がん検診の有効性評価

濱島 ちさと

近年，諸外国ではがん検診の有効性を評価し，公共政策に活用する動きが見られる．こうした流れを受け，わが国でも平成10年，11年，13年と過去3回にわたるがん検診の有効性評価が行われた．

その第3回目が，平成13年3月に公表された平成12年度厚生労働省老人保健事業推進費等補助金・がん検診の適正化に関する調査研究事業「新たながん検診手法の有効性の評価」報告書(主任研究者/久道茂)である．その評価方法は，USPSTF(『US Preventive Services Task Force』第2版)を参考にしている．そのUSPSTFにおいて，ガイドラインの更新にあたり，2001年から新しい評価方法が取り入れられた[1]．

USPSTFの新しい評価方法

ガイドラインの推奨の基準は，研究方法とその根拠を示すことで，その推奨のレベルが決定されてきた．USPSTFの第1・2版も基本的にはこの方法を踏襲したものであったが，第3版の改正では，推奨の基準と研究の評価方法が修正された．

変更点の第1は，推奨基準である．推奨基準は第2版でも5段階方式が採用されていた．このうち，A，Bは推奨，Cは保留，D，Eが非推奨であった．第3版では，この形式を修正し，**表1**の5段階を採用している．第2版と第3版の評価を比べる場合には，この推奨形式の変更に留意する必要がある．

表1　USPSTFの推奨基準(Harris RP, 2001より)

推奨	表現
A	USPSTFは，臨床家が適格な患者に対して日常的に当該サービスを提供することを強く勧告する．(USPSTFは，当該サービスが重要な健康指標を改善することを示す優良な証拠があると判断し，利益が不利益を大きく上回ると結論する)
B	USPSTFは，臨床家が適格な患者に対して日常的に当該サービスを提供することを勧告する．(USPSTFは，当該サービスが重要な健康指標を改善することを示す少なくとも相応の証拠があると判断し，利益が不利益を上回ると結論する)
C	USPSTFは，当該サービスを日常的に提供することについて，勧めることも反対することもしない．(USPSTFは，当該サービスが重要な健康指標を改善することを示す少なくとも相応の証拠があると判断するが，一般的な勧告を正当化するには利益と不利益のバランスが近接しすぎていると結論する)
D	USPSTFは，当該サービスを日常的に無症状の患者に対して提供することに反対する．(USPSTFは，当該サービスが効果がない，あるいは，不利益が利益を上回るとする少なくとも相応の証拠があると判断する)
I	USPSTFは，当該サービスを日常的に提供することについて，勧めるまたは反対する勧告を出すための証拠が不十分であると結論する．(当該サービスに効果があるとする証拠がないか，質が悪いか，あるいは，一致した結果が得られていないため，利益と不利益のバランスを判断できない)

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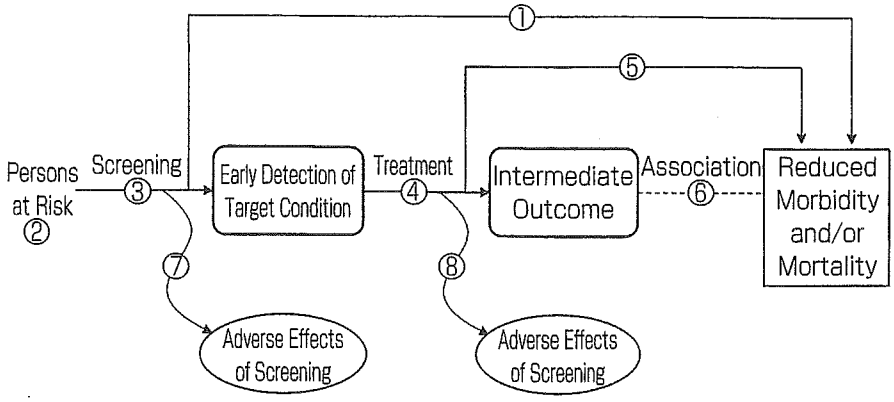

図　USPSTF における検診の Analytic Framework

[Harris RP, et al : Current methods of the U. S. Preventive Services Task Force ; A review of the process. Am J Prev Med 20 (suppl 3) : 21-35, 2001 より]

表2　USPSTF の推奨グリッド

証拠の質	利益と不利益の差(Net Benefit)			ゼロ/マイナス
	大きい	中等度	小さい	
Good	A	B	C	D
Fair	B	B	C	D
Poor＝1				

第2は研究方法ばかりではなく，研究の質を吟味することが追加された．研究方法にさらに質の検討を加え，Good・Fair・Poor の3段階で評価する．第2版までの評価方法においても，研究の質はある程度考慮されてはいたが，評価の主体はどのような研究方法により根拠が示されているかが，最も重要な点であった．この結果，無作為化比較対照試験(Randomized Controlled Trial : RCT)により評価された医療サービスの評価が最も高く，観察研究は評価が下がってしまう．RCT であれば即信頼性が裏付けられるかというと必ずしもそうではなく，一定の質が求められる．RCT 一辺倒の評価に疑問を投げかけたのが，コクランの乳がん検診の評価である．この論争を契機に，研究方法だけではなく，研究のデザインや利益・不利益を重視した評価が再認識された．USPSTF における乳がん検診の評価も，これまで最高の推奨で A であったものから，1ランク落とした B に変更された．

第3は，評価対象となる予防対策や検診について，利益と不利益を勘案した評価方法が追加された．あらゆる医療サービスには，利益・不利益があることが指摘されてきたが，その評価をガイドラインにどのように組み込むかは，必ずしも統一見解があるわけではない．しかし近年，臨床ガイドラインの作成過程においては，利益・不利益を何らかの形で評価することが求められる．

USPSTF では，推奨グリッド(表2)に基づき，研究の質と利益と不利益の差(Net Benefit)を用いて評価しようというものである．ここでいう利益とは，医療サービスが質の高い研究により，その根拠の裏づけを得ていることである．がん検診であれば，死亡率減少効果が示されていることである．利益の評価のためには信頼性に高い研究方法と質によりその判定が異なる．一方，不利益は，医療サービスがもたらすマイナスの側面で，検査の見逃しや，過剰診断，検査や治療の合併症である．これらは，従来から指摘されていた問題であった．ガイドラインの中にどのように組み込むかが明確ではなかったが，今回の推奨には「利益が不利益をどの程度上回るか」を判定することにより，推奨の段階に反映する仕組みが作られている．

第4は，直接的な根拠だけでなく，間接的根拠についても評価を行うための Analytic Framework が導入された(図)．第2版にも類似の Causal Pathways が存在していたが，第3版においては，直接的な証拠がない場合でも，Analytic Framework の各段階における Key Ques-

tionに対応する研究を積み重ねることで，検診や予防対策を評価しようというものである．

がん検診の新たな評価

USPSTF第3版の更新方法の変更が公表されて以来，第2版の評価に新たな研究を加え，評価の更新が行われつつある．2004年8月までのがん検診の更新は**表3**のとおりである．新たな推奨段階では，CとIが類似しているが，実際にCと判定される可能性は少なく，科学的根拠が不十分であるとするIの評価が多い．

USPSTFにおける大腸がん検診評価

大腸がん検診の評価を見ると，個々の検診方法の評価ではなく，大腸がん検診として推奨Aの判定を受けている[2]．ただしその方法には，便潜血検査，S状結腸鏡，便潜血検査とS状結腸鏡の併用法，全大腸内視鏡検査，注腸造影のすべてをまとめた上での評価が行われており，個別の検診方法の評価は明確ではない．しかし，3つにRCTにより有効性評価が確立している便潜血検査のみである[3]．

化学法による便潜血検査による大腸がん検診の死亡率減少効果は，3件の無作為化比較対照試験によりその直接的な根拠が証明されている．米国Minnesota[4]では，50～80歳の男女を対象に，隔年受診群(15,587例)，逐年受診群(15,570例)，対照群(15,394例)の3群について，18年間にわたる追跡を行った．対照群に比し，隔年受診群で21%(RR＝0.79；95%CI 0.62～0.97)，逐年検診で33%(RR＝0.67；95%CI 0.51～0.83)の大腸がん死亡抑制効果が認められた．英国Nottingham[5]では，45～74歳を対象とし，逐年受診群(76,224例)，対照群(76,079例)について11年間にわたる追跡を行い，隔年受診群で13%の大腸がん死亡抑制効果を認めた(RR＝0.87；95%CI 0.78～0.97)．デンマークFunen[6]では，45～75歳を対象とし，逐年受診群(30,967例)，対照群(30,966例)について13年間にわたる追跡を行い，隔年受診群で18%(RR＝0.82；95%CI 0.69～0.97)の大腸がん死亡抑制効果を認めた．スウェーデンの無作為化比較対照試験の中間報告を加えた4件の無作為化比較対照試験のメタ・アナリシス[7]では，16%の死亡率減少効果(RR＝0.84；95%CI 0.77～0.93)が認められている．ただし，USPSTFによる便潜血検査の評価は化学法を対象としたものであり，わが国に普及している免疫法は対象外となっている．

この他，S状結腸鏡，便潜血検査とS状結腸鏡の併用法，全大腸内視鏡については，症例対照研究やコホート研究による科学的根拠は示されてはいるものの，それは便潜血検査に比し薄弱なものである．また，注腸造影についても，全大腸内視鏡の代替案として評価されている．

表3　USPSTFの評価の更新

がん検診	方法	更新年	推奨段階	第2版の評価
膀胱がん	尿検査・尿細胞診・BTA・NMP22	2004	D	D(1996)
肺がん	胸部CT・胸部X線・喀痰細胞診	2004	I	D(1996)
すい臓がん	診察・US・腫瘍マーカー	2004	D	D(1996)
精巣がん	診察・US・腫瘍マーカー	2004	D	C(1996)
口腔がん	診察・自己触診	2003	I	C(1996)
子宮頸がん(21～64歳)	細胞診	2003	A	A(1996)
子宮頸がん(65歳以上)	細胞診	2003	D	C(1996)
子宮頸がん(子宮全摘後)	細胞診	2003	D	
子宮頸がん	HPV	2003	I	C(1996)
乳がん	マンモグラフィ	2002	B	50-69歳A(1996)，他の年齢C(1996)
乳がん	視触診	2002	I	C(1996)
乳がん	自己検診	2002	I	C(1996)
前立腺がん	PSA・直腸指診	2002	I	D(1996)
大腸がん	便潜血・S状結腸鏡・全大腸内視鏡・注腸造影	2002	A	便潜血・S状結腸鏡B(1996)，全大腸内視鏡・注腸造影・直腸指診C(1996)
皮膚がん	診察	2001	I	C(1996)
卵巣がん	CA-125・US	2001	I	D(1996)

まとめ

以上，USPSTFにおける新たな評価方法を概説するとともに，近年更新された推奨を提示した．新たに更新された評価の問題点として，大腸がん検診の評価の例を示した．ガイドラインの推奨方法，作成基準について，国際的な議論が活発化している．こうした動向を踏まえ，現在，わが国においてもがん検診の有効性評価の更新作業が進められている．

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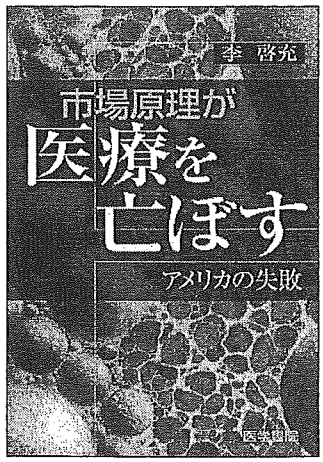
公衆衛生 Library

市場原理が医療を亡ぼす —アメリカの失敗



『市場原理が医療を亡ぼす—アメリカの失敗』李啓充(著)，医学書院，定価2,100円(本体2,000円＋税5%)，2004年

頻発する株式会社病院の「犯罪」，財力に基づく凄惨な医療差別……，医療に市場原理が導入された結果，米国医療はどうゆがんだか!? 優れた医事評論で知られる著者が，米国の事例を紹介しつつ，経済界主導で進む日本の医療のあり方に警鐘を鳴らす．「混合診療解禁」，「医療機関経営への株式会社の参入容認」など，医療における「ビジネス・チャンスの創出」を目論む勢力が主導する改革議論に正面から斬り込む．

これを読まずして医療改革は語れない!!

〈目次〉

総特集

予防医学はどこまで可能か

米国予防サービス委員会に見る大腸がん検診の経済評価

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濱島ちさと

要旨：がん検診において、有効性評価とともに経済評価が重要視されている。がん検診は有効性を評価した上で、政策に導入される。経済評価研究も、政策決定への判断材料として提供されるべき情報である。

経済評価研究の目的は限られた資源を有効に活用するための根拠を提示し、政策決定に反映させることである。近年、がん検診においても、有効性評価とともに経済評価が重要視されている。そのためには、標準化された方法による経済評価研究が前提となり、研究の質の改善が求められていた。経済評価研究の普及に対応し、96年に相次いで公表されたDrummondらによるBMJ Checklist(英)[1]、Weinsteinらによる Washington Panel (米)[2]により、その方法が集約、標準化された。

がん検診の有効性評価

がん検診をはじめとする予防対策については、各国でも有効性を評価し、その結果に基づいて、政策に導入するという方向性が確立しつつある。

わが国においても、がん検診については過去3回にわたり有効性評価が行われている。直近の成果としては、01年3月に公表されたがん検診の適正化に関する調査研究事業「新たながん検診手法の有効性の評価」報告書（以下、久道班報告書）にまとめられている。[3]

久道班報告書では、以下の3条件を踏まえ、科学的根拠に基づき、がん検診の有効性評価を行っている。

①対象は無症状の一般集団であり、「がん」を標的疾患とした検診の評価である。

②がん検診の有効性の評価を「死亡率減少効果」により判定する。

③公共政策の実施という観点からの判断材料として提供する。

評価判定の根拠は、無作為化比較対照試験や複数の観察研究が有効性を示唆するものが、「I-a：検診による死亡減少効果があるとする、十分な根拠がある」「I-b：検診による死亡減少効果があるとする、相応な根拠がある」で有効と判定されている。「II群」で保留とされているがん検診は、発見率や生存率といった報告はあるが、信頼性の高い方法による評価研究がないことから、「保留」の判定を受けている。したがって、無効とされた「I-c：検診による死亡減少効果がないとする、相応な根拠がある」「I-d：検診による死亡減少効果がないとする、十分な根拠がある」とは異なり、今後の研究によっては「有効」と判定される可能性もある。

現行のがん検診においては、視触診単独による乳がん検診と、細胞診による子宮体がん検診が無効と判定された。一方、胃X線検査による胃がん検診、細胞診による子宮頸がん検診、胸部X線検査と高危険度群による喀痰細胞診による肺がん検診、マンモグラフィと視触診併用による乳がん検診、便潜血反応による大腸がん検診が、「検診による死亡率減少効果があるとする、十分な根拠がある」あるいは「相応の根拠がある」として、有効と

●Summary
Economic evaluation of cancer screening
In cancer screening, economical evaluation is important as well as evaluation of effectiveness. Cancer screening is introduced into a policy after evaluation of the effectiveness. Economical evaluation is also considered as crucial information for policy decision making.

表3　選択すべき検診方法

研究	最も費用効果的な検診方法	選択すべき方法			
		20,000$/LSD>	20,000-30,000$/LSD	30,000-50,000$/LSD	50,000$/LSD<
Wagner 1996	FOBT＋FS	COL q10	COL q 10	FOBT+FS	FOBT+FS
Frazier 2000	FOBT＋FS	FOBT q1	FOBT q1	FOBT+FS	FOBT+FS
Knhandker 2000	COL q10 FS q5	FS q5	FOBT q1	COL q 10	
Sonnenberg 2000	COL q10	COL q10	COL q10	COL q 10	COL q 10
Vijan 2001	FOBT＋FS	FOBT q1	FOBT q1	COL 55/65	COL 55/65

（USPSTF、2002）

LSD：life-year saved　生存年／FOBT q1：便潜血検査　逐年／FS q5：シグモイドスコピー　5年毎／FOBT q1＋FS q5：便潜血検査　逐年とシグモイドスコピー　5年毎の併用／DCBE q5：注腸　5年毎／COL q10：全大腸内視鏡　10毎／COL 55／65：全大腸内視鏡　55歳・65歳対象／

表2　大腸がん検診の費用効果

検診方法	Wagner ($/LSD)	Frazier ($/LSD)	Knhandker ($/LSD)	Sonnenberg ($/LSD)	Vijan ($/LSD)
FOBT q	111,725	17,805	13,656	10,463	5,691
FS q5	12,477	15,630	12,804	39,359	19,068
FOBT q1＋FS q5	13,792	22,518	18,693	－	17,942
DCBE q5	11,168	21,712	25,624	－	－
COL q10	10,933	21,889	22,012	11,840	9,038

（USPSTF、2002）

費用はすべて2000年USドル換算／LSD：life-year saved　生存年／FOBT q1：便潜血検査　逐年／FS q5：シグモイドスコピー　5年毎／FOBT q1＋FS q5：便潜血検査　逐年とシグモイドスコピー　5年毎の併用／DCBE q5：注腸　5年毎／COL q10：全大腸内視鏡　10毎／

ち、結果の指標にQALY（Quality adjusted life-year）を用いていたのは1論文であった。費用は、すべての論文で直接費用のみが考慮されていた。

検診未実施を代替案とした費用効果（表2）では、いずれの検診方法でも、費用効果比は10,000～25,000（/life-year saved）であった。増分分析の結果、2000（/life-year saved）まで支払う意思はある場合に、選択すべき検診方法としては、逐年の便潜血、5年ごとのシグモイドスコピー、10年ごとの全大腸内視鏡であった（表3）。それ以上の支払いをしてよい場合には、シグモイドスコピーと便潜血検査の併用、全大腸内視鏡が望ましい検診方法であった。検診開始年齢は、Nessらの検討があり、男女ともに45～49歳に比し50～54歳が、より費用効果的であった。[7] Eddyによる先行研究でも、大腸がん検診の開始は40歳よりも50歳が費用効果的であることが示されている。[8] 一方、終了年齢についての検討は全くなかった。

USPSTFでは、大腸がん検診の方法として有効と評価している5方法について、いずれの方法が費用効果的という結論は出してはいない。しかし、大腸がん検診の費用効果比（検診未実施との比較）はどの方法であっても、50歳以上を対象とした乳がん検診や中等度の高血圧治療よりも費用効果的であるとしている。

予防対策のガイドラインの推奨の判断基準に経済評価を組み入れるかどうかについては、ガイドラインを作成する団体の方針や、ガイドラインの対象等について異なる。しかし、推奨の判断基準から除外された場合であっても、USPSTFのように同時に経済評価についてのレビューを行い、政策決定への判断材料として提供されるべき情報である。

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濱島ちさと（はまじま・ちさと）●83年岩手医大医卒。87年同大学院修了。87年から96年まで癌研究会付属病院検診センター、96年から97年まで慶大医学部医療政策・管理学教室、97年から02年まで聖マリアンナ医大予防医学教室を経て、現在国立がんセンターがん予防・検診研究センター情報研究部診療支援情報室。著書に「医療の経済評価」「がん検診計画ハンドブック」（共に分担）など。

表1　US Preventive Services Task Force における推奨

勧告	表現
A	USPSTFは、臨床家が日常的に適格な患者に対して当該サービスを提供することを強く勧告する。(USPSTFは、当該サービスが重要な健康指標を改善することを示す優良な証拠があると判断し、利益が不利益を大きく上回ると結論する。)
B	USPSTFは、臨床家が日常的に適格な患者に対して当該サービスを提供することを勧告する。(USPSTFは、当該サービスが重要な健康指標を改善することを示す少なくとも相応の証拠があると判断し、利益が不利益を上回ると結論する。
C	USPSTFは、当該サービスを日常的に提供することについて、勧めることも反対することもしない。(USPSTFは、当該サービスが重要な健康指標を改善することを示す少なくとも相応の証拠があると判断するが、一般的な勧告を正当化するには利益と不利益のバランスが近接しすぎていると結論する。)
D	USPSTFは、当該サービスを日常的に無症状の患者に対して提供することに反対する。(USPSTFは、当該サービスが効果がない、あるいは、不利益が利益を上回るとする少なくとも相応の証拠があると判断する。)
I	USPSTFは、当該サービスを日常的に提供することについて、勧めるまたは反対する勧告を出すための証拠が不十分であると結論する。(当該サービスに効果があるとする証拠がないか、質が悪いか、あるいは、一致した結果が得られていないため、利益と不利益のバランスを判断できない。)

(USPSTF、2001)

評価された。

また、新しいがん検診手法として取り上げられた血清ペプシノゲンによる胃がん検診、らせんCTによる肺がん検診、PSAによる前立腺がん検診などは、いずれも「検診による死亡率減少効果を判定する適切な根拠となる研究や報告が、現時点では見られない」という結果で保留と判定された。

アメリカにおいては、米国予防サービス委員会(US Preventive Services Task Force：USPSTF)が、各種がん検診の有効性や各種の予防対策についての証拠のまとめを行い、推奨を提示している。[4] 証拠のまとめについては、研究デザイン、研究の質を考慮し、good、fair、poorの3段階の評価を行っている。

さらに、検診の利益・不利益を検討した上で、5段階の推奨を付与している(表1)。大腸がん検診については、50歳以上を対象とした大腸がん検診(便潜血検査、シグモイドスコピー、シグモイドスコピーと便潜血検査の併用、全大腸内視鏡、注腸造影)を判定Aとして推奨している。[5]

有効性評価と経済評価

有効性評価の確立した予防対策については、経済評価研究により、政策決定へより具体的な提言を行うことが望まれている。USPSTFやCDCによるCommunity Preventive Services (Guide)では、有効性評価を行うとともに、経済評価のレビューも行っている。政策決定の判断材料として、経済評価研究の系統的総括を行う場合には、問題点を抽出し、それに回答を与えてくれる既存研究を有効に活用していくことが必要である。USPSTFでは、経済評価を有効性評価の判断基準には取り込んでいないが、並行して評価を進めている。

USPSTFでは、大腸がん検診については、別途検索方法や選択基準を設定し、評価のまとめを行っている。その位置づけは、有効性評価のための傍証であり、また検診が抱える問題点の回答を検討するためのものである。[6] そのためのキー・クェスチョンとして、以下を設定している。

①どのような検診方法が費用効果的か。非受診群を代替案とした費用効果分析の結果を比較する。

②経済性の優れた検診方法は何か。より適切な検診方法を行う上での判断基準となる増分分析を行う。

③検診を、いつから開始し、いつ終了とするか。年齢上限として、70歳、75歳、80歳、85歳のどの年齢に設定すべきか。開始年齢は40歳、45歳、50歳のどの年齢に設定すべきか。

93年から01年まで、経済評価の基本条件を有し、キー・クェスチョンに合致する7論文が抽出された。このうち5論文は複数の検診方法について検討していたが、2論文は内視鏡(シグモイドスコピー、全大腸内視鏡)についての検討であった。このため、すべての論文は、検診未受診の他にも、1方法ないしは複数の代替案との比較を行っていた。分析の立場は、社会の立場あるいは、第三者支払い機関の立場であった。これらの論文のう

Resting heart rate and cause-specific death in a 16.5-year cohort study of the Japanese general population

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Background Several prospective studies have reported resting heart rate (HR) to be a risk factor for certain cause-specific death, together with sex- or age-specific differences in the effects of HR on death. However, there have been few prospective data from non-Western populations.

Methods Cohort study, over 16.5 years to date of death or end of follow-up (November 15, 1998) involving 8800 men and women ≥30 years of age randomly selected throughout Japan, who participated in the National Survey on Circulatory Disorders in 1980. Resting HR was determined from 3 consecutive intervals between R waves on the 12-lead electrocardiogram.

Results For middle-aged men (30 to 59 years of age), in the highest quartile of HR, there was a significant positive association with cardiovascular (RR, 2.55; 95% CI, 1.22 to 5.31) and all-cause death (RR, 1.45; 95% CI, 1.06 to 2.00). For middle-aged women, in the highest quartile, there was a significant positive association with noncancer, noncardiovascular (RR, 2.41; 95% CI, 1.04 to 5.59), and all-cause death (RR, 1.94; 95% CI, 1.26 to 3.01). Resting HR also showed a significant positive association with cardiac events but not to stroke. These relations were not evident for elderly subjects (≥60 years of age). Results were not affected when deaths within the first 5 years of follow-up were excluded, except for noncancer, noncardiovascular death.

Conclusions High resting HR is an independent predictor of long-term death in the Japanese general population. (Am Heart J 2004;147:1024–32.)

Several prospective studies have reported resting heart rate (HR), even within the normal range, to be a risk factor for death[1-10] or morbidity[3,4] from cardiovascular disease, especially from coronary heart disease. Furthermore, some studies have reported that a high resting HR was associated with increased risk of non-cardiovascular[2,6,8-10] or all-cause death[1-3,5,6,8-10] and of osteoporotic fractures.[10] However, most of these studies were performed in Western populations.

In populations with a different lifestyle background compared with Western populations,[11] the role of HR in predicting death may be different. Our working hypothesis was that as in Western populations, resting HR was a predictor of cardiovascular or all-cause death in the Japanese general population. We examined this hypothesis using 16.5-year follow-up data from the National Survey on Circulatory Disorders, Japan.

Methods

Populations

A total of 10,546 community dwellers (4640 men and 5906 women), ≥30 years of age in 300 randomly selected districts, participated in the survey; they were followed until November 15 in 1998. The current study extended the follow-up period of NIPPONDATA80 study, the details of which have previously been reported.[12-14] Of the 10,546 participants, 1746 were excluded for the following reasons: past history of coronary heart disease or stroke (n = 280), missing infor-

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†Investigators and members of the research group are listed in References 12, 13, and 14.

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Table I. Age and age-adjusted means and prevalences for baseline characteristics

Risk characteristics	Heart rate quartiles (Stratum mean), beats/min				P
Male	<60 (54.7)	60–65 (62.7)	66–73 (69.2)	74– (81.7)	
Number of participants	960	959	995	942	
Age (y)	50.5 (12.9)	49.7 (13.0)	48.1 (12.9)	50.0 (13.3)	.001
Systolic blood pressure (mm Hg)	134.3 (0.61)	136.8 (0.61)	139.6 (0.60)	142.2 (0.61)	.024
Diastolic blood pressure (mm Hg)	81.1 (0.39)	82.8 (0.39)	84.5 (0.39)	85.8 (0.39)	<.001
Pulse pressure (mm Hg)	53.2 (0.44)	54.0 (0.44)	55.1 (0.43)	56.4 (0.45)	.008
Total cholesterol (mmol/L)	4.76 (0.03)	4.73 (0.03)	4.84 (0.03)	4.91 (0.03)	<.001
Glucose (mmol/L)	6.81 (0.06)	7.10 (0.06)	7.25 (0.06)	7.81 (0.07)	<.001
Albumin (g/L)	44.2 (0.08)	44.4 (0.08)	44.4 (0.08)	44.4 (0.08)	.083
BMI (kg/m^2)	22.3 (0.10)	22.4 (0.10)	22.7 (0.10)	22.7 (0.10)	.004
Use of antihypertensive agents (%)	8.3	10.4	8.3	10.4	.179
Hypertension (%)	42.0	46.5	48.5	58.1	<.001
Hypercholesterolemia (%)	5.6	4.9	6.0	8.2	.021
Diabetes (%)	0.7	0.7	1.0	2.2	.006
Daily drinker (%)	47.8	48.2	47.9	48.3	.996
Current smoker (%)	56.5	63.2	64.9	68.9	<.001
Female	<64 (58.8)	64–69 (66.5)	70–77 (73.2)	78– (86.5)	
Number of participants	1140	1221	1351	1232	
Age (y)	51.7 (13.0)	49.4 (13.6)	49.8 (13.5)	49.1 (13.6)	.022
Systolic blood pressure (mm Hg)	130.8 (0.55)	132.0 (0.53)	133.9 (0.51)	138.2 (0.53)	<.001
Diastolic blood pressure (mm Hg)	77.6 (0.34)	78.8 (0.33)	79.8 (0.31)	81.8 (0.32)	<.001
Pulse pressure (mm Hg)	53.2 (0.40)	53.2 (0.38)	54.1 (0.36)	56.4 (0.38)	.010
Total cholesterol (mmol/L)	4.91 (0.03)	4.91 (0.02)	4.92 (0.02)	4.96 (0.02)	.438
Glucose (mmol/L)	6.79 (0.05)	7.05 (0.05)	7.16 (0.05)	7.65 (0.05)	<.001
Albumin (g/L)	43.4 (0.07)	43.5 (0.07)	43.7 (0.07)	43.8 (0.07)	<.001
BMI (kg/m^2)	23.0 (0.10)	22.9 (0.10)	22.8 (0.09)	22.9 (0.10)	.546
Use of antihypertensive agents (%)	14.2	10.2	10.1	9.4	.001
Hypertension (%)	37.3	35.2	38.6	46.7	<.001
Hypercholesterolemia (%)	8.9	8.4	7.7	10.1	.184
Diabetes (%)	0.7	1.0	0.7	1.3	.388
Daily drinker (%)	3.1	2.8	3.3	2.5	.701
Current smoker (%)	7.3	8.5	9.8	9.8	.091

Numbers of parentheses are standard deviation for age and standard error for other variables.
*$P < .05$.

mation at baseline survey (n = 396), and lost to follow-up (n = 870). Furthermore, participants with arrhythmia affecting HR (n = 200); frequent supraventricular and/or ventricular premature beats (Minnesota code[15]; 8-1-1 and/or 8-1-2) or persistent atrial fibrillation or flutter (8-3-1 or 8-3-2) were excluded. This left 8800 participants (3856 men and 4944 women) for inclusion in the analysis.

End point determination

The underlying causes of death for the National Vital Statistics were to be coded according to the 9th International Classification of Disease (ICD-9) by the end of 1994 and the 10th International Classification of Disease (ICD-10) from the beginning of 1995. Some researchers reported that HR was strongly associated with sudden cardiac death.[2,4] It was reported that most of the cardiac sudden death tended to be described in the Japanese death certificates as "coronary heart disease" or "heart failure" as well as "unknown cause."[16,17] Furthermore, death statistics for coronary heart disease may have been underestimated by the end of 1994 by using ICD-9 because deaths coded "heart failure" might hide some coronary events.[16-19] We therefore created an extra category of deaths that combined coronary heart disease with heart failure.

Permission to use National Vital Statistics was obtained from the Management and Coordination Agency, Government of Japan. Approval for this study was obtained from the Institutional Review Board of Shiga University of Medical Science (No.12-18, 2000).

Baseline examination

During the baseline survey, resting HR was determined by measuring 3 consecutive intervals between R waves on the 12-lead electrocardiograms after the participant had sufficiently rested. Electrocardiograms were read twice by two different researchers according to the Minnesota code; in the event of disagreement, a panel of study epidemiologists and cardiologists made the final coding decision.

Nonfasting blood samples were drawn and centrifuged within 60 minutes of collection. Serum total cholesterol and albumin were analyzed in an auto analyzer (SMA12/60; Technicon, Tarrytown) at one specific laboratory (Osaka Medical Center for Health Science and Promotion, Osaka, Japan). Since April 1975, the laboratory has been certified

Table II. Number of deaths by underlying cause (ICD 9 or ICD10 †codes)

Causes of death	ICD 9 code	ICD 10 code	Total no.	Age stratification (y) 30–59 (no.)	>60 (no.)
Male					
Cardiovascular	393–459	I00–I99	291	78	213
Coronary	410–414	I20–25	57	21	36
Heart failure	428	I50	57	14	43
Stroke	430–438	I60–69	141	31	110
Cerebral infarction	433,434,437.7a,7b	I63, I69.3	83	11	72
Cerebral hemorrhage	431–432	I61, I69.1	36	11	25
Cancer	140–208	C00–D48	303	146	157
Stomach	151	C16	73	29	44
Lung	162	C33–34	69	34	35
Liver	155, 199.1c	C22	33	25	8
Pancreas	157	C25	23	15	8
Rectum	154	C19–20	15	6	9
Others			90	37	53
Noncardiovascular, noncancer			281	84	197
Pneumonia	480–486	J12–18	65	5	60
Accident, poisoning and suicide	800–999	S00–T98	46	30	16
Liver disease	570–573	K70–K77	20	9	11
Renal failure*	580–589	N00–N19	11	4	7
Diabetes	250	E10–E14	7	3	4
Others			132	33	99
Total			875	308	567
Female					
Cardiovascular	393–459	I00–I99	276	50	226
Coronary	410–414	I20–25	57	8	49
Heart failure	428	I50	63	13	50
Stroke	430–438	I60–69	123	21	102
Cerebral infarction	433,434,437.7a,7b	I63, I69.3	63	7	56
Cerebral hemorrhage	431–432	I61, I69.1	26	6	20
Cancer	140–208	C00–D48	200	93	107
Stomach	151	C16	44	20	24
Lung	162	C33–34	25	11	14
Liver	155, 199.1c	C22	13	5	8
Pancreas	157	C25	12	5	7
Rectum	154	C19–20	7	4	3
Breast	174–175	C50	15	12	3
Uterus	179–182	C53–C55	9	3	6
Others			75	33	42
Noncardiovascular, noncancer			255	53	202
Pneumonia	480–486	J12–18	54	7	47
Accident, poisoning and suicide	800–999	V01–Y89	36	19	17
Liver disease	570–573	K70–K77	11	4	7
Renal failure*	580–589	N00–N19	17	1	16
Diabetes	250	E10–E14	13	2	11
Others			124	20	104
Total			731	196	535

ICD 9 and *ICD 10*, the 9th or 10th International Classification of Disease.
*Renal failure due to diabetes was not included.

by the CDC-NHLBI Lipid standardization Program by Center for Disease Control and Prevention (CDC), Atlanta, Georgia, for the precision and accuracy of cholesterol measurements.[20] Hypercholesterolemia was defined as serum cholesterol of ≥6.21 mmol/L.

Baseline blood pressures were measured by trained observers, using a standard mercury sphygmomanometer on the right arm of seated subjects. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, use of antihypertensive agents, or any combination of these. Serum glucose was measured by the cupric-neocuproine method[21]. Diabetes was defined as serum glucose of ≥11.1 mmol/L, a history of diabetes, or both. Height in stocking feet and weight in light clothing

Table III. Relative risks (RRs) and 95% CIs for major causes of death according to resting heart rate

Heart rate (per minute) quartiles (Stratum mean)	No. of person	Person-year	Cardiovascular			
			Deaths (no.)	RR	95% CI	P
Male						
30–59 years old						
<60 (55)	715	12,335	10	1.00		
60–65 (63)	731	12,706	17	1.61	0.73, 3.53	.24
66–73 (69)	788	13,574	22	1.79	0.84, 3.82	.13
≥74 (82)	710	12,027	29	2.55	1.22, 5.31	.01
Predicted changes per 11/minute (ISD) increase				1.27	1.02, 1.58	.03
60 years old or more						
<60 (55)	245	3200	58	1.00		
60–65 (63)	228	2988	51	0.86	0.59, 1.26	.45
66–73 (69)	207	2757	48	0.93	0.63, 1.37	.72
≥74 (82)	232	2905	56	1.01	0.70, 1.48	.95
Predicted changes per 11/minute (ISD) increase				1.00	0.87, 1.15	.99
Female						
30–59 years old						
<64 (59)	816	14,315	5	1.00		
64–69 (67)	958	16,839	11	2.12	0.73, 6.11	.17
70–77 (73)	1,022	17,884	19	3.61	1.34, 9.72	.01
≥78 (86)	942	16,418	15	2.72	0.97, 7.61	.06
Predicted changes per 11/minute (ISD) increase				1.16	0.90, 1.49	.26
60 years old or more						
<64 (59)	324	4663	60	1.00		
64–69 (67)	263	3903	48	0.85	0.58, 1.25	.41
70–77 (73)	329	4658	64	0.90	0.63, 1.28	.54
≥78 (86)	290	4119	54	0.85	0.58, 1.24	.39
Predicted changes per 11/minute (ISD) increase				0.95	0.82, 1.09	.43

The relative risk (RR) was adjusted for age, serum albumin, body mass index, hypertension, hypercholesterolemia, diabetes, cigarette smoking (never, ex, ≤20 cigarettes/day, >20 cigarettes/day) and drinking (never, former, occasional, daily).

were measured. Public health nurses obtained information on smoking and drinking and medical history.

Statistical analysis

Age-adjusted mean values and prevalence of baseline characteristics were calculated in each group according to resting HR quartile, and the differences were tested by analysis of covariance or χ^2 tests. Cumulative survival rates were calculated by means of the Kaplan-Meier method with the log-rank test. The multivariate adjusted relative risk (RR) for all-cause and cause-specific death was calculated by means of the Cox proportional hazard model, adjusting for age, hypercholesterolemia, serum albumin, hypertension, diabetes, body mass index (BMI), smoking status (never, ex-, current with ≤20 cigarettes per day, and current with >20 cigarettes per day), and drinking status (never, former, occasional, and daily). Because some previous studies showed sex-[1,5–7] or age-specific[8] differences in the effects of HR on death, we stratified by sex and age at baseline (30 to 59 years and >60 years). Pulse pressure was also used as an independent variable in this model, following the report of Benetos et al[6] that the level of pulse pressure influenced the association of HR with cardiovascular death. In this model, pulse pressure was used instead of hypertension because these two variables are strongly correlated ($r = 0.55$, $P < .001$). Risks were calculated in comparison with the lowest quartile of HR as standard. Relative risks associated with a difference of 11 beats per minute (1 SD for both sexes) were also calculated. Analyses were repeated, excluding deaths within the first 5 years of follow-up to exclude the influence of preexisting diseases. The exclusion was performed by dealing deaths within the first 5 years as "censored."

The statistical Package for the Social Science (SPSS Japan Inc, Version 10.0J, Tokyo, Japan) was used for the analyses. All probability values were 2-tailed, and all confidence intervals were estimated at the 95% level.

Results

Table I shows age-adjusted means or prevalences in the baseline characteristics of all participants by quartile of resting HR. There were significant differences in

Coronary heart disease + heart failure				Noncancer, noncardiovascular				All cause			
Deaths (no.)	RR	95% CI	P	Deaths (no.)	RR	95% CI	P	Deaths (no.)	RR	95% CI	P
3	1.00			24	1.00			68	1.00		
7	2.15	0.55, 8.37	.27	11	0.47	0.23,0.96	.04	58	0.86	0.69, 1.22	.40
9	2.49	0.67, 9.24	.17	20	0.73	0.40,1.34	.31	86	1.18	0.85, 1.63	.32
16	3.99	1.14,14.0	.03	29	1.23	0.71,2.13	.46	96	1.45	1.06, 2.00	.02
	1.32	0.95, 1.84	.09		1.31	1.06,1.62	.01		1.21	1.08, 1.36	.00
19	1.00			44	1.00			144	1.00		
16	0.84	0.43, 1.65	.61	57	1.33	0.90,1.99	.16	148	1.03	0.82, 1.30	.78
18	1.05	0.55, 2.02	.88	36	0.94	0.61,1.47	.80	122	0.97	0.76, 1.24	.82
26	1.43	0.78, 2.65	.25	60	1.51	1.01,2.24	.04	153	1.14	0.90, 1.43	.28
	1.16	0.93, 1.46	.19		1.15	1.00,1.33	.05		1.05	0.97, 1.15	.25
1	1.00			8	1.00			32	1.00		
5	6.03	0.64,56.5	.12	8	0.93	0.35,2.48	.88	41	1.20	0.75, 1.91	.44
7	8.40	0.94,75.1	.06	18	2.06	0.89,4.77	.09	63	1.83	1.19, 2.80	.01
8	9.37	1.05,83.7	.04	19	2.41	1.04,5.59	.04	60	1.94	1.26, 3.01	.00
	1.43	0.99, 2.06	.06		1.29	1.01,1.64	.04		1.19	1.04, 1.35	.01
26	1.00			50	1.00			143	1.00		
24	1.02	0.58, 1.80	.94	40	0.77	0.50,1.18	.23	105	0.78	0.61, 1.01	.06
31	1.04	0.61, 1.77	.88	54	0.91	0.61,1.34	.63	152	0.92	0.73, 1.16	.49
18	0.66	0.36, 1.23	.19	58	1.10	0.74,1.62	.65	135	0.93	0.73, 1.19	.56
	0.88	0.71, 1.09	.24		1.08	0.94,1.25	.26		0.99	0.91, 1.08	.83

mean values for systolic blood pressure, diastolic blood pressure, pulse pressure, and serum glucose; they were higher in higher HR quartiles in both sexes. Mean values of BMI for men and albumin for women were also higher in higher quartiles of resting HR. Prevalence of antihypertensive agents users for women was lower in higher quartiles of HR. In addition, prevalence of hypertension, diabetes, hypercholesterolemia, and current smokers in men and hypertension in women varied significantly across HR quartiles.

Total person-years were 145,240, and mean follow-up period was 16.5 years. The number of total and cause-specific deaths is shown in Table II. During the follow-up, there were 1606 deaths (875 for men and 731 for women), of which 35% (n = 567, 33% for men and 38% for women) were due to cardiovascular diseases. There were 114 coronary heart disease deaths and 120 heart failure deaths, 20% and 21% of deaths due to cardiovascular disease, respectively, and 264 stroke deaths, 47% of deaths due to cardiovascular disease.

Among the total deaths, 31% (n = 503, 35% for men and 27% for women) were due to cancer. There were 117 stomach cancers, 94 lung cancers, and 46 liver cancers, representing 51% of deaths caused by cancer. These were the 3 major causes of cancer death. Of all deaths, 33% (n = 536, 32% for men and 35% for women) were due to noncardiovascular and noncancer diseases. There were 119 pneumonias, 82 "accidents, poisoning, and suicide," and 31 liver diseases, together representing 43% of deaths caused by noncardiovascular and noncancer diseases.

Table III shows the multivariate-adjusted RR for major noncancer causes of death according to HR quartile. For men 30 to 59 years of age, there was a trend of higher cardiovascular, noncancer, noncardiovascular, and all-cause death with higher HR, such that in the highest quartile of HR, there was a significantly raised risk of cardiovascular (RR, 2.55; 95% CI, 1.22 to 5.31) and all-cause death (RR, 1.45; 95% CI, 1.06 to 2.00). Relative risks associated with 1-SD increment of HR (11 beats/min) were 1.27 (95% CI; 1.02 to 1.58)

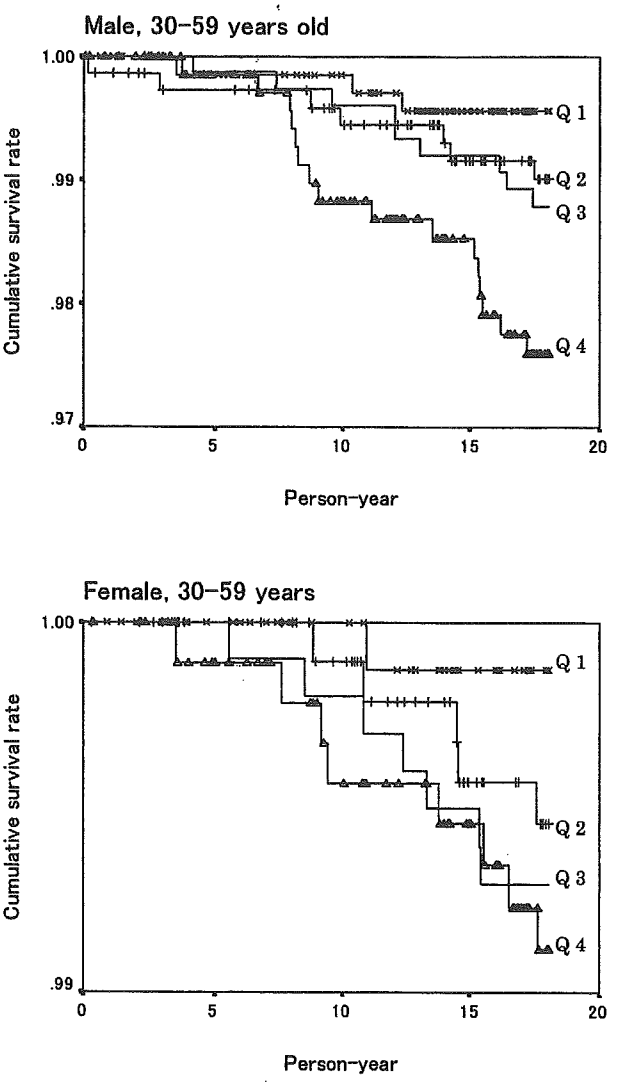
for cardiovascular disease, 1.31 (95% CI, 1.06 to 1.62) for noncancer, noncardiovascular disease, and 1.21 (95% CI, 1.08 to 1.36) for all-cause death. For women 30 to 59 years of age, there was a trend of higher noncancer, noncardiovascular, and all-cause death with higher HR, such that in the highest quartile of HR, there was a significantly raised risk of noncancer, noncardiovascular (RR, 2.41; 95% CI, 1.04 to 5.59), and all-cause death (RR, 1.94; 95% CI, 1.26 to 3.01). In addition, for cardiovascular death, there was a significantly raised risk in the second highest quartile of HR (RR, 3.61; 95% CI, 1.34 to 9.72), whereas in the highest quartile, the risk was borderline significant (P = .06). Relative risks associated with 1 SD of HR were 1.29 (95% CI, 1.01 to 1.64) for noncancer, noncardiovascular disease and 1.19 (95% CI, 1.04 to 1.35) for all-cause death. For elderly subjects (60 years old or more), only the highest quartile of HR for men showed a significant positive relation to noncancer, noncardiovascular death (RR, 1.51; 95% CI, 1.01 to 2.24). There was no association of HR to cancers in either age group and sex (data not shown).

For specific causes of cardiovascular disease death, both middle-aged men and women (30 to 59 years of age) showed raised relative risks in the highest HR quartile for coronary heart disease plus heart failure death; these were 3.99 (95 % CI, 1.14 to 14.0) and 9.37 (95% CI, 1.05 to 83.7) for men and women, based on 16 and 8 deaths, respectively. In addition, at ages ≥60 years, for men, relative risk for heart failure in the highest HR quartile was 2.61 (95% CI, 1.07 to 1.92), based on 15 deaths (data not shown). There was no relation between HR and stroke death in either age group or sex. Resting HR was not associated with cerebral infarction, cerebral hemorrhage, major site-specific cancers (stomach, lung and liver), pneumonia, "accident, poisoning, and suicide" and liver disease death (data not shown).

The results of the log-rank test for the Kaplan-Meier method were substantially consistent with the results of the Cox proportional hazard model. We showed the cumulative survival rates due to cardiac event (coronary heart disease plus heart failure death) for each HR quartiles in middle-aged participants (Figure 1).

The association between resting HR and death was investigated after excluding deaths within the first 5 years of follow-up. The pattern of results was broadly similar to that showed in Table III. For men 30 to 59 years old, the relative risks were significant for the highest quartile of HR and 1-SD increment of HR in cardiovascular disease (RR, 3.32; 95% CI, 1.41 to 7.79 for the highest quartile of HR; RR, 1.35; 95% CI, 1.07 to 1.72 for 1-SD increment), coronary heart disease and heart failure combined (RR, 6.27; 95% CI, 1.40 to 28.0; RR, 1.47; 95% CI, 1.04 to 2.08), and all-cause death (RR, 1.45; 95% CI, 1.03 to 2.05;

Figure 1



Cumulative survival rates due to cardiac event (coronary heart disease and heart failure death) for each heart rate quartile (Q1–Q4) in men and women 30 to 59 years of age. Heart rate quartiles are as follows: Q1, <60; Q2, 60–65; Q3, 66–73; Q4, ≥74 beats per minute for men; and Q1, <64, Q2, 64–69, Q3, 70–77, Q4, ≥78 beats per minute for women. Compared with Q1, Q4 in both sexes showed significantly higher mortality rates by log-rank test (P = .002 for men, P = .033 for women).

RR, 1.18; 95% CI, 1.04 to 1.34). For women 30 to 59 years old, again, patterns were similar, only results for cardiovascular disease, in the second highest HR quartile (RR, 3.97; 95% CI, 1.31 to 12.0), and for all-cause death (RR, 1.92; 95% CI, 1.19 to 3.09 for the highest quartile of HR, RR, 1.16; 95% CI, 1.01 to 1.34 for 1-SD increment) reached sta-

tistical significance. No significant relation between HR and noncancer, noncardiovascular death in men and women 30 to 59 years old was observed in this analysis.

The above-mentioned results were not substantially affected when pulse pressure was included as an independent risk factor instead of hypertension in Cox proportional hazard models.

Discussion

To our knowledge, few previous studies have examined the relation between resting HR and long-term death in Japanese living in Japan[22,23] (and Naito Y, et al, abstract in the Third International Conference of Preventive Cardiology, Oslo, 1993). However, these prior studies did not include age-specific analysis and were only limited to men. As in Western populations, higher HR was an independent predictor of all-cause death for middle-aged men and women in Japan. Resting HR also showed a significant positive correlation to coronary heart disease and heart failure death combined, but not to stroke. This coincides with results of a French study that found an association of HR with coronary death but not with stroke.[6]

In Japan, by the end of 1994, physicians used the term heart failure to not just reflect congestive heart failure, but to include sudden deaths or the mode of dying in the last stage of other diseases.[24] Therefore, it has been suggested that the death statistics for coronary heart disease have been underestimated because deaths from heart failure might include coronary events.[25] The Ministry of Health and Welfare recommended to physicians not to use "heart failure" as the mode of dying and end stage of other diseases when ICD-9 was revised to ICD-10 in 1995. Japanese vital statistics showed that coronary death rose rapidly by 25% after the ICD-10 revision in 1995, compared with the level in former periods,[26]although it still showed lower mortality rates than that of Western countries.[27,28] Because of this possible misclassification, we combined coronary heart disease with heart failure, which was associated with high HR for middle-aged men and women.

In elderly participants, high resting HR was not associated with cardiovascular death. These results are consistent with the findings of the Chicago Heart Association Detection Project in Industry.[8] The HR of elderly persons tends to be affected by various preexisting diseases, such as sinus node dysfunction or chronic obstructive pulmonary disease, which are associated with accelerated HR[29,30]; in addition, subclinical hypothyroidism is common in the elderly and is associated with decreased HR.[31] Therefore, it is difficult to interpret the relation between HR and death for older subjects even after excluding early deaths during the follow-up.

One of the mechanisms underlying excess risk for cardiovascular disease, especially for cardiac events associated with HR, is the effect of increased sympathetic nerve activity promoting atherosclerosis through a hemodynamic mechanism and producing rhythm disturbances.[32,33] A predominance of sympathetic activity over parasympathetic activity plays a critical role in the development of sudden cardiac death.[34] Sympathetic activation also increases platelet activation, which can precipitate cardiovascular events.[35] Furthermore, higher HR increases cardiac work, which increases oxygen demand and may cause myocardial ischemia.[36]

There are some limitations to the current study. First, there may be residual confounding factors affecting the relation between HR and death risk. Although we adjusted for a number of important risk factors, we could not adjust for the effect of other potential risk factors, such as forced expiratory volume as a marker of chronic obstructive pulmonary disease,[29] thyroid hormonal function,[31] physical activity,[37] and mental stress.[38] Second, the use of death data may lead to misclassification in the diagnosis of cause of deaths. However, death from stroke and cancer are known to be accurately reported on death certification in Japan.[39,40] Because of the underestimation of coronary deaths until the end of 1994 in Japan, it might be helpful in the future to examine coronary incidence as the end point. However, in the current study, we addressed this problem by combining coronary heart disease and heart failure deaths. Third, since the present study was based on HR measurement on one occasion only, the results might include regression dilution bias,[41] which might attenuate the relations of HR to long-term death. Fourth, we did not have sufficient information on the use of β-blockers at baseline, which is associated with reduced heart disease morbidity and HR,[42] although we did adjust for use of antihypertensive agents, insofar as the latter was included in the definition of hypertension. Finally, about 8% of our study population were lost to follow-up. However, we believe that this does not substantially affect the result, because the proportion of those who were lost to follow-up was not different across the HR quartiles.

In conclusion, the present study suggests that higher HR is an independent marker of cardiovascular and all-cause death for middle-aged men and women in the Japanese general population.

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Cigarette Smoking as a Risk Factor for Stroke Death in Japan
NIPPON DATA80

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Background and Purpose—Some previous Japanese cohort studies failed to show an association between smoking and stroke risk. Because such an association has been noted in other populations, this issue should be re-examined in a recent representative Japanese cohort with a higher total cholesterol level.

Methods—A total of 9638 men and women aged 30 years and older without a history of cardiovascular disease (CVD) at baseline in 1980 were followed-up for 14 years.

Results—We observed 203 stroke deaths (107 cerebral infarctions, 45 cerebral hemorrhages, and 51 others), 191 heart disease deaths, and 413 CVD deaths. The average serum total cholesterol level was ≈4.91 mmol/L. Cox proportional hazard ratios were calculated adjusting for age, systolic blood pressure, and other conventional risk factors. The hazard ratios for men who smoked 1 to 20 cigarettes/day for all strokes, cerebral infarction, and cerebral hemorrhage were 1.60 (95% CI, 0.91 to 2.79), 2.97 (CI, 1.27 to 6.98), and 0.42 (CI, 0.16 to 1.09), respectively, and for those who smoked ≥21 cigarettes/day, they were 2.17 (CI, 1.09 to 4.30), 3.26 (CI, 1.11 to 9.56), and 0.68 (CI, 0.20 to 2.33), respectively. For women who smoked ≥21 cigarettes/day, the hazard ratio for all strokes was 3.91 (CI, 1.18 to 12.90). For CVD, all heart disease, and ischemic heart disease, the hazard risks of smoking were significant (1.49 to 4.25) for men but not significant for women.

Conclusions—Smoking in a cohort with moderate serum total cholesterol level was a potent risk factor for stroke, especially cerebral infarction, for both men and women, and for CVD and ischemic heart disease for men. (***Stroke*. 2004; 35:1836-1841.)**

Key Words: epidemiology ■ cerebrovascular disorders ■ stroke ■ risk factors

It is well known that cigarette smoking is associated with an increased risk of cardiovascular disease (CVD).[1] Many epidemiological studies in Western populations have identified smoking as an independent risk factor for stroke,[2,3] and this association has also been found in people of Japanese descent living in Hawaii.[4] However, epidemiological data regarding the relationship between smoking and stroke in Japanese people living in Japan remain inconclusive.[5–8] The Hisayama study involving 1600 rural subjects followed-up for 23 years[6] did not find any association between smoking and cerebral infarction. Although smoking prevalence was high in this population, mean blood cholesterol level was low and hypertension appeared to be the sole cause of stroke from the 1960s to 1975.[7] However, recent analysis of the Hisayama study revealed that from 1961 to 1993, smoking was a risk factor for lacunar stroke.[9]

We therefore hypothesized that with the recent increase in dietary fat intake and the relative increase in the population blood cholesterol level,[10,11] the risk of stroke, particularly cerebral infarction, in smokers should be higher[8,12] than that observed in previous cohort studies.[5,6] In this study, we investigated the association between smoking and the risk of death from stroke and stroke subtype, CVD, all heart diseases, ischemic heart disease (IHD), and all causes.

Subjects and Methods

Baseline Survey

The subjects of this cohort study were the participants of the National Cardiovascular Survey of 1980 that was conducted with the National Nutrition Survey. The National Nutrition Survey in Japan is performed each year using a similar method and questionnaire. The standardized procedures used in this survey have been described elsewhere.[13] This survey was performed for all household members

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aged 30 years or older in 300 census tracts, which were randomly selected throughout Japan. The baseline survey included medical examinations, blood pressure measurements, blood tests, and a self-administered questionnaire about lifestyle from 10 897 subjects. The survey response rate was 79.4%. Trained staff at local health centers in the respective districts performed the examinations in community centers. A history of past illnesses, including heart disease, stroke, and diabetes, and smoking and drinking habits were obtained from the questionnaire. Subjects were asked to note whether they were current smokers, had quit smoking, or had never smoked. Smokers were asked to note the number of cigarettes smoked each day. With regard to drinking habits, subjects were asked to note whether they were "nonsmokers" or "ex-smokers" and if they were "sometimes" drinkers or "everyday" drinkers. Body weight was measured while the subjects wore light clothing and no shoes. Single blood pressure was measured by a standard sphygmomanometer to obtain systolic and diastolic blood pressure (SBP and DBP). Nonfasting blood samples were drawn. The measurement precision and accuracy for serum cholesterol were certified in the Lipid Standardization Program administered by the Center for Disease Control and Prevention, Atlanta, Ga.

Follow-Up Survey

A total of 10 546 subjects aged 30 years or older for whom we had complete baseline information regarding age, sex, and blood pressure in the 1980 data set were defined as the cohort (NIPPON DATA80). They were followed-up until 1994, and a follow-up survey was performed in 1994 to ascertain the vital status of cohort subjects.[13] Vital statistics for determining causes of death were obtained from the Management and Coordination Agency, Government of Japan. Approval for this study was obtained from the Institutional Review Board of Shiga University of Medical Science (number 12-8, 2000).

The underlying causes of death were coded according to the 9th International Classification of Disease. Number of deaths from all causes, CVD (ICD 9 code: 393 to 459), stroke (ICD 9 code: 430 to 438), hemorrhagic stroke (ICD 9 code: 431 to 432), cerebral infarction (ICD 9 code: 433, 434, 437.7A, 437.7B), heart disease (ICD 9 code: 393 to 398, 410 to 414, 415 to 429), and IHD (ICD 9 code: 410 to 414) were identified.

Out of 10 546 cohort subjects, the vital status of 9638 subjects (91.4%) could be ascertained in 1994. A total of 1617 subjects were excluded because of the following reasons: past history of CVD (n=697), missing information on smoking at baseline (n=12), and lost to follow-up (n=908). We analyzed the data of the remaining 8929 subjects (3972 men and 4957 women).

Although there was no difference in smoking rate between men who were and were not followed-up, there was a significant difference between women who were and were not followed-up (8.8% versus 20.0%). The mean ages (±standard deviation [SD]) at baseline were 50.0 (±13.0) and 50.2 (±13.1) years for men and women, respectively; the mean ages at the end of follow-up were 63.1 (±12.2) and 63.6 (±12.5) years, respectively.

Statistical Analysis

Subjects were divided into 4 smoking categories according to their baseline smoking habits: nonsmoker, ex-smoker, moderate smoker (1 to 20 cigarettes/d), and heavy smoker (≥21 cigarettes/d). The body mass index (BMI) was calculated as weight (kg) divided by the square of height (m). A current drinker was defined as an occasional or everyday drinker. Age-adjusted mortality rates were calculated by the direct method using the Japanese standard population of 1985. Analysis of variance was used for comparisons of several means. The χ^2 test was used to compare the frequencies among the categories. Age-adjusted and multivariate-adjusted relative risks were calculated using the Cox proportional hazard model. All P values were 2-tailed and all CIs were estimated at the 95% level. The Statistical Package for the Social Sciences (SPSS Japan Inc, version 10) was used for the analyses.

Results

There was a large difference in smoking rate between men and women: 50% to 70% of the men smoked whereas only 7% to 12% of the women smoked. The prevalence of heavy smokers, as defined by subjects who smoked ≥21 cigarettes/d, was highest in younger men (age 30 to 39 years). At the opposite end of the spectrum, the prevalence of quitters was highest in the elderly. For women, the prevalences of heavy smokers and of ex-smokers were relatively low. The drinking rate was also higher in men than in women.

Means and SDs or frequencies of selected variables by smoking habit at baseline are shown in Table 1. Among the smoking categories, the mean BMI was the highest in nonsmoking men, whereas among women, moderate smokers (≤20 cigarettes/d) had the highest BMI. SBP was significantly different among the smoking categories for both men and women: for both sexes, ex-smokers had the highest mean SBP. Serum total cholesterol significantly differed among smoking categories for men; however, the absolute differences among the categories were small.

Table 2 shows the number of deaths and age-adjusted death rates per 100 000 person-years of observation for all causes of death and cause-specific deaths according to smoking habits and sex. The mean follow-up period was 13.2 years; in total, there were 118 044 person-years of observation and 1112 deaths occurred during this period for men and women combined. Approximately one third of all deaths were CVD-related. The numbers of deaths from stroke and from heart disease were very similar. The mean ages (±SD) of stroke death cases were 76.9 (±10.9) and 77.3 (±11.2) years for men and women, respectively. Among the stroke subtypes, the incidence of cerebral infarction death was almost double for both men and women than that of hemorrhagic stroke death. The incidence of IHD death was almost one third that of total heart disease death in both men and women.

Table 3 shows the multivariate-adjusted relative risks of death from all causes and for CVD-specific death according to smoking habit. These relative risks were adjusted for age, SBP, BMI, serum total cholesterol, drinking habit, and diabetes mellitus.

For all causes of death, the adjusted risks of daily smokers for both men and women were 14% to 55% higher than those of nonsmokers, and the relative risk for male heavy smokers was 1.55 (95% CI, 1.17 to 2.04). For CVD death, ≈50% to 100% increase in risk was observed in male smokers compared with male nonsmokers, which was statistically significant. The relative risk of CVD death in female smokers was ≈40% to 135% higher than in female nonsmokers, although significance was borderline.

For all stroke death, the relative risks for male moderate and heavy smokers were 1.60 (95% CI, 0.91 to 2.79) and 2.17 (95% CI, 1.09 to 4.30), respectively, whereas that for ex-smokers was 1.56 (95% CI, 0.84 to 2.90). The relative risk of cerebral infarction for men was higher than that of all strokes: 3.06 for ex-smokers, 2.97 for moderate smokers, and 3.26 for heavy smokers compared with nonsmokers ($P<0.05$ for all). For women, the relative risk for stroke death for heavy smokers was significantly higher (relative risk [RR], 3.91; 95% CI, 1.18 to 12.90) than that for nonsmokers; however,

TABLE 1. Distribution of Selected Risk Factors (Mean±SD or Percentage) by Smoking Habits at Baseline in 1980, NIPPON DATA80

			Smoker		
Men	Nonsmoker	Ex-Smoker	1–20 Cigarettes/d	≥21 Cigarettes/d	Significance
No. of subjects	724	721	1536	991	
Age (y)	50.4±14.0	52.8±13.5	51.1±13.1	46.0±10.8	$P<0.001$
Body mass index (kg/m^2)	23.1±2.9	22.6±3.0	22.0±2.8	22.7±2.8	$P<0.001$
Systolic blood pressure (mm Hg)	138.1±20.7	139.8±21.2	139.3±21.3	134.8±18.7	$P<0.001$
Diastolic blood pressure (mm Hg)	84.2±11.9	84.5±11.9	83.3±12.7	82.3±11.9	$P<0.01$
Serum total cholesterol (mmol/L)	4.86±0.82	4.94±0.90	4.69±0.81	4.87±0.85	$P<0.001$
Drinking (%)	68.1	71.9	76.7	79.4	$P<0.001$
Diabetes (%)	5.7	6.0	7.3	7.6	NS
			Smoker		
Women	Nonsmoker	Ex-Smoker	1–20 Cigarettes/d	≥21 Cigarettes/d	Significance
No. of Subjects	4421	103	398	35	
Age (y)	50.05±13.0	54.0±14.5	51.2±13.6	49.7±13.7	$P<0.01$
Body mass index (kg/m^2)	22.9±3.3	22.9±3.7	22.3±3.7	23±3.0	$P<0.05$
Systolic blood pressure (mm Hg)	133.2±21.2	139.3±25.4	133.2±21.4	133.7±24.0	$P<0.05$
Diastolic blood pressure (mm Hg)	79.5±11.8	80.1±11.4	78.5±12.5	80.4±13.6	NS
Serum total cholesterol (mmol/L)	5.14±0.88	5.07±0.92	4.93±0.87	5.09±0.87	NS
Drinking (%)	17.3	38.8	41.0	60.0	$P<0.001$
Diabetes (%)	3.9	7.8	3.3	11.4	$P<0.05$

P values are of ANOVA or χ^2 test.
Diabetes was defined as a nonfasting serum glucose level ≥11.1 mmol/L, a past history of diabetes, or both.

moderate smokers had a 42% higher risk of stroke death, although this was not statistically significant. Smoking was not associated with hemorrhagic stroke in either men or women, even in heavy smokers.

For all heart disease, the relative risk of death gradually increased in men from ex-smokers (0.98) to moderate smokers (1.40) to heavy smokers (2.15) ($P<0.05$). Similarly, the risk of IHD-associated death for men also showed a graded increase from ex-smokers (1.00) to moderate smokers (1.56) to heavy smokers (4.25) compared with nonsmokers ($P<0.05$). The relative risk of IHD-associated death in women was higher in smokers than in nonsmokers, but this was not statistically significant.

Discussion

In the present study, we demonstrated that smoking is an independent risk factor for stroke death in both men and women. The graded association was clearly evident for both cerebral infarction and IHD death as well as for total CVD death. In addition, our study results showed that heavy smoking in women is also a risk factor for all stroke death. These findings reveal a recent trend among Japanese smokers, because the NIPPON DATA80 was the first follow-up study for a representative Japanese population randomly selected throughout Japan. Therefore, the death rate and cause-specific death determinations made in this study represent the actual figure in Japan.

Both 12-year and 20-year follow-up studies of the Honolulu Heart Program involving Japanese Americans living in Hawaii showed smoking to be a risk factor for cerebral infarction and for hemorrhagic stroke.[4,14] These findings combined with those of the present study have led us to conclude that smoking is a risk factor for stroke in Japanese people.

Previously, some cohort studies in Japan revealed smoking to be a risk factor for IHD, but they failed to demonstrate a convincing association between smoking and all strokes, hemorrhagic stroke, or nonhemorrhagic stroke.[5,6] It was puzzling that these studies did not show smoking to be a risk factor for stroke in Japan. One possible explanation for this result may be that associations between smoking and stroke risk are only evident in populations with moderate or high levels of serum total cholesterol. Recent changes in lifestyle and environmental conditions in Japanese people have caused an increase in fat consumption.[10] In 1965, the per-capita energy intake from fat in Japan was ≈15% according to the National Nutrition Survey.[10] This figure is now 26% overall and close to 30% for the younger generation.[11,15,16] Additionally, a gradual change in the occurrence of stroke subtype has occurred; that is, the number of deaths from hemorrhagic stroke has decreased sharply since ≈1965, and at present it is only one third of the total number of cerebral infarction-associated deaths.[16–18] Individuals who smoke are much more susceptible to cerebral infarction or lacunar stroke than to hemorrhagic stroke.[18,19] Therefore, in previous Japanese cohort studies, which were performed in a population with low cholesterol, a high mean blood pressure, and a relatively high occurrence of hemorrhagic stroke, an association between

TABLE 2. Number of Deaths and Age-Adjusted Death Rates per 100 000 Person-Years for All-Cause and Cardiovascular Disease Deaths According to Smoking Habit in Japan During 1980–1990, NIPPON DATA80

			Smoker		
Men	Nonsmoker	Ex-Smoker	1–20 Cigarettes/d	≥21 Cigarettes/d	Total
Person-years of observation	9245	9280	19 911	13 159	51 774
No. of deaths (age-adjusted death rate)					
All-cause	108 (777.1)	129 (883.0)	256 (944.0)	115 (1145.6)*	608 (954.3)
Cardiovascular diseases	37 (249.8)	42 (295.6)	99 (366.8)	40 (436.9)*	218 (346.5)
All stroke	18 (119.3)	25 (173.0)	50 (186.8)	19 (209.6)	112 (178.3)
Infarction	7 (46.6)	17 (118.9)*	31 (117.0)*	8 (113.8)	63 (121.7)
Hemorrhagic	10 (64.2)	6 (41.3)	8 (28.6)	4 (38.2)	28 (43.3)
Others	1 (4.9)	2 (32.5)	11 (31.5)	7 (32.4)	21 (27.3)
All heart disease	17 (116.8)	17 (122.6)	43 (159.6)	21 (227.3)*	98 (156.1)
Ischemic heart disease	5 (34.1)	6 (46.8)	12 (44.3)	13 (116.9)*	36 (56.3)
			Smoker		
Women	Nonsmoker	Ex-Smoker	1–20 Cigarettes/d	≥21 Cigarettes/d	Total
Person-years of observation	59 267	13 333	5215	455	66 270
No. of deaths (age-adjusted death rate)					
All-cause	421 (543.9)	20 (687.4)	58 (725.6)	5 (748.6)	504 (559.2)
Cardiovascular diseases	159 (203.8)	8 (252.2)	24 (286.3))	4 (602.3)	195 (216.7)
All stroke	73 (94.8)	5 (160.6)	10 (119.1)	3 (525.8)*	91 (102.1)
Infarction	34 (43.9)	3 (103.3)	6 (70.7)	1 (76.4)	44 (48.9)
Hemorrhagic	16 (20.2)	1 (28.6)	0	0	17 (18.8)
Others	23 (30.2)	1 (37.0)	4 (23.0)	2 (263.2)	30 (33.3)
All heart disease	76 (95.8)	3 (91.6)	14 (167.2)*	0	93 (102.0)
Ischemic heart disease	28 (34.9)	1 (28.6)	4 (47.0)	0	33 (35.9)

*Age-adjusted relative risk for death is significantly higher than that of nonsmoking group at the level of alpha=0.05.

smoking and stroke did not emerge. A similar situation currently exists in China. Although China has a very high smoking rate, a recent report from a cohort study in rural areas of China failed to show a significant association between smoking and stroke.[20]

Hypertension is a well known risk factor for stroke. Our data clearly show that smoking is also a potent risk factor for cerebral infarction, even in populations with moderate cholesterol levels such as those in certain Asian and other developing countries. Therefore, reducing the incidence of smoking as well as hypertension should be a high priority in attempts to overcome the increase in CVD in developing countries and for reducing the number of disabled people in most industrialized countries.

To identify cause of death, we used underlying cause of death determined by a government officer through a review of death certificates written by medical doctors. Misdiagnosis of stroke and its subtypes as well as IHD by a clinician occasionally occurred, which may have caused underestimation or overestimation of the number of cause-specific deaths. We could not validate the recorded cause of death with autopsy findings in this cohort. However, most of the stroke cases in Japan are referred to hospitals for admission and computerized tomography (CT) is performed on >90% of the admitted cases, even in rural areas.[17,21] The >9000 CT machines available throughout Japan in 1996 made this possible.[22] It has also been reported that according to autopsy studies, the death certificate diagnosis for stroke in the Hisayama and Hiroshima/Nagasaki studies were quite accurate.[23,24] Therefore, we believe that the diagnoses of stroke as well as its subtypes were mostly correct. In contrast, IHD may have been underestimated to some extent; however, Japanese people do have the lowest incidence of and mortality from IHD in the world.[7,16,25,26]

The effect of smoking on the risk of CVD may have been underestimated in our cohort study because smoking habits were identified only once at baseline by a questionnaire in 1980.[27] In addition, the lost female subjects had a higher smoking rate than those who were followed-up, and some of the individuals who smoked at baseline may have quit during the follow-up period. Because the risk of CVD after smoking cessation approaches that of nonsmokers within a few years,[2,28] the risk of CVD in smokers may have been underestimated because those who quit were still considered to be smokers in this study. Actually, the prevalence of male and female ex-smokers increased by 3.9% and 0.6%, respectively, between 1980 and 1990.[27] A similar underestimation may have occurred regarding the risk of hypertension because of an increased treatment rate for hypertension (from 12.8% to 15.6% between 1980 and 1990 in men and women combined) and regarding hypercholesterolemia for IHD