ously treated with fluoropyrimidine plus platinum-based chemotherapy. Am J Clin Oncol. 2010 Mar 19 [Epub ahead of print].

107) Richly H, Schultheis B, Adamietz IA, et al. Combination of sorafenib and doxorubicin in patients with advanced hepatocellular carcinoma: results from a phase I extension trial. Eur J Cancer. 2009; 45: 579-87.

108) Hoffmann K, Glimm H, Radeleff B, et al. Prospective, randomized, double-blind, multi-center, Phase III clinical study on transarterial chemoembolization (TACE) combined with sorafenib versus TACE plus placebo in patients with hepatocellular cancer before liver transplantation -HeiLivCa [ISRCTN24081794]. BMC Cancer. 2008; 8: 349.

109) Hsu CH, Shen YC, Lin ZZ, et al. Phase II study of combining sorafenib with metronomic tegafur/ uracil for advanced hepatocellular carcinoma. J Hepatol. 2010; 53: 126-31.

110) Vincenzi B, Santini D, Russo A, et al. Early skin toxicity as a predictive factor for tumor control in hepatocellular carcinoma patients treated with sorafenib. Oncologist. 2010; 15: 85-92.

111) Yau T, Chan P, Ng KK, et al. Phase 2 open-label study of single-agent sorafenib in treating advanced hepatocellular carcinoma in a hepatitis B-endemic Asian population: presence of lung metastasis predicts poor response. Cancer. 2009; 115: 428-36.

112) Maksimovic O, Schraml C, Hartmann JT, et al. Evaluation of response in malignant tumors treated with the multitargeted tyrosine kinase inhibitor sorafenib: a multitechnique imaging assessment. AJR Am J Roentgenol. 2010; 194: 5-14.

113) Koeberle D, Montemurro M, Samaras P, et al. Continuous sunitinib treatment in patients with advanced hepatocellular carcinoma: a Swiss Group for Clinical Cancer Research (SAKK) and Swiss Association for the Study of the Liver (SASL) multicenter phase II trial (SAKK 77/06). Oncologist. 2010; 15: 285-92.

114) Bekaii-Saab T, Markowitz J, Prescott N, et al. A multi-institutional phase II study of the efficacy and tolerability of lapatinib in patients with advanced hepatocellular carcinomas. Clin Cancer Res. 2009; 15: 5895-901.

115) Thomas MB, Morris JS, Chadha R, et al. Phase II trial of the combination of bevacizumab and erlotinib in patients who have advanced hepatocellular carcinoma. J Clin Oncol. 2009; 27: 843-50.

116) Hsu CH, Yang TS, Hsu C, et al. Efficacy and tolerability of bevacizumab plus capecitabine as first-line therapy in patients with advanced hepatocellular carcinoma. Br J Cancer. 2010; 102: 981-6.

117) Pinter M, Wichlas M, Schmid K, et al. Thalidomide in advanced hepatocellular carcinoma as antiangiogenic treatment approach: a phase I/II trial. Eur J Gastroenterol Hepatol. 2008; 20: 1012-9.

3）慢性肝炎患者をどのように指導するか

池上　正，松﨑靖司

　わが国には現在200万とも300万ともいわれる数の肝臓病患者がいる．そして，毎年4万人近くの患者が肝臓病で死亡している．先進国中この数は突出しており，したがってわが国において，肝臓病は専門領域を問わず日常診療でよく遭遇するcommon diseaseであるといえる．第2章までに述べられたように積極的な抗ウイルス療法の導入，あるいは肝庇護療法による病態進展の予防を行うことで肝硬変や肝臓癌の発生を抑制できる時代に突入している．

　治療の多くは肝臓専門医によって行われているが，一方で，上述したように日常診療において肝臓病患者に遭遇する機会は多く，その際にこれを見逃さず，いかに必要な診療体系，あるいは治療システムにのせていくのかはかかりつけ医や肝臓病を専門としない医師の認識の差に依存するところが大きい．また，抗ウイルス療法などの治療以外の診療をかかりつけ医や肝臓病を専門としない医師が担当する機会も多く，より生活に密着した形で診療を行うこれらの医師にとって，慢性肝炎患者の指導は重要な役割のひとつと思われる．本稿では，これらの慢性肝炎患者をどのように指導するのかについて，日常生活上の注意事項を含めてまとめてみる．なお，食事についての詳細は第3章-4）C型慢性肝炎患者の食事指導を参照されたい．

1 通院の継続について

　慢性肝炎患者の多くは無症状であり，検診や他疾患で医療機関を受診した際に偶然ウイルス感染を発見されて紹介されることが多い．マスコミを中心にした啓発活動の成果もあって，治療が必要であるという認識が一般にも広まってきてはいるがまだ十分とはいえず，また診療ガイドラインは毎年改訂されており，他疾患のガイドラインにも目を通す必要のある一般臨床医にとって，これをキャッチアップしていくのは大変かもしれない．これらを考えると，慢性ウイルス性肝炎を診た場合は，今後のフォローアップ方針や治療の是非について，一度専門医を受診させた方がよい．専門医にて治療方針が決定された後はその方針にしたがって治療，もしくはフォローアップのスケジュールを設定する．

1）C型肝炎患者の場合

　診療ガイドラインに沿って考えたときに，無症候性キャリアと判断されたものは，3～6カ月ごとのフォローアップを受けることになるが，このフォローアップが途切れないように配慮をすべきである．C型肝炎については，肝機能が正常（ALT＜30 IU/L，血小板数15万以上）の患者でも，経過フォロー中にALTの上昇をみるものがほとんどであり，また，病態としても炎症が持続していることが多い．図1は当院で肝生検を施行したPNALT（persistent normal ALT）症例の生検結果の内訳であるが，90％以上の患者については肝組織上，何らかの変化が現れており，これを裏付けている．抗ウイルス療法や肝庇護療法を継続している患者の場合，通院継続は至極当然であるが，キャリアとし
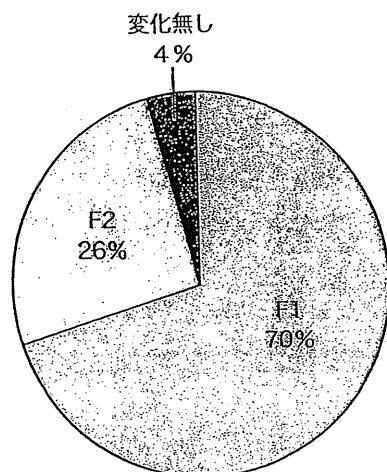
図1◆ 当院におけるALT＜31 IU/L症例の
肝生検結果

平均年齢：52.5歳，男：女＝14：15
線維化の評価は第1章-5を参照

てフォローする場合も途切れず受診を続けるように指導する.

　さらに，治療が必要な患者については，治療の必要性についてよく説明し，専門医受診を勧める. 治療に伴う経済的負担を不安視する患者もいるため，治療費助成制度による公的サポートの存在を伝える. また，最近は多くのメーカーから患者指導用の資料が作成，配布されており，これを利用することで患者の理解を深め，治療意欲をもたせるなどの工夫が可能である.

pitfall　インターフェロン (IFN) 治療を拒否したC型慢性肝炎患者に対し，IFN療法を行わず，肝細胞癌の早期発見の検査を怠った過失により死亡したとして，担当医が敗訴になるという判例がある. HCV抗体陽性患者が存在したら，HCV RNA検査によりウイルス感染の持続を確認したうえで，患者に治療を勧める，あるいは専門医への受診を勧告すべきである. また，このこれらの事柄についてカルテにきちんと記載しておくこと.

コツ 抗ウイルス療法導入の前に
　C型慢性肝炎患者に抗ウイルス療法を勧める際に注意するのは，1回の診察ですべてを決めてしまわないことである. 患者の病気の状態，推奨される治療，その効果と副作用，治療を行わないときの不利益について時間をかけて説明し，自宅に持ち帰ってよく考え，家族と相談する時間を与える.

　一方で，抗ウイルス療法が奏効し，SVRを得た症例はどのようにすべきであろうか. 抗ウイルス療法は明らかに病態の進行を抑制し，肝発癌を抑制するが，0になるわけではない. 特に抗ウイルス療法開始時にすでに線維化が進行している症例や，高齢者の場合はウイルス排除に至っても発癌に至る可能性が高い. このため，抗ウイルス療法終了後も引き続き画像検査などで早期に肝癌を発見するためのサーベイランスを継続する必要があり，このことは治療中から患者に対してよく説明されるべきである.

　さらに，何らかの理由で抗ウイルス療法が行えなかった症例，あるいは抗ウイルス療法によってもウイルス排除が得られなかった症例については，肝庇護療法にて積極的に肝機能の安定化を目指すが，これらは多くの場合長期間・頻回の注射，外来通院を要する. これらの治療の必要性についてよく説明し，また定期的な画像検査受診の必要性を説明する.

2) B型肝炎患者の場合

　B型肝炎患者については，核酸アナログなどの抗ウイルス療法を受けている患者については，治療の中断による肝炎の再燃などのリスクについてよく伝え，通院を継続することの必要性を強調する．また，無症候性キャリアのうち，HBV DNA が低値であり，HBe抗体が陽性の症例でも経過観察中にウイルス量の増加，肝炎の再燃をみることを経験するため，これらの比較的low risk と思われるキャリアでも，6カ月に1回程度の受診を継続するように指導する．

3) かかりつけ医の役割

　病識に乏しく，専門医受診を勧めてもなかなか受診しない者がいる一方，患者によっては，非常に病識の高い者も多く，自分でインターネットを調べたり，いろいろな本を読んだりし，治療法に関しても積極的に考える者が増えてきている．ただし，この場合に逆に知識が増えすぎてしまって自分自身で整理ができなくなってきていることがあり，この交通整理をするのも医師の役割であるといえる．

　以上のように，慢性肝炎患者に関しては，現在安定しているからといって「問題なし」との判断を容易に与えると，患者によっては「通院は不要」と解釈する者もあることから，定期的な通院の必要性について説明し，自分の専門外であるならば，専門医（消化器内科医，肝臓専門医）への紹介を促し，適切なフォローアップ，治療へと結びつけるようにすることが重要である．

2 運動・仕事・日常生活

1) 運動

　慢性肝疾患患者の運動量について具体的な運動強度についての設定について根拠をもって示された報告はない．慢性肝炎と一言でいっても，病態的にはかなりの幅があり，ほとんど肝機能には影響のない無症候性キャリアから，代償性肝硬変に近い状態のものまでさまざまであるため，一様には運動量について決められない．しかし，おおむね以下のような内容で指導を行う．患者に肝疾患の状態について把握をさせることが重要である．

a. 無症候性キャリア〜 軽度（ALT＜100 IU/L）肝障害を呈する慢性肝炎患者

　運動制限の必要はない．近年の研究の結果，特にC型慢性肝炎と内臓脂肪，肝脂肪化の関連について知られるようになった．軽度の運動やカロリー制限による内臓脂肪の減少は肝機能データの改善につながることが示されており，むしろこの状況では積極的に運動を勧めてよい．

b. 中等度以上（ALT≧100 IU/L）の肝障害を呈する慢性肝炎患者

　特に強い運動制限は行わないが，翌日などに強い疲労感が残るような激しい運動を避ける．

2) 仕事

　仕事についてもほぼ上記と同様に考えてよく，デスクワーク主体の仕事の場合には特に業務を中止，あるいは短縮させる必要はない．肉体労働を伴う場合，内容の強度によっては制限させる必要が出てくるが，これはケースバイケースである．中等度以上の肝硬変患者の場合，通勤ラッシュなどにおいて立ちっぱなしでいることは避け，座るようにした方がよい．

3) 日常生活

a. 食後・入浴

　高度に進行した肝硬変患者の場合，食後20〜30分ほどは横臥した方がよいとされているが，慢性肝炎，あるいは軽度の肝硬変の患者については食後すぐ動くのではなく，20〜30分程度安静にして

リラックスする時間をとるとよい．入浴に関しては高度進行肝硬変患者以外では特に制限はないが，熱い湯に長湯をしないことが望ましい．

b. こむら返り

代償性肝硬変患者や，比較的線維化の進行した慢性肝炎患者のなかには，夜間などに下腿を中心にした筋肉の痙攣（＝こむら返り）を経験するものがいる．一般的にこむら返りは，多量発汗，下痢，脱水などによって誘発される，高ナトリウム血症，低カリウム血症，低カルシウム血症などの電解質異常や，ビタミンB1欠乏状態の際に神経や筋肉が興奮しやすくなるため起こるとされている．

また，運動負荷により筋肉内に蓄積した乳酸とアンモニアによる筋肉細胞の酸性化により，神経筋接合部での膜不安定化が起こり，興奮性が増す結果とも考えられている．肝疾患患者にこれが多く起きる理由は明らかになっていないが，われわれは肝疾患モデルラットを使った実験から，運動負荷によりこれらのラット筋肉中のBCAA濃度，タウリン濃度の低下が起こることを明らかにした[1]．さらに，ラットにタウリンの投与を行うことにより筋疲労が改善することを示した[2]．これらの基礎的データに基づき，こむら返りを呈する肝硬変患者12名に1日6gのタウリン投与を行ったところ，8名の患者について，こむら返りの消失，症状軽減をみた[3]．BCAA製剤の投与についても同様の報告があるが，BCAA顆粒は保険診療上肝硬変患者のみの適応という制限があり，処方には難があるが，市販品として購入可能なBCAA richな栄養剤も販売されており，これらを薦めてもよいだろう．強いこむら返りには芍薬甘草湯が効果があることが知られているが，同薬剤は甘草の作用による偽アルドステロン症による高血圧などの副作用が知られており，短期間の投与にとどめるべきである．

いずれにしても，これらの患者に対しては，過度の筋疲労を避けるよう生活指導がなされるべきである．

3 飲酒

1）HCVキャリア

HCVキャリアに関しては，飲酒は病状の進行を加速させ，病態の悪化要因となるため禁酒とさせる．C型肝硬変患者において，1日80g以上の飲酒を5年以上行っている群は，80g以下の飲酒を行う群に比べてオッズ比で3.24倍肝癌の発生率が高かったという報告をしている．抗ウイルス療法後SVRに至った症例についての飲酒の許可については意見の分かれる点であるが，治療開始時，あるいは終了時に線維化がある程度進行していると考えられる症例，高齢者では摂取制限は継続すべきであるし，一般的にアルコール単独でも肝硬変・肝癌に至る症例があることを考えると，若年者であってもやはり制限は必要である．治療が終了した者でも，肝癌リスクが0になったわけではない，という点を強調すべきである．

2）HBVキャリア

HBVキャリアについては，むしろHBVそのものの発癌性の方が勝っているとも考えられ，飲酒についてリスクファクターとして取り上げた報告はない．近年では，アルコールはHBV感染患者の肝細胞癌リスクを増加させない，とする韓国からの報告もある．無症候性キャリアであれば，常識的な範囲内の飲酒は許可してもよいが，ある程度線維化が進行していると考えられる症例に関してはHCV同様，飲酒を制限すべきである．

4 喫煙

疫学データによると，喫煙者は非喫煙者に比べて 1.5 倍の危険率で肝発癌が増加することが示されている[4]．C型肝炎患者では喫煙指数が 400 以上の者では非喫煙者に比べ，2.46 倍の危険率で肝発癌率が増加する．同様の成績は台湾，韓国，フランスなどでも発表されており，その機序は不明であるが，肝癌予防の観点からは禁煙を勧めるべきである．

> **memo** **喫煙指数**
>
> 　喫煙が人体に与える影響は，それまでに吸い込んだたばこの煙の総量と関係している．総量は，A.一日あたりの平均喫煙量（本数）と，B.喫煙をしていた年数をかけ合わせたもの（喫煙指数＝ブリンクマン指数）が目安として用いられる．1日20本を20年間吸い続けると喫煙指数は400となり，一般的にはこの値が400を超えると要注意と考えられている．

5 薬物の服用，健康食品，サプリメントの摂取について

1）薬物の服用

　慢性肝疾患の進行により，代謝能の低下が起こるため，薬物によっては副作用が起こりやすくなることがある．通常慢性肝炎の状態ではあまり問題にならないことが多いが，たとえば抗真菌薬のように肝機能障害が比較的多い薬剤を使用する場合に皮膚科医から問い合わせを受ける機会が多い．ウイルスキャリアであっても，肝機能障害のない場合はあまり問題にならないが，進行した肝炎の場合は，薬剤による肝障害の悪化により病状進行に結びつく可能性がある．**肝予備能が低下していると考えられる者，ALT値が100 IU/L以上の高値である症例については，原則として投与を見合わせる．また，肝炎以外の病気があり，使用する薬剤がkey drugすなわち他に代替薬のないものであり治療をしないことが著しく患者にとって不利益であると判断できる場合は，肝臓専門医に相談のうえ，薬剤の投与を許可するかどうかを決定する．**

2）サプリメントや健康食品の摂取

　サプリメントや健康食品もよく相談を受ける事柄のひとつである．第3章-4でも説明されるが，C型慢性肝炎や脂肪性肝炎患者では鉄分の過剰摂取が肝内での活性酸素の増加につながり，肝障害の悪化をもたらす可能性が指摘されており，**鉄分摂取の制限が推奨されている**．肝炎患者の多くが服用しているサプリメントのなかには鉄分を多く含有するものがあり注意が必要である．標準的なウコンは1日量で鉄1.5〜3 mgを含むとされ，これは摂取推奨量（一日6.5mgまで）の1/3程度にあたる．また，サプリメントや健康食品自体でも薬物性肝障害を起こす事例があり，注意を促すべきである．

6 感染の予防

　職場や家庭での他人への感染が心配であるという相談をよく受ける．B型肝炎，C型肝炎ともにそれぞれのウイルスを含む血液が皮膚や粘膜などの感染防御機構を破り，体内に侵入することで感染発症する．感染力については，HBVの場合，HBe抗原陽性者の血液は血液1 mLを1億倍に希釈しても感染力があることが証明されているが，一方HBe抗体陽性者の血液は1 mLの10倍希釈では感染しなかったとするものがあり，ウイルス学的な状態により感染のしやすさには差があることが確認されている．また，HCVは1,000倍希釈したら感染が成立しなかったことがチンパンジーを用いた実験で

証明されており，感染力は弱いと考えられている．

したがって，これらのウイルスに関しては，ウイルスキャリアの血液が他者の粘膜や皮膚などの傷に触れた場合，一定のリスクで感染の危険がある，としかいえず，日常生活のなかでこのような機会はかなり限定されるといってよい．また，唾液についても唾液中のウイルス量は感染成立力価以下と考えられ，感染予防目的で回し飲みやキスなどを禁止する必要はない．日常生活以外の点で，以下の点を患者に指導すべきである．

①HBVキャリアの場合，セックスパートナーに感染させる可能性があるため，HBV未感染かつHBs抗体をもたない相手にHBVワクチン接種を受けるよう指導する

②血液付着物，具体的には鼻出血，生理，外傷時の出血を処置した際のガーゼ，タオルなどは他人に触れさせないこと．可能な限り患者自身でビニール袋などに入れて，医療廃棄物として処理させるか，自身で焼却させる

③タオル，安全剃刀を同居人と共用することのないようにする

その他，歯科医を受診する際にも注意が必要である．歯牙を切削する高速回転の器具は，唾液や血液を周囲にまき散らすことが多く，医療従事者のみならず，他の患者への交叉感染が起きないように留意が必要である．2004年度の厚生労働省研究班「歯科診療におけるB型およびC型肝炎防止体制の確立に関する研究」の内容は，「歯科診療における院内感染対策CDCガイドライン」として刊行され，また日本歯科医師会もスタンダードプレコーションの必要性について強調している．しかし一般歯科診療所における院内感染対策のための保険点数の加算は認められていない．今後行政が十分な措置を講じる必要があるが，現状では，歯科での治療を開始したが，ひょんなことから肝炎ウイルスキャリアであることが歯科医師の知るところとなり，前もって言った言わないでトラブルになったケースも存在することを認識すべきである．

7 さいごに

慢性肝炎，特にウイルス性肝炎患者の多くがもつ感情に「どうして私だけが」という理不尽さへの怒りや悩み，また最終的には病気の進行による「死の恐怖」があり，これらの感情のためさまざまな迷いを訴える患者も少なくない．かかりつけ医としての役割はまず適切な判断を行い，専門医紹介を含め適切な診療方針に導くことであるが，それ以前に，患者のこういった感情をよく理解しようとすることから信頼関係の構築が始まると思う．

また，患者の啓発を目的とした市民公開講座などが多く開催されているため，これらの機会への参加を促すことで，同じ病をもつ人が数多く存在し，各々が熱心に治療を続けていることを伝え，患者の孤独感を薄め，治療意欲を高めることができる．また，経済的・時間的な負担が大きい慢性肝炎の治療には，家族の協力が不可欠であり，本稿で述べた内容を家族にも周知してもらうことが必要である．

Point

▶「どうして私だけが」という理不尽さへの怒り，病気の進行による「死の恐怖」といったウイルス性肝炎患者のもつ感情をよく理解することから信頼関係の構築が始まる

▶ 患者の啓発を目的とした市民公開講座などへの参加を促し，患者の孤独感を薄め，治療意欲を高めることが必要である

▶ 慢性肝炎の治療は経済的，時間的な負担が大きく，家族の協力が不可欠であり，家族にも患者同様，通院や治療の必要性を理解してもらう必要がある

文 献

1) Miyazaki, T., et al. : Hepatol. Res., 27 : 230-237, 2003
→ ラット肝硬変モデルで運動負荷により筋肉中のアミノ酸組成が変化することを示した論文.

2) Matsuzaki, Y., et al. : Med. Sci. Sports Exerc., 34 : 793-797, 2002
→ 上記同様, ラットモデルにタウリンを投与すると運動負荷に対する耐用性が増したとする論文.

3) Matsuzaki, Y., et al. : Am. J. Gastroenterol., 88 : 1466-1467, 1993
→ こむら返りを訴える肝硬変患者に対してタウリンを投与し, これがこむら返りの予防に有用だったとする臨床試験.

4) Chiba, T., et al. : Am. J. Gastroenterol., 91 : 1195-1203, 1996
→ 喫煙量により肝発癌リスクが上昇することを示した疫学的研究.

5) 「患者さんの質問に答える慢性肝疾患診療 改訂2版」(松﨑靖司 編), 南山堂, 2008
→ 手前味噌だが, 患者さんの視点からの質問にどのように回答すべきか, また詳細な内容について根拠をあげて記述してあり, 一般内科医, 後期研修医向けである.

Profile　　池上　正 (Tadashi Ikegami)
東京医科大学茨城医療センター消化器内科 准教授

1988年 筑波大学医学専門学群卒業
研究テーマは肝疾患と脂質代謝, 胆汁酸とシグナル伝達など

松﨑靖司 (Yasushi Matsuzaki)
東京医科大学茨城医療センター センター長, 同消化器内科 教授

1980年 筑波大学医学専門学群卒業. 筑波大学大学院人間総合科学研究科准教授を経て現職

【雑　　誌】

Total Numbers of Undiagnosed Carriers of Hepatitis C and B Viruses in Japan Estimated by Age- and Area-Specific Prevalence on the National Scale

Junko Tanaka[a] Tomiko Koyama[d] Masaaki Mizui[b] Shigeru Uchida[f]
Keiko Katayama[a] Junko Matsuo[a] Tomoyuki Akita[a] Ayumu Nakashima[a]
Yuzo Miyakawa[e] Hiroshi Yoshizawa[c]

[a]Department of Epidemiology, Infectious Disease Control and Prevention, Hiroshima University Graduate School of Biomedical Sciences, [b]Japanese Red Cross Hiroshima Blood Center, and [c]Hiroshima University, Hiroshima, [d]Health Service Association, Iwate, [e]Miyakawa Memorial Research Foundation, and [f]Japanese Red Cross Society Blood Service Headquarters, Tokyo, Japan

Abstract

Objective: To estimate total numbers of undiagnosed carriers of hepatitis C virus (HCV) and hepatitis B virus (HBV) in Japan. *Methods:* Area- and age-specific prevalence of HCV as well as HBV was determined in the first-time blood donors [20–39 years (n = 2,429,364)] and examinees of periodical health check-ups [40–74 years (6,204,968 for HCV and 6,228,967 for HBV)] in Japan. Prevalence in adolescents [5–19 years (79,256 for HCV and 68,792 for HBV)] was determined in a single prefecture, and that of HCV in the elderly (≥75 years) was estimated by the exponential model. HBV infection was determined by the detection of hepatitis B surface antigen, and HCV infection by either the algorithm or assuming persistent infection in 70% of the individuals with antibody to HCV. *Results:* Of the total population of 127,285,653 in 2005, 807,903 (95% CI 679,886–974,292) were estimated to be infected with HCV at a carrier rate of 0.63%, and 903,145 (837,189–969,572) with HBV at that of 0.71%. *Conclusion:* Ac-

curate estimation of undiagnosed HCV and HBV carriers in the general population would help to predict the future burden of liver disease, and take appropriate measures for improving healthcare.

Introduction

Hepatitis C virus (HCV) and hepatitis B virus (HBV) are estimated to infect 170 and 350 million people over the world, respectively [1, 2]. Most infections with HCV or HBV do not induce clinical liver disease, while ~30% of them develop severe liver disease such as cirrhosis and hepatocellular carcinoma [3, 4]. Hence, there is a pressing need to identify the individuals who have undiagnosed HCV or HBV infection, and take effective measures for terminating viral infections and preventing the progression of liver disease.

For management of persistent HCV and HBV infections in a given country, it is necessary to know their exact numbers for assessing medical and financial needs in the foreseeable future. Prevalence of undiagnosed HCV or HBV

Junko Tanaka
Department of Epidemiology, Infectious Disease Control and Prevention
Hiroshima University Graduate School of Biomedical Sciences
1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551 (Japan)
Tel. +81 82 257 5161, E-Mail jun-tanaka@hiroshima-u.ac.jp

infection has been estimated by survey of blood donors in Japan [5] and a representative population in the USA [6].

In the present study, area- and age-specific prevalence of HCV or HBV infection was determined in 8 jurisdiction areas of the Japanese Red Cross Blood Center. Then, the total numbers of undiagnosed HBV and HCV infections were estimated by compiling the results in the first-time blood donors and examinees of the periodical health check-up program. Of the 127,285,653 Japanese registered in 2005, 807,903 (0.63%) were estimated to be infected with HCV and 903,145 (0.71%) with HBV.

Materials and Methods

Japanese Population

Japan is divided into 8 areas, along its north-to-south axis, according to jurisdiction of the Japanese Red Cross Blood Center, into Hokkaido, Tohoku, Kanto, Hokuriku/Tokai, Kinki, Chugoku, Shikoku and Kyushu. Populations in 5-year age groups in each jurisdiction area were obtained from the registry at the National Census 2005.

First-Time Blood Donors

During 6 years from January 2001 to December 2006, 3,748,422 individuals (aged 16–64 years) donated whole blood or apheresis products for the first time, and their sera were tested for markers of HCV and HBV infections. Ongoing HCV infection was estimated by assuming the detection of HCV RNA in 70% of individuals with the antibody to HCV (anti-HCV), in accordance with a previous report [5].

Examinees of Hepatitis Virus Infections

Since the fiscal year 2002 in Japan, individuals who turned 40, 45, 50, 55, 60, 65 and 70 years were offered to take tests for hepatitis viruses at periodical health check-ups by a 5-year national project. During 5 years through 2006, 6,204,968 individuals received tests for HCV and 6,228,967 for HBV, corresponding to ~30% of the eligible Japanese, and their area- and age-specific prevalence of HCV or HBV infection was determined.

School Children and Adolescents

In the Iwate prefecture located in the north of Japan, biochemical markers of diseases dependent on the lifestyle were examined in children and adolescents at the entrance to schools. Their serum samples had been stored frozen, and were tested for markers of hepatitis virus infections. Carrier rates of HCV and HBV among them were calculated, with their ages adjusted to those in 2005; infants aged <5 were represented by the children aged from 5 to 9 years. Designs and procedures of this investigation were approved by the Ethics Committee of Hiroshima University.

Simulation of HCV and HBV Infections in the Elderly

By its age-specific profile, the prevalence of HCV was deduced to be an exponential function of the age. Accordingly, age-specific prevalence of HCV in the individuals aged ≥75 years was simulated by an exponential function model; it was constructed on the prevalence of HCV in each age group ≥50 years.

The formula was constructed as:

$$\log y(x) = a + bx$$

where x is the 5-year age code, $y(x)$ is an estimator of HCV prevalence in x, and a and b are coefficients.

The equation is transformed into:

$$y(x) = e^{a}e^{bx}$$

in which e^{a} represents the HCV prevalence when $x = 0$ (in the group aged 0–4 years), since $y(0)$ is equal to e^{a}. By replacing x for $x + 1$ in the above equation, it is converted to $y(x + 1) = e^{a}e^{b(x + 1)}$.

Then, the following equation can be constructed:

$$y(x + 1) = e^{b}y(x)$$

where e^{b} is the slope of HCV prevalence increasing with age. Thus, the HCV prevalence is multiplied by a factor e^{b} for an increment of the age code by 1.

The simulation model was applied to estimate age-specific prevalence of HCV in each of 8 areas in the individuals ≥75 years.

Prevalence of HBV in the individuals ≥75 years was represented by that in those aged 70–74 years, since it stayed constant from 65 through 75 years.

Markers of Hepatitis Virus Infections

In blood donors, anti-HCV was determined by passive hemagglutination of the second generation with commercial assay kits (HCV PHA; Abbott Laboratories, North Chicago, Ill., USA) with a cutoff limit set at 2^{5}, as well as by particle agglutination with commercial assay kits (HCV PA Test-II; Fujirebio, Inc., Tokyo, Japan). HBsAg was determined by reversed passive hemagglutination with reagents prepared by the Japanese Red Cross.

In examinees of periodical health check-ups, ongoing HCV infection was determined by the algorithm with anti-HCV and HCV RNA [7]. Anti-HCV was determined by passive hemagglutination of the second generation with commercial assay kits (HCV PHA; Abbott Laboratories), and since 2002, it was determined by enzyme immunoassay with commercial assay kits (AxSYM HCV Dinapack-III; Abbott Laboratories). Samples with high anti-HCV titers contain HCV RNA, and therefore, only those with low and middle titers were examined for HCV RNA. HBsAg was determined by reversed-passive hemagglutination with commercial assay kits (Institute of Immunology Co., Ltd, Tokyo, Japan).

Statistical Analyses

Statistical analyses for the evaluation of R^{2} values were performed with JMP 8.0 (SAS Institute, Inc., Cary, N.C., USA) and DeltaGraph 5.5 (RedRock Software, Inc., Salt Lake City, Utah, USA). A p value > 0.05 was considered significant.

Results

Age-Specific Prevalence of HCV in the First-Time Blood Donors and Examinees of Periodical Health Check-Ups

Figure 1 illustrates age-specific prevalence of HCV in the first-time blood donors (aged 15–69 years in 2005) and examinees of periodical health check-ups (39–73 years in 2005); 70% of individuals with anti-HCV were considered
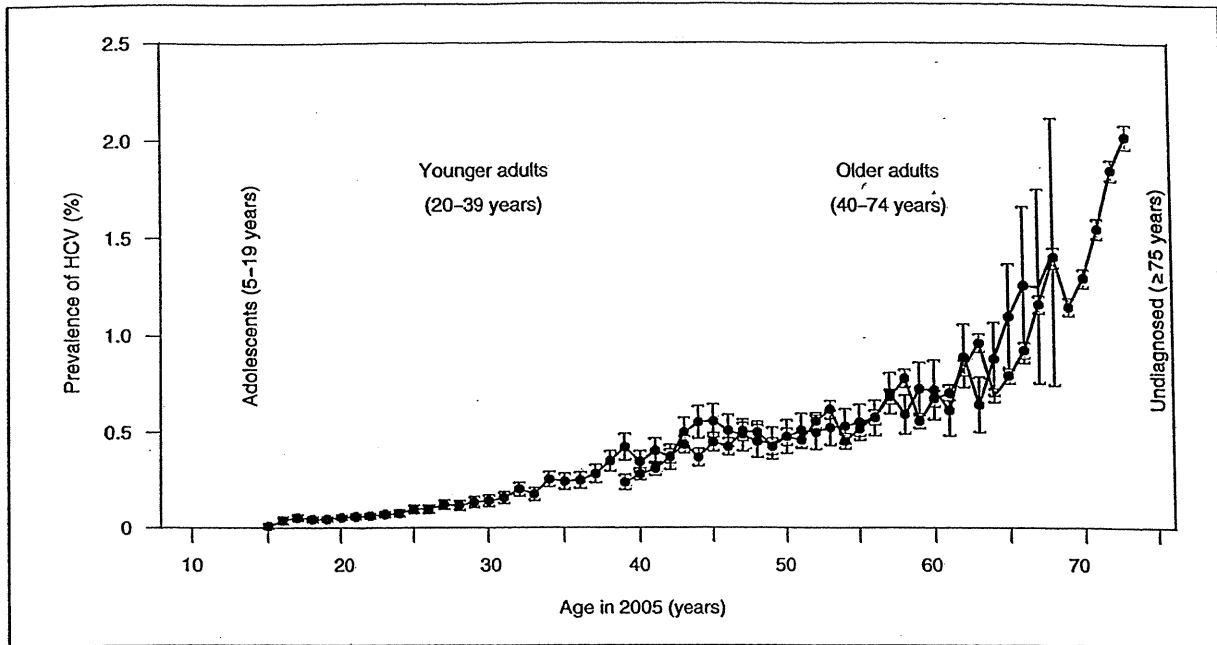
Fig. 1. Age-specific prevalence of HCV in Japan. The prevalence of HCV was determined in the first-time blood donors aged from 15 to 68 years (blue dots) and examinees of periodical health check-ups aged from 39 to 73 years (red dots). Their ages were adjusted to those in the year 2005. Bars indicate ranges of 95% CI.

to possess HCV RNA in serum [5]. Results of two distinct populations were well in accord. For the first-time blood donors, however, the variation (95% CI) widened increasingly with age. It would have reflected decreases in the first-time blood donors with age, since the majority of these (83.5%) were aged ≤39 years. As the prevalence of HCV in blood donors ≥40 years was unreliable in them, that in examinees of periodical check-ups was adopted for estimating the national prevalence of HCV.

Area-Specific Prevalence of HCV in Eight Jurisdiction Areas

In view of distinct geographic distribution of HCV, the prevalence of HCV in the general population would not be applicable to every area in Japan. Figure 2 compares results in the first-time blood donors and recipients of health check-ups among 8 jurisdiction areas spanning from north (Hokkaido) to south (Kyushu). They unfolded a wide variety in the age-specific prevalence of HCV. Although the prevalence of HCV increased with age in all areas, the slope of increase differed widely among them. Hence, it was necessary to employ a distinct age-specific prevalence in each of the 8 areas for estimating HCV carriers precisely.

Table 1. Age-specific prevalence of HCV in three different populations

Age in 2005	n	HCV-positive, n	Prevalence, % (95% CI)
School children			
5–9	17,390	2	0.012 (0.000–0.027)
10–14	29,817	3	0.010 (0.000–0.021)
15–19	32,049	7	0.022 (0.006–0.038)
Blood donors			
20–24	1,205,966	1,122	0.065 (0.061–0.070)[a]
25–29	536,560	874	0.114 (0.105–0.123)[a]
30–34	408,814	1,089	0.186 (0.173–0.200)[a]
35–39	278,024	1,190	0.300 (0.279–0.320)[a]
HCV screening			
40–44	611,146	2,127	0.348 (0.333–0.363)
45–49	495,032	2,292	0.463 (0.444–0.482)
50–54	675,350	3,485	0.516 (0.499–0.533)
55–59	947,438	5,974	0.631 (0.615–0.646)
60–64	1,081,854	8,423	0.779 (0.762–0.795)
65–69	1,264,496	13,722	1.085 (1.067–1.103)
70–74	1,054,472	17,649	1.674 (1.649–1.698)

[a] The prevalence in blood donors was based on an assumption of HCV infection persisting in 70% of those with anti-HCV [5].

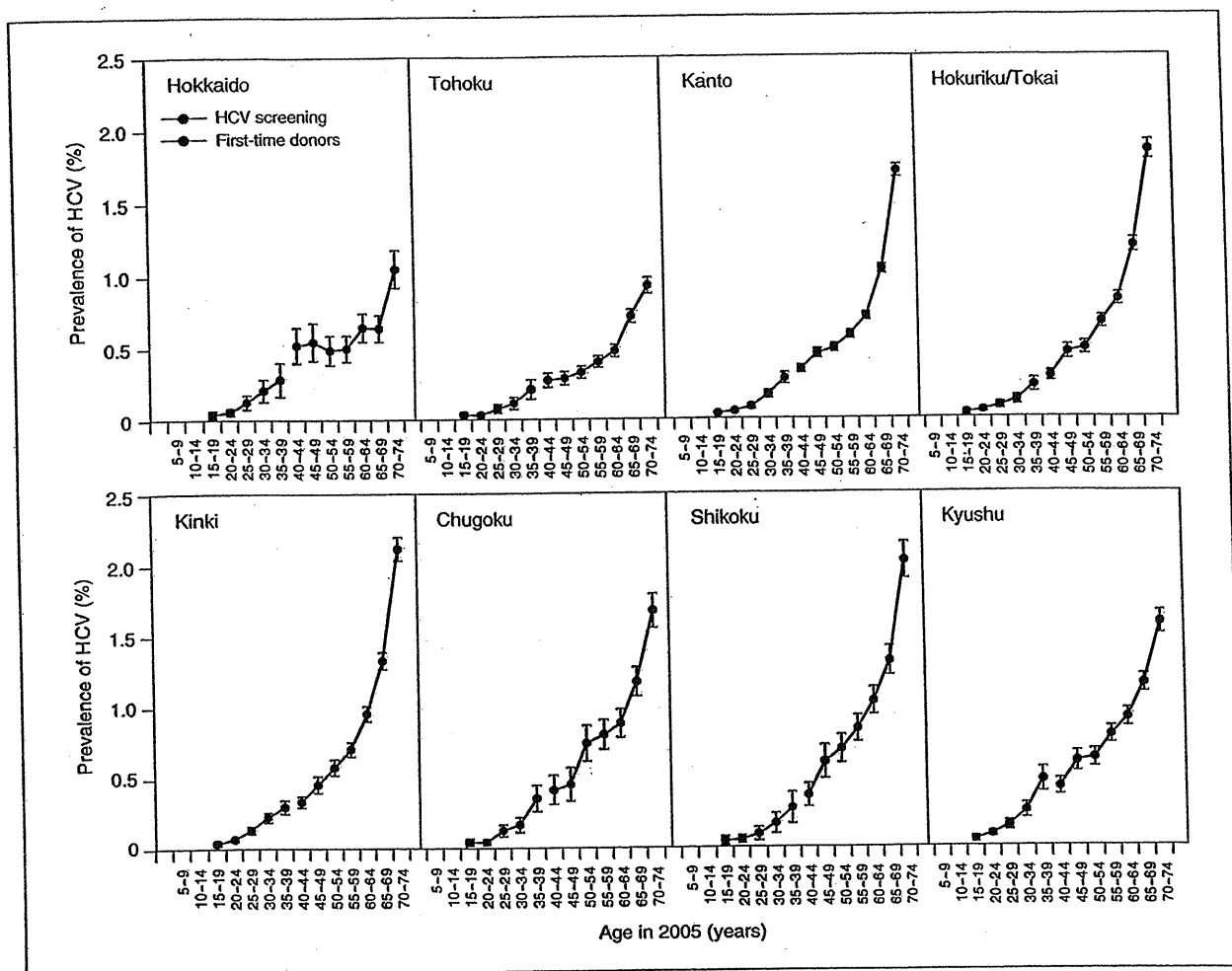Undiagnosed HCV and HBV Carriers in Japan

Fig. 2. Age-specific prevalence of HCV in 8 jurisdiction areas in Japan. The prevalence of HCV is calculated in each of twelve age groups notched by 5 years. The prevalence in five groups ≤39 years was represented by the first-time blood donors, and that in seven groups ≥40 years by recipients of HCV screening. Bars indicate ranges of 95% CI.

Prevalence of HCV in Adolescents

Since blood donors were restricted to 16–64 years of age, and health examinees were targeted on 40–70 years, they did not cover individuals aged ≤15 or ≥75 years in the year 2005. To fill in an opening on the younger side, the age-specific prevalence of HCV was determined in school children and adolescents in the Iwate prefecture (table 1). The prevalence in infants aged 0–4 years was assumed similar to that in the children aged 5–9 years; an extremely low prevalence of HCV (0.012%) would support such an assumption.

Simulating Prevalence of HCV in the Elderly

The prevalence of HCV appeared to be an exponential function of the age, according to its profiles in the first-time blood donors and examinees of health check-ups (fig. 1). Based on this assumption, a formula was constructed to simulate the prevalence of HCV in age groups ≥75 years for each of the 8 jurisdiction areas in Japan (see Materials and Methods).

Figure 3 compares actual (dots) and simulated data (red line) of five age groups from 50 to 74 years (corresponding to age codes 10–14) among the 8 areas. There was a high coefficient of determination between them,
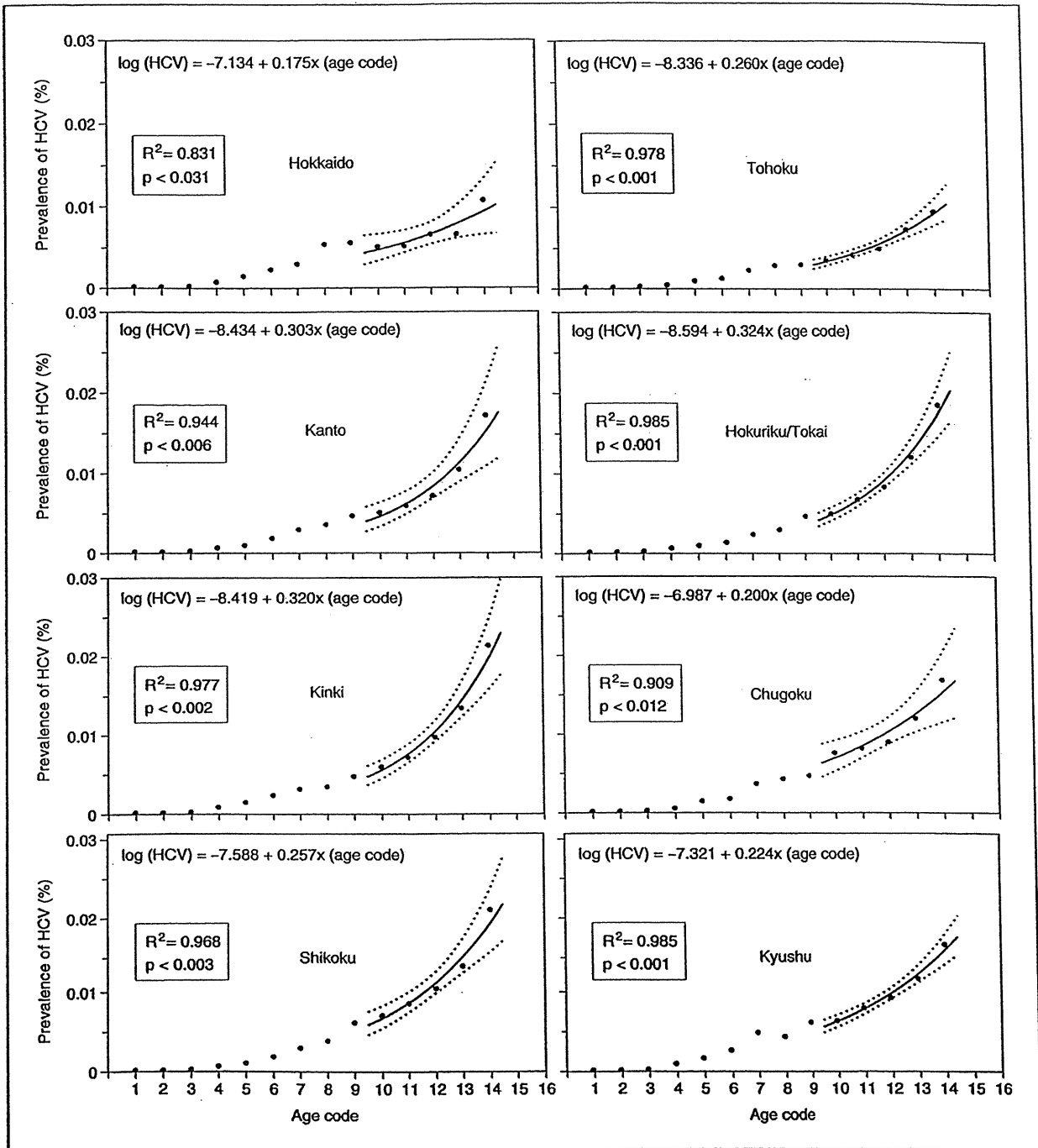
Fig. 3. Simulation of age-specific prevalence of HCV in the elderly. Prevalence of HCV in the first-time blood donors as well as examinees of periodical health check-ups (dots) and that simulated by formulation (red line with ranges of 95% CI in dotted line) are shown for 8 jurisdiction areas in Japan. Formula is shown at the top of each area. Age codes are: 1, 5–9 years; 2, 10–14 years; 3, 15–19 years; 4, 20–24 years; 5, 25–29 years; 6, 30–34 years; 7, 35–39 years; 8, 40–44 years; 9, 45–49 years; 10, 50–54 years; 11, 55–59 years; 12, 60–64 years; 13, 65–69 years; 14, 70–74 years, and 15, 75–79 years.

Table 2. Regional and total HCV carriers in Japan

Areas	Population	HCV carriers (95% CI)	Carrier rate
Hokkaido	5,620,813	26,097 (19,356–34,413)	0.46%
Tohoku	12,047,975	50,688 (42,754–59,953)	0.40%
Kanto	41,247,892	235,328 (195,408–293,611)	0.57%
Hokuriku/Tokai	19,294,443	132,434 (114,216–154,446)	0.69%
Kinki	22,657,542	173,808 (147,548–207,173)	0.52%
Chugoku	7,650,977	53,296 (42,299–67,698)	0.70%
Shikoku	4,083,698	35,159 (28,746–43,004)	0.86%
Kyushu	14,682,313	101,092 (89,379–113,993)	0.80%
Total	127,285,653	807,903 (679,886–974,292)	0.63%

Table 3. Age-specific prevalence of HBV in three different populations

Age in 2005	n	HBV-positive, n	Prevalence, % (95% CI)
School children			
5–9	17,363	3	0.017 (0.000–0.037)
10–14	29,817	14	0.047 (0.022–0.072)
15–19	32,049	12	0.037 (0.016–0.059)
Blood donors			
20–24	1,205,966	1,826	0.151 (0.144–0.158)
25–29	536,560	1,650	0.308 (0.293–0.322)
30–34	408,814	1,759	0.430 (0.410–0.450)
35–39	278,024	1,327	0.477 (0.452–0.503)
HBV screening			
40–44	613,960	5,491	0.894 (0.871–0.918)
45–49	497,589	5,373	1.080 (1.051–1.109)
50–54	679,893	8,700	1.280 (1.253–1.306)
55–59	950,508	12,891	1.356 (1.333–1.379)
60–64	1,085,119	13,282	1.224 (1.203–1.245)
65–69	1,268,304	12,406	0.978 (0.961–0.995)
70–74	1,057,469	9,545	0.903 (0.885–0.921)

with R^2 values ranging from 0.831 to 0.985 (p < 0.031 and p < 0.001, respectively), attesting to the validity of this simulation. Of note, the factor b in formula (by which age codes were multiplied) varied broadly among the 8 areas. Thus, it was the highest in Hokuriku/Tokai at 0.324 and lowest in Hokkaido at 0.175, with close to twofold differences between them.

Estimation of Undiagnosed HCV Carriers in Eight Areas and the Entire Nation

Based on age- and area-specific prevalence of HCV, numbers of undiagnosed HCV carriers were calculated for 8 jurisdiction areas, and they were compiled in the entire nation (table 2). The prevalence of HCV in each of three age groups (75–79, 80–84 and ≥85 years) was simulated by the formula, while that of HBV was represented by the prevalence in the group of 70–74 years. As of the year 2005, 127,285,653 were registered in the national census of Japan, and 807,903 of these are estimated to have undiagnosed HCV infection at an overall carrier rate of 0.63%. There was an increasing gradient in the prevalence of HCV along the north-to-south axis of Japan.

Age-Specific Prevalence of HBV

Figure 4 depicts age-specific prevalence of HBV in 2005. It was deduced from HBsAg in the first-time blood donors (15–69 years) and examinees of periodical health check-ups (39–73 years). Since the prevalence of HBV in the elderly did not increase with age so sharply as that of HCV (fig. 1), it was presumed not to increase further and stay around 1% in the individuals ≥75 years. The age-specific prevalence of HBV tabulated in three different
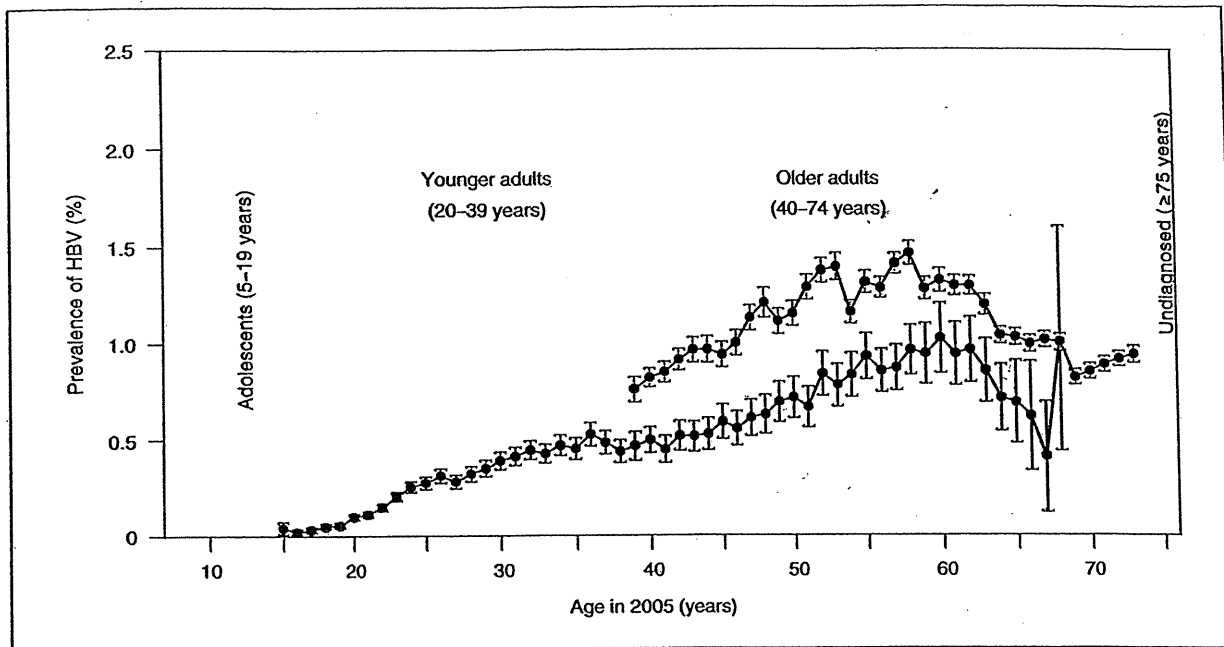
Fig. 4. Age-specific prevalence of HBV in Japan during 2002–2006. The prevalence of HBV was determined in the first-time blood donors aged from 15 to 68 years (blue dots) in the year 2005 and examinees of periodical health check-ups aged from 39 to 73 years (red dots) in the year 2005. Bars indicate ranges of 95% CI.

populations is listed in table 3. There was a constant decline with decreasing age in the frequency of HBV in individuals ≤39 years, and it was particularly low in children ≤9 years (0.017%).

In examinees of periodical health check-ups, the age-specific prevalence of HBV did not diverge and stayed within a narrow 95% CI (fig. 4). By contrast, that in the first-time blood donors dispersed widely. Such a variation in the age-specific prevalence of HBV would have been ascribed to the first-time blood donors who clustered in age groups ≤40 years.

Area-Specific Prevalence of HBV in Eight Jurisdiction Areas

The age-specific prevalence of HBsAg varied widely among 8 jurisdiction areas (fig. 5). HBsAg was most frequent in the age group of 55–59 years in every area, and reached 3.1% in the northern-most Hokkaido. The peak frequency decreased in central Japan (1.1% in Kanto and Hokuriku/Tokai), and increased towards the southern end (1.9% in Kyushu). Thus, the prevalence of HBsAg was determined individually along the axis of Japan in estimating the total number of HBV carriers in Japan.

Estimation of Undiagnosed HBV Carriers in Eight Areas and the Entire Nation

Numbers of undiagnosed HBV carriers were complied by multiplying age-specific prevalence of HBsAg by corresponding subpopulations in 8 jurisdiction areas (table 4). In total, 903,145 of the 127,285,653 (0.71%) individuals are estimated to have undiagnosed HBV infection in Japan in 2005.

Shift of Undiagnosed HCV and HBV Carriers during 5 Years (2000–2005) in Japan

Table 5 compares numbers of HCV and HBV carriers aged 15–69 years between 2000 and 2005 for 8 jurisdiction areas in Japan. Data for the year 2000 were extracted from a previous survey [5]. Data for the year 2005 were obtained in the first-time blood donors during 2001–2006 in this study by the same method as in the previous survey [5]. Undiagnosed HCV and HBV carriers decreased during 5 years by 55 and 47.5%, respectively. The overall carrier rate of HCV declined sharply from 0.95 to 0.44%, and that of HBV from 1.04 to 0.55% in Japan.
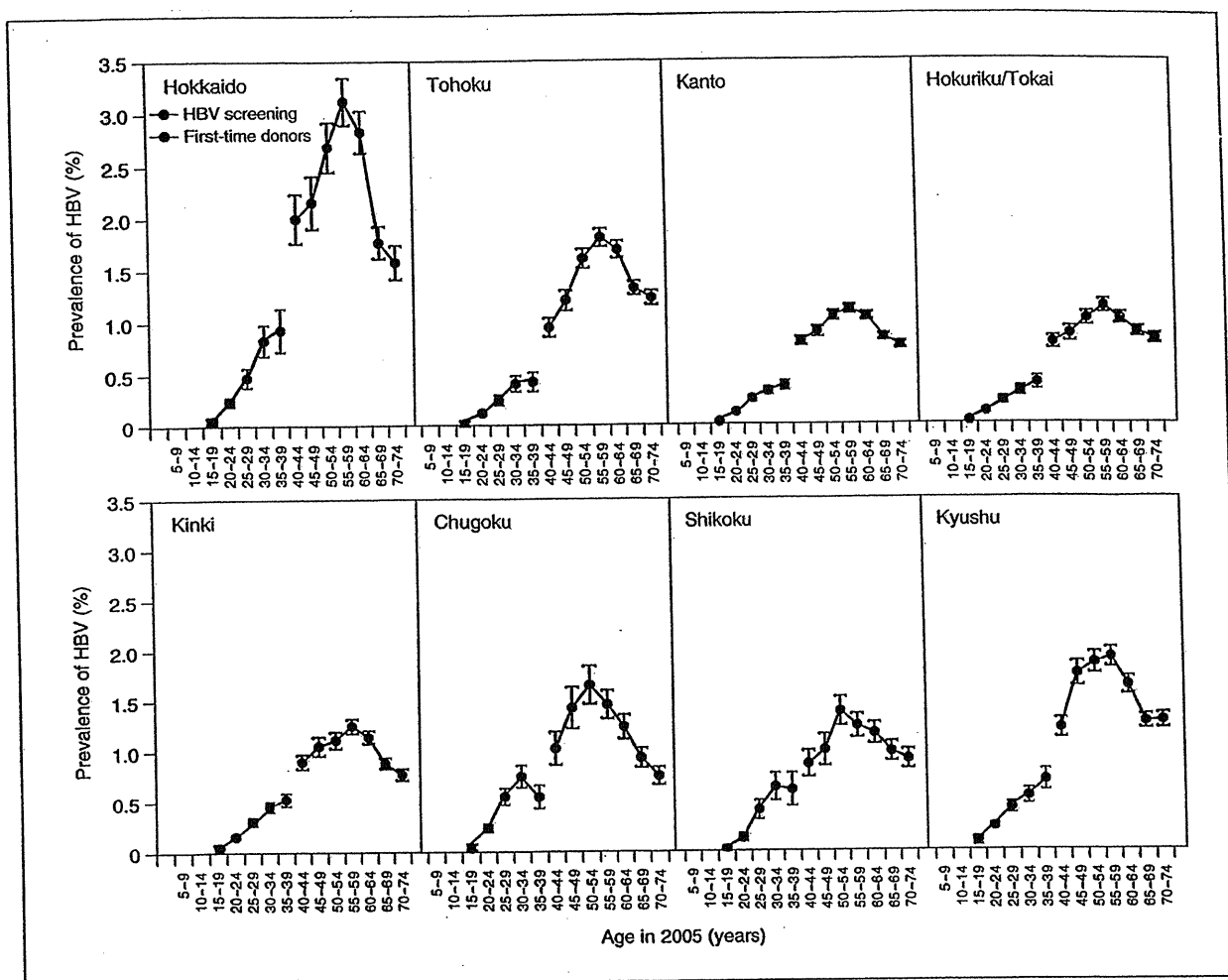

Undiagnosed HCV and HBV Carriers in Japan

Fig. 5. Age-specific prevalence of HBV in 8 jurisdiction areas in Japan. The prevalence of HBV is calculated in each of twelve age groups notched by 5 years. The prevalence in five groups ≤39 years was represented by the first-time blood donors and that in seven groups ≥40 years by recipients of HCV screening. Bars indicate ranges of 95% CI.

Table 4. Regional and total HBV carriers in Japan

Areas	Population	HBV carriers (95% CI)	Carrier rate
Hokkaido	5,620,813	80,573 (72,314–88,765)	1.43%
Tohoku	12,047,975	104,736 (97,742–111,816)	0.87%
Kanto	41,247,892	231,799 (220,129–244,105)	0.56%
Hokuriku/Tokai	19,294,443	109,709 (101,722–117,581)	0.56%
Kinki	22,657,542	144,965 (134,387–155,464)	0.64%
Chugoku	7,650,977	59,948 (52,705–67,121)	0.78%
Shikoku	4,083,698	29,776 (26,080–33,437)	0.73%
Kyushu	14,682,313	141,639 (132,111–151,282)	0.96%
Total	127,285,653	903,145 (837,189–969,572)	0.71%

Tanaka et al.

Table 5. Decrease of undiagnosed HCV and HBV carriers in the 15- to 69-year-old population in Japan

	Survey in 2000[a]		Survey in 2005		Difference	
	number estimated	carrier rate in area[b]	number estimated	carrier rate in area[b]	number estimated	balance
Shift of HCV carriers during 5 years from 2000 to 2005						
Hokkaido	41,139	0.99%	17,658	0.44%	-23,481	-57.1%
Tohoku	61,658	0.71%	30,525	0.37%	-31,133	-50.5%
Kanto	277,644	0.90%	126,283	0.41%	-151,361	-54.5%
Hokuriku/Tokai	88,724	0.64%	48,360	0.35%	-40,364	-45.5%
Kinki	178,871	1.06%	70,526	0.43%	-108,345	-60.6%
Chugoku	72,431	1.32%	24,595	0.47%	-47,836	-66.0%
Shikoku	43,497	1.49%	16,504	0.59%	-26,993	-62.1%
Kyushu	120,989	1.16%	64,115	0.63%	-56,874	-47.0%
Total	884,954	0.95%	398,567	0.44%	-486,387	-55.0%
Shift of HBV carriers during 5 years from 2000 to 2005						
Hokkaido	106,896	2.56%	54,557	1.35%	-52,339	-49.0%
Tohoku	104,923	1.21%	48,490	0.58%	-56,433	-53.8%
Kanto	255,207	0.83%	132,414	0.43%	-122,793	-48.1%
Hokuriku/Tokai	78,481	0.56%	51,477	0.37%	-27,004	-34.4%
Kinki	165,915	0.98%	85,083	0.52%	-80,832	-48.7%
Chugoku	90,041	1.64%	37,706	0.71%	-52,335	-58.1%
Shikoku	38,411	1.32%	19,162	0.69%	-19,249	-50.1%
Kyushu	127,879	1.23%	77,941	0.77%	-49,938	-39.1%
Total	967,753	1.04%	506,830	0.55%	-460,923	-47.6%

[a] Data for the year 2000 were extracted from a previous survey of hepatitis virus infections in Japan [5].
[b] The carrier rate specific for respective jurisdiction area was applied.

Discussion

There are many constraints in estimating total HCV and HBV infections in a given nation. Since it is not feasible to test every member for serological markers of hepatitis virus infection, populations representative of the entire nation have served for the estimation. Volunteer blood donors are recruited, but they have a restricted age range (16–64 years in Japan). Students attending schools and universities can close the opening in younger generations, but infants younger than the school age are not enrolled. Moreover, there are no means of estimating carrier rates of hepatitis virus infections in the individuals aged beyond the eligibility of blood donation. In addition, blood donors are selected individuals who are leading healthy lives above the average. In the survey of inhabitants in sentinel counties of the USA [6], who represent the average Americans, patients with liver disease and persons with restricted activities, such as those incarcerated or institutionalized, are not included.

Patients with clinical liver disease, as well as individuals found with HCV or HBV infection by health check-ups, can receive the medical care. However, many blood donors found with viral infections have developed severe liver disease already, and therefore, cannot receive efficient medical interventions [7, 8]. Hence, it is necessary to detect undiagnosed HCV and HBV infections hidden in the society. For this purpose, periodical health check-ups for screening hepatitis virus markers were started in April 2002 on the individuals, who turned 40, 45, 50, 55, 60 and 70 years, by a 5-year national project in Japan. The target age range (40–70 years) was selected due to a high incidence of hepatocellular carcinoma [9]. Since by far the majority of the first-time blood donors were younger than 40 years, the prevalence of HCV or HBV beyond that age dispersed widely (fig. 1, 4). In this study, therefore, the coverage by the first-time blood donors was confined to 20–39 years of age, and it was taken place by examinees of health check-ups aged 40–74 years; they left age groups ≤15 and ≥75 years uncovered, however.

The national prevalence of hepatitis virus infections in individuals ≤19 years was presumed to be similar to that in the Iwate prefecture situated in northern Japan. Since the prevalence of HCV or HBV infection in them was extremely low and stayed between 0.01 and 0.02%, such an assumption would not have affected the overall results to any significant extent. The prevalence of HCV in age groups ≥75 was simulated by a premise that it would be an exponential function of the age. Consequently, the formula based on profiles in five age groups from 50 to 74 years (at a 5-year notch) was extrapolated to three age groups ≥75 years. The simulation matched closely with the prevalence determined in corresponding age groups, with R^2 values ranging from 0.83 to 0.99 ($p < 0.05$ and $p < 0.01$, respectively) throughout 8 jurisdiction areas in Japan (fig. 3).

Japan has an axis spanning 2,000 kilometers from the north-east towards the south-west over the four major islands (Hokkaido, Honshu, Shikoku and Kyushu). Within a rather small land, the prevalence of HCV or HBV is not uniform all over Japan. The prevalence of HCV had an increasing gradient from north to south, and was the highest in Kyushu (table 2), while that of HBV was the highest in Hokkaido, decreased in between and then increased towards Kyushu (table 4). Reflecting such local differences, age-specific prevalence of HCV or HBV differed widely among 8 jurisdiction areas (fig. 2, 5).

Based on the results obtained on the area- and age-specific prevalence of HCV or HBV, carriers of these hepatitis viruses in 8 jurisdiction areas were tabulated separately over age groups from 20 to 74 years. Those in age groups ≤19 years were represented by the Iwate prefecture. The prevalence of HCV in age groups ≥75 years was simulated by the formula, and that of HBV was represented by individuals aged 70–74 years. Japan was populated by 127,767,994 people in 2005. Of these, 807,903 (95% CI 679,886–974,292) were estimated to have undiagnosed HCV infection at an overall prevalence of 0.63%, and 903,145 (837,189–969,572) to possess undiagnosed HBV infection at that of 0.71%. These estimates are much less than publically inferred numbers of HCV and HBV carriers in Japan at 1.5–2.0 million each. Leaving aside HCV and HBV carriers who have developed liver disease and stayed outside the scope of the present study, our estimates based on reasonable scientific grounds are much smaller; they add up barely half of generally referred figures around 1.5–2.0 million in Japan.

Based on the sex- and age-specific prevalence of hepatitis virus markers in the 3,478,422 first-time blood donors during 2001–2006, with the same criteria used in the previous study [5], we have estimated the number of undiagnosed HCV carriers aged 15–69 years in the year 2005 to be 398,567 (95% CI 295,410–501,453) and that of undiagnosed HBV carriers to be 506,830 (95% CI 398,115–616,113). In the previous study [5], undiagnosed HCV and HBV carriers aged 15–69 years in the year 2000 were assessed to be 884,954 (95% CI 725,082–1,044,826) and those with HBV to be 967,753 (95% CI 806,760–1,128,745). They decreased by 55.0 and 47.6%, respectively, during 5 years (table 5). In support of this view, the incidence of HCV or HBV infection during 10 years (1994–2000) in Japan is very low and estimated at 1.86 (95% CI 1.06–3.01) or 2.78 (1.87–4.145) per 100,000 person-years [10]. Decreases in undiagnosed HCV and HBV carriers in Japan would have been attributed to increased chances of receiving tests for hepatitis virus infections at health checkups and medical institutions, as well as increased awareness due to educational programs or other healthcare campaigns or screening programs in high-risk individuals. Additionally, there would have been a cohort effect in individuals aged 15–69 years who have shifted by 5 years during the observation period.

The results of the Third National Health and Nutrition Survey (HANES III, 1988–1994) [11] and those of more recent HANES (2001–2002) [6] in the USA are essentially similar with respect to age-specific profiles of HCV infection, and shifted by 10 years. The incidence of de novo HCV and HBV infections may have decreased substantially both in the USA and Japan, driven partly by the introduction of the nucleic acid amplification test and a more stringent questionnaire on donors to exclude blood donations in the window period of infection [12–17]. The national burden of HCV infection has been reported in Great Britain [18], where the prevalence of anti-HCV in hospitalized patients was 3.4% and that in the first-time blood donors was 0.03% in the year 2008.

In spite of many improvements in the control of hepatitis virus infections, there are many HCV and HBV carriers buried in the society who need immediate identification for receiving timely and efficient medical interventions. Treatment of viral hepatitis keeps improving, especially for liver disease induced by HCV. The sustained virological response in the patients infected with HCV of genotype 1, who have received triple therapy with pegylated interferon, ribavirin and protease inhibitors, has increased to 70% or higher, from 50% with the state-of-care therapy with pegylated interferon and ribavirin [19, 20]. With the advent of new antiviral drugs that will enter the scene in the foreseeable future, the virological response is expected to increase further. There would be

nothing like early detection of HCV and HBV infections for appropriate and timely medical care to prevent the progression of liver disease. Such a rational strategy will benefit not only patients themselves, but also merit the society and government, which are going to be burdened with ever-increasing morbidity and mortality along with skyrocketing costs.

Acknowledgements

References

1 World Health Organization: Hepatitis C (Global Alert and Response, 2002). Geneva, WHO, 2002. Updated February 2010 (http://www.who.int/csr/disease/hepatitis/whocd-scsrlyo2003/en/index.html).

2 World Health Organization: Hepatitis B (Factsheet No. 204). Geneva, WHO, Revised August 2008 (http://www.who.int/ media-centre/factsheets/fs204/en/index.html).

3 Lok AS: Chronic hepatitis B. N Engl J Med 2002;346:1682–1683.

4 Seeff LB: Natural history of chronic hepatitis C. Hepatology 2002;36:S35–46.

5 Tanaka J, Kumagai J, Katayama K, Komiya Y, Mizui M, Yamanaka R, Suzuki K, Miyakawa Y, Yoshizawa H: 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. Intervirology 2004;47:32–40.

6 Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ: The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. Ann Intern Med 2006;144:705–714.

7 Yoshizawa H, Tanaka J: A national project for the management of viral hepatitis toward prevention of hepatocellular carcinoma in Japan; in Morrisey RF (ed): International Kilmer Conference Proceedings. Laval, Polyscience Publications, 2004, vol 8, pp 247–264.

8 Mizui M, Tanaka J, Katayama K, Nakanishi T, Obayashi M, Aimitsu S, Yoshida T, Inoue J, Yokoyama T, Tsuji K, Arataki K, Yamaguchi S, Miura T, Kitamoto M, Takezaki E, Orimen S, Sakata T, Kamada K, Maruhashi A, Tamura T, Nakamura T, Ishida K, Teramen K, Miyakawa Y, Yoshizawa H: Liver disease in hepatitis C virus carriers identified at blood donation and their outcomes with or without interferon treatment: study on 1,019 carriers followed for 5–10 years. Hepatol Res 2007;37:994–1001.

9 Yoshizawa H: Hepatocellular carcinoma associated with hepatitis C virus infection in Japan: projection to other countries in the foreseeable future. Oncology 2002;62(suppl 1):8–17.

10 Tanaka J, Mizui M, Nagakami H, Katayama K, Tabuchi A, Komiya Y, Miyakawa Y, Yoshizawa H: Incidence rates of hepatitis B and C virus infections among blood donors in Hiroshima, Japan, during 10 years from 1994 to 2004. Intervirology 2008;51:33–41.

11 Wong JB, McQuillan GM, McHutchison JG, Poynard T: Estimating future hepatitis C morbidity, mortality, and costs in the United States. Am J Public Health 2000;90:1562–1569.

12 Busch MP, Glynn SA, Stramer SL, Strong DM, Caglioti S, Wright DJ, Pappalardo B, Kleinman SH: A new strategy for estimating risks of transfusion-transmitted viral infections based on rates of detection of recently infected donors. Transfusion 2005;45:254–264.

13 Busch MP, Glynn SA, Wright DJ, Hirschkorn D, Laycock ME, McAuley J, Tu Y, Giachetti C, Gallarda J, Heitman J, Kleinman SH: Relative sensitivities of licensed nucleic acid amplification tests for detection of viremia in early human immunodeficiency virus and hepatitis C virus infection. Transfusion 2005;45:1853–1863.

14 Yoshikawa A, Gotanda Y, Itabashi M, Minegishi K, Kanemitsu K, Nishioka K: HBV NAT positive [corrected] blood donors in the early and late stages of HBV infection: analyses of the window period and kinetics of HBV DNA. Vox Sang 2005;88:77–86.

15 Biswas R, Tabor E, Hsia CC, Wright DJ, Laycock ME, Fiebig EW, Peddada L, Smith R, Schreiber GB, Epstein JS, Nemo GJ, Busch MP: Comparative sensitivity of HBV NATs and HBsAg assays for detection of acute HBV infection. Transfusion 2003;43:788–798.

16 Kleinman SH, Busch MP: Assessing the impact of HBV NAT on window period reduction and residual risk. J Clin Virol 2006; 36(suppl 1):S23–S29.

17 Yugi H, Mizui M, Tanaka J, Yoshizawa H: Hepatitis B virus screening strategy to ensure the safety of blood for transfusion through a combination of immunological testing and nucleic acid amplification testing – Japanese experience. J Clin Virol 2006; 36(suppl 1):S56–64.

18 http://www.hpa.org.uk/web/HPAweb&HPAwebStandard/HPAweb_C/125915222116.

19 Hezode C, Forestier N, Dusheiko G, Ferenci P, Pol S, Goeser T, Bronowicki JP, Bourliere M, Gharakhanian S, Bengtsson L, McNair L, George S, Kieffer T, Kwong A, Kauffman RS, Alam J, Pawlotsky JM, Zeuzem S: Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. N Engl J Med 2009;360:1839–1850.

20 McHutchison JG, Everson GT, Gordon SC, Jacobson IM, Sulkowski M, Kauffman R, McNair L, Alam J, Muir AJ: Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. N Engl J Med 2009;360: 1827–1838.