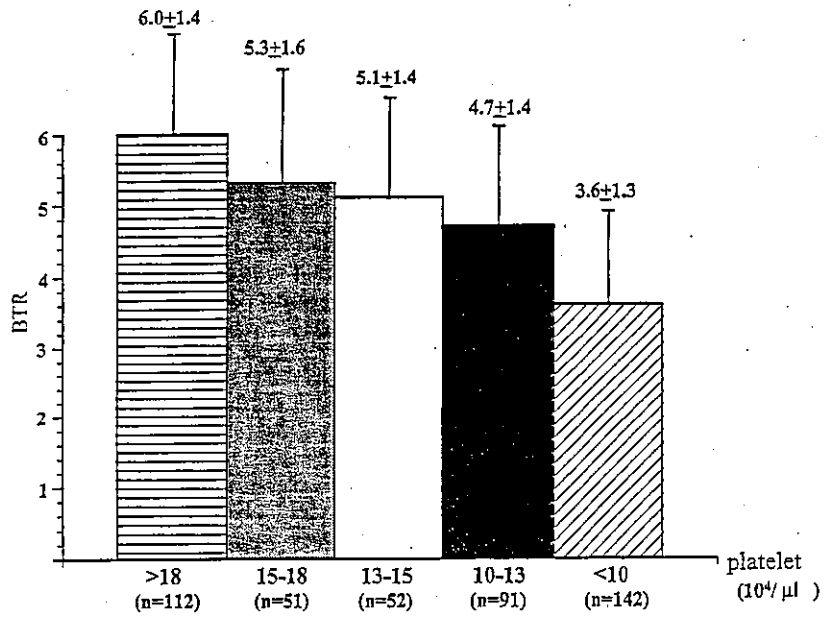

Fig. 4. The mean BTR of patients with HCV-related chronic liver diseases ($n = 448$), who were classified using platelets counts (mean ± S.D.). We used platelet counts to classify 448 patients with HCV-related chronic liver diseases, who were outpatients of our hospital, and analyzed the mean BTR in each class. The BTR of healthy people is considered to be 5.82–8.64 (mean ± 1 S.D.) or 4.41–10.05 (mean ± 2 S.D.). It has been demonstrated that BTR regularly and gradually decreases as liver diseases progress.

as other chronic diseases which progress gradually, such as type 2 diabetes mellitus and essential hypertension, starting appropriate nutritional interventions in the early stages of chronic liver diseases is expected to improve prognosis and to maintain QOL. The reason for this is that these interventions are very effective when they are started in patients with glucose intolerance and in patients with borderline hypertension, who exhibit no organ-related symptoms (Fig. 3).

A diet containing abundant BCAAs has been invented as an approach for nutritional therapy [33]. However, it has been reported that it is difficult to effectively correct amino acid metabolism using this diet alone [34].

We used platelet counts to classify 448 patients with HCV-related chronic liver diseases, who were outpatients of our hospital, and analyzed the mean BTR in each class [27] (Fig. 4). The BTR of healthy people is considered to be 5.82–8.64 (mean ± 1 S.D.) or 4.41–10.05 (mean ± 2 S.D.). It has been demonstrated that BTR regularly and gradually decreases as liver diseases progress. As nutritional supplements, BCAAs have universal effects, such as protein anabolic action, which are commonly recognized. It has been demonstrated that BCAAs not only promote albumin synthesis, but also improve the QOL and prognosis of patients with liver cirrhosis [18]. For obtaining better correction of disorders of amino acid metabolism and protein metabolism, which are associated with chronic liver diseases, an interesting issue is when is the optimal timing of nutritional interventions with appropriate amounts of BCAA supplementation.

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なる傾向がある.

1. 感染予防　HBV は血液を介して感染し，血液による汚染対策が最も重要である．病院内で血液と接する機会が多いほどその危険性は高く，また感染源となるウイルスキャリアが多い病棟では特に注意が必要である．事故の多くは針刺し事故であり，リキャップをしない，血液に汚染された注射針を放置しないなど注意が必要である．一般的な注意事項と対策は，下記のごとくである．

(a) 感染源対策：病院内での患者の血液検査結果（ウイルスなどの感染情報）はプライバシーを考慮しつつ医療従事者には参照できるようにする．

(b) 感染経路対策：洗浄，滅菌・消毒，ゴム手袋などの使用により汚染を避ける．

(c) 医療従事者の管理：定期的なウイルスマーカーの検査とワクチンの接種．

2. 曝露後の対策　医療従事者が HBV の汚染を受けた場合，まず汚染部位の血液を搾り出し，流水で十分洗浄する．汚染を受けた者が HBs 抗体陰性の場合は事故後 48 時間以内に HBIG を投与する．感染源となった血液中のウイルス量が多い場合は HBIG に加え 0，1，2 か月後に HB ワクチンを投与する．

なお汚染事故は労務災害であり，事務手続きも含めた感染対策マニュアルを整備しておく必要がある．

HCV キャリアの指導，管理および院内感染事故対策

Management of HCV Carrier and Prevention of Nosocomial Infection with HCV

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病態と診断

C 型肝炎ウイルス（HCV）キャリアとは，広義には C 型慢性肝炎を含めた HCV - RNA 陽性者全体をさすが，本稿では HCV - RNA 陽性にもかかわらず一定期間 ALT 値が正常値を維持している狭義の「無症候性」のキャリアについて解説する．住民検診において HCV 抗体が測定されるようになり，HCV キャリアが数多く発見されている．HCV 抗体陽性者で肝機能正常の場合には，感染既往の可能性があるため，診断に際しては必ず HCV - RNA あるいは HCV コア抗原が陽性であることを確認する．また，慢性肝炎との境界は不明瞭であり，無症候性キャリアといえども，肝組織像は軽度の炎症と線維化を有していることが多い．

C 型急性肝炎は約 7 割が遷延化し，上述のキャリアの時期を経て慢性肝炎に進展する．慢性肝炎に進展してからではインターフェロン（IFN）の著効率が低いため，最近，HCV 感染の早期から IFN 治療を行うことが推奨されている．

治療方針

A. HCV キャリアへの指導と治療

HCV キャリアは，原則として肝庇護薬や IFN の投与は必要なく，経過観察のみでよい．日常生活の指導は，アルコール摂取を制限し，脂肪肝を合併させないように食事指導と適度の運動を勧める．仕事や日常生活への制限はない．腹部エコーで，肝の形態変化を伴う場合には積極的に肝生検を行う．肝組織が慢性肝炎の所見を呈した場合には慢性肝炎として IFN 治療を考慮する．しかし，ALT 正常者における IFN の著効率は異常者（慢性肝炎）に比べ低率である．また，IFN 投与後 HCV が消失しない場合は，ALT 値の異常が出現する場合もある．このため，IFN の著効率が高い HCV のセロタイプ 2 型か HCV 量がアンプリコアモニター法で 200 KIU 以下の低値例に，現時点では投与対象を限定すべきである．

標準処方例　下記のいずれかを用いる

1) スミフェロン注　1 回 900 万 IU　1 日 1 回　筋注　2 週間連日投与後，週 3 回 22 週間投与

2) アドバフェロン注　1 回 1,800 万 IU　1 日 1 回　皮下注　2 週間連日投与後，週 3 回 22 週間投与

投与 4 週時点で HCV - RNA が陽性の場合は 48 週まで延長．1 日投与量は，副作用が強い場合には減量する．

患者説明のポイント

・自覚症状がなく検査値が正常であっても，自然寛解はまれで，慢性肝炎へ移行する症例が多い．HCV 消失がみられるまで，半年に一度の血液検査と腹部エコー検査を勧める．

B. 院内感染対策および急性肝炎への治療

1. 曝露前対策　針刺し事故などの院内感染対策の基本は，事故そのものの発生防止対策が基本である．「院内感染への対応マニュアル」を作成し，B 型肝炎へのワクチン接種や職員教育を行っておく．注射針のリキャップを行わず専用の廃棄容器を設置するなどの対策を講じ，事故が起こりにくい環境を整備する．

2. 曝露後対策　B 型肝炎と異なり，C 型肝炎に対する中和抗体やワクチンはない．また，針刺し事故直後の IFN 投与は，HCV 感染の成立が 1%程度であることと短期間の IFN 投与では感染防止効果も実証されていないため，推奨できない．受傷した時

点で，直ちに流水で受傷部位を洗浄し，血液を搾り出す．感染事故直後より，2-4週ごとに6か月まで肝機能とHCV抗体を測定し，経過を観察する．HCV感染が成立した場合は，ALT値のピークが過ぎた時点でPCRにてHCV-RNA陽性を再確認し，労務災害扱いでIFN治療を開始する．HCV型が多くセロダイプI型であっても，IFN単独療法でも著効率が高く，リバビリンの併用は必要ない．また，一般のC型急性肝炎でも感染事故例と同様，IFNの有効性が報告されている．しかし，現時点では保険適用はない．

(R) 処方例) 下記のいずれかを用いる

1) フエロン注 1回600万IU 1日1回 静注 8週連日投与

2) イントロンA注 1回1,000万IU 1日1回 筋注 4週連日投与後，週3回12週投与

労務災害では4週間投与しか認められていないが，長期投与が望ましい．

肝疾患患者の生活指導

Management and Guidance of Daily Life in the Patients with Liver Injuries

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原因や病態により肝疾患の治療もさまざまである．ここでは代表的な肝疾患であるウイルス性肝炎や肝硬変，アルコールや薬物による肝疾患，脂肪肝について述べるが，患者には病態や予後，検査や投薬治療などが十分に説明されていることを前提とする．

A. ウイルス性肝炎

1. 急性肝炎 急性炎症のため肝は肉眼的に赤く腫大し，組織学的に細胞浮腫，類洞狭窄，微小循環障害などによる中心静脈域の変性・壊死をみる．そのため肝血流を減らさない安静が最重要となる．安静の程度や期間は症状や肝機能検査値などからみた重症度によるが当初は入院・ベッド上安静（肝血流は起床のみで30%減）が基本となる．GOT・GPT値の正常化は肝細胞破壊の進行がようやく治まったことを示しているだけで，破壊された肝組織修復にはさらなる時間を要する．すぐに安静を解除すると肝機能が再度増悪するので，安静の解除は徐々に負荷をかけながら行う．通常の生活復帰にはGOT・GPT値正常化後1-2月位を目安にするが，組織所見からすると6か月間は慎重な生活が望ましいとされる．急性肝炎は一時的な肝不全状態で倦怠感や食欲不振が強い．その極期も多くは2週以内で，その間のみ補液を要する．食欲が回復するに伴い蛋白やビタミンに富んだ常食にもどすが，運動不足の時期だけにカロリー過剰にならないようにする．

2. 慢性肝炎 慢性肝炎はほぼ正常な機能の部と障害された部（線維化も含め）とが混在し，F0-1のように前者が主の肝炎からF3のように後者が主の肝炎まで幅広く存在する．F0-2の肝予備能は日常生活に特別な支障がなく，年余にわたる長い病気なことから，増悪の時期以外，過激な勤務やスポーツでなければ晩酌も含め特に制限せず，その人の人生を大切にすることが肝要である．F3ではストレスや過度な肉体的負荷を避ける．ただ，いたずらに制限せず負荷前後の肝機能を患者と共有しそれに基づいた指導をする．なお，感染予防のためけがなど出血時の対応やカミソリ・歯ブラシの共用禁止を教育しておく．

3. 代償期肝硬変 F3に準じるがより肝予備能が少ないので，丁寧に臨床所見や検査成績などから肝予備能を把握し，慎重に肝機能の推移をみながら指導することが望まれる．食事はバランスのとれた常食で構わない．

4. 非代償期肝硬変 肝予備能がさらに低下し生命維持に必須な代謝が障害されているので，程度に差はあれ安静とホメオスターシス維持の治療が基本となる．肝細胞数低下のためGOT・GPT値はそれほど上昇せずに病態が増悪するので，症状や臨床所見を大切にして早め早めに入院させ治療する．肝性脳症が懸念される患者には便秘や電解質異常に注意し，食事は蛋白を制限する．また浮腫や腹水時は内科的治療と同時に水分や塩分の制限を行う．

B. アルコール性肝障害・薬物性肝障害

炎症の強い急性期は断酒もしくは薬物中止とし急性肝炎に準じて指導するが，アルコール例では線維化のある症例に増悪したacute on chronicが多いので，その際は慢性肝炎や肝硬変に準じた指導を行う．起因薬物が判明すればそれを患者に教え，病院にかかる時には必ず医師にみせるよう指導する．アルコールではほろ酔い気分になるまで飲みたい患者には初めの1杯目から止めさせることが必須となる．

C. NASH・脂肪肝

食事と運動が基本となるが，遺伝的なことや心因的なこともあり改善しにくいことも多い．食事指導が最も大切であり，基礎代謝率と仕事量から算出されたエネルギーを下回るバランスがとれた食事にする．運動はNASHなどGOT・GPT値が高いときは急性肝炎に準じて行い，通常の脂肪肝では積極的に行わせる．しかし，運動で消費するエネルギーは期待ほど多くなく，終了後反動で食べたり飲んだりして逆効果もあるので注意する．

5 インターフェロンによる肝細胞癌の再発予防

西口修平　久保正二

はじめに

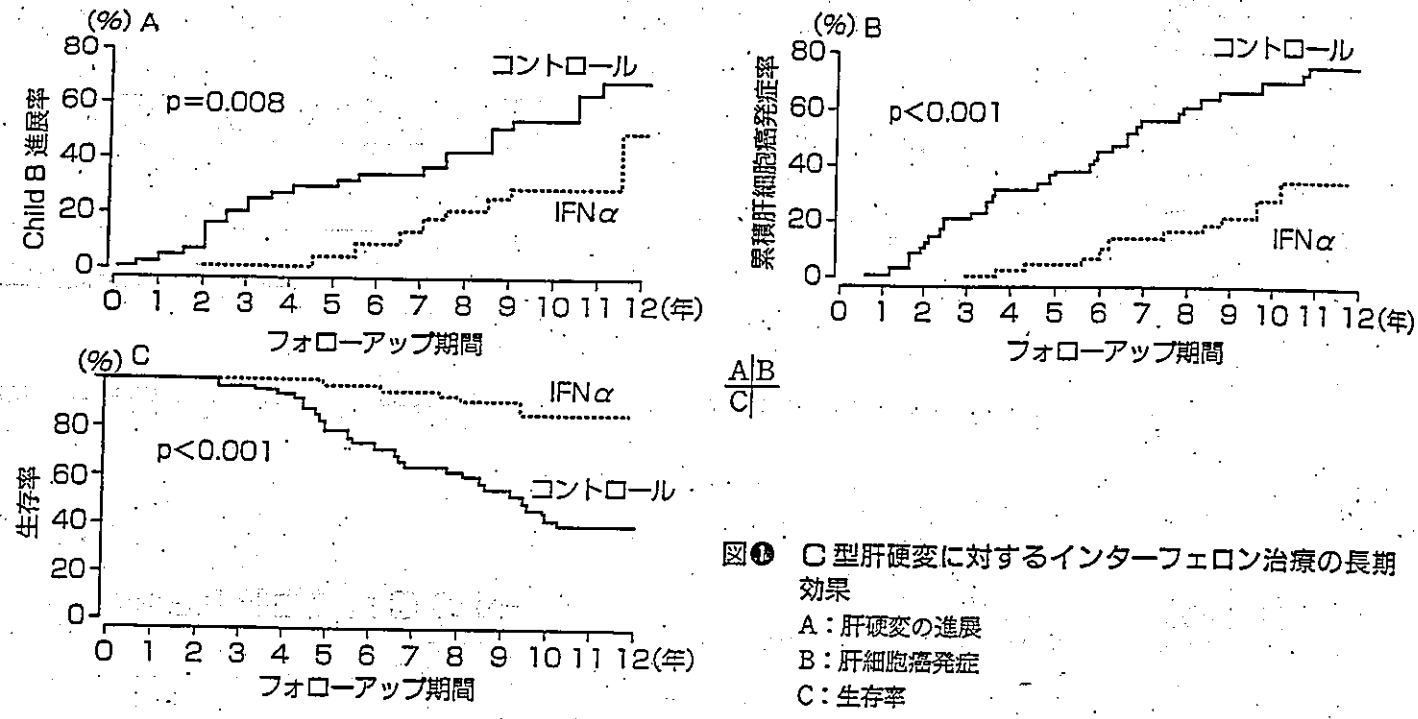
C型肝硬変での年率発癌率は7%に達する．発癌のハイリスク症例を対象に集中的に画像診断がおこなわれているため，2 cm以下の微小肝細胞癌で発見される症例が多くなっている．しかし，これらの症例に治癒切除などの適切な癌治療をおこなっても，生命予後の延長には限界がある．その理由は，長期生存には肝硬変の進行によって生ずる非代償化，すなわち肝不全死の問題と，非癌部から年率25%程度生じてくる術後再発の問題が解決できていないからである．このため，肝細胞癌症例を含めたC型慢性肝疾患の予後延長のためには，肝硬変までの時点においては慢性肝炎から肝硬変への進展抑制と肝細胞癌発症の阻止であり，肝細胞癌発症後は肝不全や術後再発を予防することが必要となる．

ここでは，われわれがおこなった二つの臨床研究，すなわち術前に投与したインターフェロン(IFN)の術後再発へ影響をretrospectiveに検討した研究と，治癒切除後にIFNを投与したprospectiveな再発抑制の臨床研究を中心に紹介し，文献的な考察を加えて概説する．

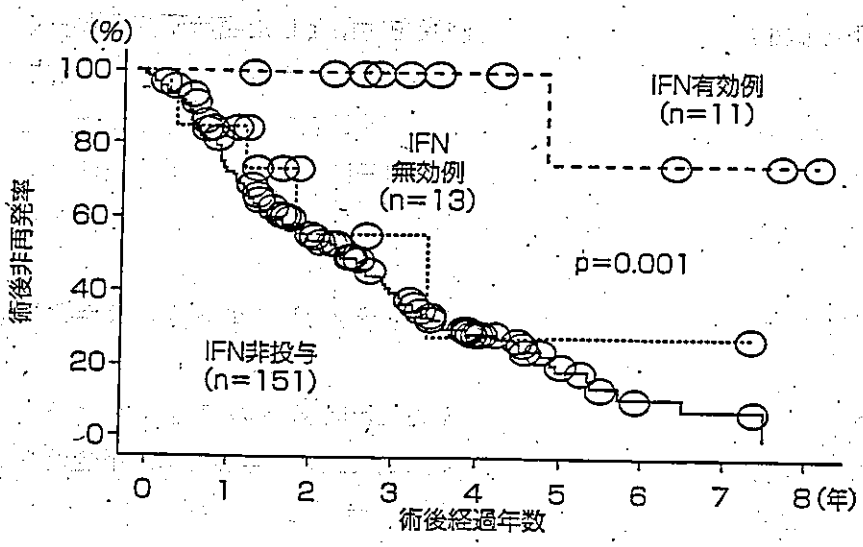
1. IFNのC型慢性肝疾患への臨床的効果

IFNの発癌抑制効果について，C型慢性肝炎あるいは肝硬変を対象とした臨床研究は数多く報告されている．われわれは，よく代償された非A非B型（C型）肝硬変を対象に検討した[1)2)]．組み込み時点の背景因子は，2群間で有意差はなく，平均観察期間は両群とも約10年である．その結果，IFN投与群からは45例中7例にHCV-RNA消失がみられ，血清ALT値の安定化は半数の症例に認められた．IFNは肝硬変の進展を阻止し(Child AからChild Bへの進展)，発癌率を低下させた．さらに，IFN投与群では肝不全死や肝細胞癌死が減少し，全死亡率の改善が生じた(図❶)．IFN投与群の非投与群に対するリスク比を統計学的に求めると，肝硬変の進展を0.250倍，肝細胞癌の発症を0.256倍，全死亡率を0.135倍に改善させることが示された．

本研究を契機として，IFNの発癌抑制効果についてC型慢性肝炎・肝硬変を対象とした多くの大規模臨床研究がおこなわれ，IFNの発癌抑制効果，肝硬変への進展抑制効果が実証された[3)]．さらにYoshidaら[4)]は，IFN投与群では肝臓関連死のみならず，全死亡も有意に改善することを明らかにした[5)]．これらの効果は，IFNによってHCV-



図❶ C型肝硬変に対するインターフェロン治療の長期効果
A：肝硬変の進展
B：肝細胞癌発症
C：生存率



図❷ 発癌前のインターフェロン治療歴と術後再発との関係
IFN有効例とはIFN投与後血清ALT値が持続正常化，無効例とは血清ALT異常値を呈する症例．(Kubo S *et al*, 2001[6]より引用)

RNAの陰性化の有無にかかわらず血清ALTが安定化した症例により強く認められた．

2. 発癌前のIFN投与が術後再発へ及ぼす影響

残肝部における高い再発率と肝硬変の進行が障壁となり，肝細胞癌の生存率の改善は頭打ちとなっている．このため，再発と肝不全を抑制する非癌部への対策が重要であるが，われわれはC型慢性肝炎や肝硬変においては病態の進展や発癌抑制効果が実証されているIFNに注目した．

当院消化器外科にて肝切除された175症例を対象に，IFN投与の既往のある症例と既往のない症例についての術後再発率を調査した．IFN投与歴のある症例では，肝機能が正常化した11例において1例しか再発しなかったが，IFN投与によっても肝機能異常が持続している症例ではIFN投与歴のない症例とほぼ同等の再発率であった（図❷）[6]．再発に寄与する因子を多重ロジスティック回帰分析すると，Child-Pugh分類のChild Aの

再発率はChild Bにくらべ0.64倍，腫瘍数が単発の症例では多発にくらべ0.59倍，IFN治療が有効例は無治療にくらべ0.07倍であった（表❶）．従来より，非癌部の発癌ポテンシャルは肝硬変の進展例や肝細胞癌の多発例で高いとされてきた．今回，これらの臨床指標よりIFNの有効性が最も再発に寄与することが示された．この結果は，C型慢性肝炎や肝硬変に対するIFNの発癌抑制効果の結果から容易に予測可能であり，発癌が生じた症例においてもウイルス持続消失（sustained viral response：SVR）例では発癌ポテンシャルが低下しているため，その後の再発頻度が少ないことを意味している．

表❶ 再発に寄与する因子（多重ロジスティック回帰分析）

寄与因子	リスク比（95%CI）	p値
Child-Pugh分類		
Child B	1	
Child A	0.64（0.43—0.95）	0.026
腫瘍数		
多発	1	
単発	0.59（0.40—0.87）	0.008
IFN治療		
治療歴なし	1	
IFN有効例	0.07（0.01—0.53）	0.009
無効例	0.80（0.32—1.99）	0.631

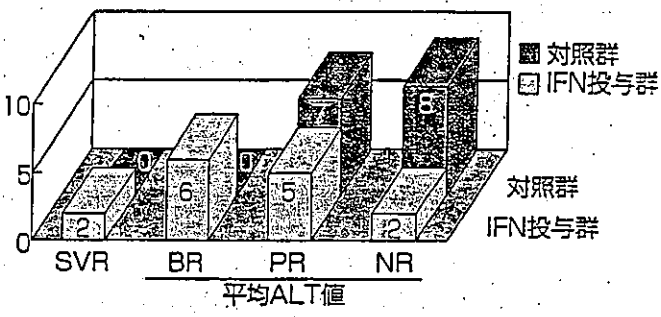
3. 発癌後のIFN投与の臨床的効果

われわれは発癌後のIFNの再発抑制効果を明らかにするために，治癒切除されたC型肝細胞癌30例をIFN投与群と対照群の2群に分け，prospective stydyをおこなった[6]．IFNはヒトリンパ芽球インターフェロン（HLBI）6 MIU/日を術後より2週間連日，14週間は週3回投与し，さらに週2回投与を88週間追加し，計2年間の投与をおこなった．対照群では，従来の肝庇護療法を継続した．エントリーの基準は①長径5 cm未満の単発の肝細胞癌，②HBs抗原とヒト免疫不全ウイルス（human immunodeficiency virus：HIV）抗体陰性で，HCV-RNA陽性，③慢性肝炎あるいは代償期肝硬変，④血小板数5万/μl以上，⑤治癒切除（術後4週のCTにて，限局性病変を認めない）などの5条件とした．

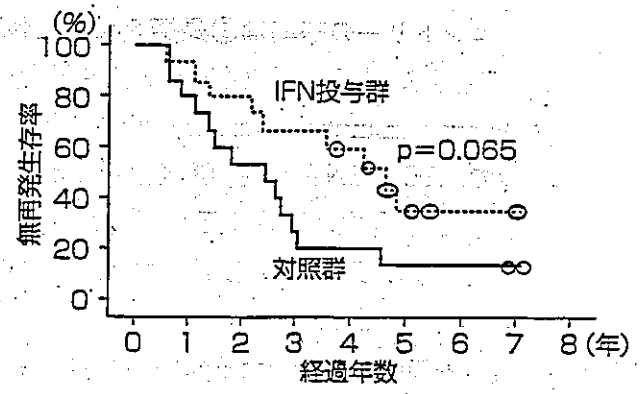
エントリー時点での背景因子は両群間で有意差はみられなかった（表❷）．患者の平均年齢はIFN投与群では61.9歳，対照群では60.0歳であり，

表❷ インターフェロン投与群と対照群の臨床背景

	IFN投与群	対照群	p値
年齢±SD，y	61.9±5.8	60.0±4.8	0.33
性別（男：女）	15：0	15：0	>0.99
アルブミン g/dl	3.6（3.3，4.3）	3.6（3.3，4.1）	0.77
ALT，IU/l	105（45，131）	86（58，151）	0.49
血小板，×万/μl	14.7（7.5，23.1）	11.2（6.1，20.9）	0.14
AFP，>100 ng/l，n	4	4	>0.99
Child-Pugh分類A：B	11：4	12：3	>0.99
腫瘍径，cm	2.5（1.9，3.5）	2.6（2.4，3.5）	0.68
分化度，n			
高/中/低	1/11/3	2/11/2	0.77
非癌部組織像，n			
炎症，1/2/3	4/6/5	1/7/7	0.33
線維化，1-3/4	8/7	7/8	>0.99



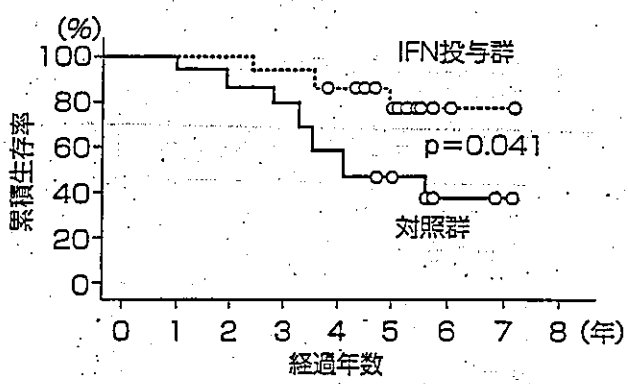
図❸ インターフェロン投与群と対照群との治療効果比較
SVR(HCV完全消失)，BR(血清ALT値のみ持続正常化)，PR(血清ALT値が軽度異常)，NR(平均血清ALT値80 IU/l以上)



図❹ インターフェロンによる術後再発への抑制効果

表❸ 発癌時点の肝機能検査の比較

検査項目	IFNα投与群 (n=9)	対照群 (n=13)	p
アルブミン値	4.0 (3.6, 4.2)	3.7 (2.8, 3.9)	0.05
総ビリルビン値	0.7 (0.6, 1.0)	1.1 (0.6, 2.1)	0.04
血清ALT値	57 (26, 110)	70 (59, 160)	0.12
血小板数	11.5(7.9, 20.2)	12.3(6.8,21.5)	0.85
p-3-p値	0.8 (0.6, 1.2)	1.1 (0.6, 1.9)	0.32
再発時腫瘍数 (3ヵ所以上)	1 (11%)	6 (46%)	0.16



図❺ インターフェロンによる累積生存率の改善

全例が男性である．アルブミンの中央値は両群とも3.6 g/dlと若干低値で，血清ALT値は全例異常値を呈した．外科症例であるため，肝予備能が比較的よく，血小板の中央値は10万/μl以上を保っており，非癌部の肝組織像も約半数はステージ3までの慢性肝炎であった．2年間のIFN治療の効果は，SVR例がIFN投与群では15例中2例に認められた．さらに，IFNを長期に投与したためウイルスが消失しなかった症例のなかからも肝機能の正常化（biochemical response：BR）が6例に生じた（図❸）．

術後再発はIFN投与群では15例中9例に，対照群では15例中13例に再発が認められ，IFNによって再発が遅延する傾向がみられた(図❹)．両群ともに肝機能が正常値を維持している症例からの再発はまれであり，慢性肝炎や肝硬変での知見と同様，肝機能の安定化が再発抑制にも重要であることが明らかとなった．また，今回の臨床試験の再発パターンから，IFNの投与時点に画像で確認できないレベルの微小肝細胞癌が残肝部に存在する症例の場合には，IFN単独では抗腫瘍効果は期待しがたいと考えられた．しかし，発癌症例における発癌時点の肝機能検査所見は，IFN投与群ではアルブミン値，ビリルビン値が対照群にくらべて良好であり，再発した腫瘍数も少ない傾向が認められた(表❸)．IFNは肝予備能に関しても改善作用を有しており，発癌抑制効果と相まって予後の延長が認められた(図❺)．Mutoら[7]は，肝細胞癌の再発に対する非環式レチノイドの効果を検討し，IFNと同等の発癌抑制効果を報告している．本剤の場合は，微小肝細胞癌をアポトーシスに陥らせると推測されており，今後IFNとの併用

効果の検討が必要である.

おわりに

われわれは慢性肝炎から肝細胞癌に至るどの病期においても,IFN を中心とした積極的な発癌抑制対策を講じるべきであると考えている.多くの臨床研究をメタ分析した結果からも,少なくとも慢性肝炎についてはその効果がすでに実証されている.このような IFN による発癌抑制効果は,ウイルスの非消失例であっても血清 ALT 値が正常化した症例では HCV 消失例と同等の抑制効果が認められ[3],無効例でも線維化の進展が抑制される.すでに,ウルソデオキシコール酸 (UDCA) や小柴胡湯などの肝機能改善薬の発癌抑制効果は基礎研究のみならず,臨床研究においても抑制効果が報告されている[8].少なくとも短期間の発癌抑制のためには,ウイルスの排除は必ずしも必要ではなく,血清 ALT の安定化や炎症の鎮静化が重要と考えられる.肝細胞癌症例に対する IFN の発癌抑制効果は慢性肝炎などの癌化の過程が進んでいない症例にくらべ弱いものの,われわれの成績でも弱い再発抑制が認められた.IFNβ を用いて同様の検討をおこなった Ikeda ら[9]の成績では,IFN の再発抑制効果はわれわれの結果より顕著であった.また,経皮エタノール注入療法 (PEIT) 後の再発をみた Shiratori ら[10]は,IFN 著効例においても一度目の再発は抑制せず,2 回目以降の再発については明らかな抑制効果を発揮することを報告している.われわれは,IFN の発癌抑制効果よりもむしろ肝不全への進展阻止効果に注目している.IFN 投与例では発癌時点の肝予備能がよく,再発に対する十分な根治療法が可能であった.このため,IFN 投与によって生命予後の改善がみられた.

わが国でも 2001 年 12 月にリバビリン (Rib) やコンセンサスインターフェロン (コンセンサス IFN),ペグインターフェロン (PEG-IFN) などの新薬が認可され,今後も PEG-IFN/Rib 併用の承認が予定されている.これらの新薬によって,全体の SVR 率は 50%程度に向上すると予測されている.これに伴い IFN の発癌抑制の更なる増強が期待できる.一方で,わが国の C 型の肝細胞癌は高年齢化しており,IFN や Rib による副作用の出現率が欧米より高いことが問題となっている.このため,副作用の少ない,患者にやさしい治療,たとえば IFN を SVR ではなく肝機能の BR を目的に投与する少量長期投与が注目を集めている.

発癌抑制をめざし,肝疾患患者の予後延長をはかるためには,年齢や身体条件,肝機能改善薬への反応性,肝病変の進展度など種々の条件を考慮し,個々の患者に応じたオーダメード医療が必要である.IFN をどの時期にどのように投与するのか,さらに Rib を併用するのか,あるいは SVR をあきらめ BR をめざすのか,それぞれの患者に応じた綿密な治療戦略の立案が必要である.

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【雑誌】

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Sex- and Age-Specific Carriers of Hepatitis B and C Viruses in Japan Estimated by the Prevalence in the 3,485,648 First-Time Blood Donors during 1995–2000

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Key Words
Hepatitis B virus · Hepatitis C virus · Hepatocellular carcinoma · Transfusion

Abstract
Objective: Carriers of hepatitis B virus (HBV) and hepatitis C virus (HCV) in Japan were estimated on a national basis. ***Methods:*** Sera from the first-time blood donors aged 16–64 years in eight jurisdictions of the Japanese Red Cross Blood Center during 1995–2000 were tested for hepatitis B surface antigen (HBsAg) and antibody to HCV (anti-HCV). Viremia with HCV was estimated to be present in 70% of donors with anti-HCV. ***Results:*** HBsAg was detected in 22,018 of 3,485,648 (0.63%) blood donors including 12,990 of 1,780,149 (0.73%) men and 9,028 of 1,705,499 (0.53%) women, and anti-HCV in 17,010 (0.49%) including 8,504 (0.48%) men and 8,506 (0.50%) women. Multiplying the carrier rate by the population registered in the Census 2000, the total HBV carriers aged 15–65 years were estimated at 967,753 (95% confidence interval 806,760–1,128,745), of whom 571,210 (479,267–663,152) were men and 396,543 (327,494–465,593) were women. Likewise, the total HCV carriers were estimated at 884,954 (95% confidence interval 725,082–1,044,826), of whom 464,363 (377,927–550,799) were men and 420,591 (347,156–494,027) were women. ***Conclusion:*** Estimated numbers of HBV and HCV carriers would help plan to prevent the development of hepatocellular carcinoma in Japan.

Introduction

Hepatocellular carcinoma (HCC) develops by far the most frequently against the background of advanced chronic hepatitis or liver cirrhosis induced by two blood-borne hepatitis viruses, i.e. hepatitis B virus (HBV) and hepatitis C virus (HCV). Deaths due to HCC keep increasing in Japan, principally as the results of a widespread HCV infection during 1940–1990 [1]. The past epidemic of HCV in the Japanese population manifests itself at present. Yearly deaths due to HCV-associated HCC started to increase in 1975 and reached 27.5/100,000 population in the year 2001. HCC ranks as the forth most frequent cause of death due to malignancy in men and the fifth most frequent one in women in Japan.

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About 76% of HCC cases are due to HCV infection and 17% due to HBV infection; the cause is unknown for the remaining 7%. What is seen in Japan today may represent the tip of the iceberg. Approximately half a million people die of HCC worldwide, and it ranks sixth among malignant neoplasms in men and ninth in women [2].

To cope with ever-increasing deaths due to HCC in Japan, surveys of HBV and HCV infections in people of cancer-bearing age were started at the health checkups they undergo every 5 years after they reach the age of 40. In order to plan and scale measures for preventing the development of HCC in hepatitis virus carriers, it is imperative to know how many are infected with HBV or HCV in Japan, especially amongst those in the cancer-baring age group (40–65 years old).

For the purpose of estimating total numbers of HBV and HCV carriers in Japan, hepatitis B surface antigen (HBsAg) and antibody to HCV (anti-HCV) were determined in all the 3,485,648 first-time blood donors who visited local offices in the eight jurisdictions of the Japanese Red Cross Blood Center during 1995–2000. The sex- and age-specific prevalence rates of HBsAg and anti-HCV thus obtained were multiplied by numbers of respective subpopulations surveyed at the Census 2000, for the purpose of estimating the total HBV and HCV carriers in men and women of different age groups.

Materials and Methods

Subjects

During 6 years from January 1995 to December 2000, 3,485,648 individuals visited local offices of the Japanese Red Cross Blood Center for the first time with the intention to donate blood. Their sera were tested routinely for serum markers of HBV and HCV infections, in addition to examinations of biochemical parameters and infections with other microbes. The study design conformed to the 1975 Declaration of Helsinki. The ethical justification for the use of virological data of sera from anonymous blood donors has been agreed upon legally, provided that they contribute to the good and health of human beings.

Serum Markers for Hepatitis Virus Infections

HBsAg was determined by reversed-passive hemagglutination with reagents made in-house by the Japanese Red Cross Blood Center. Anti-HCV was determined by passive hemagglutination with commercial kits [the second generation HCV PHA (Dinabott, Tokyo, Japan) and HCV PA (Ortho Diagnostics, Tokyo, Japan)]. The cutoff level for the hemagglutination test for HBsAg was 2^2 and that for anti-HCV was either 2^5 or 2^4.

Estimation of the Number of Hepatitis Virus Carriers in Each Subpopulation

The Japanese Red Cross Blood Center has eight jurisdictions (Hokkaido, Tohoku, Kanto, Chubu/Tokai, Kiniki, Chugoku, Shikoku and Kyushu), and accepts blood donations from individuals aged from 16 to 64 years. The ages of the blood donors during the 6 years from 1995 to 2000 were extrapolated to those of the year 2000. Blood donors were stratified by the two sexes and six age groups (<20, 20–29, 30–39, 40–49, 50–59 and ≥60 years). Carriers of HBV were defined by the detection of HBsAg in the serum, while those of HCV were estimated at 70% of the blood donors who test positive for anti-HCV in serum.

Prevalence rates of HBV and HCV carriers thus obtained, for subpopulations of male and female blood donors in the respective age groups, were multiplied by the total number of Japanese who were in the corresponding sex and age group in the year 2000. In this manner, numbers of HBV and HCV carriers of different sex and various age groups were estimated in the eight jurisdictions and collectively in Japan. The 95% confidence interval (CI) was calculated for the estimation of the carrier number of each subpopulation.

Table 1. Sampling ratio of the first-time blood donors in the eight jurisdictions of the Japan Red Cross Blood Center

Jurisdiction	Donors (16–69 years)	Population (15–69 years)	Ratio, %
Hokkaido	163,003	4,172,190	3.9
Tohoku	294,369	8,699,070	3.4
Kanto	961,732	30,847,095	3.1
Chubu/Tokai	668,644	13,926,448	4.8
Kinki	673,108	16,865,894	4.0
Chugoku	152,693	5,473,745	2.8
Shikoku	133,130	2,914,857	4.6
Kyushu	438,969	10,426,271	4.2
Total	3,485,648	93,325,570	3.7

Results

Proportion of the First-Time Blood Donors to the Population in the Eight Jurisdictions

The number of the first-time blood donors and the total population in the eight jurisdictions are shown in table 1, along with the ratio between them. There were marked differences in the population, with Kanto accounting for 28% of the total first-time blood donors followed by Kinki and Chubu/Tokai both at 19%; together they reached 70% of the total first-time blood donors in Japan. The proportion of the first-time blood donors to the local population (sampling ratio) ranged from 2.8 to 4.6% and averaged at 3.7%. Thus, the present investigation was on a large scale, involving approximately 4% of all the people aged from 15 to 69 years in Japan.

Table 2. Age-specific total and sex-specific prevalence of HBsAg in the first-time blood donors in Japan during 1995–2000

Age groups (year of birth)	Total		Men		Women	
	n	HBsAg	n	HBsAg	n	HBsAg
16–19 (1981–1984)	582,415	1,327 (0.23) [0.22–0.24]	273,842	709 (0.26)	308,573	618 (0.20)
20–29 (1971–1980)	1,929,147	10,054 (0.52) [0.51–0.53]	1,004,986	5,955 (0.59)	924,161	4,099 (0.44)
30–39 (1961–1970)	472,447	3,988 (0.84) [0.82–0.87]	277,627	2,828 (1.02)	194,820	1,160 (0.60)
40–49 (1951–1960)	247,020	2,950 (1.19) [1.15–1.24]	120,576	1,796 (1.49)	126,444	1,154 (0.91)
50–59 (1941–1950)	198,477	2,984 (1.50) [1.45–1.56]	80,336	1,388 (1.73)	118,141	1,596 (1.35)
60–69 (1931–1940)	56,142	715 (1.27) [1.18–1.37]	22,782	314 (1.38)	33,360	401 (1.20)
Total	3,485,648	22,018 (0.63) [0.62–0.64]	1,780,149	12,990 (0.73)	1,705,499	9,028 (0.53)

Figures in parentheses represent percentages, those in square brackets the 95% CI.

Table 3. Estimated numbers of individuals who carry HBV in Japan stratified by sex and age

Age at 2000	Total		Men		Women	
	n	carriers	n	carriers	n	carriers
≤14	18,472,499		9,459,102		9,013,397	
15–19	7,488,165	17,225 (13,623–20,827)	3,833,984	9,947 (7,923–11,971)	3,654,181	7,278 (5,700–8,856)
20–29	18,211,769	94,074 (87,002–101,146)	9,272,519	54,543 (50,781–58,305)	8,939,250	39,531 (36,221–42,841)
30–39	16,891,475	142,302 (125,003–159,601)	8,533,104	91,354 (82,133–100,576)	8,358,371	50,948 (42,870–59,025)
40–49	16,716,227	211,435 (181,881–240,990)	8,391,943	134,384 (117,121–151,647)	8,324,284	77,051 (64,760–89,343)
50–59	19,176,162	304,118 (260,670–347,566)	9,500,277	173,856 (148,024–199,688)	9,675,885	130,262 (112,646–147,878)
60–69	14,841,772	198,598 (138,581–258,615)	7,106,809	107,125 (73,285–140,964)	7,734,963	91,474 (65,296–117,651)
≥70	14,899,213		5,864,835		9,034,375	
15–69	93,325,570	967,753 (806,760–1,128,745)	46,638,636	571,210 (479,267–663,152)	46,686,934	396,543 (327,494–465,593)

Figures in parentheses represent 95% CI.

Prevalence of HBV Carriers among Blood Donors Stratified by Sex and Age

In view of the influence of age on the prevalence of HBsAg, the ages of all the first-time blood donors during 1995–2000 were extrapolated to those in the year 2000. Their sex- and age-specific prevalence rates of HBsAg are shown in table 2. Overall, HBsAg was detected in 0.63% of the 3,485,648 blood donors. The prevalence of HBsAg was significantly higher (χ^2 test, $p < 0.001$) in men (0.73%) than in women (0.53%), and increased with age until 60 years in both of them. HBsAg was the least frequent in the blood donors aged younger than 20 in 2000 at 0.26% and 0.2% in men and women, respectively.

Figure 1 illustrates the prevalence of HBsAg in blood donors as a function of their age notched by 1 year. The prevalence of HBsAg was the highest with an average of 1.5% in the cancer-bearing age groups from 40 to 69 years in both men and women.

The total number of HBV carriers in Japan aged from 15 to 69 years in the year 2000 is estimated in table 3. The numbers of HBV carriers in subpopulations stratified by sex and age are also listed. The estimation was based on the prevalence of HBsAg in a given subpopulation multiplied by the number of individuals belonging to that category registered in the Census 2000. The total number of HBV carriers aged from 15 to 69 years was estimated close to a million at 967,753. The number of HBV carriers was highest in the age group of 50–59 in both men and women. Due to the number in this subpopulation being highest in both men and women registered in the Census 2000 in combination with the highest prevalence of HBsAg in this age group, the total number of HBV carriers stood out prominently in comparison with those in the other age groups. Of the HBV carriers aged from 15 to 69 years in Japan in the year 2000, carriers of the cancer-bearing age of 40–69 years accounted for 73.8%.

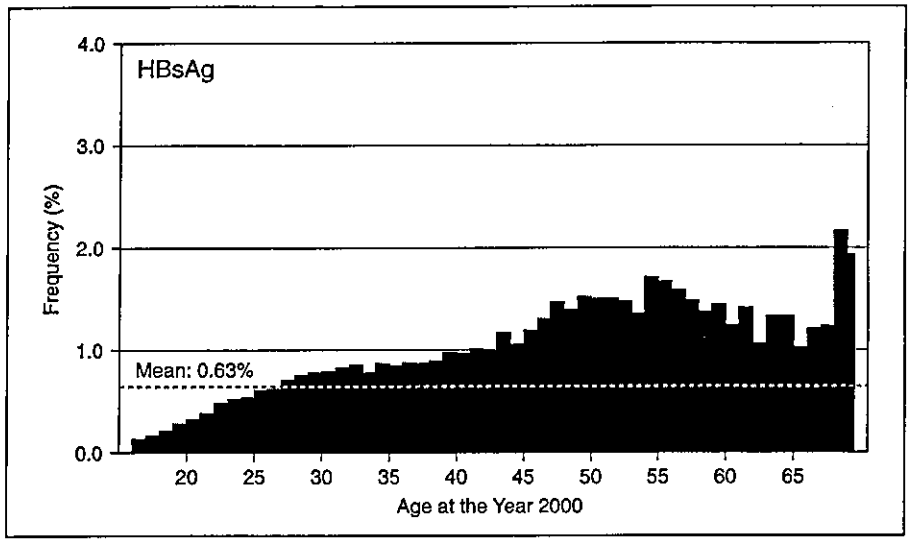

Fig. 1. Age-specific prevalence of HBsAg in the first-time blood donors with their ages extrapolated to the year 2000.

Table 4. Age-specific total and sex-specific prevalence of antibody to HCV in the first-time blood donors in Japan during 1995–2000

Age groups (year of birth)	Total		Men		Women	
	n	HCV	n	HCV	n	HCV
16–19 (1981–1984)	582,415	737 (0.13) [0.12–0.14]	273,842	294 (0.11)	308,573	443 (0.14)
20–29 (1971–1980)	1,929,147	4,012 (0.21) [0.20–0.21]	1,004,986	1,976 (0.20)	924,161	2,036 (0.22)
30–39 (1961–1970)	472,447	3,633 (0.77) [0.74–0.79]	277,627	2,288 (0.82)	194,820	1,345 (0.69)
40–49 (1951–1960)	247,020	3,165 (1.28) [1.24–1.33]	120,576	1,704 (1.41)	126,444	1,461 (1.16)
50–59 (1941–1950)	198,477	3,565 (1.80) [1.74–1.85]	80,336	1,455 (1.81)	118,141	2,110 (1.79)
60–69 (1931–1940)	56,142	1,898 (3.38) [3.23–3.53]	22,782	787 (3.45)	33,360	1,111 (3.33)
Total	3,485,648	17,010 (0.49) [0.48–0.50]	1,780,149	8,504 (0.48)	1,705,499	8,506 (0.50)

Figures in parentheses represent percentage, those in square brackets the 95% CI.

Prevalence of Anti-HCV among Blood Donors Stratified by Sex and Age

Sex- and age-specific prevalence rates of anti-HCV among blood donors are shown in table 4. Overall, anti-HCV was detected in 0.49% of the blood donors. As for HBsAg, the prevalence of anti-HCV increased with age in both men and women. Unlike HBsAg, however, the prevalence of anti-HCV did not reach a plateau in the age group of 50–59 years. It was by far the highest in the oldest age group examined (60–69 years) at 3.45% in men and 3.33% in women.

When the prevalence of anti-HCV was plotted against the age notched by 1 year (fig. 2), the increase of anti-HCV with age became more prominent in comparison with the age profile of HBsAg (fig. 1). In particular, the increase of anti-HCV was almost exponential in the blood donors aged older than 55 years in 2000.

Assuming 70% of the individuals with anti-HCV would have an ongoing infection with HCV RNA in the serum, the numbers of HCV carriers were estimated on the basis of anti-HCV prevalence and the population/subpopulation in Japan at the Census 2000 (table 5). The total number of HCV carriers was estimated at 884,954. Due to the prevalence of anti-HCV markedly increasing with age, the estimated numbers of HCV carriers were highest in the age groups older than 50 years in both men and women. Amongst the HCV carriers aged from 15 to 69 years in Japan in the year 2000, therefore, carriers aged from 40 to 69 years accounted for 85.8%.

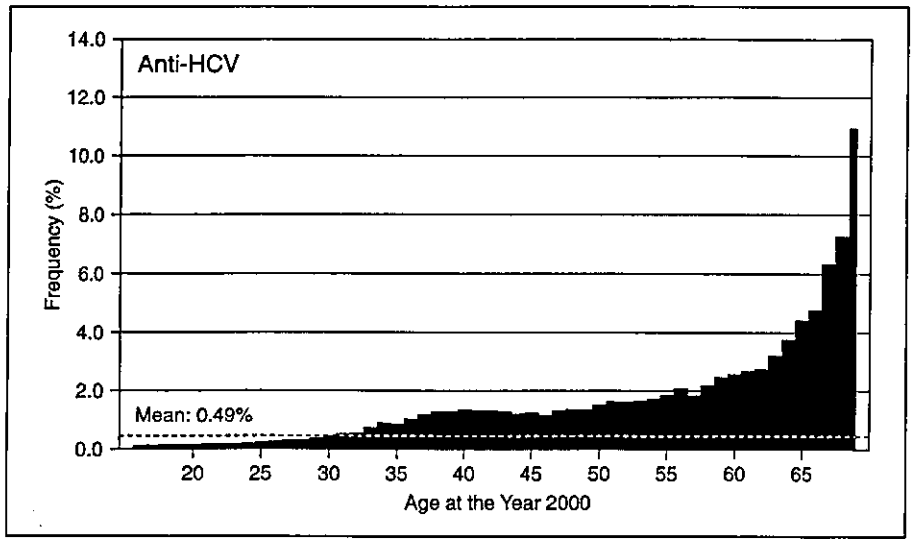

Fig. 2. Age-specific prevalence of anti-HCV in the first-time blood donors with their ages extrapolated to the year 2000.

Table 5. Estimated numbers of individuals who carry HCV in Japan stratified by sex and age

Age at 2000	Total		Men		Women	
	n	HCV	n	HCV	n	HCV
≤14	18,472,499		9,459,102		9,013,397	
15–19	7,488,165	6,716 (4,568–8,864)	3,833,984	2,905 (1,864–3,946)	3,654,181	3,811 (2,704–4,917)
20–29	18,211,769	26,807 (23,203–30,410)	9,272,519	12,967 (11,226–14,708)	8,939,250	13,840 (11,977–15,703)
30–39	16,891,475	92,115 (78,268–105,962)	8,533,104	51,457 (44,693– 58,220)	8,358,371	40,658 (33,575– 47,742)
40–49	16,716,227	155,653 (130,907–180,399)	8,391,943	89,515 (75,894–103,136)	8,324,284	66,138 (55,013– 77,263)
50–59	19,176,162	246,336 (208,241–284,430)	9,500,277	128,800 (107,083–150,516)	9,675,885	117,536 (101,159–133,914)
60–69	14,841,772	357,327 (279,894–434,760)	7,106,809	178,720 (137,166–220,273)	7,734,963	178,608 (142,728–214,488)
>70	14,899,213		5,864,835		9,034,378	
15–69	93,325,570	884,954 (725,082–1,044,826)		464,363 (377,927–550,799)		420,591 (347,156–494,027)

Figures in parentheses represent 95% CI.

Regional Differences in the Prevalence Rates and Carrier Numbers of Hepatitis Virus Infections in Japan

Blood donors were examined for serum markers of HBV and HCV infection in the eight jurisdictions in Japan (table 1). Sex- and age-specific prevalence rates of HBsAg, as well as numbers of HBV carriers in each of the eight jurisdictions are illustrated in figure 3a and b, and those of anti-HCV in figure 4a and b. Although the prevalence of both HBsAg increased with age and exhibited similar patterns in all the eight jurisdictions, it was highest in Hokkaido representing the northernmost island, and lowest in the Chubu/Tokai district, the geographical center of Japan (fig. 3a).

The prevalence of anti-HCV was very different from that of HBsAg (fig. 4a). It was higher in Chugoku, Shikoku and Kyushu, in the southwestern areas of Japan, than in the other districts.

Discussion

Transmission of HBV for establishing the persistent carrier state has been prevented effectively by the national program for passive and active immunoprophylaxis of perinatal transmission of HBV from carrier mothers to their babies implemented in 1986 in Japan [3, 4]. Unlike HBV infection that tends to perpetuate in the infancy but

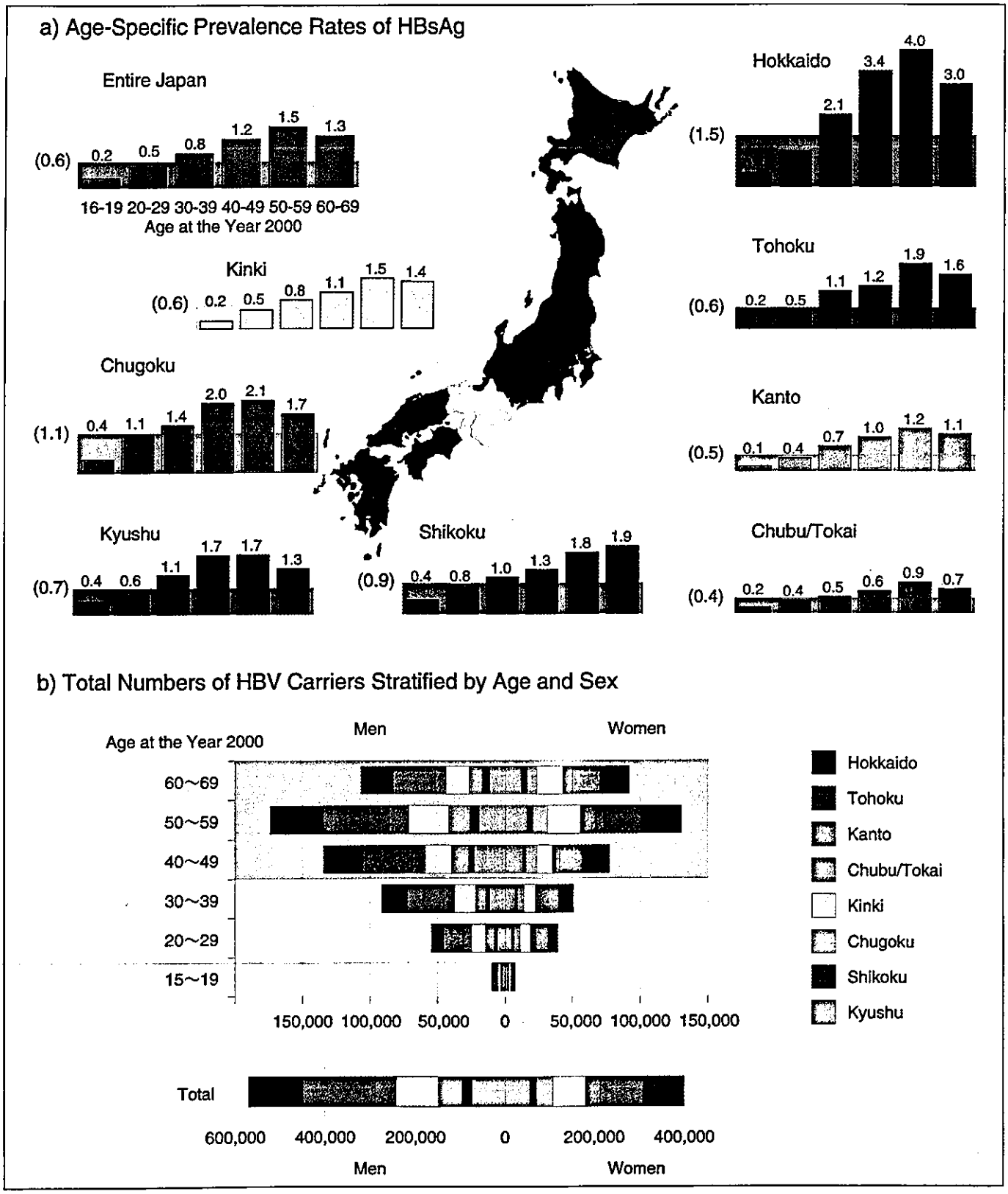

Fig. 3. Sex- and age-specific prevalence of HBsAg in the first-time blood donors from the eight jurisdictions in Japan during 1995–2000 (**a**) and estimated total numbers of HBV carriers stratified by sex and age (**b**).

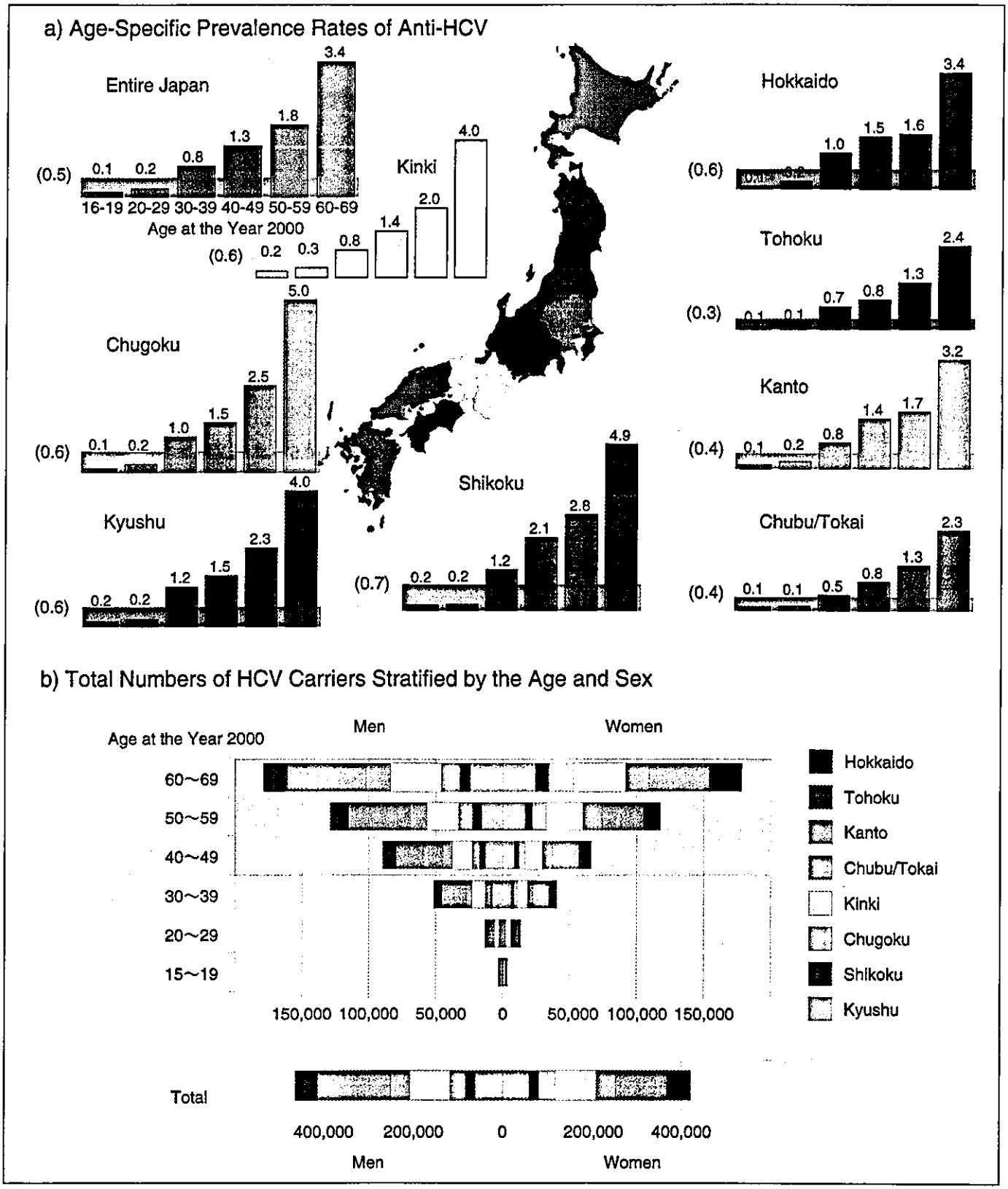

Fig. 4. Sex- and age-specific prevalence of anti-HCV in the first-time blood donors from the eight jurisdictions in Japan during 1995–2000 (**a**) and estimated total numbers of HCV carriers stratified by sex and age (**b**).

resolves spontaneously in most cases of adulthood infection, infection with HCV in adults has a high propensity to become persistent (70–80%) [5, 6]. Thrust by rare perinatal transmission of HCV [7, 8], the incidence of de novo HCV infection has become extremely rare in Japan [1]. There are, however, many individuals who have been infected with HBV and HCV persistently in Japan.

HCC is rare among malignancies because people at risk are easily identified. Unlike in the United States where one half of HCC cases develop in patients with cryptogenic liver cirrhosis [9], such cases occur in less than 10% in Japan. Approximately 75% of HCC cases are accounted for by HCV infection and 16% by HBV infection [1]. Hence there is a need to identify individuals infected with HBV or HCV who are at high risk of HCC, follow them closely and take measures to prevent and treat HCC immediately as required. Since HCC develops later in life, screening for HBV and HCV infection is reasonably indicated for Japanese individuals when they reach 40 years of age.

As a result, the national program to test for HBsAg and HCV RNA was started as of April 2002. All individuals are offered to undergo tests for HBsAg and HCV RNA at the regular health checkups they are given when they reach 40 years of age and every 5 years thereafter. Thus, the program will cover all individuals aged ≥40 years in March 2007; only those who reach the age of 40 years will receive tests annually thereafter. Additionally, tests for HBsAg and HCV RNA have been extended to include individuals who are also at risk of developing HCC for different reasons, such as those with elevated transaminase levels or having a history of transfusion with blood or blood products, or family members of patients with liver disease, even if they do not qualify for the 5-year health checkups.

In order to have an idea of how many HBV or HCV carriers are identified by the national screening, and to plan medical and financial measures to deal with them to prevent the development of HCC and treating it if necessary, it is of crucial importance to estimate their total numbers in Japan. The blood donation system conducted by the Japanese Red Cross Association offers a unique and rare opportunity to survey the extent of HBV and HCV infections on a national basis. Tests for serological markers have been performed with the same reagents (since 1970 for HBsAg with hemagglutination and since 1992 for anti-HCV with the second-generation immunoassay) on approximately 6 million units of donated blood annually for securing the safety of transfusions and infusion with blood products.

Worldwide, approximately 1.9 million people are estimated to be infected with HCV [10]. Of the 45 surveys conducted on blood donors from various countries, 22 tested more than 10,000 donors and only 7 examined more than 100,000 donors [11]. The prevalence of anti-HCV in sizable blood donor groups varies widely from 0.005 in Germany [12] to 1.85% in India [13]. Even in the same country, the reported prevalence rate of anti-HCV ranges from 0.17 to 0.5% in the United States [14–16] and from 0.19 to 2.2% in Japan [17–19]. In the present survey, anti-HCV was detected in 0.6% of some 3.5 million first-time blood donors in Japan with the use of the standardized method for detection. In order to estimate carriers of HCV as well as HBV carriers in a given country, caution is needed to avoid variations due to local differences and methods for detecting viral markers.

In view of the fact that HCC develops 4 times more frequently in men than in women, and preferentially in ages older than 55 years for HBV-associated and 65 years or older for HCV-associated HCC [1], the prevalence rates of HBsAg and anti-HCV were determined in blood donors stratified by sex and age. Since the Japanese Red Cross Association operates in the eight jurisdictions, sex- and age-specific prevalence rates of viral markers were complied in each of them separately. Such an attempt may reveal local differences, if any, in the exposure to and persistence of HBV and HCV infections.

On the basis of prevalence rates of HBsAg and anti-HCV in the first-time blood donors, and the number of men and women in different age groups determined in the Census 2000, there were an estimated 967,753 HBV carriers and 884,954 HCV carriers aged from 15 to 69 years in Japan. Those of cancer-bearing age, who were 40–69 years old and targeted in the screening program, accounted for 73.8% of HBV carriers and 85.8% of HCV carriers among the respective carriers aged from15 to 69 years in Japan. Hence, the screening program would be able to efficiently identity Japanese people at risk of developing HCC associated with HBV or HCV infection.

Although profiles of the sex- and age-specific distribution of both HBsAg and anti-HCV were comparable among blood donors in the eight jurisdictions, there was a wide variety of the mean prevalence of these viral markers between them. Thus, the mean prevalence rate of HBsAg varied from 0.4% in Chubu/Tokai in the center of Japan to 1.5% in Hokkaido in the north. Anti-HCV, in contrast, tended to be more prevalent in southwestern regions of Japan represented by Chugoku (0.6%), Shikoku (0.7%) and Kyushu (0.6%); they may be responsible, at least in part, for the fact that the incidence of

HCC increases from the northeast to southwest along the Japan Islands [20].

It has to be pointed out, however, that the estimation on the basis of the first-time blood donors is subject to cohort effects in that only persons who wish to donate blood can be examined. Although the first-time blood donors tested for viral markers covered approximately 4% of the Japanese aged from 15 to 69 years in toto, they had an uneven age distribution and were biased in favor of younger generations with a low representation of older ages. They covered 7.8% of individuals in the age group of 15–19 years, 10.5% of 20–29 years and 2.8% of 30–39 years; the representation was low at 1.5% of individuals in the age group of 40–49 years, 1.0% of 50–59 years and merely 0.4% of 60–69 years. Hence, the reliability becomes lower in the estimation of HBV and HCV carriers in older age groups who are at high risk of developing HCC. As data on the prevalence of HBsAg and anti-HCV are accumulating during 2002 through 2006 in the national survey, it will be evaluated how closely the prevalence rates of viral markers in the first-time blood donors in this study represent those that are established in larger populations. At present, however, there are no better cohorts for estimating the prevalence rates of persistent hepatitis virus infections than the first-time blood donors, both in scale and quality.

Now that the number of HBV and HCV carriers has been reasonably estimated, measures to manage them need to be planned both in their magnitude and regarding costs. It would be the duty of the medical domain and the government to see to it that carriers of HBV or HCV are regularly screened for HCC and receive treatment to prevent the development of HCC as well as treatment for HCC if necessary. Knowing that HCV infection accounts for 75% of HCC cases at present [1] and that a large proportion of HCV infections in the past occurred after blood transfusion and inadequate medical practices in Japan, physicians and ministries in charge are obliged to do their best in working toward the goal of preventing and curing HCC associated with HCV infection.

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