また，身長，体重，既往歴も調査し，肥満や糖尿病などの合併症の影響についても検討を行った．

肝硬変の診断は，剖検，腹腔鏡，画像検査により形態的に明らかなもの，および臨床的に食道静脈瘤，腹水，脳症などを有するか血液，凝固，生化学検査で肝硬変と診断できるものとした．肝炎ウイルスマーカーで，少なくともHBs抗原とHCV抗体が陰性が判明しているものを肝炎ウイルスマーカー陰性群とし，HBc抗体，HBs抗体など他の肝炎ウイルスマーカー陽性が判明しているものはこの群から除外した．

純エタノール換算で一日飲酒量60 g以上-110 g未満のものを常習飲酒群，一日飲酒量110 g以上のものを大量飲酒群と定義した．

年齢や飲酒期間についてはStudent t-test，飲酒量（常習飲酒群と大量飲酒群），合併症などの関係については乖二乗検定を用いて有意差を検討した．P値が0.05未満の場合を有意差ありとした．

3. 結　果

郵送対象施設数1234施設に対して，有効な回答のあった施設は98施設で，回答率は7.9%であった．飲酒量の調査しえた肝炎ウイルスマーカー陰性アルコール性肝硬変例1207例について検討した．初回入院時の平均年齢は，男性55.3歳，女性50.2歳と女性が有意に若かった（Table 1）．1日平均飲酒量は男性が平均129 g/日，女性が131 g/日と有意差はなかったが，常習飲酒期間は，男性が平均31.2年に対し女性は22.5年であり，女性は短い飲酒期間で肝硬変に罹患していた．合併症の割合では，糖尿病の有病率は，男性では全男性アルコール性肝硬変患者のうち25.8%を占めているのに対し，女性は12.1%であった（Table 2）．特に常習飲酒群では，糖尿病の有病率は，男性常習飲酒群では45.2%を占めているのに対し，女性は16.7%で有意に少なかった．肥満（Body Mass Index：BMI 25以上）の割合は，男性42.4%，女性47.4%と有意差を認めなかった．しかし，常習飲酒群のうち肥満合併者の割合は51.1%を占めたのに対し，大量飲酒群では37.3%と有意に少なかった．糖尿病，胃切除，肥満（BMI 25以上）のいずれかが合併している率は，常習飲酒群では，男性が85.9%を占めたのに対し，女性は62.1%で，有意に女性の方が少なかった（Table 2）．一方，合併症毎の常習飲酒群と大量飲酒群の比率を見ると（Table 3），糖尿病合併群では，常習飲酒群が68.9%を占めているのに対し，糖尿病非合併群は31.1%であった．肥満については糖尿病よりは肝硬変進展への関与は少ないものの，BMI 25以上の群では常習飲酒群が48.6%に対して，BMI 25未満の肥満群では常習飲酒群が35.0%と，肥満群で常習飲酒群の比率が大量飲酒群よりも多かった．合併症のない群では，男性の85.6%を大量飲酒群が占め，常習飲酒群で肝硬変に至る例は14.4%と少数であった．

Table 1 Daily Alcohol Intake, Duration in Alcoholic Liver Cirrhosis

	Total	Male	Female
Number	1207	1091	116
Age (y/o)	54.8	55.3＊	50.2
Daily intake (g)	129	129	131
Duration (y)	30.4	31.2＊	22.5

Data is expressed as mean value.
Daily alcohol intake expressed as 100% ethanol/day.
＊P<0.05 vs female

4. 考　察

肝疾患におけるアルコール性肝障害の比率と成人一人あたりのアルコール消費量の相関をみると，最近は成人一人あたりの飲酒量の増加は上げ止まったものの，年々肝疾患におけるアルコール性肝障害の比率は増加しており，2002年度には20%を超えて22.8%に達した[3]．また，アルコール性肝硬変におけるアルコール単独とアルコール＋ウイルス性の比率が，アルコール単独によるものが1998年度[5]は45%であったが，本研究の1次調査の結果でも69%とその比率が上昇し，最近はアルコール性肝硬変への進展に肝炎ウイルスの病態への影響は少なくなってきていると考えられる[6]．

アルコール性肝障害において肝炎ウイルス感染の合併が減少する中，全肝疾患におけるアルコール性肝障害の比率が飲酒量の増加なく増えている一つの理由として，女性の飲酒者数の増加が考えられる．疫学的には，飲酒量が同等の場合，女性においてアルコール性肝障害が進展しやすいことが報告されている[7)~9)]．週に7-41単位（日本酒換算で1日0.5-3合）の飲酒においては，女性においてアルコール性肝障害のリスクが男性の約2倍に高まるとの報告がある[8]．わが国において女性の飲酒率が増加しており，それに伴ってアルコール性肝障害患者における女性の割合が増加している[4]．居酒屋や屋台といった主に中年男性の飲酒場所への女性進出の他に，ワインバーやイタリアンレストランなどの増加，既製の缶入りカクテルの販売など，アルコー

Table 2 Complications in Alcoholic Liver Cirrhosis

Number (%)	Total	Male	Female
Complications			
Diabetes Mellitus (+)	296 (24.5%)	282 (25.8%)*	14 (12.1%)
60－110 g	204 (41.4%)	193 (45.2%)*	11 (16.7%)
≧ 110 g	92 (12.9%)	89 (13.4%)	3 (6.0%)
Diabetes Mellitus (－)	911 (75.5%)	809 (74.2%)	102 (87.9%)
60－110 g	289 (58.6%)	234 (54.8%)*	55 (83.3%)
≧ 110 g	622 (87.1%)	575 (86.6%)	47 (94.0%)
Obesity (BMI, 25 ≦)	518 (42.9%)	463 (42.4%)	55 (47.4%)
60－110 g	252 (51.1%)#	221 (51.8%)#	31 (47.0%)
≧ 110 g	266 (37.3%)	242 (36.4%)	24 (48.0%)
Obesity (BMI, < 25)	689 (57.1%)	628 (57.6%)	61 (52.6%)
60－110 g	241 (48.9%)#	206 (48.2%)#	35 (53.0%)
≧ 110 g	448 (62.7%)	22 (63.6%)	26 (52.0%)
Any complications	743 (61.6%)	675 (61.9%)	68 (58.6%)
60－110 g	408 (82.8%)#	367 (85.9%)*	41 (62.1%)
≧ 110 g	335 (46.9%)	308 (46.4%)	27 (54.0%)
No complication	464 (38.4%)	416 (38.1%)	48 (41.4%)
60－110 g	85 (17.2%)#	60 (14.1%)*	25 (37.9%)
≧ 110 g	379 (53.1%)	356 (53.6%)	23 (46.0%)

Daily alcohol intake expressed as 100% ethanol/day.
*$P < 0.005$ vs female.
#$P < 0.05$ vs ≧ 110 g group.
Complications include diabetes mellitus, obesity, and/or past history of gastorectomy.

ルを提供する側の変化も関与していると思われる．女性の社会進出に伴う飲酒機会の増加と女性に好まれる食・飲酒習慣への変化により，今後女性のアルコール性肝障害患者の増加が予想される．実際，2003年度の調査では，KASTによるスクリーニングテストで女性の問題飲酒者と判定される人数が，1984年度の約2倍に増加している[4]．今回の検討でも，初回入院時の平均年齢はそれぞれ男性55.3歳，女性50.2歳と女性が有意に若く，常習飲酒期間が男性31.2年に対し女性22.5年であり，女性は短期間の飲酒で肝硬変に至ることが示唆された．

また，合併症の割合では，肥満（BMI 25以上）の割合は，男性42.4%，女性47.4%と性差を認めなかった．肥満の合併率は，常習飲酒群では全患者の51.1%を占めたのに対し，大量飲酒群では37.3%で有意に少なかった．糖尿病の有病率は，男性が25.8%を占めるのに対し，女性は12.1%であった．特に常習飲酒群では，糖尿病の有病率は男性常習飲酒群では45.2%を占めるのに対し，女性常習飲酒群は16.7%で有意に少なかった．糖尿病，胃切除，肥満（BMI 25以上）のいずれかが合併している率は，常習飲酒群では，男性が85.9%を占めるのに対し，女性は62.1%で，有意に女性の方が少なかった．これらの結果から，女性は糖尿病，胃切除，肥満などのアルコール性肝硬変進展促進因子とは独立した危険因子であることが示唆された．

BMIと脂肪肝の有病率や程度も正の相関を示し，肥満も肝障害を誘発する重要な因子といえる．肥満などに起因する非飲酒者（1日エタノール換算で20 g以下の飲酒者）の脂肪肝患者の一部に，炎症，壊死，線維化を伴いアルコール性肝炎に類似する組織所見を呈するnon-alcoholic steatohepatitis（NASH）を認める．NASHは，1980年にLudwigら[10]により提唱され，その後肝硬変から肝細胞癌に至る例もあることが報告された．日本人は欧米人と比較して基礎代謝量が低くなる倹約遺伝子（β3アドレナリン遺伝子多型）をもち，つまり少ない食事量で生存可能である[11]．こうした背景も受けて，わが国でも人口の約3%がNASHに罹患していると推計されている[12]．本邦でのBMIが30以上の肥満者は約

Table 3 Relationship between Daily Alcohol Intake and Complications in Alcoholic Liver Cirrhosis

Number (%)	Total	Male	Female
Number	1207	1091	116
Daily alcohol intake			
60–110 g	493 (40.8%)	427 (39.1%)	66 (56.9%)
≧ 110 g	714 (59.2%)	664 (60.9%)	50 (43.1%)
Diabetes Mellitus (+)	296	282	14
60–110 g	204 (68.9%)*	193 (68.4%)*	11 (78.6%)
≧ 110 g	92 (31.1%)	89 (31.6%)	3 (21.4%)
Diabetes Mellitus (−)	911	809	102
60–110 g	289 (31.7%)	234 (28.9%)	55 (53.9%)
≧ 110 g	622 (68.3%)	575 (71.1%)	47 (46.1%)
Obesity (BMI, 25 ≦)	518	463	55
60–110 g	252 (48.6%)**	221 (47.7%)	31 (56.4%)
≧ 110 g	266 (51.4%)	242 (52.3%)	24 (43.6%)
Obesity (BMI, < 25)	689	628	61
60–110 g	241 (35.0%)	206 (32.8%)#	35 (57.4%)
≧ 110 g	448 (65.0%)	422 (67.2%)	26 (42.6%)
Any complications	743	675	68
60–110 g	408 (54.9%)***	367 (54.4%)	41 (60.3%)
≧ 110 g	335 (45.1%)	308 (45.6%)	27 (39.7%)
No complication	464	416	48
60–110 g	85 (18.3%)	60 (14.4%)#	25 (52.1%)
≧ 110 g	379 (81.7%)	356 (85.6%)	23 (47.9%)

Daily alcohol intake expressed as 100% ethanol/day.
*P < 0.001 vs Diabetes Mellitus (−) group.
**P < 0.05 vs Obesity (−) (BMI < 25) group.
***P < 0.001 vs No complication group.
#P < 0.05 vs female.
Complications include diabetes mellitus, obesity, and/or past history of gastorectomy.

250万人と推計され，1日エタノール換算で120 g以上（日本酒換算で5.5合以上）の大量飲酒者の推計数とほぼ同等である[13]．このNASHから肝硬変の流れも重要であり，本邦でも非ウイルス性，非アルコール性の肝硬変や肝細胞癌も，一般臨床の場で少なからず経験するようになってきている．このような群に飲酒が加われば，肝硬変の進展が早まることは十分に考えられる．

アルコール性肝硬変の危険因子として，飲酒量や年齢，性差のほかに，高脂肪食や体重過多が関与しているとの報告があり，肥満は直接アルコール性肝硬変の危険因子となる可能性がある[14)~16)]．飲酒に伴う栄養障害としては，栄養素の欠乏や低栄養状態が取り上げられてきたが，現代の先進国においてはむしろ過栄養による肥満や糖尿病が問題となっており，こうした過栄養がアルコール性肝障害の進展を増強することが示唆されている．BMIが25を少し越した程度で，飲酒量も2合程度の脂肪肝，肝炎患者は，厳密にはNASHやNAFLD（non-alcoholic fatty liver disease）にも，アルコール性肝障害にも含まれない．（NASHは1合以下，アルコール性肝障害は3合以上の飲酒者とされている．）今後はこうした，overlap steatohepatitisとでも呼ぶべきsub-clinicalな肝障害患者にも目を向ける必要があろう．

実際，常習飲酒群では，糖尿病の有病率は男性では45.2%を占め，大量飲酒群の13.4%より有意に高く，肥満（BMI 25以上）の合併率も51.8%と大量飲酒群の36.4%より高かった（Table 2）．また，常習飲酒群のうち糖尿病，胃切除，肥満（BMI 25以上）のいずれかが

合併している率は，男性が85.9%であったのに対し女性は62.1%であり，また男性の大量飲酒群の46.4%と比較しても高かった(Table 2)．一方，合併症毎の常習飲酒群と大量飲酒群の比率を見ると，糖尿病合併群では，常習飲酒群が68.9%と，糖尿病非合併群の31.7%に比して有意に高かった(Table 3)．肥満については糖尿病よりは肝硬変進展への関与は少ないものの，BMI 25以上の肥満群では常習飲酒群が48.6%に対して，BMI 25未満の群では常習飲酒群が35.0%と，BMI 25以上の肥満群で常習飲酒者の比率が多かった．合併症のない群では，男性では85.6%が一日110 g以上の飲酒者であり，常習飲酒群で肝硬変に至る例は14.4%と少数であった．これらの結果から，男性の常習飲酒群では，糖尿病，胃切除，肥満などのアルコール性肝硬変進展促進因子との合併により比較的少量(60–110 g)の飲酒で肝硬変に進展していることが示唆された．

5. 結　語

常習飲酒群で肝硬変に至った群では，糖尿病，肥満などのアルコール性肝硬変進展促進因子の合併が多く，これらの因子が肝硬変進展に関与していることが示唆された．糖尿病合併アルコール性肝硬変患者が飲酒を継続した場合予後が有意に悪いことも報告されている[17]．糖尿病，肥満などの生活習慣病の予防と合わせた生活指導，節酒指導が重要であり，こうした生活習慣病合併アルコール性肝硬変患者への断酒指導も重要と考えられた．

また，女性のアルコール性肝硬変は男性と比較し短期間で進行し，女性は糖尿病，胃切除，肥満などのアルコール性肝硬変進展促進因子とは独立した危険因子であることが示唆された．近年の女性を中心とした飲酒者数の増加を見ると，飲酒者への適正飲酒の指導が重要であり，また潜在化している問題飲酒者への禁酒，節酒の教育・指導は，今後はさらに重要になると考えられる．特に女性の飲酒問題が重要で，妊娠による胎児への影響の問題に加え，医療機関受診率の低さや大量飲酒を認めない否認傾向も問題となっている．社会全体での女性の飲酒問題への取り組みが不可欠と思われる．

謝辞：今回のアンケート調査にご協力いただいた，下記の医療機関に対して，心より謝意を表します．

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文　献

1) 国税庁課税部酒税課.「平成20年度酒のしおり」2008
2) 厚生統計協会. 厚生の指標「国民衛生の動向」2000, p92
3) 堀江義則，石井裕正，日比紀文. わが国のアルコール性肝障害の現状についての検討. 日本アルコール・薬物医学会雑誌　2004；39：505—510
4) 尾崎米厚，松下幸生，白坂知信，他. わが国の成人飲酒行動およびアルコール症に関する全国調査. 日本アルコール・薬物依存医学会雑誌　2005；40：455—470
5) 小林健一，他編.「肝硬変の成因別実態1998」中外医学社，1999
6) 堀江義則，山岸由幸，菊池真大，他. 飲酒の肝硬変進展への影響—C型肝炎とアルコール性肝硬変の関係について. 日本アルコール・薬物依存医学会雑誌　2009；44：38—42
7) Morgan MY, Sherlock S. Sex-related differences among 100 patients with alcoholic liver disease. Br Med J 1977; 1: 939—941
8) Becker U, Deis A, Sorensen TI, et al. Prediction of risk of liver disease by alcohol intake, sex, and age: a prospective population study. Hepatology 1996; 23: 1025—1029
9) Kwo PY, Ramchandani VA, O'Connor S, et al. Gender differences in alcohol metabolism: relationship to liver volume and effect of adjusting for body mass. Gastroenterology 1998; 115: 1552—1557
10) Ludwig J, Viggiano TR, McGill DB, et al. Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. Mayo Clin Proc 1980; 55: 434—438
11) 西原利治，大西三郎. 肝胆膵の代謝・機能と生活習慣—本邦の現状. 肝胆膵　2005；51：855—860
12) Nozaki Y, Saibara T, Nemoto Y, et al. Polymorphisms of interleukin-1 beta and beta 3-adrenergic receptor in Japanese patients with nonalcoholic steatohepatitis. Alcohol Clin Exp Res 2004; 28: 106S—110S
13) 厚生労働省.「国民栄養調査」2002
14) Rotily M, Durbec JP, Berthezene P, et al. Diet and alcohol in liver cirrhosis: a case-control study. Eur J Clin Nutr 1990; 44: 595—603
15) Iturriaga H, Bunout D, Hirsch S, et al. Overweight as a risk factor or a predictive sign of histological liver damage in alcoholics. Am J Clin Nutr 1988; 47: 235—238
16) Naveau S, Giraud V, Borotto E, et al. Excess weight risk factor for alcoholic liver disease. Hepatology 1997; 25: 108—111
17) Yokoyama A, Ishii H, Takagi T, et al. The impact of diabetes mellitus on the prognosis of alcoholics. Alcohol Alcohol 1994; 29: 181—186

Current status of alcoholic liver cirrhosis and factors involved in the progression

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We addressed the recent trend in alcoholic liver cirrhosis (LC) in Japan. Nation wide survey was carried by asking the hospitals that are qualified by the Japanese Society of Gastroenterology for the number of hospitalized-patients of LC in 2007 and etiology of LC. Concerning alcoholic LC, we also obtained the amount of daily alcohol intake and period of habitual drinking.

There was no significant gender difference in daily alcohol intake, while the period of habitual drinking in female patients with LC was shorter than that in male patients. Among the patients whose daily alcohol intake was less than 110 g/day, prevalence of diabetes mellitus and/or obesity (BMI≧25) were significantly higher.

Shorter period of alcohol drinking was found in the female alcoholic LC compared with male LC. Obesity and diabetes mellitus appeared to be involved in the progression of alcoholic LC. Education of low risk drinking and improvement of total life style are important to decrease the prevalence of alcoholic liver disease.

Key words: alcohol liver cirrhosis gender difference diabetes mellitus obesity

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一般医療現場での対応

堀江義則*

abstract

アルコール使用障害を認める患者が最初に医療機関を受診する場合，そのほとんどが身体症状や健康診断での異常値を主訴に内科外来を受診するか，外傷などで救急外来や整形外科を受診する．外来においては，まずは節酒を指導する．節酒指導では，Brief Interventionと呼ばれる行動変化をもたらすことを目標とした短時間のカウンセリングを行う．「健康」を主なテーマとして飲酒量低減の具体的な目標を自ら設定してもらう．そのために毎日の飲んだ時間，量，誰と飲んだかなど飲酒日記をつけるとよい．過剰飲酒を防ぐ方法を日記をもとに具体的に検討する．あまりに厳しい指導は外来通院の中断につながるおそれがある．「褒める」「励ます」「共感する」がキーワードである．しかし，初期のうちは禁酒により速やかに改善するため，患者が病状を深刻に考えず，再度，使用障害に至ることも多い．病状が進行した後も，単に臓器障害の治療を行うのみでは，ほとんどの場合，再飲酒をきたし入退院を繰り返す．節酒できず肝機能の改善がない場合や，肝硬変，慢性膵炎など病状が進んだ段階ではアルコール依存症の可能性が高いことを説明し，精神科やアルコール症専門病院を紹介する必要がある．

はじめに

わが国には，問題飲酒（アルコール使用障害）者は約300～400万人，アルコール依存症患者は約80万人いると推計されているが[1]，精神科にてアルコール依存の治療を行っている患者数は2万人程度である．アルコール使用障害が原因で入院している患者は21万人で，外来患者は119万人と推計されており[2]，その多くは精神科やアルコール専門病院ではなく，内科などの一般診療科で治療されている．アルコール使用障害を認める患者が最初に医療機関を受診する場合，身体症状や健康診断での異常値を主訴に内科外来を受診するか，外傷などで救急外来や整形外科を受診することがほとんどである．アルコール使用障害を認識した時点で自ら節酒できる人にはスムーズに診療が行われるが，自ら節酒できない人が大多数である．自ら節酒できない人の診療で問題となるのが，初期のうちは禁酒により速やかに改善するため，患者が病状を深刻に考えず，症状が消失すると通院を中断し，再度，使用障害に至る点である．アルコール性臓器障害の進展は個人差が大きく，他人は同じ飲酒量で臓器障害がないのに，自分だけに発症したことに納得がいかないことも問題となる．節酒ができない理由として，飲酒期間が10年，20年といった長期にならないと症状が出ないため，すでに依存が生じている点と，今までと同じ量を飲酒しているにもかかわらず突然症状が出たことに対し飲酒が原因と素直に受け止められない点が挙げられる．

内科外来におけるアルコール医療はアルコール性

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消化器疾患	
食道	：食道潰瘍，食道炎，食道癌，食道静脈瘤，Mallory-Weiss症候群
胃・十二指腸	：胃・十二指腸潰瘍，胃・十二指腸炎，急性胃粘膜病変（出血性胃炎）
小腸・大腸	：びらん，下痢，吸収障害，大腸癌
肝臓	：脂肪肝，肝炎（重症型アルコール性肝炎），肝線維症，肝硬変，肝細胞癌
膵臓	：急性膵炎，慢性膵炎
脳神経障害	：ビタミン欠乏 Wernicke-Korsakoff症候群，小脳変性症，ペラグラ，多発神経炎 （下肢遠位部から侵され，鈍い持続痛） アルコール性認知症 アルコール性大脳萎縮（前頭葉に顕著である）
アルコール性筋症（ミオパチー）	：赤色筋，下肢近位筋に多い
骨疾患	：骨粗鬆症，大腿骨骨頭壊死
循環器疾患	：高血圧症，アルコール性心筋症，虚血性心疾患，不整脈
造血器障害	：巨赤芽球性貧血，溶血性貧血，血小板減少
代謝障害	：高中性脂肪血症，VLDL上昇，pre・リポ蛋白分画増加，高乳酸血症，高尿酸血症

表
習慣性の大量飲酒に伴う臓器障害

臓器障害を治療する役割をもつが，このような特徴から他の臓器障害の治療にはない困難性があり，投薬などの治療内容は同じでも異なるアプローチが必要である．

内科診療におけるアルコール症治療の問題点

内科におけるアルコール医療では，患者に病識がなく，健康診断などで異常を指摘されていても病気を治そうとする意思がないことが問題となる．病気を治そうと受診するときは自覚症状を認める段階であり，そのためにかなり病状が進んでいることが多い．肝硬変や慢性膵炎，心筋症や脳神経障害など病状が進んだ段階ではアルコール依存症の可能性が高く，断酒が必要である．このような患者は，精神科（できればアルコールの専門機関）への紹介が必要となるが，またここにも問題があり，断酒の必要性が高い依存症者ほど断酒できない傾向にある．

比較的病状が進んでいない状態では，節酒できる可能性もあり，まず節酒を勧める．2週間ごとに通院してもらい，肝機能の推移を確認する．この段階では家族が自ら同伴してくることは少ないが，外来受診時に家族を同伴させると効果的なことが多い．節酒できない旨の自己申告があった場合や，肝機能の改善がない場合には，依存症の可能性が高いことを説明しアルコール症専門病院を紹介する．プレアルコホリック（家庭不和，無断欠勤，飲酒運転などのアルコール関連の社会的問題をもつが，連続飲酒発作や離脱症状のないもの）は，内科で治療をするか専門病院を紹介するかの境目の段階にあるが，どちらで治療するにしても早期介入すれば，依存症の予防につながるし，治療期間も短縮できる[3]．しかし，現代医療では臓器別に細分化，専門化が進んでおり，専門医は多臓器にわたる病態をもつ患者に興味をもちにくい．アルコール症では多臓器に障害があることが多く（表），複数の医師で診察に当たることがある．この場合，最終責任を誰がもつかが不明瞭となり，介入の遅れから依存症が進行するリスクが高い．単に臓器障害の治療を行うのみでは，ほとんどの場合，再飲酒をきたし，入退院を繰り返すこととなる（図1）．これでは臨床医の役割は，飲める体に戻してあげることになり，治療を遅らせるだけでなく医療費の無駄遣いとなる．内科を受診する体調の悪い時期は，患者も救いを求めている時期であり，節酒や断酒の説得のチャンスである．行動変化をもたらすための精神的な介入が，この悪循環を断つために必要である．

外来での接し方（介入方法）

アルコール使用障害を認める患者の外来診療においては，まず問診（特に飲酒歴の聴取）が重要であ

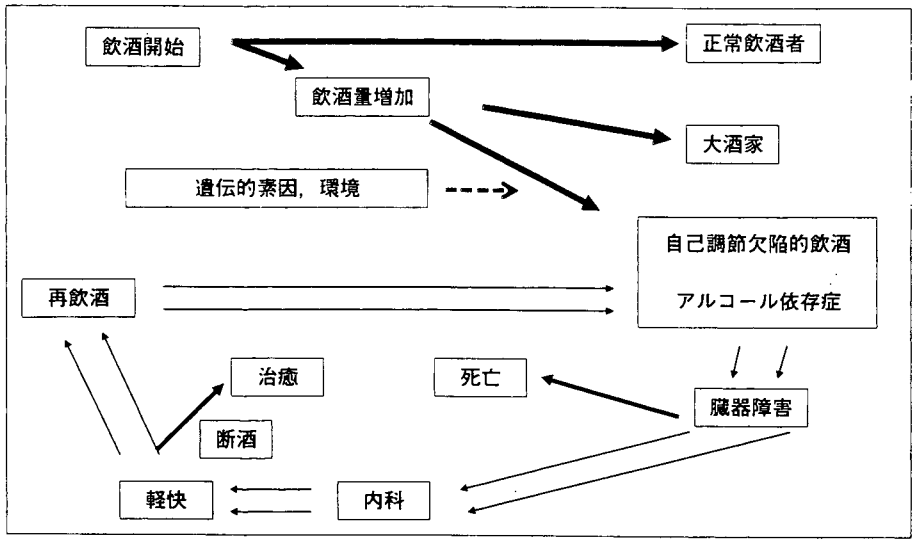

図1
アルコール依存症の自然史
単に臓器障害の治療を行うのみでは，ほとんどの場合，再飲酒をきたし，入退院を繰り返すこととなる．精神的な介入により断酒させることが，この悪循環を断つために必要である．

る．問診は診断のためだけでなく，患者に自分の飲酒習慣を振り返って反省してもらうための治療行為としても重要であり，機械的な聴取ではなく時間をかけて具体的に聞く必要があり，忙しい外来診療の合間では困難を極めるため，看護師やソーシャルワーカーなどの協力を得て行う必要がある．飲酒量の問診では，「一日どのくらい飲みますか？」ではなく，「最高に飲んだときは？」，「何を飲みますか？」「ボトルは何日で空きますか？」と具体的な質問をする．「今はやめています」とか，「最近は1合に減らしています」などと答えた際は，「いつからですか？」と飲酒期間を具体的に聞く必要がある．それでも過少申告していることが多く，家族からの情報も重要である．

初診の段階で依存症と診断がつく患者には，「あなたの病気はアルコールが原因です．お酒をやめる決意があるなら一生懸命治しますが，もし，やめる気がないなら協力できません」ときっぱりいう．依存症患者には節酒指導は行わない．断酒指導が必要であり，自信がなくても「やめます」と本人にいわせることが重要である．

依存症ではない場合は節酒を指導することになるが，とりあえず2週間は禁酒してもらう．2～3日で離脱症状が出たり，2週間禁酒できない場合は依存症のことが多く，断酒の必要性を説明し，アルコール症専門病院の受診を勧める．寝酒として飲酒習慣のある人も多いため，就寝前にジアゼパムなどの抗不安薬を処方するとよい．2週間の禁酒で多くの合併症（高血圧，高脂血症，糖尿病など）は軽快傾向を示すことが多い．また安易な投薬は「自分は臓器障害なんだ」と飲酒問題から目を逸らすリスクもあることから，外来での合併症治療の投薬は必要最低限に抑えるべきである．2週間禁酒できた場合はそのことを大いに褒め，食事がおいしい，体調がよいなど，禁酒してよかった点を聞き出す．そして，本格的な節酒指導へと移行する．

節酒指導では，Brief Interventionとよばれる行動変化をもたらすことを目標とした短時間のカウンセリングを行う．Brief Interventionの有効性はいくつかの論文で示されており，アメリカ予防医療専門委員会も臨床での実施を推奨するBランクの評価を与えている[4)～6)]．断酒ではなく飲酒量の低減（節酒）が目的であり，専門家ではなく一般診療科の医師や保健師など，ヘルスケアの従事者が行うのが特徴である．そのため依存症者の介入には用いられない．

その介入にはいくつかの留意点がある．まず，本人にとってどのような問題があるのか，「肝機能の数値が基準の3倍を超え，線維化がすでに始まっている」など，現在の身体状況を具体的に説明する．そのうえで，本人の責任意識をはっきりさせる必要があり，「今の状況はあなた自身のせいで，よくするにはあなた自身が行動を変えるしかない」と自己責任であることを強調する．しかし，飲酒問題の直面化は避け，「健康」を主なテーマとして飲酒量低

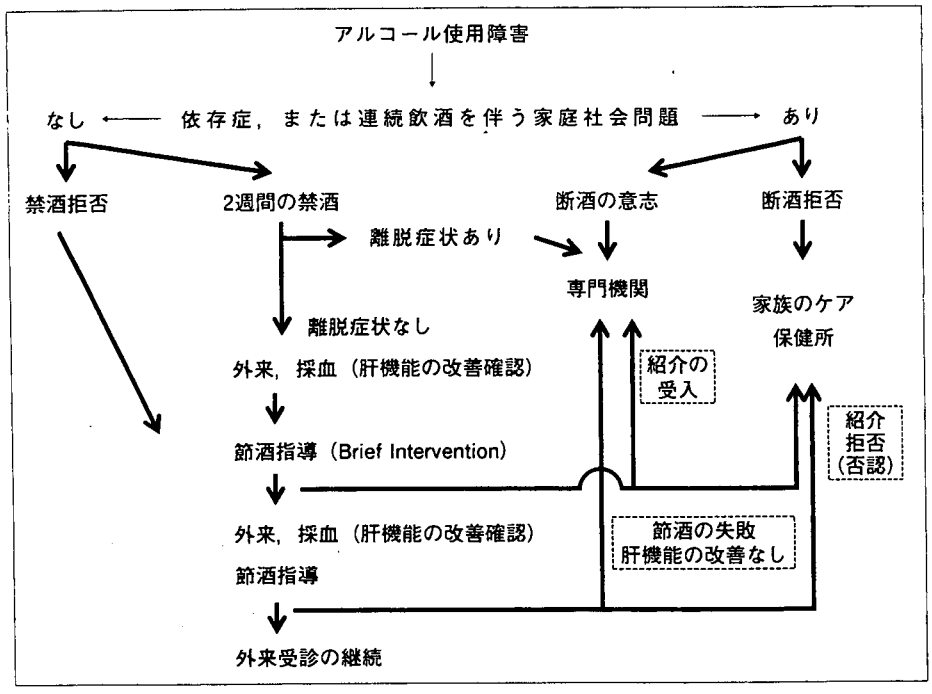

図2
アルコール使用障害者への治療介入フローチャート

減の具体的な目標を自ら設定してもらう．「健康」をテーマに早期介入すると否認や抵抗が少ない．

目標の自己設定が基本だが，必要に応じて医療者側が，わかりやすく，具体的で，しかも実現可能な戦略を，本人が選べるよう複数の選択肢をもって示すことも必要な場合がある．具体的なテクニックとしては，毎日の飲んだ時間，量，誰と飲んだか，その時の気分など飲酒日記をつけるとよい．飲酒量が増えたときはどんなときか，反省の材料にも使える．二次会を断る，濃い酒は薄めて飲む，食事と一緒に飲む，行きつけの店の前を通らないで帰るなど，ただ「控えなさい」ではなく過剰飲酒を防ぐ方法を日記をもとに具体的に検討する．実行可能な目標を立てる必要があり，あまりに厳しい指導は外来通院の中断につながるおそれがある．患者を叱るのではなく，患者の自己決定を尊重し，節酒のために自分でできることを提案してもらい，少しずつでもうまくいっているなら肝機能データの改善などを医師はフィードバックし，大いに褒める．うまくいっていないなら行動目標の切り替えを相談する．本を読む，運動をするなど，お酒以外の生活習慣にも目を向けさせるとよい．共感をもって接することが必要で，「あなたならきっとできる」といったように自己達成感を感じられるまで勇気づける，励ますことが重要である．「褒める」「励ます」「共感する」がキーワードである．

アルコール症専門病院への紹介

節酒ができない場合は依存症と診断し，きっぱりと断酒の必要性を説明する．糖尿病などが合併していると，「まずは食事指導から」などと逃げる人が多いので，「あなたの病気はアルコールが原因である」ときっぱりと伝え，もう一生分の飲酒をしてしまったこと，酒なしでも楽しい生活が送れること，アルコール依存症は人生の脱落者ではなく，むしろうつ病と同じように働き過ぎ，ワーカホリックの人がストレス解消の過程として移行することが多いこと，早期にきちんと治療すれば生命予後は良好なことを話す．肝硬変に至っていても，飲酒を続ければ5年生存率は30％程度なのに対し，断酒をすれば90％近い生存率があり，健常者とほとんど差がない[7]．

プレアルコホリックならはじめは一般内科で経過を診てもよいが，あなたは依存症なのでアルコールの専門病院の受診が必要な旨を説明する．精神科に偏見がある人が多いため，「入院する，しないは自

分の希望でよいので，まずは専門医の意見を聞いてみては」と敷居を低くして専門医の外来を受診させる．依存症から逃げるのではなく，依存を認め真正面から治療していくことが重要で，そのための最も有効な手立ては，専門医の受診であることを内科医は認識しておく必要がある．

おわりに

アルコール使用障害を認める患者の外来診療において，最も問題となるのが否認である．「全くそんなことはない，自分の飲酒量，飲酒行動には全く問題ない」とする完全否認もあれば，「過剰飲酒は認めるが，依存症ではない」といった縮小化する否認もある．一般診療では問診に対し症状を過少申告することはないが，アルコール症では依存症と診断されることを嫌い，飲酒量は少なめに答え，臓器障害の病名を付けられることに安心し，症状を抑える投薬のみを希望することが多い．多くの内科医は，こうした患者を見ると診療に値しない患者と判断し，除外してしまう．しかし，この否認こそがアルコール依存症の根底にある特有のサインである．お酒をやめることは，しらふで現実と対峙することになるため，それを回避するための心の防衛反応ともいえる．仮に過剰飲酒を認めたとしても，それは夫の非協力性や，妻の理解のなさ，さらには会社の不合理などを理由に挙げ，自分の非は少ないことを強調する．患者が病気（依存症）であることを認め，治療（断酒）を受け入れることで初めて回復に向かう．ただし，回復した時点で，私は依存症でなかったのではないかという第二の否認に至る例も多いので安心してはいけない．この否認の連鎖を断ち切ることが，唯一この病気の治療につながる．家族の否認（私のせいで夫は飲み過ぎてしまう，私が何とかできるなど）や治療者（医師，医療従事者）の否認（肥満が半分くらい関係している，食べ過ぎが一部この病気を悪化させている，1合程度なら飲んでも治せるなど）も本人の否認を増強することも理解しておかねばならない．

参考文献

1) 尾崎米厚ほか：わが国の成人飲酒行動およびアルコール症に関する全国調査．日本アルコール・薬物医学会雑誌 **40**：455-470, 2005
2) 角田　透：潜在するアルコール関連問題者数の推定について．我が国のアルコール関連問題の現状―アルコール白書（河野裕明ほか編）p42-53，厚健出版，1993
3) 丸山勝也：精神科と内科の学際領域としてのアルコール医療―アルコール関連疾患を伴うプレアルコーリックに対する医療．医学のあゆみ　アルコール医学・医療の最前線．（竹井謙之編）p114-119，医歯薬出版 東京，2008
4) Fleming MF, Barry KL, Manwell LB, et al：Brief physician advice for problem alcohol drinkers. A randomized controlled trial in community-based primary care practices. JAMA **277**：1039-1045, 1997
5) Fleming MF, Mundt MP, French MT, et al：Brief physician advice for problem drinkers：long-term efficacy and benefit-cost analysis. Alcohol Clin Exp Res **26**：36-43, 2002
6) U.S. Preventive Services Task Force：Screening and behavioral counseling interventions in primary care to reduce alcohol misuse：recommendation statement. Ann Intern Med **140**：554-556, 2004
7) Yokoyama A, Ishii H, Takagi T, et al：The impact of diabetes mellitus on the prognosis of alcoholics. Alcohol Alcohol **29**：181-186, 1994

Health Risk Appraisal Models for Mass Screening of Esophageal Cancer in Japanese Men

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Abstract

Background: **Because early squamous cell carcinoma (SCC) of the esophagus is detectable by endoscopic esophageal iodine staining with high accuracy and is easily treated by endoscopic mucosectomy, it is important to develop efficient methods for screening candidates for the endoscopic examination. Inactive aldehyde dehydrogenase-2 (ALDH2) is a very strong risk factor for esophageal SCC in alcohol drinkers and thus may be suitable as a screening tool.**

Purpose: **To assess the performance of health risk appraisal (HRA) models in screening for esophageal SCC in the Japanese male population.**

Methods: **Two types of HRA models were developed based on our previous case-control study, which included assessment of ALDH2 activity and selected risk factors (HRA-G and HRA-F: activities of ALDH2 assessed by genotype and questionnaire for alcohol flushing, respectively). Each individual's risk of esophageal SCC was calculated quantitatively as a risk score. The sensitivity and specificity of the HRA models at various cutoff values of risk score was estimated by a leave-one-out cross-validation. The positive predictive value was estimated assuming the prevalence of esophageal SCC in the whole population to be 0.17% or 0.39% according to literatures.**

Results: **When individuals ranked in the top 10% of the HRA-F risk score was screened, the sensitivity was 57.9% and positive predictive value was 0.93% or 2.12% according to the above assumptions, respectively. The sensitivity was slightly better by the HRA-G model than by the HRA-F model.**

Conclusion: **The HRA models may provide an important approach to early intervention strategies to control esophageal SCC in Japanese men.** (Cancer Epidemiol Biomarkers Prev 2008;17(10):2846–54)

Introduction

Because early squamous cell carcinoma (SCC) of the esophagus and oropharyngolarynx can be treated by endoscopic mucosectomy (1, 2) or endoscope-guided mucosectomy (3), it is important to develop methods to identify individuals at increased risk of cancer of the upper aerodigestive tract to provide detailed examinations by the upper aerodigestive tract endoscopy combined with esophageal iodine staining. Without using the esophageal iodine staining, more than half of intraepithelial or mucosal esophageal SCC would be missed (2, 4). A possible approach to mass screening of high-risk individuals is to classify them according to exposure to risk factors such as heavy alcohol drinking and smoking. However, the prevalence of drinkers and smokers in Japanese men is so high (e.g., 35.7% of men drink every day and 43.3% are current smokers in 2004; ref. 5) that it is not practical to conduct detailed endoscopic examinations on all of them; therefore, a more effective screening method is required.

A mutant allele encoding an inactive subunit of aldehyde dehydrogenase-2 (*ALDH2**2) is prevalent (42%) in the Japanese population (6), and the ALDH2 genotype determines an individual's blood acetaldehyde concentration (7). Acetaldehyde has been established as a carcinogen in experimental animals (8) and is suspected of playing a critical role in cancer development in humans (9). Case-control studies in Japanese (10-13) and Taiwanese (13-16) individuals and prospective studies in which esophageal iodine staining has been used in Japanese alcoholics (17-19) have consistently shown a very strong link between the risk of esophageal SCC and alcohol drinking in people possessing the *ALDH2**1/*2 genotype. Alcohol drinking together with the *ALDH2**1/*2 genotype has been reported to be a risk factor for multiple cancerization in the upper aerodigestive tract (13, 17, 19-21) and for oropharyngolaryngeal SCC (13, 18, 20, 22, 23). The IARC has recently concluded that substantial mechanistic evidence in humans with inactive ALDH2 indicates that acetaldehyde derived

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from the metabolism of ethanol in alcoholic beverages contributes to esophageal cancer (9). Because drinking a small amount of alcohol results in acetaldehydemia and unpleasant alcohol flushing responses in persons with inactive ALDH2, the activity of ALDH2 can be assessed by a simple questionnaire that asks about both current and past facial flushing (24, 25). This simple questionnaire about flushing as a marker of inactive ALDH2 is a highly reliable means of detecting inactive ALDH2 and predicting the risk of SCC in the upper aerodigestive tract (11, 18, 22, 25-27).

Increased mean corpuscular volume (MCV) is associated with alcohol drinking, especially drinking by inactive ALDH2 heterozygotes, and with smoking, low body mass index, and poor nutrition, all of which increase the risk of SCC in the upper aerodigestive tract (26, 27). We showed recently that MCV is a marker for drinkers who are at high risk of SCC in the upper aerodigestive tract (18, 26-28).

Based on our previous case-control study of esophageal SCC in Japanese men (12, 25), we developed simple health risk appraisal (HRA) models that predicted an individual's risk of developing esophageal cancer based on logistic regression analyses. In addition to drinking habits, smoking habits, and diet, the HRA models included either ALDH2 genotype or the results of a simple questionnaire about alcohol flushing (26). Each individual was ranked according to his risk of esophageal SCC. Persons in the top 10% risk category for esophageal SCC, as estimated by the HRA model that included ALDH2 genotype, were selected with high sensitivity by two simple criteria, that is, the combination of moderate/heavy drinking plus "heavy smoking or alcohol flushing" and the combination of moderate/heavy drinking plus "heavy smoking or MCV ≥ 99 fl" (26). If these models are valid for the screening of high-risk individuals for esophageal SCC, a detailed examination by endoscopy of such high-risk individuals may provide an efficient method for detecting early esophageal SCC. In the present study, we assessed the performance of screening methods with our HRA models in terms of sensitivity, specificity, and positive predictive value (PPV) to identify individuals with and without esophageal SCC.

Materials and Methods

Data of Case-Control Study

Study Subjects. We previously conducted a case-control study of 234 male cases with esophageal SCC and 634 male cancer-free controls and reported the results (12). The case participants were male Japanese patients with primary esophageal SCC undergoing treatment at the National Cancer Center Hospital, National Cancer Center Hospital East, Kawasaki Municipal Hospital, or National Osaka Hospital. The cancer-free controls were men who came to two Tokyo clinics for annual health checkups, and most of them were ordinary residents or workers living in Tokyo or surrounding areas. The age-adjusted prevalences of current smokers and habitual drinkers in the controls were very similar to those in the Tokyo metropolis assessed by the National Nutrition Survey in Japan, a nationwide population-based survey using representative samples (29). Thus, the controls represented the general population of Tokyo well, at least with regard to drinking and smoking habits (12). The ethics committee of each collaborating institute reviewed and approved the proposal for this study, and each of the participants gave his informed consent.

Measurement of Risk Factors. Each participant independently completed a structured questionnaire concerning his drinking, smoking, and dietary habits; those with cancer were instructed to report on their habits before they got sick. The contents of the questionnaire and the method of calculating alcohol consumption (1 unit = 22 g, the ethanol content of one serving of *sake*) were described previously (12). The subjects were classified as never/rare drinkers, ex-drinkers, or current drinkers who consumed 1 to 8.9 units/wk (light drinkers), 9 to 17.9 units/wk (moderate drinkers), or ≥18 units/wk (heavy drinkers). MCV was measured during the health checkups in the

Table 1. Risks of esophageal SCC according to selected risk factors including ALDH2 genotype or alcohol flushing

Model		Estimated multivariate risks of esophageal SCC, OR* (95% confidence interval)
Risk factors		
Multivariate model including *ALDH2* genotype		
ALDH2 genotype	Alcohol drinking	
2*1/*1	Never/rare	0 (not calculable)
	Light	1 (reference)
	Moderate	5.58 (1.54-20.25)
	Heavy	10.38 (2.85-37.84)
	Ex-drinker	8.81 (1.53-50.76)
2*1/*2	Never/rare	0.75 (0.14-4.11)
	Light	5.82 (1.59-21.38)
	Moderate	55.84 (15.40-202.51)
	Heavy	88.88 (23.97-329.57)
	Ex-drinker	50.50 (9.18-277.95)
2*2/*2	Never/rare	1.44 (0.22-9.54)
	Light	0 (not calculable)
Strong alcoholic beverages†		4.58 (2.10-9.99)
Smoking‡		2.36 (1.52-3.65)
Green-yellow vegetables§		1.63 (1.00-2.66)
Fruit§		1.73 (1.01-2.94)
Multivariate model including alcohol flushing		
Flushing	Alcohol drinking	
Any	Never/rare	1 (reference)
Never	Light	1.27 (0.27-5.88)
	Moderate	10.12 (3.45-29.69)
	Heavy	15.61 (5.19-46.91)
	Ex-drinker	27.31 (5.24-142.46)
Current/former	Light	6.69 (2.21-20.20)
	Moderate	42.66 (14.17-128.42)
	Heavy	72.86 (23.75-223.57)
	Ex-drinker	37.00 (7.66-178.76)
Strong alcoholic beverages†		3.59 (1.63-7.87)
Smoking‡		2.62 (1.71-4.00)
Green-yellow vegetables§		1.65 (1.03-2.64)
Fruit§		1.57 (0.94-2.62)

* Simultaneously adjusted for all the variables (including age; not shown) in each multiple logistic regression model. These ORs were estimated by our previously reported case-control study. See refs. 12 and 25 for details.
† Frequent versus never/sometimes (reference).
‡ ≥30 versus <30 pack-years (reference).
§ Not every day versus almost every day (reference).

Risk factors		Score (select one each for A-E)	
ALDH2 genotype and alcohol drinking			
*ALDH2*1/*1*			
Never/rare	(<1 unit/w)	-12.94	A
Light	(1-8.9 units/w)	0.00	
Moderate	(9-17.9 units/w)	1.72	
Heavy	(18+ units/w)	2.34	
Ex-drinker		2.18	
*ALDH2*1/*2*			
Never/rare	(<1 unit/w)	-0.29	
Light	(1-8.9 units/w)	1.76	
Moderate	(9-17.9 units/w)	4.02	
Heavy	(18+ units/w)	4.49	
Ex-drinker		3.92	
*ALDH2*2/*2*			
Never/rare	(<1 unit/w)	0.37	
Light	(1-8.9 units/w)	0.00	
Drinks strong alcoholic beverages frequently			
	Yes	1.52	B
	No	0.00	
Smoked 30 pack-years or more			
	Yes	0.86	C
	No	0.00	
Eats green-yellow vegetable almost every day			
	Yes	0.00	D
	No	0.49	
Eats fruit almost every day			
	Yes	0.00	E
	No	0.54	

Total score = A + B + C + D + E

Predicted risk	Total score
Bottom 25%	≤1.02
25-49%	1.03-2.33
50-74%	2.34-3.60
75-89%	3.61-4.56
Top 10%	4.57+

Figure 1. HRA model for esophageal cancer that includes ALDH2 genotype. The risk score is calculated as the sum of scores A to E. The higher the score, the higher the risk. For example, if an individual's risk is ≥4.57, his risk of esophageal SCC is in the top 10% in this study population.

controls and at the time of diagnosis of esophageal SCC in the cases. The activity of ALDH2 was assessed by ALDH2 genotype and a facial flushing response to alcohol drinking. The PCR-restriction fragment length polymorphism method had been done on lymphocyte DNA samples to determine the ALDH2 genotype (12). The flushing response was assessed by two questions (25): (*a*) Do you have a tendency to flush in the face immediately after drinking a glass of beer (yes, no, or unknown)? (*b*) Did you have a tendency to flush in the face immediately after drinking a glass of beer during the first to second year after you started drinking (yes, no, or unknown)? The designation "current flushing" was applied to individuals who answered "yes" to question (*a*) and "former flushing" to those who answered "no" or "unknown" to question (*a*) and "yes" to question (*b*). The remaining subjects were classified as "never flushing." Current or former flushing individuals were assumed to have inactive ALDH2.

This approach identified inactive ALDH2 genotype with 90% sensitivity and 88% specificity in the cancer-free controls (25). Data on ALDH2 genotype were available for 234 cases and 634 controls (12); data on alcohol flushing were available for 233 cases and 610 controls (25). The distribution of ALDH2 genotypes in the control subjects was similar to that reported in other Japanese studies (6, 10, 23).

HRA Models

Scoring Each Individual's Risk of Esophageal SCC. Table 1 summarizes the estimated odds ratios (OR) of selected risk factors for esophageal SCC in our previously reported case-control study (12, 25). We calculated the risk of esophageal SCC for each cancer-free control subject by the previously reported method (26) based on alcohol drinking, ALDH2 genotype (or alcohol flushing), smoking, and intake of vegetables and fruit, using the formula: $RR_i = \exp[z_i - z_0]'\hat{\beta}$, where RR_i is the ith individual's OR [vs. the reference individual, who is a light drinker with the *ALDH2*1/*1* genotype (or a never/rare drinker with any category of alcohol flushing), does not drink strong alcohol beverages frequently, smoked less than 30 pack-years, and eats vegetables and fruit every day]; z_i is an observed vector of the ith individual's risk factors; z_0 is a vector of the reference individual's risk factors; and $\hat{\beta}$ is the vector of logistic regression coefficients estimated in our previously reported case-control study (12, 25). In other words, the ith individual is RR_i times more likely to develop esophageal SCC than the reference individual. In actual practice, the above formula is equivalent to simply calculating the product of RRs that correspond to the individual's risk factors. For example, computation with the estimation model that includes the ALDH2 genotype is illustrated below. When the ith individual is a moderate drinker with

*ALDH2*1/*2* [log OR = 4.02 (OR = 55.84); see Table 1 and Fig. 1], does not drink strong alcohol beverages frequently (log OR = 0), smoked ≥30 pack-years (log OR = 0.86), and does not eat vegetables and fruit every day (log OR = 0.49 and 0.54, respectively), his risk is calculated as the sum of these log ORs (log RR_i = 4.02 + 0 + 0.86 + 0.49 + 0.54 = 5.91). Hereafter, each subject's RR_i (for the *i*th individual versus the reference subject) is designated as RR_{ind} to express his risk of esophageal SCC. The subjects were classified into five risk categories based on the percentiles of the log RR_{ind} value among all controls in our previous case-control study (12, 25): bottom 25%, 25% to 49%, 50% to 74%, 75% to 89%, and top 10%.

The procedures used to make these calculations are summarized in Figs. 1 and 2. Although the calculations are relatively simple, because an electronic calculator may be required to sum the scores with two decimal places and it may be inconvenient in clinical situations or for mass-screening purposes, we further simplified the HRA model that included alcohol flushing by converting the scores to small integers ("integer score" in Fig. 2). The integer score was obtained by multiplying the original score by a constant, 2.265, and then rounding to the nearest integer, with the constant having to meet the following three conditions: (*a*) each integer score must be between 0 and 10, so that most people are able to sum them in their head; (*b*) the Spearman rank correlation coefficient between totals of the original scores and totals of the integer scores must be close to 1.0; and (*c*) a cutoff value that divides the subjects into the approximately top 10% and bottom 90% should be established because we intend to identify the top 10% risk individuals from the population and conduct a detailed examination of them by endoscopy with esophageal iodine staining. When 2.265 was used as the constant, it yielded a Spearman rank correlation coefficient of 0.997 and a cutoff value of 11, which selected 11.1% of the subjects.

Cross-Validation Study. The performance of the HRA models was assessed in terms of sensitivity (the percentage of subjects predicted to have a cancer among the cancer cases), specificity (the percentage of subjects predicted to be cancer-free among the cancer-free controls), and PPV (the percentage of patients with cancer among the selected high-risk individuals). The maximum likelihood estimates of the logistic regression model most effectively predict the data that generated them but do not perform so well when used for predictions on new data (30). Therefore, the sensitivity and specificity were estimated by the cross-validation method, which is a data-oriented method to more correctly assess the performance of a statistical model for predicting new data (30). We used the leave-one-out cross-validation method as follows:

1. Let *Q* be the percentage of subjects ($0 < Q < 100\%$) to be selected as candidates for detailed examinations by endoscopy.
2. Remove one subject from the case-control data (*n* subjects in total) and generate a HRA model, as described above, using the remaining cases and controls (*n* - 1 subjects in total). Calculate RR_{ind} for each of the remaining controls and the left-out subject using this HRA model.
3. If the RR_{ind} for the left-out subject is above or equals to the (1 - Q) × 100th percentile of the RR_{ind} for the remaining controls, the left-out subject is predicted to have a cancer; otherwise to be cancer-free.
4. Repeat nos. 2 and 3 by removing each of the cases and controls *n* times in total.

Risk factors		Score (select one each for A-E)		
Alcohol flushing and drinking		Original score	*(Integer score)*	
Any flushing				
Never/rare	(<1 unit/w)	0.00	*(0)*	A
Never flushing				
Light	(1-8.9 units/w)	0.24	*(1)*	
Moderate	(9-17.9 units/w)	2.31	*(5)*	
Heavy	(18+ units/w)	2.75	*(6)*	
Ex-drinker		3.31	*(7)*	
Current/former flushing				
Light	(1-8.9 units/w)	1.90	*(4)*	
Moderate	(9-17.9 units/w)	3.75	*(9)*	
Heavy	(18+ units/w)	4.29	*(10)*	
Ex-drinker		3.61	*(8)*	
Drinks strong alcoholic beverages frequently				
	Yes	1.28	*(3)*	B
	No	0.00	*(0)*	
Smoked 30 pack-years or more				
	Yes	0.96	*(2)*	C
	No	0.00	*(0)*	
Eats green-yellow vegetable almost every day				
	Yes	0.00	*(0)*	D
	No	0.50	*(1)*	
Eats fruit almost every day				
	Yes	0.00	*(0)*	E
	No	0.45	*(1)*	

Total score = A + B + C + D + E

Predicted risk	Total score	
	Original	*Integer*
Bottom 25%	≤1.18	*0-2*
25-49%	1.19-2.78	*3-5*
50-74%	2.79-3.80	*6-8*
75-89%	3.81-4.70	*9-10*
Top 10%	4.71+	*11+*

Figure 2. HRA model for esophageal cancer that includes alcohol flushing. The risk score is calculated as the sum of scores A to E. The higher the score, the higher the risk. The integer score is prepared for a self-administered questionnaire in mass screening, where each participant calculates his risk score in his head.

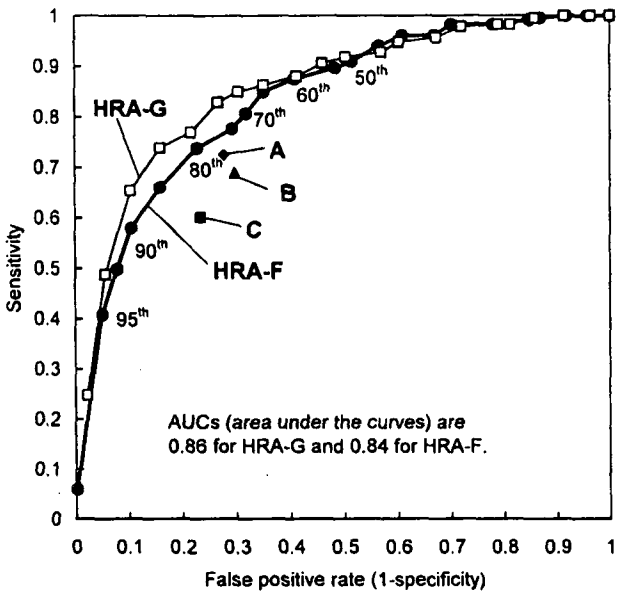

Figure 3. Sensitivity and specificity for screening esophageal SCC by two HRA models (HRA-G and HRA-F) and three other simple criteria (A-C). The ROC curves are for HRA models, where the sensitivities and specificities are calculated by the leave-one-out cross-validation method; the cutoff values for screening (denoted as 50th, 60th, etc.) are percentiles of the HRA risk score in the cancer-free control subjects. HRA-G: activity of ALDH2 assessed by genotype. HRA-F: activity of ALDH2 assessed by a questionnaire for alcohol flushing. **A.** Moderate-to-heavy drinking plus either smoking ≥30 pack-years or flushing. **B.** Moderate-to-heavy drinking plus either smoking ≥30 pack-years or MCV ≥ 99 fl. **C.** Moderate-to-heavy drinking and smoking ≥30 pack-years.

The percentage of models that correctly predict the left-out cases to have a cancer is the cross-validated sensitivity; the percentage that correctly predict the left-out controls to be cancer-free is the cross-validated specificity. We computed the receiver operating characteristic (ROC) curve for the HRA models by changing Q from 0 to 100% for calculation of cross-validated sensitivity and specificity. The area under the curve was computed via numerical integration of the ROC curve.

If PPV is extremely low, the esophagoscopy with iodine staining would not be practical in terms of cost efficiency. Therefore, we estimate PPV, which is a function of sensitivity, specificity, and prevalence of disease in a whole population (p) according to the following formula (31):

$$\mathrm{PPV} = \frac{p \times \text{sensitivity}}{p \times \text{sensitivity} + (1-p)(1-\text{specificity})}$$

The data on sensitivity and specificity are available as explained above. However, data on prevalence of the esophageal cancer in the whole population are very limited, and mass screening for targeting esophageal cancer by the esophageal iodine staining technique has not been conducted for the whole population. The detection rate of esophageal cancer by endoscopy in men ages ≥40 years was 0.39% in the Research Center for Cancer Prevention and Screening Program (32), where esophageal iodine staining was applied when the mucosal surface appeared abnormal. The detection rates of stomach cancer by mass screening using endoscopy were 0.87% among 11,679 people ages ≥40 years in Niigata city in 2004 (33). Because the incidence of esophageal cancer was only 19.3% of that of stomach cancer in men ages ≥40 years and the incidence of stomach cancer was higher in men than in women in Japan in 2001 (34), the detection rate of esophageal cancer would be higher than 0.17% (0.87% × 0.193) according to these data. Thus, we assumed two different detection rates of 0.17% and 0.39% (lower and higher assumptions, respectively) for the detection rate of esophageal cancer ($\approx p$ by esophageal endoscopy with iodine staining) in the whole population.

We also calculated the sensitivity and specificity of three simple combinations of criteria for estimating the risk of cancer: moderate-to-heavy drinking plus smoking ≥30 pack-years; moderate-to-heavy drinking plus "smoking ≥30 pack-years or alcohol flushing"; and moderate/heavy drinking plus "smoking ≥30 pack-years or MCV ≥ 99 fl" (26). The sensitivity is the percentage of cases who met the criterion; the specificity is that of controls who did not meet it.

All statistical analyses were done with the SAS statistical package version 9.1 (SAS Institute).

Results

Figure 3 shows the cross-validated ROC curves of the two HRA models (HRA-G: activity of ALDH2 assessed by the genotype and HRA-F: activity of ALDH2 assessed by the flushing questionnaire) for predicting esophageal cancer. The ROC curve of HRA-F model showed that when people in the top 10% of risk scores were selected for detailed endoscopic examinations, 57.9% (sensitivity at cutoff value of 90th percentile) of cancer cases in the whole population were expected to be included in them. The HRA-G model selected cancer cases with a higher sensitivity (65.4%) at this cutoff value. When the 80th percentile was used as the cutoff value, 73.8% (HRA-F model) or 76.9% (HRA-G model) of all cancer cases were selected as candidates for detailed endoscopic examinations, mildly improving the sensitivity at the cost of a doubled false-positive rate. It should be noted that the specificity is approximately equal to the cutoff value (denoted as the percentile) by definition but could be slightly different because of ties (equal ranking) of scores (e.g., 23% of controls are above or equal to the 80th percentile by the HRA-F model). The area under the curve was slightly higher for the HRA-G model than HRA-F model (0.86 and 0.84, respectively).

The sensitivity and specificity for the simple combinations of criteria are also shown in Fig. 3: (A) moderate-to-heavy drinking plus "smoking ≥30 pack-years or alcohol flushing," (B) moderate/heavy drinking plus "smoking ≥30 pack-years or MCV ≥ 99 fl," and (C) moderate-to-heavy drinking plus smoking ≥30 pack-years. Criterion (C) showed relatively low sensitivity (60.1%) and false-positive rate (23.3%); criterion (A) showed relatively high sensitivity (72.5%) and false-positive rate (27.7%). All

criteria were below the ROC curves of HRA models, indicating that these combinations of risk factors were not as useful as the HRA models.

Figure 4 shows the expected PPV among individuals selected by the HRA-F model at different cutoff values. When people in the top 10% of risk scores were selected for detailed endoscopic examinations (cutoff value = 90th percentile), the expected PPV were 0.93% and 2.12% according to the lower and higher assumptions for the prevalence in the whole population, respectively.

In the HRA-F model, the top 10% of individuals were selected by the original score of 4.71 or above, whereas 96% of them were selected by the integer scores of ≥11 (data not shown), showing that the integer score can be used instead of the original score for the mass-screening purpose.

Discussion

This study assessed the performance of screening methods for detecting individuals who have a high risk of esophageal cancer using HRA models that were developed based on our previous case-control study (12, 25). Because each individual's risk is calculated as a quantitative score and the risks differ extraordinarily among the individuals (e.g., RR_{ind} ranked at the bottom 25th and top 10th percentiles differ 83-fold by the HRA-G model), we can give a higher priority for detailed examination to those who have the higher scores. The sensitivity and specificity of the HRA-G model are slightly superior to those of the HRA-F model, but the low-cost is a significant advantage of the latter. When we select individuals with the top 10% risk scores of HRA-F, the sensitivity is 57.9%. This means that approximately 60% of esophageal cancer in the whole population can be detected by examining only 10% of them. Furthermore, the expected detection rate of esophageal cancer among the screened high-risk men (PPV) is 0.93% based on a lower assumption and may be more than 2% through the use of advanced diagnostic technology including esophageal endoscopy combined with iodine staining (higher assumption). If these indexes of screening are true, the application of our HRA models for the mass screening of esophageal cancer would be highly cost-efficient.

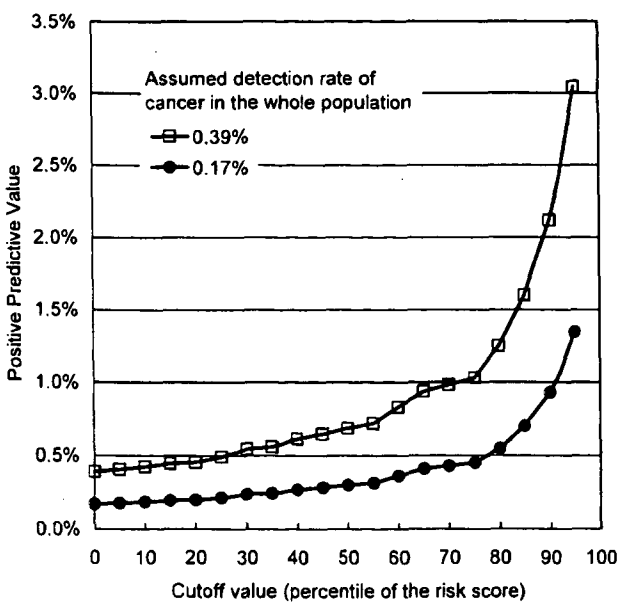

Figure 4. Expected PPV among individuals selected by the HRA-F model at different cutoff values. Because the overall detection rate of esophageal cancer in the whole population by endoscopy is unknown, two rates were assumed according to the literatures (0.17% and 0.39%). For example, if the overall detection rate in the whole population is 0.17% and the 90th percentile of risk score (that is, upper 10%) is used as the cutoff value, the expected PPV is 0.93%.

The generalizability of our estimates of sensitivity, specificity, and PPV depends on the difference in distributions of risk factors between the background population of our case-control study and the target population to which the HRA models are applied. Especially, the prevalence of inactive ALDH2 and alcohol drinking would strongly affect the performance of screening using the HRA models. The magnitude of the ALDH2-associated risk depends on the extent of the association between the evaluated cancer and alcohol consumption and the proportion of alcohol drinkers with inactive ALDH2. Case-control studies in high-risk rural regions in China, where alcohol drinking plays a less important role in esophageal carcinogenesis than in Japan and Taiwan, showed moderate-to-modest positive or no associations (35-37) between inactive heterozygous ALDH2 and esophageal cancer risk. A case-control study in a Thai population, where only 18% of the controls have inactive ALDH2, also showed a marginally significant modest positive association (38). The inhibitory effect of inactive heterozygous ALDH2 on alcohol drinking is influenced by sociocultural factors; thus, only 3% of Japanese alcoholics had the inactive heterozygous ALDH2 in 1979 as opposed to 8% in 1986 and 13% in 1992 (39).

This phenomenon inversely suggests the possibility, using the HRA models, that alcohol consumption by inactive ALDH2 heterozygotes is decreased by social intervention such as public education. Thus, the HRA models that include inactive ALDH2 or alcohol flushing should be changed according to different regions and different eras in Asia. ALDH2-related susceptibility to esophageal SCC has been shown in Japanese female heavy drinkers (11). However, a much smaller proportion of women with heterozygous ALDH2 are drinkers in comparison with men, resulting in a smaller population attributable risk of esophageal SCC for alcohol drinking plus heterozygous ALDH2 in women than in men (11, 12). Therefore, we intended to apply our HRA models for screening esophageal cancer in Japanese male populations. The proportion of people selected by our cutoff value for the top 10% risk may be smaller than 10% in a population where the prevalence of drinkers is small or vice versa. However, the importance of screening for esophageal cancer in such a low-risk population would be relatively small. The age-adjusted death rates from esophageal cancer differ considerably among the 47 prefectures in Japan (40) and are strongly correlated with annual per capita consumption of alcoholic beverages in each prefecture (ref. 41; Spearman's rank correlation coefficient = 0.68; $P < 0.0001$). Further studies are needed to clarify the geographical difference

in the distribution of HRA risk score among Japanese male populations.

From a cost-efficiency point of view, the HRA-F to detect esophageal cancer in a mass screening has the advantage that it is available almost at no cost and deliverable not only at the clinic but also via mass media, Internet, and other sources. For the screened top 10% high-risk individuals, the cost of endoscopic esophageal iodine staining is 12,000 Japanese yen (JPY; 1 US$ ≈ 105-108 JPY in June 2008) per person. Thus, the cost to identify one case of esophageal cancer is roughly estimated, by dividing 12,000 JPY by the PPV, to be 570,000 to 1,290,000 JPY (higher and lower assumptions, respectively), which is less expensive than that of gastric cancer by endoscopic screening (1,608,000 JPY) and photofluorography (3,290,000 JPY) in a Japanese population (33). As for the HRA-G, the expected PPV (2.40% and 1.06% for higher and lower assumptions, respectively, with the cutoff value of the top 10%) is slightly better; thus, the estimated cost of endoscopic examination to identify one case of esophageal cancer is somewhat smaller (500,000-1,130,000 JPY, respectively) than that of HRA-F. However, a large *initial* cost would be required for genotyping of ALDH2 for all individuals in the target population. The additional cost to identify one case of esophageal cancer is estimated as the unit cost of genotyping divided by the detection rate of cancer among all subjects, and this may far exceed the cost of endoscopic examination. However, it should be emphasized that genotyping is needed only once in a lifetime and the data are available repeatedly; and the unit cost would be largely discounted when a huge number of samples is analyzed.

On the other hand, we have no data to analyze the *effectiveness* of mass screening to decrease mortality from esophageal cancer because there has been no large-scale screening of esophageal cancer conducted in Japan. When an asymptomatic high-risk population was screened by a combination of endoscopy and esophageal iodine staining, 76% of the esophageal cancer detected did not invade the submucosa (4). Such early esophageal cancer can be safely treated by endoscopic mucosal resection, and the patients are generally hospitalized for only a week or less (1) with relatively low medical costs. Notably, the cause-specific survival rates 5 years after endoscopic mucosal resection for esophageal cancer not invading the submucosa have been reported to be 95% to 98% (1, 42), whereas the 5 year-survival rate of esophageal cancer based on data from a population-based cancer registry was reported to be 25% among seven prefectures of Japan (43). Therefore, it is expected that implementation of screening for esophageal cancer could improve the prognosis and decrease the mortality substantially. However, the actual effectiveness, considering the costs, must be analyzed based on the results of mass screening in a large population in the future.

A parallel study on oral and pharyngeal SCC conducted in men who came to the same clinics and hospitals showed that hypopharyngeal SCC and esophageal SCC shared several common risk factors including ALDH2 genotype, alcohol flushing, drinking habits, smoking habits, and diet (12, 22, 25). Figure 5 shows the ROC curves for detecting hypopharyngeal SCC by the HRA models for esophageal SCC. The sensitivity was 62.7% when the top 10% was screened by the HRA-F

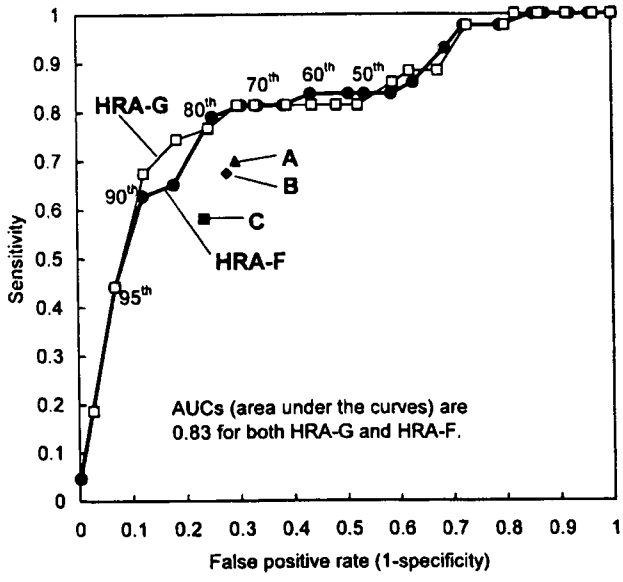

Figure 5. Sensitivity and specificity for screening hypopharyngeal cancer by two HRA models (HRA-G and HRA-F) and three other simple criteria (A-C). HRA-G: activity of ALDH2 assessed by genotype. HRA-F: activity of ALDH2 assessed by a questionnaire for alcohol flushing. **A.** Moderate-to-heavy drinking plus either smoking ≥30 pack-years or flushing. **B.** Moderate-to-heavy drinking plus either smoking ≥30 pack-years or MCV ≥ 99 fl. **C.** Moderate-to-heavy drinking and smoking ≥30 pack-years.

model and the areas under the curve are very similar to those of esophageal SCC. Although the HRA models were designed based on the results of a case-control study of esophageal SCC, they can be applied to hypopharyngeal SCC as well.

The combination of alcohol flushing and MCV with the traditional risk factors of drinking and smoking improved the predictive power of esophageal and pharyngeal SCC in comparison with the combination of drinking and smoking alone, which was in good agreement with our previous study (26). However, a substantially greater proportion (28.2% and 30.6%) of subjects met the two criteria, which is a disadvantage when using these criteria to select candidates for cancer screening.

One of the limitations of our study may be that the HRA models are not based on a prospective cohort study, but a case-control study that could have some biases in principle. However, it is unlikely that the potential biases affect the results notably because the estimated RRs are exceptionally strong. Another limitation is that we could not assess the risk of age. Because the incidence rate of esophageal cancer increases above the age of 50 years (34) and the majority of esophageal cancer patients in our case-control data is older than 50 years (12, 25), it may be appropriate that our HRA models are used for mass screening in those age groups. The age distributions of cases and controls did not match well in our case-control study, especially at ages 70 to 79 years; hence, there was concern that statistical

adjustment for age might have unexpected effects. To address this issue, we repeated the cross-validation study for men ages 70 to 79 years and confirmed that, at the cutoff value of top the 10%, the sensitivity was similar to (60.0% and 57.5% for HRA-G and HRA-F, respectively) and the specificity was somewhat better than (93.3% and 96.7%, respectively) those of other age groups, showing a good performance of our HRA models even in this old age group. However, the sample sizes in these groups are so small (40 cases and 30 controls) that further investigations are needed for the elderly ages ≥70 years.

Although alcohol flushing is a marker of inactive ALDH2, the sensitivity and specificity of the flushing questionnaire for identifying inactive ALDH2 in a Japanese male population was 90% and 88%, respectively (25). The advantage of the model that included alcohol flushing over the model that included ALDH2 genotype is that it facilitates risk estimation and can easily be applied to both public education and screening. Our HRA functions, which are very easily calculated on a simple sheet of paper (Figs. 1 and 2), may not only provide a means of screening the high-risk individuals but also help persuade those people to change their drinking habits, smoking habits, and diet. Cessation of drinking and smoking has been shown to reduce the risk of cancer of the upper aerodigestive tract (44, 45). Early cancer of the esophagus (1, 2) and pharynx (3) can be easily treated by endoscopic mucosectomy or endoscope-guided mucosectomy, and the HRA models we used may provide an important approach to early intervention strategies to control these high-mortality cancers in Japanese men. Further study is needed to confirm the effectiveness of this new approach in large Japanese populations.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

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References

1. Makuuchi H. Endoscopic mucosal resection for mucosal cancer in the esophagus. Gastrointest Endosc Clin N Am 2001;11:445–58.
2. Yokoyama A, Ohmori T, Makuuchi H, et al. Successful screening for early esophageal cancer in alcoholics using endoscopy and mucosa iodine staining. Cancer 1995;76:928–34.
3. Sato Y, Omori T, Yokoyama A, et al. Treatment of superficial carcinoma in the pharynx and the larynx [in Japanese with English abstract]. Shokaki Naishikyo 2006;18:1407–16.
4. Yokoyama A, Omori T, Yokoyama T, et al. Esophageal melanosis, an endoscopic finding associated with squamous cell neoplasms of the upper aerodigestive tract, and inactive aldehyde dehydrogenase-2 in alcoholic Japanese men. J Gastroenterol 2005;40:676–84.
5. Ministry of Health Labour and Welfare. The National Health and Nutrition Survey 2004, Japan [in Japanese]. Tokyo: Ministry of Health, Labour and Welfare 2006.
6. Higuchi S, Matsushita S, Murayama M, Takagi S, Hayashida M. Alcohol and aldehyde dehydrogenase polymorphisms and the risk for alcoholism. Am J Psychiatry 1995;152:1219–21.
7. Mizoi Y, Yamamoto K, Ueno Y, Fukunaga T, Harada S. Involvement of genetic polymorphism of alcohol and aldehyde dehydrogenases in individual variation of alcohol metabolism. Alcohol Alcohol 1994;29:707–10.
8. IARC. Allyl compounds, aldehydes, epoxides and peroxides. In: IARC monographs on the evaluation on the carcinogenic risk of chemicals to humans. Lyon: IARC; 1985. p. 101–32.
9. Baan R, Straif K, Grosse Y, et al. Carcinogenicity of alcoholic beverages. Lancet Oncol 2007;8:292–3.
10. Yang CX, Matsuo K, Ito H, et al. Esophageal cancer risk by ALDH2 and ADH2 polymorphisms and alcohol consumption: exploration of gene-environment and gene-gene interactions. Asian Pac J Cancer Prev 2005;6:256–62.
11. Yokoyama A, Kato H, Yokoyama T, et al. Esophageal squamous cell carcinoma and aldehyde dehydrogenase-2 genotypes in Japanese females. Alcohol Clin Exp Res 2006;30:491–500.
12. Yokoyama A, Kato H, Yokoyama T, et al. Genetic polymorphisms of alcohol and aldehyde dehydrogenases and glutathione *S*-transferase M1 and drinking, smoking, and diet in Japanese men with esophageal squamous cell carcinoma. Carcinogenesis 2002;23:1851–9.
13. Yokoyama A, Omori T. Genetic polymorphisms of alcohol and aldehyde dehydrogenases and risk for esophageal and head and neck cancers. Jpn J Clin Oncol 2003;33:111–21.
14. Chen YJ, Chen C, Wu DC, et al. Interactive effects of lifetime alcohol consumption and alcohol and aldehyde dehydrogenase polymorphisms on esophageal cancer risks. Int J Cancer 2006;119:2827–31.
15. Wu CF, Wu DC, Hsu HK, et al. Relationship between genetic polymorphisms of alcohol and aldehyde dehydrogenases and esophageal squamous cell carcinoma risk in males. World J Gastroenterol 2005;11:5103–8.
16. Lee CH, Lee JM, Wu DC, et al. Carcinogenetic impact of ADH1B and ALDH2 genes on squamous cell carcinoma risk of the esophagus with regard to the consumption of alcohol, tobacco and betel quid. Int J Cancer 2008;122:1347–56.
17. Yokoyama A, Ohmori T, Muramatsu T, et al. Short-term follow-up after endoscopic mucosectomy of early esophageal cancer and aldehyde dehydrogenase-2 genotype in Japanese alcoholics. Cancer Epidemiol Biomarkers Prev 1998;7:473–6.
18. Yokoyama A, Omori T, Yokoyama T, et al. Risk of squamous cell carcinoma of the upper aerodigestive tract in cancer-free alcoholic Japanese men: an endoscopic follow-up study. Cancer Epidemiol Biomarkers Prev 2006;15:2209–15.
19. Yokoyama A, Omori T, Yokoyama T, Sato Y, Kawakubo H, Maruyama K. Risk of metachronous squamous cell carcinoma in the upper aerodigestive tract of Japanese alcoholic men with esophageal squamous cell carcinoma: a long-term endoscopic follow-up study. Cancer Sci 2008;99:1164–71.
20. Muto M, Takahashi M, Ohtsu A, Ebihara S, Yoshida S, Esumi H. Risk of multiple squamous cell carcinomas both in the esophagus and the head and neck region. Carcinogenesis 2005;26:1008–12.
21. Yokoyama A, Omori T, Tanaka Y, et al. p53 Protein accumulation, cancer multiplicity, and aldehyde dehydrogenase-2 genotype in Japanese alcoholic men with early esophageal squamous cell carcinoma. Cancer Lett 2007;247:243–52.
22. Asakage T, Yokoyama A, Haneda T, et al. Genetic polymorphisms of alcohol and aldehyde dehydrogenases, and drinking, smoking and diet in Japanese men with oral and pharyngeal squamous cell carcinoma. Carcinogenesis 2007;28:865–74.
23. Hiraki A, Matsuo K, Wakai K, Suzuki T, Hasegawa Y, Tajima K. Gene-gene and gene-environment interactions between alcohol drinking habit and polymorphisms in alcohol-metabolizing enzyme genes and the risk of head and neck cancer in Japan. Cancer Sci 2007;98:1087–91.
24. Yokoyama A, Muramatsu T, Ohmori T, Kumagai Y, Higuchi S, Ishii H. Reliability of a flushing questionnaire and the ethanol patch test in screening for inactive aldehyde dehydrogenase-2 and alcohol-related cancer risk. Cancer Epidemiol Biomarkers Prev 1997;6:1105–7.
25. Yokoyama T, Yokoyama A, Kato H, et al. Alcohol flushing, alcohol and aldehyde dehydrogenase genotypes, and risk for esophageal squamous cell carcinoma in Japanese men. Cancer Epidemiol Biomarkers Prev 2003;12:1227–33.
26. Yokoyama A, Yokoyama T, Kumagai Y, et al. Mean corpuscular volume, alcohol flushing, and the predicted risk of squamous cell carcinoma of the esophagus in cancer-free Japanese men. Alcohol Clin Exp Res 2005;29:1877–83.
27. Yokoyama A, Yokoyama T, Muramatsu T, et al. Macrocytosis, a new predictor for esophageal squamous cell carcinoma in Japanese alcoholic men. Carcinogenesis 2003;24:1773–8.

28. Yokoyama M, Yokoyama A, Yokoyama T, et al. Mean corpuscular volume and the aldehyde dehydrogenase-2 genotype in male Japanese workers. Alcohol Clin Exp Res 2003;27:1395–401.
29. Tokyo Metropolitan Government. Nutritional status of the people in Tokyo metropolitan: results of National Nutrition Survey in 2000 [in Japanese]. Tokyo: Bureau of Public Health, Tokyo Metropolitan Government; 2001. p. 31–2.
30. Bailey R, Harding S, Smith G. Cross-validation. In: Kotz S, editor. Encyclopedia of statistical sciences. 2nd edition. Hoboken (NJ): John Wiley & Sons; 2006. p.1454–8.
31. Greenland S. Basic methods for sensitivity analysis and external adjustment. In: Rothman KJ, Greenland S, editors. Modern epidemiology. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 1998. p. 353–5.
32. Hamashima C, Sobue T, Muramatsu Y, Saito H, Moriyama N, Kakizoe T. Comparison of observed and expected numbers of detected cancers in the research center for cancer prevention and screening program. Jpn J Clin Oncol 2006;36:301–8.
33. Tashiro A, Sano M, Kinameri K, Fujita K, Takeuchi Y. Comparing mass screening techniques for gastric cancer in Japan. World J Gastroenterol 2006;12:4873–4.
34. The Editorial Board of the Cancer Statistics in Japan. Cancer incidence rate by age and site (2001). In: Cancer statistics in Japan: 2007. Tokyo: Foundation for Promotion Cancer Research; 2007. p. 72–3.
35. Cai L, You NC, Lu H, et al. Dietary selenium intake, aldehyde dehydrogenase-2 and X-ray repair cross-complementing 1 genetic polymorphisms, and the risk of esophageal squamous cell carcinoma. Cancer 2006;106:2345–54.
36. Guo YM, Wang Q, Liu YZ, Chen HM Qi Z, Guo QH. Genetic polymorphisms in cytochrome P4502E1, alcohol and aldehyde dehydrogenases and the risk of esophageal squamous cell carcinoma in Gansu Chinese males. World J Gastroenterol 2008;14:1444–9.
37. Yang SJ, Wang HY, Li XQ, et al. Genetic polymorphisms of ADH2 and ALDH2 association with esophageal cancer risk in southwest China. World J Gastroenterol 2007;13:5760–4.
38. Boonyaphiphat P, Thongsuksai P, Sriplung H, Puttawibul P. Lifestyle habits and genetic susceptibility and the risk of esophageal cancer in the Thai population. Cancer Lett 2002;186:193–9.
39. Higuchi S, Matsushita S, Imazeki H, Kinoshita T, Takagi S, Kono H. Aldehyde dehydrogenase genotypes in Japanese alcoholics. Lancet 1994;343:741–2.
40. Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labour and Welfare. Age-adjusted death rate by prefecture, specified report of vital statistics 2005. Tokyo: Ministry of Health, Labour and Welfare; 2007.
41. National Tax Agency. Liquor tax, volume of sales (consumption) by prefectures. In: The 131th, National Tax Agency Annual Statistics Report 2005. Tokyo: National Tax Agency; 2007. p. 190–1.
42. Katada C, Muto M, Momma K, et al. Clinical outcome after endoscopic mucosal resection for esophageal squamous cell carcinoma invading the muscularis mucosae: a multicenter retrospective cohort study. Endoscopy 2007;39:779–83.
43. The Editorial Board of the Cancer Statistics in Japan. International comparisons of cancer survival rates. In: Cancer statistics in Japan: 2007. Tokyo: Foundation for Promotion Cancer Research; 2007. p. 46.
44. Castellsague X, Munoz N, De Stefani E, et al. Smoking and drinking cessation and risk of esophageal cancer (Spain). Cancer Causes Control 2000;11:813–8.
45. Rehm J, Patra J, Popova S. Alcohol drinking cessation and its effect on esophageal and head and neck cancers: a pooled analysis. Int J Cancer 2007;121:1132–7.