者がより野菜を摂取する可能性があると考えたが、本研究では苦み感受性は一部の野菜の嗜好と関連あるものの全体の野菜摂取量や葉酸、ビタミン等との関連性はないことが示された。幼児を対象に栄養指導を行う上で、苦みへの感受性を考慮した個別の指導法はそれほど有効でないと考えられた。

7. 食事・運動習慣の改善を目指した介入研究に参加した閉経後女性における血清女性ホルモン濃度に関する横断研究

身体特徴、特に肥満と関連する特徴と血中の女性ホルモン濃度との関連における日本人の知見は少ない。本研究では、欧米人における検討とほぼ同様に、肥満と関連のある測定項目が特に E2 との間に正の相関が認められた。この事は、内因性のエストロゲンが日本人集団でも欧米人と同様肥満に関連する要因の影響を受けていることを示唆すると考えられる。本邦における閉経後のホルモン関連である乳がんにおいて、肥満がリスク要因として確実な関連を示していることと併せて考えても矛盾のない結果と言える。ただし、BMI に関しては、今回の検討者数が少なかったこともあり、示唆的な傾向は認めるものの有意な差とはならなかったことは注目する必要がある。日本人女性における BMI は欧米人のそれと比べると、全体的に低くまたそのばらつきも小さいことが知られる。腰部周囲長や体重、肥満度の方が BMI よりもホルモン濃度に関して感度が高いことを示しているのかも知れない。今後別集団で大規模に検討すべき課題と考えられる。

Ⅶ. 生活習慣と遺伝的要因との交互作用を検討する分子疫学研究

1. 大腸腺腫の遺伝・環境要因の症例・対照研究―遺伝・環境相互作用を中心に―

飲酒と大腸腺腫発生とを関連づけるメカニズムはまだ明らかになっていないが、エタノール及びその代謝産物であるアセトアルデヒドを介する直接的な経路だけでなく、葉酸代謝を介する間接的な経路が考えられている。本研究では、飲酒と葉酸代謝遺伝子多型(MTHFR)の交互作用が認められ、アルコールと大腸腺腫との関連は、葉酸代謝を介する可能性が示唆される。

2. 大腸がんの生活習慣と遺伝的要因との交互作用

大腸がんと NKG2D 遺伝子、および、喫煙、飲酒、葉酸摂取、家族歴、BMI、運動との交互作用に関する研究では、NK 活性が高い方が大腸がんリスクが低い、という知見を得た。また、統計学的有意ではないものの、運動との関連を得たことは、運動の大腸がんリスクに対するメカニズムを考える上で示唆的と考えられる。今後、他がんでの結果を踏まえた上で更なる検討が期待できると考える。

E.結論

日本人における野菜・果物以外の食品摂取・体格・運動・感染症と主要部位(胃・大腸・肺・乳・肝)がんとの関連、および、喫煙・飲酒・野菜・果物・体格・野菜果物以外の食品摂取とがん(食道・膵・前立腺)との関連に関する文献レビューとその要約と総括評価をおこなった。喫煙は食道がんと convincing な、膵がんと probable な正の関連と判定した。飲酒は食道がんと convincing な正の関連と判定した。野菜・果物は食道がんと probable な負の関連と判定した。野菜・果物以外の食品摂取について、コーヒーは肝がんと probable な、大腸がんと possible な負の関連、食塩と胃がんは probable な正の関連、加工肉は大腸がんと possible な正の関連、大豆は乳がんと前立腺がんと possible な負の関連と判定した。体格について、肥満は大腸がんと probable な、閉経後乳がんと convincing な正の関連と判定した。運動について、大腸がんと probable な負の関連と判定した。ヘリコバクター・ピロリ菌感染は胃がんと convincing な正の関連、HBV 感染、HCV 感染は、ともに、肝がんと convincing な正の関連、結核は肺がんと possible な正の関連と判定した。その他、糖尿病と肝がんは probable な正の関連、授乳と乳がんは probable な負の関連と判定した。文献の追加や新たなエビデンス

の構築などにより、果物と胃がんの負の関連は probable から possible に、飲酒と大腸がんの正の関連は probable から convincing に変更した。その他の要因については、判定するには証拠が不十分であった。

新たなエビデンスの構築と関連の強さを量的に推定するため、BMI・野菜・果物・塩分・緑茶・飲酒について現行コホートプール解析を行った。BMIと全がんについては、21未満の男性で1.3-1.5倍の全がん死亡リスク上昇(23-24.9を基準)を認めた。大腸がんでは、25以上の男性で1.2-1.5倍の大腸がん罹患リスク上昇(25未満を基準)、乳がんでは、27以上の女性で1.3-1.6倍の乳がん罹患リスク上昇を認めた。全野菜＋果物および果物(果物はジュース除く)で、喫煙・エネルギー摂取量調整後も男性肺がん死亡リスクとの間に負の関連を認めた。男性の遠位部胃がんと野菜・果物摂取でリスクの低下傾向を認めた。塩分と胃がんでは男女とも関連を認めなかった。緑茶では、男性では関連がみられなかったが、女性では、1日5杯以上の飲用で胃がんリスクの低下を認めた。飲酒と肝がん・大腸がんでは、ともに、飲酒量と罹患リスクに正の関連を認めた。

国際的な評価、及び、本研究班で行った評価を踏まえ「日本人のためのがん予防法」を提示した。

喫煙・飲酒・BMIの組み合わせでがん罹患割合を予測モデルで推計したところ、3要因の1つでも健康的な要素を持つ人の罹患割合は低かった。

野菜・果物摂取と減塩の食事指導では、関連の栄養素摂取量が増加しその効果が3-4年後も維持されることが示唆された。メラトニン高含有野菜摂取介入研究では、2ヵ月後介入・観察の両群で、介入前後の尿中メラトニン代謝物に統計学的有意な変化を認めた。都市部住民における食物摂取頻度調査票の開発とその妥当性の評価を行ったところ、地域住民を対象とした妥当性とほぼ同等か、上回る結果であった。食生活・運動習慣に関する職域介入研究では、6ヶ月後介入群で体重減少と運動時間の増加を認めた。食事・運動の個別・集団指導では、3ヵ月後介入群で緑黄色野菜摂取量増加、運動量増加を認めた。幼児の苦味の感受性と食習慣の把握を行ったところ、苦味の感受性は食品群・栄養素に関連はなかった。

大腸腺腫と飲酒、および、葉酸遺伝子多型に関する研究では、非飲酒と比較して多量飲酒者で大腸腺腫リスクの上昇をみとめ、さらに、飲酒と葉酸代謝に関わる遺伝子多型に交互作用がみられた。大腸がんとNKG2D遺伝子、および、生活習慣との交互作用に関する研究では、NK活性が高いアリルでリスクの有意な低下が認めたが、飲酒、喫煙、家族歴、葉酸、BMI、運動の何れも有意な交互作用は認めなかった。

生活習慣によるがんの予防可能性をより適切に伝えていくための手法を開発していくと同時に、がん予防情報の蓄積を積極的におこない、結果については、本研究班において開設したホームページ(http://epi.ncc.go.jp/can_prev/)やがん情報サービス(http://ganjoho.jp/public/pre_scr/prevention/evidence_based.html)で公開し、国民への還元を図っている。

F. 健康危険情報

なし

G. 研究発表

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H. 知的財産権の出願・登録状況

なし

表 A. 生活習慣とがんとの関連についての評価のまとめ

	全がん	肺がん	肝がん	胃がん	大腸がん			乳がん			食道がん	膵がん	前立腺がん
						(結腸)	(直腸)		(閉経前)	(閉経後)			
喫煙	convincing ↑	convincing ↑	probable ↑	convincing ↑	possible ↑	insufficient	possible ↑	possible ↑			convincing ↑	probable ↑	insufficient
飲酒	convincing ↑	insufficient	convincing ↑	insufficient	convincing ↑	convincing ↑	convincing ↑	insufficient			convincing ↑	insufficient	insufficient
野菜	insufficient	insufficient	insufficient	possible ↓	insufficient			insufficient			probable ↓	insufficient	insufficient
果物	insufficient	possible ↓	insufficient	possible ↓	insufficient			insufficient			probable ↓	insufficient	insufficient
緑茶	insufficient			insufficient				insufficient					insufficient
コーヒー			probable ↓		possible ↓	possible ↓	insufficient						
大豆		insufficient	insufficient					possible ↓					possible ↓
脂肪・肉類					(肉類) insufficient			(脂肪・肉類) insufficient					
加工肉					possible ↑								
魚					insufficient			insufficient					
塩・塩蔵品				probable ↑									
乳製品					insufficient	insufficient	insufficient	insufficient					insufficient
BMI	insufficient	insufficient	insufficient	insufficient	probable ↑				insufficient ↑	convincing ↑			insufficient
運動	insufficient	insufficient			probable ↓	probable ↓	insufficient	insufficient					
感染症		(肺結核) possible ↑	(HBV) convincing ↑ (HCV) convincing ↑	(H. ピロリ菌) convincing ↑									
その他	(心理社会学的要因) insufficient		(糖尿病) probable ↑		(高身長) insufficient			(授乳) probable ↓					

評価の変更履歴 (2008.07.04) (班会議、東京)　新しいプール分析の結果により、飲酒と大腸がんの評価を、「probable」から「convincing」に変更。

(班会議、東京)　エビデンスの追加とサマリーテーブルの見直しにより、果物と胃がんの評価を、「probable」から「possible」に変更。

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書 籍 名	出版社名	出版地	出版年	ページ

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
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Alcohol Drinking and Liver Cancer Risk: An Evaluation Based on a Systematic Review of Epidemiologic Evidence among the Japanese Population

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Background: Although alcohol consumption has been recognized as a risk factor for primary liver cancer, it will be informative to summarize relevant epidemiologic data in the Japanese who have characteristic environmental determinants (e.g. hepatitis C virus infection) and genetic traits (e.g. presence of poor acetaldehyde metabolizers).
Methods: We systematically reviewed epidemiologic studies on alcohol drinking and liver cancer among Japanese populations. Original data were obtained through searches of the MEDLINE (PubMed) and *Ichushi* databases, complemented with manual searches. The evaluation was performed in terms of the magnitude of association ('strong', 'moderate', 'weak' or 'no association') in each study and the strength of evidence ('convincing', 'probable', 'possible' or 'insufficient'), together with biological plausibility as previously assessed by the International Agency for Research on Cancer.
Results: Among 22 cohort studies identified, 14 (64%) reported weak to strong positive associations between alcohol and liver cancer risk, 3 (14%) reported no association and five (23%) reported weak to moderate inverse associations; such inverse associations were found mostly in follow-up studies of patients with chronic liver disease (particularly, cirrhotic patients), yet recent studies on patients with chronic hepatitis C presented fairly consistent positive associations. Of 24 case–control studies identified, 19 (79%) showed weak to strong positive associations, whereas the remainder demonstrated no association ($n = 4$) or a moderate inverse association ($n = 1$).
Conclusion: We conclude that there is 'convincing' evidence that alcohol drinking increases the risk of primary liver cancer among the Japanese population.

Keywords: systematic review – epidemiology – alcohol – liver cancer – Japanese

INTRODUCTION

Alcohol has long been viewed as a hepatotoxic agent, and its heavy consumption is known to cause hepatocellular injury that can lead to enhanced fibrosis and eventually to liver cirrhosis through various mechanisms presumed (1). Alcohol drinking has also been implicated in the etiology of primary liver cancer that often develops from cirrhosis (2). In the most recent evaluation by the International Agency for Research on Cancer (IARC), the occurrence of liver cancer has been 'causally' related to the consumption

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of alcoholic beverages (3). In the second report published by the World Cancer Research Fund and the American Institute for Cancer Research, the Panel has judged that alcohol consumption is 'probably' a direct cause of liver cancer (4).

Primary liver cancer is one of the most common cancers in Japan (5). More than 90% of primary liver cancers in this country are hepatocellular carcinomas (HCCs) that are mostly attributable to chronic infections with hepatitis C virus (HCV) and hepatitis B virus (HBV) (6,7); HCV and HBV infections are estimated to account for 70 and 15%, respectively, of the recent occurrences of HCC in Japan (6). This tendency clearly contrasts with the situation in south-east Asia and sub-Saharan Africa where HBV represents a dominant risk factor of HCC, and with that in Western countries where HCV infection plays an increasingly important role (2,8). The role of alcohol in hepatocarcinogenesis might differ between Japan and such areas. Moreover, ~50% of the Japanese are poor metabolizers of acetaldehyde (9), the first metabolite of ethanol, which has been recognized as being possibly carcinogenic to humans (10). Such poor metabolizers have not been found in Africans or Caucasians (9), and thus the Japanese as Mongoloids might be more susceptible to alcohol than other ethnic groups.

The aim of the present study was to review and summarize epidemiologic findings on alcohol drinking and liver cancer among Japanese populations. This work was conducted as part of a project of systematic evaluation of the epidemiologic evidence regarding lifestyles and cancers in Japan (11).

PATIENTS AND METHOD

The details of the evaluation method have been described elsewhere (11). In brief, original data for this review were identified through searches of the MEDLINE (PubMed) and *Ichushi* (*Japana Centra Revuo Medicina*) databases, complemented by manual searches of references from relevant articles where necessary. All epidemiologic studies on the association between alcohol drinking and liver cancer incidence/mortality among the Japanese from 1950 (or 1983 for the *Ichushi* database) to June 2008, including papers in press if available, were identified using the following as keywords: alcohol, liver, hepatocellular, cohort, follow-up, case–control, Japan and Japanese. Papers written in either English or Japanese were reviewed, and only studies on Japanese populations living in Japan were included. The individual results were summarized in the tables separately as cohort or case–control studies.

The evaluation was made based on the magnitudes of association and the strength of evidence. First, the former was assessed by classifying the relative risk (RR) in each study into the following four categories, while considering statistical significance (SS) or no statistical significance (NS): (i) 'strong' (symbol ↓↓↓ or ↑↑↑) when $RR < 0.5$ (SS) or $RR > 2.0$ (SS); (ii) 'moderate' (symbol ↓↓ or ↑↑) when $RR < 0.5$ (NS), $0.5 \leq RR < 0.67$ (SS), $1.5 < RR \leq 2.0$ (SS) or $RR > 2.0$ (NS); (iii) 'weak' (symbol ↓or ↑) when $0.5 \leq RR < 0.67$ (NS), $0.67 \leq RR \leq 1.5$ (SS) or $1.5 < RR \leq 2.0$ (NS) and (iv) 'no association' (symbol −) when $0.67 \leq RR \leq 1.5$ (NS); the RR used in this paper denotes ratio measures of effect, including risk ratios, rate ratios, hazard ratios and odds ratios. When RRs for three or more exposure levels were reported, that for the highest level was employed for this classification. In the case of multiple publications of analyses of the same or overlapping data sets, only data from the largest or most updated results were included. Studies that reported RRs for indefinite exposure levels, or did not provide RRs or data necessary for the present authors to calculate relevant RRs, were excluded.

After this process, the strength of evidence was evaluated in a manner similar to that used in the WHO/FAO Expert Consultation Report (12), in which evidence was classified as 'convincing', 'probable', 'possible' and 'insufficient'. We assumed that biological plausibility corresponded to the judgment of the most recent evaluation from the IARC (3). Despite the use of this quantitative assessment rule, an arbitrary assessment cannot be avoided when considerable variation exists in the magnitudes of association among the results of each study. The final judgment, therefore, was made based on a consensus of the research group members, and it was therefore not necessarily objective. When we reach a conclusion that there is 'convincing' or 'probable' evidence of an association, we conduct a meta-analysis to obtain summary estimates for the overall magnitude of association.

MAIN FEATURES AND COMMENTS

We identified a total of 22 cohort (13–34) (Table 1) and 24 case–control studies (35–58) (Table 2). Of those cohort studies, two presented the results by sex (19,31), seven for men only (13–16,26,29,32) and 13 for men and women combined (17,18,20–25,27,28,30,33,34). The respective numbers for the case–control studies are two (45,54), nine (36–38,42,44,48–51) and 13 (35,39–41,43,46,47,52,53,55–58). Several studies showed the results separately according to study areas (16), different age categories (31), the severity of chronic liver disease (CLD) (33) or different control groups (49,54,56).

Study populations in the cohort studies, except for one study based on male alcoholics (26), were classified broadly into two categories: mostly healthy subjects ($n = 7$) such as local residents (14,16,25,31,32), physicians (13) and atomic bomb survivors (19) and patients with CLD (15,17,18,20–24, 27–30,33,34) ($n = 14$) (Table 1). Chronic infections with both HCV and HBV were taken into account in 12 studies, all of which followed patients with CLD (18,20–24, 27–30,33,34). In the case–control studies, excluding one study based on military men exposed to thorotrast (38), a

Table 1. Cohort studies on alcohol drinking and liver cancer among Japanese

Reference	Study period	Study population				Category	Number among cases	Relative risk (95% CI or *P*)	*P* for trend	Confounding variables considered	Comments
		Number of subjects for analysis	Source of subjects	Event followed	Number of incident cases or deaths						
Kono et al. (13)	1965–83	5130 men	Male physicians in western Japan	Death	51 men (primary 9, unspecified 42)	Never/past		1.00		Age, smoking	HBsAg and anti-HCV were not tested.
						Occasional		1.34 (0.61–2.98)			
						<2 go/day		1.80 (0.80–4.02)			
						≥2 go/day		2.36 (1.04–5.35)			
Hirayama (14)	1966–82	122261 men	95% of the census population in 29 health-center-covered areas in six prefectures	Death	788 men (liver cancer) or 123 men (primary liver cancer)	For liver cancer				Age	HBsAg and anti-HCV were not tested
						Not daily		1.00			
						Daily		1.25 ($P < 0.01$)			
						For primary liver cancer					
						Not daily		1.00			
						Daily		1.89 ($P < 0.01$)			
Inaba et al. (15)	1973–88	270 men	Patients with liver cirrhosis at Juntendo University Hospital	Death	46 men	Never		1.00		Age, HBsAg, histories of blood transfusion, hepatitis and surgical operation, smoking	Anti-HCV was not tested
						Current/past		0.41 (0.08–2.20)			
Shibata et al. (16)	1958–86	639 men in a farming area and 677 men in a fishing area	Residents in a farming area or a fishing area in Kyushu	Death	11 men (farming area) and 22 men (fishing area)	Farming area					HBsAg and anti-HCV were not tested
						Non-drinker	2	1.0	>0.1	Age	
						Sake <1 go/day	6	1.1 (0.2–5.5)			
						Sake 1–2 go/day	2	1.6 (0.2–11.6)			
						Sake ≥2 go/day	1	1.1 (0.1–13.5)			
						Fishing area					
						Non-drinker	2	1.0		Age	
						Sake <1 go/day	0	–			
						Sake 1–2 go/day	0	–			
						Sake ≥2 go/day	1	5.5 (0.6–51.1)			

						Fishing area					
						Shochu none	4	1.00	<0.01	Age, smoking	
						Shochu <2 go/day	14	5.85 (1.31–26.18)			
						Shochu ≥2 go/day	4	14.02 (2.34–83.89)			
Kato et al. (17)	1987–90	1784	Patients with decompensated liver cirrhosis or post-transfusion hepatitis	Incidence	122	Never drinker	46	1.00		Sex, age	HBsAg and anti-HCV status was unknown. The total alcohol index was obtained by multiplying the daily ethanol intake (ml) by the number of years of drinking
						Past drinker	19	0.58 (0.32–1.04)			
						Occasional drinker	4	0.43 (0.15–1.24)			
						Current drinker	5	0.41 (0.16–1.06)			
						Total alcohol index					
						0	46	1.00	0.046		
						1–1999	10	0.49 (0.23–1.02)			
						2000+	13	0.53 (0.27–1.04)			
Tsukuma et al. (18)	1987–91	917 (548 men and 369 women)	Patients with chronic hepatitis or compensated cirrhosis at Center for Adult Diseases, Osaka	Incidence	54	Nondrinker		1.00		Age, sex, stage of disease, serum alpha-fetoprotein, HBsAg, anti-HBc, anti-HCV, smoking	HBsAg and anti-HCV status was adjusted for.
						Occasional drinker		0.77 (0.20–2.99)			
						Former drinker					
						<80 g ethanol/day		1.46 (0.56–3.79)			
						≥80 g ethanol/day		1.66 (0.69–3.96)			
						Current drinker					
						<80 g ethanol/day		1.10 (0.39–3.07)			
						≥80 g ethanol/day		1.15 (0.35–3.78)			
Goodman et al. (19)	1980–89	36133	Atomic bomb survivors	Incidence	242 (156 men and 86 women)	For men				Sex, city, age at the time of bombing, age, radiation dose to the liver	HBsAg and anti-HCV were not tested.
						Never-drinker	25	1.00			
						Ever-drinker	126	1.11 (0.72–1.70)			
						Ex-drinker	25	2.33 (1.34–4.07)			
						Quit ≥16 years ago	4	0.96 (0.33–2.77)			

Continued

Table 1. *Continued*

Reference	Study period	Study population				Category	Number among cases	Relative risk (95% CI or *P*)	*P* for trend	Confounding variables considered	Comments
		Number of subjects for analysis	Source of subjects	Event followed	Number of incident cases or deaths						
						Quit 11–15 years ago	8	2.08 (0.93–4.67)			
						Quit ≤10 years ago	12	7.87 (3.89–16.0)			
						Present drinker	100	0.98 (0.63–1.52)			
						<135 ml/week	37	1.09 (0.65–1.81)			
						135–299 ml/week	37	1.11 (0.67–1.86)			
						≥300 ml/week	37	1.12 (0.67–1.87)			
						For women					
						Never/past drinker	56	1.00			
						Present drinker	27	1.25 (0.78–1.98)			
						<27 ml/week	1	0.28 (0.04–2.02)			
						27–69 ml/week	6	1.20 (0.52–2.79)			
						≥70 ml/week	9	2.02 (0.99–4.09)			
Chiba et al. (20)	1977–93	412 (249 men and 163 women)	Patients with HCV-associated chronic hepatitis or compensated cirrhosis at Tsukuba University Hospital	Incidence	63 (54 men and 9 women)	Nondrinker		1.00		Sex, age, stage of disease, serum alpha-fetoprotein, anti-HBs, anti-HBc, histories of blood transfusion, surgical procedure and liver cancer in family, smoking	All subjects were anti-HCV-positive and HBsAg-negative.
						<150 kg ethanol		1.33 (0.60–2.93)			
						150–449 kg ethanol		1.50 (0.71–3.17)			
						≥450 kg ethanol		0.98 (0.43–2.23)			
Ikeda et al. (21)	1980–?	2215 (1544 men and 671 women)	Patients with chronic hepatitis at Toranomon Hospital	Incidence	89	All subjects	($n = 2215$)			Stage of hepatitis, gamma-glutamyl transpeptidase	HBsAg and anti-HCV status was available for all subjects.
						<500 kg ethanol		1.00			
						≥500 kg ethanol		3.04 (1.79–5.14)			
						HBsAg(+) anti-HCV(−) subjects	($n = 610$)			Indocyanine green retention rate	

						<500 kg ethanol		1.00			
						≥500 kg ethanol		8.37 (2.70–25.93)			
						HBsAg(−) anti-HCV(+) subjects	($n = 1500$)			Stage of hepatitis, γ-glutamyl transpeptidase, history of blood transfusion, albumin	
						<500 kg ethanol		1.00			
						≥500 kg ethanol		1.96 (1.06–3.62)			
Tanaka et al. (22)	1985–95	96 (62 men and 34 women)	Patients with liver cirrhosis at Kyushu University Hospital	Incidence	37 (27 men and 10 women)	Never	16	1.00		Sex, age, years since LC diagnosis, department, hospitalization status, serum albumin, AST, alpha-fetoprotein, HBsAg, anti-HCV, smoking	HBsAg and anti-HCV status was adjusted for. The relative risks were not described in the original paper, and were reestimated by one of the authors (KT). One 'drink' corresponds to 23 ml of ethanol.
						Past	17	0.59 (0.20–1.73)			
						Current					
						<2.4 drinks/day	1	0.06 (0.01–0.57)			
						≥2.4 drinks/day	3	0.17 (0.02–1.42)			
Matsushita et al. (23)	1985–94	267 (165 men and 102 women)	Patients with liver cirrhosis at Kanazawa University Hospital	Incidence	67	Type B or C cirrhosis	($n = 202$)			Age, anti-HCV	All subjects analyzed were positive for anti-HCV or HBsAg.
						Positive drinking history		1.83 (1.00–3.36)			
						Type C cirrhosis	($n = 140$)			Age	
						Positive drinking history		2.36 (1.23–4.54)			
Aizawa et al. (24)	1981–98	153 (115 men and 38 women)	Patients with chronic hepatitis or cirrhosis positive for anti-HCV at Jikei University Hospital	Incidence	Not described	Habitual heavy drinking				Sex, age, ALT, interferon therapy, histologic staging, irregular regeneration	All subjects were anti-HCV-positive and HBsAg-negative. Habitual heavy drinking was defined as an average daily consumption of 65 g of ethanol for >5 years.
						No		1.00			
						Yes		3.04 (1.31–7.09)			
Mori et al. (25)	1992–97	3052 (974 men and 2078 women)	Residents in a town in Saga prefecture	Incidence	22 (14 men and 8 women)	History of habitual alcohol consumption				Sex, age	Anti-HCV and HBsAg status was available but not adjusted for.
						No	10	1.00			
						Yes	22	1.27 (0.46–3.47)			
						Never drinker	10	1.00	0.87		One 'drink' corresponds to a glass of sake.
						1–19 drink-years	3	2.05 (0.48–8.79)			
							9				

Continued

Table 1. *Continued*

Reference	Study period	Study population				Category	Number among cases	Relative risk (95% CI or *P*)	*P* for trend	Confounding variables considered	Comments
		Number of subjects for analysis	Source of subjects	Event followed	Number of incident cases or deaths						
						≥20 drink-years		1.14 (0.40–3.26)			
Noda et al. (26)	1972–92	306 men	Alcoholics in Takatsuki city, Osaka, who had been diagnosed at a psychiatric institution	Death	Not described	O/E ratio for hepatocellular carinoma		1.6 (0.3–4.7)		Age, calendar year	Anti-HCV and HBsAg were not tested.
Hamada et al. (27)	1980–2000	469 (227 men and 242 women)	Patients with clinically compensated chronic hepatitis C due to blood transfusion at National Nagasaki Medical Center	Incidence	52	Alcohol consumption				Age, serum bilirubin, platelets, interferon therapy, duration from infection, fibrosis	All subjects were anti-HCV-positive and HBsAg-negative. Excessive alcohol consumption was defined as an alcohol consumption of >50 g/day for 5 years.
						Not excessive		1.00			
						Excessive		2.21 (1.00–3.58)			
Takimoto et al. (28)	1989–?	356	Patients with histologically proven chronic hepatitis C at Niigata University Hospital and one hospital in Niigata, who did not respond to interferon therapy	Incidence	Not described	Alcohol drinking				Age, sex, blood transfusion, viral load, viral subtype, stage of fibrosis, ALT, platelets, interferon dose	All subjects were anti-HCV-positive and HBsAg-negative. Alcohol drinking was defined as having consumed >80 g ethanol daily for >5 years.
						No		1.00			
						Yes		4.30 ($P = 0.048$)			
Uetake et al. (29)	1988–2000	91 men	Patients with HBsAg-negative anti-HCV-negative alcoholic cirrhosis at Jikei University Hospital	Incidence	13 men	Cumulative alcohol intake (kg)				Anti-HBc	All patients were HBsAg-negative, anti-HCV-negative, and alcoholic. The hazard ratio (and 95% confidence interval) was not described in the original paper, and was estimated by one of the authors (KT).
						1200 kg increase		7.7 (1.9–31.5)	0.0047		
Iwasaki et al. (30)	1986–2003	792 (533 men and 259 women)	Hepatitis C patients with or without Child A cirrhosis at Okayama University Hospital and participating institutions, with sustained response to interferon	Incidence	23 (20 men and 3 women)	Alcohol consumption				Fibrosis staging, age	All subjects were anti-HCV-positive and HBsAg-negative.
						<50 g/day		1.00			
						≥50 g/day		3.86 (1.58–9.44)			
Ogimoto et al. (31)	1988–99	66974 (28343 men and 38631 women)	Residents in 45 areas throughout Japan	Death	184 (number by sex and age not described)	Male, 40–59 years	($n = 16715$)			Collaborating institute	HBsAg and anti-HCV were not tested.
						Never drinker		1.00			
						Ex-drinker		8.11 (3.17–20.77)			
						Current drinker		0.65 (0.27–1.52)			