3.82(95%CI : 2.60~5.63), 膀胱癌 2.73(95%CI : 1.58~4.71), 腎臓・腎盂・尿管・その他及び部位不明の泌尿器癌 5.11(95%CI : 2.92~8.93)で男性が有意に高く、甲状腺癌では 0.51(95%CI : 0.16~1.57)で男性が低かった。年齢・喫煙を調整すると泌尿器癌 1.95(95%CI : 1.09~3.47), 腎臓・腎盂・尿管・その他及び部位不明の泌尿器癌 2.95(95%CI : 1.30~6.69), 膀胱癌 1.25(95%CI : 0.55~2.86)と年齢調整のみと比べハザード比が低くなっている。膀胱癌では有意差はなくなっている。甲状腺癌は 0.93(95%CI : 0.19~4.62)で有意差はないがハザード比は少し高くなっている。年齢・飲酒で調整すると泌尿器癌 3.70(95%CI : 2.31~5.95), 腎臓・腎盂・尿管・その他及び部位不明の泌尿器癌 4.06(95%CI : 2.05~8.05)は年齢調整のみのハザード比と比べ同じかやや低くなっていた。膀胱癌 3.32(95%CI : 1.71~6.44), 甲状腺癌 0.99(95%CI : 0.26~3.75)は年齢調整のみのハザード比と比べ少し高くなっていたが有意差はなかった。年齢・喫煙・飲酒で調整すると泌尿器癌 2.22(95%CI : 1.17~4.18), 腎臓・腎盂・尿管・その他及び部位不明の泌尿器癌 2.64(95%CI : 1.08~6.45)で年齢・喫煙で調整したハザード比とほぼ同様の結果で、膀胱癌 1.83(95%CI : 0.74~4.55)はやや高いが有意差はない。甲状腺癌は 1.37(95%CI : 0.25~7.62)で有意差はないが、他の調整のハザード比と比べやや高くなっている。

D．考察

年齢調整のみの結果は胆嚢癌、甲状腺癌以外の全ての癌で男性のハザード比が有意に高く性差が認められた。

年齢・喫煙で調整した場合、性差のあるほとんどの癌のハザード比は低くなり、依然性差はあるものの、食道癌、結腸癌、膵臓癌、膀胱癌、その他及び部位不明の胆道癌、胆嚢・その他及び部位不明の胆道癌でハザード比の低下が認められ、これらの癌に喫煙の影響があると考えられる。喉頭癌、気管・気管支及び肺の癌でハザード比は顕著に低下した。これらの癌は喫煙の影響が大きいと考えられる。

年齢・飲酒で調整した場合、食道癌、腎臓・腎盂・尿管・その他及び部位不明の泌尿器癌でハザード比の低下が認められたが、年齢調整のみと比べほぼ同じ結果を示し、飲酒の影響は小さいと思われる。

年齢・喫煙・飲酒で調整した場合、ほぼ年齢・喫煙と同様の結果であった。喫煙を含めて、調整しても性差がリスクであった癌は食道癌、胃癌、直腸癌、肝癌、気管・気管支及び肺の癌、泌尿器癌、腎癌で、本質的に男性が高いか、または喫煙以外に影響する交絡要因があると考えられる。

E．結論

本研究で性差のリスクには喫煙の影響が大きく、飲酒の影響はそれほどでもなかった。今後、性差をリスク要因とした時の喫煙・飲酒以外の交絡要因を検討していきたい。
また、罹患情報も加えて分析することを検討してみたい。

F．健康危険情報

なし

G．知的財産権の出願・登録状況
（予定を含む）

特許取得	なし
実用新案登録	なし
その他	なし

表１　部位別癌死亡別にみた性差のリスク（１）

死因/ICD		対象数	死亡数	HR1	95%CI	HR2	95%CI	HR3	95%CI	HR4	95%CI
食道癌/C15	女	61315	23	1.00		1.00		1.00		1.00	
	男	46452	108	6.95	1.43-10.90	2.89	1.53-5.45	4.66	2.74-7.91	2.17	1.11-4.25
胃癌/C16	女	64252	285	1.00		1.00		1.00		1.00	
	男	46316	575	3.03	2.63-3.49	2.58	2.09-3.13	2.93	2.46-3.49	2.56	2.03-3.23
結腸癌/C18	女	64305	150	1.00		1.00		1.00		1.00	
	男	46447	142	1.43	1.14-1.80	1.27	0.89-1.82	1.47	1.10-1.96	1.30	0.87-1.92
直腸Ｓ上結腸移	女	64297	61	1.00		1.00		1.00		1.00	
行部･直腸･肛門	男	46444	122	2.97	2.19-4.05	2.65	1.67-4.21	3.04	2.07-4.48	2.53	1.53-4.19
及び肛門管の癌											
/C19 C20 C21											

HR：Hazard Rate　HR1：年齢調整のみのハザード比

HR2：年齢・喫煙で調整したハザード比

HR3：年齢・飲酒で調整したハザード比

HR4：年齢・喫煙・飲酒で調整したハザード比

表２　部位別癌死亡別にみた性差のリスク（２）

死因/ICD		対象数	死亡数	HR1	95%CI	HR2	95%CI	HR3	95%CI	HR4	95%CI
肝及び肝内胆管	女	64320	161	1.00		1.00		1.00		1.00	
の癌/C22	男	46461	365	3.38	2.80-4.06	2.44	1.82-3.27	3.57	2.82-4.54	2.41	1.75-3.32
膵癌/C25	女	64323	156	1.00		1.00		1.00		1.00	
	男	46462	161	1.55	1.24-1.93	0.93	0.66-1.31	1.32	1.01-1.75	0.89	0.61-1.29
喉頭癌/C32	女	48840	2	1.00		1.00		1.00		1.00	
	男	34640	10	7.63	1.67-34.85	2.33	0.30-18.20	7.58	1.40-41.18	2.46	0.28-21.27
気管･気管支	女	64307	200	1.00		1.00		1.00		1.00	
及び肺の癌	男	46435	638	4.80	4.10-5.63	1.91	1.50-2.43	4.87	4.02-5.90	1.98	1.53-2.56

HR：Hazard Rate　HR1：年齢調整のみのハザード比

HR2：年齢・喫煙で調整したハザード比

HR3：年齢・飲酒で調整したハザード比

HR4：年齢・喫煙・飲酒で調整したハザード比

表3　部位別癌死亡別にみた性差のリスク（3）

死因/ICD		対象数	死亡数	HR1	95%CI	HR2	95%CI	HR3	95%CI	HR4	95%CI
胆嚢癌/C23	女	64323	74	1.00		1.00		1.00		1.00	
	男	46462	49	1.00	0.69-1.43	0.71	0.40-1.28	1.00	0.63-1.59	0.64	0.34-1.22
その他及び部位	女	64323	74	1.00		1.00		1.00		1.00	
不明の胆道癌	男	46462	91	1.85	1.36-2.52	1.45	0.88-2.37	2.12	1.43-3.14	1.56	0.90-2.69
/C24											
胆嚢・その他及	女	64323	140	1.00		1.00		1.00		1.00	
び部位不明の胆	男	46462	148	1.42	1.13-1.79	1.07	0.74-1.56	1.55	1.15-2.09	1.07	0.71-1.62
道癌/C23 C24											

HR：Hazard Rate　HR1：年齢調整のみのハザード比

HR2：年齢・喫煙で調整したハザード比

HR3：年齢・飲酒で調整したハザード比

HR4：年齢・喫煙・飲酒で調整したハザード比

表４　部位別癌死亡別にみた性差のリスク（4）

死因/ICD		対象数	死亡数	HR1	95%CI	HR2	95%CI	HR3	95%CI	HR4	95%CI
泌尿器癌/C64	女	56760	36	1.00		1.00		1.00		1.00	
C65C66C67C68	男	40443	91	3.82	2.60-5.63	1.95	1.09-3.47	3.70	2.31-5.95	2.22	1.17-4.18
膀胱癌/C67	女	39727	20	1.00		1.00		1.00		1.00	
	男	28319	36	2.73	1.58-4.71	1.25	0.55-2.86	3.32	1.71-6.44	1.83	0.74-4.55
腎臓・腎盂・尿管・	女	56765	16	1.00		1.00		1.00		1.00	
その他及び部位不	男	40458	54	5.11	2.92-8.93	2.95	1.30-6.69	4.06	2.05-8.05	2.64	1.08-6.45
明の泌尿器癌											
/C64C65C66C68											
甲状腺癌/C73	女	39716	12	1.00		1.00		1.00		1.00	
	男	28329	4	0.51	0.16-1.57	0.93	0.19-4.62	0.99	0.26-3.75	1.37	0.25-7.62

HR：Hazard Rate　HR1：年齢調整のみのハザード比

HR2：年齢・喫煙で調整したハザード比

HR3：年齢・飲酒で調整したハザード比

HR4：年齢・喫煙・飲酒で調整したハザード比

Ⅳ. 事 務 局 記 録

事務局の活動記録および会議開催状況

（平成17年 3月20日現在）

平成16年	7月 7日	第１回研究打ち合わせ会議（東京）
	12月 1日	第２回研究打ち合わせ会議（東京）
	7月14日	平成16年度国庫補助金内示
平成17年	1月27日	厚生労働省より補助金交付決定通知
	3月 1日	厚生労働省より補助金交付

Ⅴ．研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Yagyu K, Lin Y, Obata Y, Kikuchi S, Ishibashi T, Kurosawa M, Inaba Y. et al.	Bowel movement frequency, medical history and the risk of gallbladder cancer death: A cohort study in Japan.	Cancer Sci	95(8)	674-678	2004
Fujino Y, Tamakoshi A, Hoshiyama Y, Mikami H, Okamoto N, Ohno Y, Yoshimura T, for the Japan Collaborative Cohort Study Group.	Prospective study of transfusion history and thyroid cancer incidence among females in Japan.	Int J Cancer	112(4)	722-725	2004
Nagata C, Takatsuka N, Shimuzu N, Shimizu H.	Sodium intake and risk of death from stroke in Japanese men and women.	Stroke	35	1543-1547	2004
Nagata C, Hirokawa K, Shimuzu N, Shimizu H.	Soy, fat and other dietary factors in relation to premensturual symptoms in Japanese women.	BJOG	111	594-599	2004
Nagata C, Hirokawa K, Shimuzu N, Shimizu H.	Associations of menstrual pain with intakes of soy, fat and dietary fiber in Japanese women.	Eur J Clin Nutr	59	88-92	2005

Ⅵ. 研究成果の刊行物・別刷

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

Kiyoko Yagyu,[1] Yingsong Lin,[1] Yuki Obata,[1] Shogo Kikuchi,[1,5] Teruo Ishibashi,[2] Michiko Kurosawa,[3] Yutaka Inaba[3] and Akiko Tamakoshi[4] for the JACC Study Group

[1]Department of Public Health, Aichi Medical University School of Medicine, 21 Karimata, Yazako, Nagakute-cho, Aichi-gun, Aichi 480-1195; [2]Asama General Hospital, 1862-1 Iwamurada, Saku 385-5885; [3]Department of Epidemiology and Environmental Health, Juntendo University School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421; and [4]Department of Preventive Medicine/Biostatistics and Medical Decision Making, Field of Social Life Science, Program in Health and Community Medicine, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550

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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-

[5]To whom correspondence should be addressed.
E-mail: kikuchis@aichi-med-u.ac.jp

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.

The present members of the JACC Study and their affiliations are as follows: Dr. Akiko Tamakoshi (present chairman of the study group), Nagoya University Graduate School of Medicine; Dr. Mitsuru Mori, Sapporo Medical University School of Medicine; Dr. Ichiro Tsuji, Tohoku University Graduate School of Medicine; Dr. Yoshikazu Nakamura, Jichi Medical School; Dr. Hiroyasu Iso, Institute of Community Medicine, University of Tsukuba; Dr. Haruo Mikami, Chiba Cancer Center; Dr. Yutaka Inaba, Juntendo University School of Medicine; Dr. Yoshiharu Hoshiyama, Showa University School of Medicine; Dr. Hiroshi Suzuki, Niigata University Graduate School of Medical and Dental Sciences; Dr. Hiroyuki Shimizu, Gifu University School of Medicine; Dr. Hideaki Toyoshima, Nagoya University Graduate School of Medicine; Dr. Shinkan Tokudome, Nagoya City University Graduate School of Health Sciences; Dr. Yoshinori Ito, Fujita Health University School of Health Sciences; Dr. Shuji Hashimoto, Fujita Health University School of Medicine; Dr. Shogo Kikuchi, Aichi Medical University School of Medicine; Dr. Akio Koizumi, Graduate School of Medicine an Faculty of Medicine, Kyoto University; Dr. Takashi Kawamura, Kyoto University Center for Student Health; Dr. Yoshiyuki Watanabe and Dr. Tsuneharu Miki, Kyoto Prefectural University of Medicine Graduate School of Medical Science; Dr. Chigusa Date, Faculty of Human Environmental Sciences Mukogawa Women's University; Dr. Kiyomi Sakata, Wakayama Medical University; Dr. Takayuki Nose, Tottori University Faculty of Medicine; Dr. Norihiko Hayakawa, Research Institute for Radiation Biology and Medicine, Hiroshima Univesity; Dr. Takesumi Yoshimura, Institute of Industrial Ecological Sciences, University of Occupational and Environmental Health, Japan; Dr. Katsuhiro Fukuda, Kurume University School of Medicine; Dr. Naoyuki Okamoto, Kanagawa Cancer Center; Dr. Hideo Shio, Moriyama Municipal Hospital; Dr. Yoshiyuki Ohno (former chairman of the study group), Asahi Rosai Hospital; Dr. Tomoyuki Kitagawa, Cancer Institute of the Japanese Foundation for Cancer Research; Dr. Toshio Kuroki, Gifu University; and Dr. Kazuo Tajima, Aichi Cancer Center Research Institute. The past investigators of the study group were listed in reference 36 except for the following seven members (affiliations are those at the time when they participated in the study): Dr. Takashi Shimamoto, Institute of Community Medicine, University of Tsukuba; Dr. Heizo Tanaka, Medical Research Institute, Tokyo Medical and Dental University; Dr. Shigeru Hisamichi, Tohoku University Graduate School of Medicine; Dr. Masahiro Nakao, Kyoto Prefectural University of Medicine; Dr. Takaichiro Suzuki, Research Institute, Osaka Medical Center for Cancer and Cardiovascular Diseases; Dr. Tsutomu Hashimoto, Wakayama Medical University; and Dr. Teruo Ishibashi, Asama General Hospital. The authors wish to express their appreciation to Dr. K. Aoki, Professor Emeritus, Nagoya University School of Medicine and the former chairman of the Monbusho ECC (steering committee of the JACC study, i.e., the Research Committee on Evaluation of Risk Factors for Cancer by Large-scale Cohort Study) and to Dr. Haruo Sugano, former Director of the Cancer Institute of the Japanese Foundation of Cancer Research, who contributed greatly to the initiation of the study, and also to Ms. M. Endo and Ms. K. Takaba for their assistance. The JACC study has been supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan (Monbusho/Monbukagakusho) (Nos. 61010076, 62010074, 63010074, 1010068, 2151065, 3151064, 4151063, 5151069, 6279102, 11181101, 12218237).

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SHORT REPORT

PROSPECTIVE STUDY OF TRANSFUSION HISTORY AND THYROID CANCER INCIDENCE AMONG FEMALES IN JAPAN

Yoshihisa FUJINO[1,2,*], Akiko TAMAKOSHI[3], Yoshiharu HOSHIYAMA[4], Haruo MIKAMI[5], Naoyuki OKAMOTO[6], Yoshiyuki OHNO[7], Takesumi YOSHIMURA[1] and the Japan Collaborative Cohort Study Group[8]

[1]*Department of Clinical Epidemiology, Institute of Industrial Ecological Sciences, University of Occupational and Environmental Health, Japan*
[2]*Department of Epidemiology, Statistics and Public Health, University of Wales College of Medicine, United Kingdom*
[3]*Department of Preventive Medicine/Biostatistics and Medical Decision Making, Field of Social Life Science, Program in Health and Community Medicine, Nagoya University Graduate School of Medicine, Nagoya, Japan*
[4]*Department of Public Health, Showa University School of Medicine, Japan*
[5]*Head Division of Epidemiology, Chiba Cancer Center Research Institute, Chiba, Japan*
[6]*Department of Epidemiology, Research Institute, Kanagawa Cancer Center, Yokohama, Japan*
[7]*Labour Welfare Corporation Asahi Rosai Hospital, Asahi, Japan*
[8]*See Acknowledgements*

A link between hepatitis C virus (HCV) infection and thyroid cancer was recently reported in a series of case-control studies in southern Italy. A prospective study could reinforce these findings. However, cohort studies that began before 1990 rarely assessed serological HCV infection. In addition, thyroid cancer is rare and generally has a good prognosis. Therefore, incidence outcome data are required, rather than mortality data, to evaluate the risk of thyroid cancer. Blood transfusion history might be a possible substitute measure to evaluate the cancer risks associated with HCV infection because blood transfusions were the major HCV transmission route in Japan until 1992. The purpose of our study was therefore to examine the association between transfusion history and thyroid cancer. A baseline survey of members of the JACC Study was conducted from 1988 until 1990, which involved 110,792 participants from 45 areas throughout Japan. Data were collected from a total of 37,983 women with no history of cancer at the baseline (337,906 person-years) and 79 cases of thyroid cancer were identified among this group. A history of blood transfusion marginally increased the risk of thyroid cancer [risk ratio (RR) = 1.77, 95% confidence interval (CI) = 0.95–3.30], and a history of transfusion and/or liver disease significantly increased the thyroid cancer risk (RR = 1.84, 95% CI = 1.07–3.16). These results indirectly support an association between HCV and thyroid cancer. In addition, our data reveal an association between blood transfusion and thyroid cancer, which might be facilitated by transfusion-associated immunomodulation.

Key words: *thyroid cancer; blood transfusion; hepatitis C virus; immunomodulation; Japanese population*

Infection with the hepatitis C virus (HCV) is a strong risk factor for liver cancer[1] and several studies have reported associations between HCV and other cancers, including non-Hodgkin lymphoma and multiple myeloma.[2,3] In addition, a novel link between HCV and thyroid cancer was recently reported in a series of case-control studies in southern Italy.[4–6] For example, Montella *et al.*[4] carried out a hospital-based study in an area of southern Italy with a high prevalence of HCV (up to 12.6%) among the general population. Their study group comprised 106 female patients who had been histologically diagnosed with thyroid cancer and 116 controls who were hospitalised without any history of cancer. The odds ratio (OR) for the relationship between serological HCV-positive status and thyroid cancer among females was 4.0 [95% confidence interval (CI) = 1.1–8.8].

A prospective study could confirm the association between HCV and thyroid cancer. However, cohort studies that began before 1990 rarely assessed serological HCV infection, as the virus was only identified in 1988. In addition, thyroid cancer is relatively rare and generally has a good prognosis. Therefore, incidence rather than mortality data are required to evaluate the thyroid cancer risk associated with HCV infection.

Blood transfusion history might be a possible alternative measure for evaluating the cancer risks associated with HCV infection. Several studies have revealed an association between transfusion history and liver cancer, which might be explained by the proposed link between transfusion history and HCV infection. Blood transfusions were the major transmission route for HCV in Japan before 1992.[7] The purpose of our study was therefore to examine the association between blood transfusion history and thyroid cancer.

MATERIAL AND METHODS

The JACC study

The details of the Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC Study), sponsored by the Ministry of Education, Science, Sports and Culture of Japan, have been described previously.[8–13] Briefly, this cohort study involved a total of 110,792 subjects (46,465 male and 64,327 female) who were aged 40–79 years at recruitment. Subjects were enrolled between 1988 and 1990 on the basis of participation in general health check-ups that were periodically provided by the 45 municipalities involved.

The vital status of each participant was checked annually using data held at each regional research centre, with permission from the Ministry of Public Management, Home Affairs, Post and Telecommunications, to review the population register sheets. The incidence of cancer was ascertained in 24 study areas (with a total of 65,184 subjects) and coded according to the tenth revision of the International Classification of Disease (ICD-10) and the second edition of the International Classification of Diseases for Oncology (ICD-O). The analysis in the present study also included follow-up data collected before 1999.

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*Correspondence to: Department of Clinical Epidemiology, IIES, UOEH 1-1, Iseigaoka, Yahatanishi-ku, Kitakyushu, 807-8555, Japan. Fax: +81-93-603-0158. E-mail: zenq@med.uoeh-u.ac.jp

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The informed consent procedures were approved by the Ethics Committee of Medical Care and Research, University of Occupational and Environmental Health, Kitakyushu, Japan, and the Ethical Board of the Nagoya University School of Medicine, Japan.

Data retrieval for analysis

In order to identify the appropriate data for our analysis, we first restricted the subjects to those who lived in the study areas for which cancer incidence was ascertained. We then further restricted the data to include only those participants who provided information concerning their age and sex, and who lacked a previous history of cancer. Our final dataset comprised data from 37,983 women (a total of 379,135 person-years) and thyroid cancer cases were identified among this group using code C73 of the ICD10. Of a total of 79 thyroid cancer cases, 4 individuals died during the follow-up period: 2 as a result of thyroid cancer, 1 as a result of lung cancer and 1 as a result of ovarian cancer. The crude incidence for thyroid cancer in females was 20.8 per 100,000 person-years, whereas the crude estimated thyroid cancer incidence in Japan, based on data obtained from 12 population-based cancer registries between 1986 and 1997, was 7–11 per 100,000.[14] The older age of the JACC cohort at study entry (40–79 years) may explain the higher incidence in this population.

History of blood transfusion and liver disease

Participants with a history of blood transfusion were identified at the baseline by a positive response to a question about previous transfusions (n = 3,504). Information was also obtained about certain other diseases, including hepatitis and liver cirrhosis: respondents indicated on a checklist those diseases with which they had been diagnosed either currently or previously.

Statistical analysis

The Cox proportional hazards model was used to estimate the age-adjusted risk ratio (RR) of a history of blood transfusion for thyroid cancer incidence. The risk of thyroid cancer following liver disease was also estimated. Subjects were divided into 3 groups: individuals with neither a history of transfusion nor of liver disease; individuals with a history of transfusion and/or liver disease; and individuals who had no transfusion history but whose history of liver disease was unknown, or who had no history of liver disease but whose transfusion history was unknown. All calculations were performed using the SAS statistical software package.[15]

RESULTS

As shown in Table I, the prevalence of history of liver disease among subjects with a history of blood transfusion (11.5%) was twice that of those without a history of transfusion (5.3%; p <0.001 derived from chi-squared test).

Table II shows that a history of transfusion was associated with an increased risk of thyroid cancer, although this relationship was not statistically significant (RR = 1.77, 95% CI = 0.95–3.30). No increase in the risk of thyroid cancer was associated with a history of liver disease. However, subjects with a history of transfusion and/or liver disease had a significantly increased risk of thyroid cancer compared with those with neither a history of transfusion nor liver disease (RR = 1.84, 95% CI = 1.07–3.16). When the thyroid cancer data were restricted to only the 59 cases of papillary adenocarcinoma using the ICD-O classification, the results were similar although the risk was higher (RR = 1.96, 95% CI = 1.06–3.63). In addition, after the exclusion of subjects who died as a result of liver cancer, in order to avoid competing risk, the results remained similar (RR = 1.85, 95% CI = 1.08–3.18).

The RRs for liver cancer mortality were also estimated. The risk of a transfusion history for liver cancer was 3.84 (95% CI = 2.34–6.31) and the risk of liver disease for liver cancer was 25.9 (95% CI = 15.8–42.3).

TABLE I – BASELINE CHARACTERISTICS BY HISTORY OF TRANSFUSION

	Transfusion history		
	No n = 29,169	Yes n = 3,504	Unknown n = 5,310
Mean age (SD)	55.5 (10.1)	58.6 (9.9)	61.8 (9.5)
History of liver disease (%)[1]			
No	89.4	75.8	49.3
Yes	5.3	11.5	5.7
Unknown	5.3	12.7	45.0
Number of deaths due to liver cancer	49	23	7
Number of incidences of thyroid cancer	58	12	9

[1] p value derived from chi-squared test <0.001.

DISCUSSION

Our study revealed a marginal association between blood transfusion history and thyroid cancer among females in Japan. Two possible underlying pathways for this association are discussed below.

The first possible mechanism is the transmission of HCV. Chronic HCV infections have been linked with various autoimmune disorders, including autoimmune thyroid diseases and autoimmune hepatitis.[2,3,16,17] Autoimmune thyroiditis is thought to be a preneoplastic condition for thyroid carcinoma[18] and the oncogenetic potential of HCV might partly be explained by modulating effects of the host immune system.[6,19] In addition, autoimmune hepatitis is also associated with thyroiditis: according to a nationwide survey in Japan, chronic thyroiditis was seen in 12% of all cases of autoimmune hepatitis.[20,21]

Transfusion history was used as a proxy for HCV infection in our study, as blood transfusions have been an important transmission route for HCV in Japan. Like Italy, Japan has a high prevalence of HCV, with most cases being present in older individuals. The screening of donated blood for anti-HCV antibodies by the Japanese Red Cross commenced in 1989 with a first-generation ELISA, and the process was improved in 1992 when a second-generation assay was adopted. One previous study estimated that 33% of all HCV infections were acquired through blood transfusions.[22]

An HCV transmission rate of approximately 7–18% following blood transfusion has been reported in Japan.[7,23] Among blood donors with a history of transfusion, 7.4% were found to be positive for anti-HCV antibodies, whereas the anti-HCV-positive rate was only approximately 1.0% among more than 10 million blood donations screened throughout Japan.[7] In addition, the present study showed that individuals with a history of transfusion had higher rates of liver disease and an increased risk of liver cancer. These results also support the hypothesis that transfusion history is a reasonable proxy for HCV infection, as more than 80% of all liver cancer patients in Japan have antibodies to HCV.[24]

The second possible mechanism underlying the association between blood transfusion history and thyroid cancer is based on the hypothesis that blood transfusion-induced immunomodulation promotes the carcinogenic progression from thyroiditis to cancer. Allogeneic blood transfusions induce clinically significant immunosuppression in recipients; this clinical syndrome is referred to as transfusion-associated immunomodulation and its effects have been shown to increase the rate of cancer recurrence.[25]

In our study, a history of liver disease alone did not increase the risk of thyroid cancer. Although liver disease could be a proxy for HCV, other factors, such as HBV and alcohol consumption, are also associated with liver disease, which might lead to a weak association between a history of liver disease and thyroid cancer if the proposed association between HCV and thyroid cancer is genuine. However, when these categories were combined, subjects with a history of transfusion and/or liver disease had a higher risk

TABLE II - THE RISK OF HISTORY OF TRANSFUSION AND LIVER DISEASES FOR THYROID CANCER

	n	Person-years	Thyroid cancer	RR	95% CI	
History of transfusion						
No	29,169	291,920	58	Reference		
Yes	3,504	34,287	12	1.77	0.95	3.30
Unknown	5,310	52,928	9	0.91	0.45	1.84
History of liver disease						
No	31,363	315,766	64	Reference		
Yes	2,257	21,590	6	1.39	0.60	3.21
Unknown	4,363	41,780	9	1.13	0.55	2.30
Transfusion and liver disease						
Neither transfusion nor liver disease	26,088	262,190	50	Reference		
Transfusion and/or liver disease	5,357	52,061	18	1.84	1.07	3.16
Other[1]	6,538	64,885	11	0.95	0.49	1.84

[1]Subjects who did not have a transfusion history and whose history of liver disease was unknown, or subjects who did not have liver disease and whose transfusion history was unknown.

of thyroid cancer compared with those with no history of either. We propose that the combined category of individuals with a history of liver disease and transfusion captured more HCV-positive subjects, even if the sensitivity of HCV detection was relatively low. In addition, an HCV-negative reference group, comprising individuals with a history of neither transfusion nor liver disease, might have been more inclusive than only those with no history of transfusion, as blood transfusion is not the exclusive route of HCV transmission.[22]

A potential limitation of our study is that the participants reported their own blood transfusion history. However, a previous report[26] calculated the sensitivity and specificity of self-reported transfusion histories as 93% and 78%, respectively. In addition, misclassification would tend to weaken any association between a history of transfusion and thyroid cancer; therefore, the actual risk might be greater than that reported here.

This prospective cohort study indirectly supports the association between HCV and thyroid cancer suggested by a recent series of case-control studies in southern Italy. In addition, our results raise a new hypothesis: the association between blood transfusions and thyroid cancer is facilitated by transfusion-associated immunomodulation. Detailed epidemiological studies will be necessary to further examine the interactions between thyroid cancer, HCV and blood transfusion, including immunomodulation effects.

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