, life style factors and medical history, and were followed up until the end of 1999. During the follow-up period, the vital status of participants was determined from the residential registration records. Cause of death was confirmed by examining death certificates held at the regional health center, with the permission of the Director-General of the Prime Minister's Office, Ministry of Public Management, Home Affairs, Post and Telecommunications. Cause of death was classified according to the International Classification of Disease, 9th revision: ICD-9[37] and 10th revision: ICD-10.[38]

Participants. The end point in this study was death from gallbladder cancer (156.0 for ICD-9, C23 for ICD-10). The person-time of follow-up for each participant was calculated from the day of enrollment to the day of death from gallbladder cancer or any other cause, or to the time the person moved out of the study area, or to the end of 1999, whichever came first. Participants who died from causes other than gallbladder cancer or who moved out of the study area were treated as censored cases. We excluded subjects who had a history of digestive cancer (stomach, esophageal, liver, pancreas, colon, and rectum) at baseline. To remove a cancer-related effect, we also excluded subjects who died from gallbladder cancer within 2 years from baseline (7 males and 12 females). The number of participants finally included in the present analysis was 113,394 (47,673 males and 65,721 females), ranging in age from 40 to 89 years at entry.

Questionnaire. At baseline, a questionnaire was used to collect data on demographic characteristics, medical history of selected diseases (hepatic disease, gallstone or cholecystitis, diabetes mellitus, gastric or duodenal ulcer, dysentery, and typhoid), his-

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tory of blood transfusion, frequency of stool, and a tendency toward diarrhea. With regard to the medical history of selected diseases and history of blood transfusion, participants were asked to answer yes or no to each question. Stool was classified by frequency into three categories: more than once per day, once in 2–3 days, and less than once per 4 days. Subjects were asked to describe their tendency toward diarrhea: no, yes, or intermediate.

Statistical analysis. Statistical analysis was performed using the SAS Software System.[39] Person-years for each participant was calculated from the date of enrollment to the primary endpoint, death, moving away or December 31, 1999. Hazard ratio (HR) and 95% confidence intervals (95% CI) were estimated using Cox proportional hazard models.[40] HR by gender was adjusted for age and overall HR was adjusted for age and gender in all analyses. All variables were entered as dummy variables. All tests of significance were two-sided and a P value less than 0.05 was considered statistically significant.

Results

The demographic characteristics of study subjects at the start of follow-up are shown in Table 1. A total of 116 deaths (46 males and 70 females) from gallbladder cancer were identified during a follow-up of 1,104,858.7 person-years. The mean follow-up period was 9.7 years (standard deviation, 2.4). The crude mortality rate was estimated to be 10.07 per 100,000 population among males and 10.80 per 100,000 population among females. Among gallbladder cancer deaths, the rate for those who had a medical history of hepatic disease, diabetes mellitus, gastric or duodenal ulcer, dysentery, and typhoid was higher among males than among females. There were no gallbladder cancer deaths among males with a stool frequency of less than once per 4 days.

Table 2 shows the HRs for gallbladder cancer death according to medical history of selected diseases and history of blood transfusions. Overall, those with a history of hepatic disease showed a significantly elevated risk for gallbladder cancer death (HR: 2.28; 95% CI: 1.24–4.21; P=0.008). Except for hepatic disease, medical history of selected diseases and history

Table 1. Demographic characteristics of subjects at baseline

	Males			Females		
	N	(%)	Death from gallbladder cancer[1)]	*N*	(%)	Death from gallbladder cancer[1)]
Age group						
40–49	11,793	24.7	1	15,401	23.38	7
50–59	13,969	29.2	4	19,742	30.0	13
60–69	13,859	29.0	23	19,442	29.51	18
70–79	6647	13.9	15	9102	13.82	27
80–89	1546	3.2	3	2191	3.3	5
Overall	47,814	100.0	46	65,878	100.0	70
Medical history						
Hepatic disease						
No	34,532	91.7	23	48,972	94.2	48
Yes	3141	8.3	6	3038	5.8	6
Gallstone or cholecystitis						
No	37,739	95.6	31	51,464	94.2	51
Yes	1745	4.4	2	3151	5.8	4
Diabetes mellitus						
No	38,582	92.8	32	54,409	95.6	54
Yes	2974	7.2	4	2524	4.4	6
Gastric or duodenal ulcer						
No	32,239	77.2	26	50,101	88.5	51
Yes	9530	22.8	9	6497	11.5	8
Dysentery						
No	37,690	97.6	32	52,448	98.4	55
Yes	913	2.4	2	832	1.6	0
Typhoid						
No	37,974	98.4	32	52,620	98.7	55
Yes	634	1.6	2	667	1.3	0
History of blood transfusion						
No	35,410	89.7	28	48,430	89.0	43
Yes	4079	10.3	7	5967	11.0	8
Stool frequency						
More than once per day	33,756	88.3	22	36,973	69.1	36
Once per 2–3 days	4008	10.5	7	14,268	26.6	14
Less than once per 4 days	482	1.2	0	2263	4.3	5
Tendency toward diahrrea						
No	24,611	63.8	27	42,210	79.5	49
Intermediate	6687	17.3	5	6064	11.4	4
Yes	7288	18.9	1	4832	9.1	2

1) Seven males and 12 females who died within 2 years from baseline were excluded.

Table 2. The hazard ratio of death from gallbladder cancer in relation to medical history of selected diseases

	Male[1]					Female[1]					Overall[2]		
	Person-year	No. of deaths	Hazard ratio	(95% CI)	*P* value	Person-year	No. of deaths	Hazard ratio	(95% CI)	*P* value	Person-year	No. of deaths	Hazard ratio
Hepatic disease													
No	327,619.6	23	1.00			475,332.0	48	1.00			802,951.6	71	1.00
Yes	27,961.2	6	3.06	(1.24–7.51)	0.015	28,364.9	6	1.86	(0.79–4.34)		56,326.1	12	2.28
Gallstone or cholecystitis													
No	361,260.2	31	1.00			505,421.1	51	1.00			8666,681.3	82	1.00
Yes	15,924.6	2	1.23	(0.27–4.71)		30,002.8	4	1.05	(0.38–2.90)		45,927.4	6	1.07
Diabetes mellitus													
No	372,974.4	32	1.00			538,888.2	54	1.00			911,862.6	86	1.00
Yes	26,866.9	4	1.36	(0.48–3.86)		23,058.1	6	1.84	(0.79–4.30)		49,925.0	10	1.60
Gastric or duodenal ulcer													
No	309,919.8	26	1.00			495,009.8	51	1.00			804,929.6	77	1.00
Yes	91,433.4	9	1.11	(0.52–2.36)		63,074.1	8	1.10	(0.52–2.31)		154,507.5	17	1.09
Dysentery													
No	352,055.5	32	1.00			504,399.7	55	1.00			856,455.2	87	1.00
Yes	8,493.9	2	1.95	(0.47–8.16)		7974.1	0	—	(—)		16,468.0	2	1.02
Typhoid													
No	355,060.6	32	1.00			506,157.8	55	1.00			861,218.4	87	1.00
Yes	5526.3	2	2.05	(0.49–8.67)		6269.1	0	—	(—)		11,795.4	2	1.03
History of blood transfusion													
No	338,783.4	28	1.00			473,279.2	43	1.00			812,062.6	71	1.00
Yes	36,090.1	7	1.78	(0.77–4.08)		56,854.5	8	1.47	(0.69–3.12)		92,944.6	15	1.62

1) Adjusted for age.
2) Adjusted for age and gender.

Table 3. The hazard ratio of death from gallbladder cancer in relation to bowel movement frequency

	Male[1]				Female[1]				Overall[2]			
	Person-year	No. of deaths	Hazard ratio	(95% CI)	Person-year	No. of deaths	Hazard ratio	(95% CI)	Person-year	No. of deaths	Hazard ratio	(95% CI)
Stool frequency												
More than once per day	318,542.4	22	1.00		357,335.2	36	1.00		675,877.6	58	1.00	
Once per 2–3 days	35,202.2	7	2.24	(0.95–5.29)	136,568.8	14	1.07	(0.58–1.98)	171,771.0	21	1.35	(0.81–2.24)
Less than once per 4 day	3748.0	0	—	(—)	20,905.4	5	2.39	(0.94–6.10)	24,653.4	5	2.06	(0.82–5.18)
		P for trend		0.208		*P* for trend		0.088		*P* for trend		0.050
Tendency toward diahrrea												
No	230,058.7	27	1.00		407,817.0	49	1.00		637,875.7	76	1.00	
Intermediate	62,712.5	5	0.84	(0.32–2.18)	57,326.6	4	0.61	(0.22–1.68)	120,039.1	9	0.71	(0.35–1.42)
Yes	68,760.7	1	0.18	(0.02–1.31)	45,969.7	2	0.37	(0.08–1.83)	114,730.4	3	0.26	(0.08–0.83)
		P for trend		0.079		*P* for trend		0.063		*P* for trend		0.014

1) Adjusted for age.
2) Adjusted for age and gender.

of blood transfusions were not associated with the risk.

The HRs for gallbladder cancer death according to bowel movement frequency are shown in Table 3. For stool frequency, the HR was elevated for those who had a stool once per 2–3 days in males. The HR was substantially elevated for those who had a stool less than once in 4 days in females. Overall, compared with those who had a stool at least once a day, the HR was 1.35 (95% CI: 0.81–2.24) for those who had a stool once in 2–3 days, and 2.06 (95% CI: 0.82–5.18) for those who had a stool less than once per 4 days. This trend was statistically significant (*P* for trend=0.050). A tendency toward diarrhea by gender was inversely associated with the risk of gallbladder cancer death. Overall, it was significantly and inversely associated with the risk of gallbladder cancer death (*P* for trend=0.014), i.e., those with such a tendency showed a markedly decreased risk (HR: 0.26; 95% CI: 0.08–0.83; *P*=0.023).

Discussion

In the present study, we focused on the association between medical history or bowel movement frequency and the risk of death from gallbladder cancer and found that a history of hepatic disease, infrequent stool and frequent diarrhea were associated with that risk. Initially, the analyses were carried out for each gender. As we obtained similar results for male and female subjects, we carried out subsequent analyses for all subjects combined.

A weakness of the present study is that the end point was set up as death from gallbladder cancer. However, that may have little influence on the results, since the prognosis for gallblad-

der cancer is so severe. To remove the effect of pre-existing gallbladder cancer at baseline, we excluded subjects who died from gallbladder cancer within 2 years from baseline.

We observed that participants with a history of hepatic disease had a significantly elevated risk for gallbladder cancer death. It has been suggested that chronic viral hepatitis may play a role in the development of gallbladder cancer since the damaged liver might produce a carcinogen. However, since we lacked any information about chronic viral hepatitis infection, we could not examine such an association in detail.

Previous epidemiological studies have suggested that a history of gallstones[16, 23–26, 30] and cholecystitis[20, 22] are potential risk factors for gallbladder cancer. Since data on the medical history of diseases such as gallstones were obtained by self-reporting, it is likely that those who did not experience clinical symptoms were overlooked, which may explain the low frequency of gallstones observed in the present study.

We observed no association of a history of diabetes mellitus, or gastric or duodenal ulcer with gallbladder cancer risk, in accordance with several previous studies.[14, 20, 30]

Typhoid infection[14, 15, 21, 31–34] may be a risk factor for gallbladder cancer. We could not examine the role of typhoid or dysentery infection in gallbladder cancer development, since the prevalence of these diseases is extremely low in Japan.[41] For that reason, even if typhoid infection may be a risk factor for gallbladder cancer, its influence is considered to be limited in Japan.

As several studies have implied that viral infection may play a role in gallbladder carcinogenesis,[34, 42, 43] some viral infections may have occurred through blood transfusion in some patients. However, we observed no significantly elevated risk among those who had a history of blood transfusion.

One case-control study has shown that loose stools or reporting two or more bowel movement per day was associated with an increased risk of gallbladder cancer.[20] In contrast, we found that stool infrequency seriously elevated that risk. The association between gallbladder cancer and stool infrequency can be explained by the role of bile acids; secondary bile acids (deoxycholic acid and lithocholic acid) in particular may be involved in this association. Secondary bile acids are formed in the large bowel by the bacterial degradation of primary bile acids, and are normally present in small quantities in the gallbladder. One study showed that patients with gallbladder cancer had a significantly higher concentration of secondary bile acids than control patients.[44] A hypothesis described in another report was that lipophilic bile acids (lithocholate and deoxycholate) are excreted in bile, and if retained over a long enough period in the gallbladder, may be carcinogenic.[45] Furthermore, it has been reported that secondary bile acids may be a causal factor in the development of colon cancer,[46] and that there was a positive association between constipation and an increased risk for colon cancer.[47] Because of long retention, stool infrequency may increase re-absorption into the bile of secondary bile acids formed in large quantities in the colon, via enterohepatic circulation, suggesting that an increase of secondary bile acids induced by stool infrequency may elevate the risk of gallbladder cancer.

Although diarrhea has been shown to be associated with an increased risk of gallstones,[19] its role in gallbladder carcinogenesis is disputed.[20, 48, 49] The present study showed that diarrhea actually decreased the risk, through the mechanism of this effect remains unclear. However, when the factor of stool frequency is combined, the results would seem to be consistent with the finding of an increased risk of gallbladder cancer associated with constipation. Further studies are required to confirm this association conclusively.

In conclusion, this prospective cohort study indicated that both constipation and a history of hepatic disease may be positive risk factors for gallbladder cancer death. On the other hand, a history of blood transfusion and a medical history of selected diseases, other than hepatic diseases, were not associated with that risk.

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