30年にわたる
日系人と日本人の
健康調査研究結果のまとめ

日本人はアメリカ日系人より健康か？

シアトル市パシフィックリム疾病予防センターと日本健康増進財団の共同研究

行方　令
（なめかた・つかさ）

日本健康増進財団リサーチフェロー
シアトル市パシフィックリム疾病予防センター元デレクター
シアトル市ワシントン大学元臨床准教授

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序にかえて

行方令博士の米国シアトル市における疫学研究の総まとめである「シアトルにおける 30 年にわたる日系人と日本人の比較健康調査報告」を、予防医学広報事業団の DVD として上梓することになったのは誠に大きな喜びである。

移民の疫学的研究は米国におけるがん死亡率の大きな人種差を究明するため、米国 NCI 生物学部長ウイリアム・ヘンセル先生が、がんという原因不明の慢性病は生活習慣と密接に関連するとして、何年もかけて生活習慣調査をベースとする症例対照研究の方法論を確立され、まず消化器がんの発生要因を日系米人と米白人、次いで、日本人との比較研究、さらに大規模な国際研究でいくつかの主要な発生要因を突き止められた。明らかになった発生要因はきわめて説得力があり、実際の予防対策の道を開かれたのである。画期的な業績であり、近代疫学研究が誕生したわけである。私はヘンセル先生の共同研究者であった故瀬木三雄東北大学教授の要請もあり、日本側の協力者として大腸がんの症例対照研究を分担し、その研究方法の科学性と斬新さに驚嘆した一人である。

その後、米国白人に高率で日本人にきわめて低い心疾患死亡率や、逆に日本人に高い脳卒中死亡率の原因究明に、Ni―Hon―San Study が計画され、1975 年には主要なリスク要因や発生機序が解明され、その後の予防対策に大きく貢献したことは周知である。

行方博士はこの Ni―Hon―San Study に刺激され、担当した地域の米国シアトル市ではどのようになっているかの研究を計画された。1986 年のことである。日本の疫学の権威や日本健康増進財団の協力を得られ、新しい検査法を多く取り入れ、綿密な計画を立てられ、シアトル市の住民の大きな協力を得て、1989 年研究はスタートした。多くの研究者が長年にわたり協力を惜しまなかったのは行方博士のお人柄もあったと思う。ご苦労続きであつたと思うが、多くの難関を突破され、次々に業績を発表され、30 年かかり目的を達成された。定年退職の時期を迎えられ、日本健康増進財団前専務理事、鈴木賢二特別顧問とともに、この偉業を日本語でまとめられた。副題は、「日本人の健康に、アメリカからのメッセージ、シアトル日系人健康調査からの教訓　～見えてきた将来の日本人の健康像～」とされた。行方博士の業績は逐年紹介されていたが、こうしてまとまった読み物となると、誠に素晴らしく、広く日本の若手の疫学者に読んでもらいたいと思っていた。たまたま私がお送りした当事業団の DVD、玉腰暁子北大教授の編集になる「JACC Study これまでの成果とあゆみ」、これは日本疫学会会員が協力した 13 万人余の大規模ながんコホート研究の 30 年間の成果のまとめであるが、これを見られて、シアトルの成果をこうした DVD で残せないかとの相談を寄せられた。事業団の役員会に諮り、全員一致の承諾を得た。改めて、行方先生に新しく編集していただき、行方先生の共同研究者の承諾も得られたので、この DVD が出来上がったのである。

行方博士は新潟大学教育学部を卒業後、東京大学大学院健康教育学科で修士、博士課程を終了後、米国イリノイ大学で Ph.D.を取得され、イリノイ大学の公衆衛生学部で環境疫学を研究、ワシントン州シアトル市、パテル記念研究所で疫学研究、1989 年

からシアトル市パシフィック・リム疾病予防センター所長となられ、この健康調査に専心された。研究経過と成果の詳しい内容は、列挙された英文論文に詳しいので、ぜひこれも参考にしていただきたい。

私が行方博士を知ったのは、1987 年、日本で開催された國際シンポジアム“The International Conference on Indoor Air Quality”の機会である。私は会長の故春日斉先生から Epidemiology of Passive Smoking and Lung Cancer という session の司会を依頼された。同時に学会から Co-chairman として行方先生が推薦された。当時はこの passive smoking 説は、国際的にはまだ認められていない時代であり、難しい問題であった。会議では案の定、故平山雄先生らの研究成果に対して、世界から集まった疫学の権威者から忌憚のない意見と、鋭い批判が相次ぎ、議論をまとめるのは容易ではなかった。行方博士はすでに第 10 回 IEA 総会で大気汚染と健康障害についての workshop で座長を務め、その記録も著書として発刊されておられたこともあり、こうした論議をうまくバランスを取られ進行を助けられた。おかげで無難なまとめにもってゆくことができた。その後、各国での研究が進み、passive smoking は広く認められることになった。私は行方博士の力量と人柄に感じ、その後研究情報の交換を続けることになった。そして、シアトルでの活動を知ったわけである。これには東大名誉教授故前田和甫先生のお陰によるところも大きい。

この DVD が多くの疫学者の目に触れ、参考になることを期待している。

また、この DVD の内容は、行方博士のシアトルのホームページに載せられるが、日本では名古屋大学予防医学教室のホームページで閲覧できる。

令和 4 年 3 月

予防医学広報事業団理事長　　青木國雄

青木國雄

1928 年 7 月 28 日名古屋市で出生

1952 年	名古屋大学医学部卒業 医学博士(名古屋大学)　Diploma（米国ペンシルベニア大学予防医学・公衆衛生学部）FFPHM（英国王室医師協会）
1976 年	名古屋大学医学部教授 予防医学講座主任 医学部長兼任（1987～1989）
1990 年	愛知県がんセンター総長（4 年間）その後複数の公的医療機関役員を務める
研究領域	疫学　予防医学　社会福祉　その他
受賞	日本結核病学会今村荒男賞　日本癌学会長与又郎賞　日本疫学会功労賞　荒記俊一賞(社会医学振興財団)　中富健康科学振興賞　中日文化賞　東海テレビ文化賞　保健文化賞　Certificate (国際際対がん連合)　叙勲：瑞宝中綬賞　その他
役員	国際疫学学会理事・理事長・会長　UICC(国際対がん連合：がん予防プログラム委員長、理事)16 年間　WHO がん専門委員会顧問　日本学術会議専門委員会委員　放射線影響研究所評議員（広島）　その他
名誉称号	名古屋大学名誉教授　愛知県がんセンター名誉総長　愛知医科大学客員教授　名古屋市社会福祉協議会名誉理事長　国際疫学会名誉会員　中国医科大学顧問教授・予防医学基地名誉理事長　中国本鋼総医院顧問　国内学会名誉会員(日本結核学会、日本癌学会、日本公衆衛生学会、日本衛生学会、日本肺がん学会、日本胸部疾患学会、他)　同功労会員（日本老年学会、日本医学史学会、他）

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シアトル市ダウンタウンの風景

レニア山（ワシントン州）

広島城

富士山

行方　令

（なめかた・つかさ）

日本健康増進財団リサーチフェロー
シアトル市パシフィックリム疾病予防センター元デレクター
シアトル市ワシントン大学元臨床准教授

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はじめに

令和2年（2020年）6月

行方　令

荒井親雄先生に診断していただきました。心臓踝血管弾性指標（CAVI）についての解析と論文作成にはCAVI研究の第一人者である白井厚治先生に多大なるご指導を賜りました。シアトルにおける胃がんリスク要因の研究においては三木一正先生と渡邊能行先生にピロリ菌とペプシノゲン検査の便宜を計っていただき、親身な研究指導を受けました。また、本研究に一貫して注目し激励していただいた元国立公衆衛生院長・元東京大学教授高石昌弘先生及び元日本疫学会長・元国際疫学会長である名古屋大学名誉教授青木國雄先生に厚くお礼申し上げます。他にも多くの方々のご協力をいただき心より謝意を表する次第です。

アメリカの日系人の健康問題に興味を持ったのは、1975年にAmerican Journal of Epidemiology に発表されたサイム（Syme）とマーモット（Marmot）らのNi-Hon-San Study（日本、ホノルル、サンフランシスコに住む日本人と日系人の男性の比較研究）を読んだことがきっかけです。結論として、虚血性心疾患（狭心症と心筋梗塞）の有病率は広島の日本人男性、ホノルルの日系人男性、サンフランシスコの日系人男性の順に高く、アメリカ本国に近いほど多くなりますが、シアトルの日系人はどうなのかという疑問を持ちました。

そこで、1986年から準備を進め、訪日の機会に日本人の国民性に関する国際比較研究を長年やられている文部科学省統計数理研究所元所長の故林知己夫先生にお会いし、日本健康増進財団の鈴木賢二氏を紹介していただきました。全面的な研究協力が得られることになり、この財団と同じにシアトル日系人の健診を行い、財団の健診データと比較できるようにプランを立てました。こうして、30年間にわたる研究を遂行することができた次第です。研究論文は多くが英文の学術誌に公開しましたので、一般の人たちに分かりやすく書くことを勧められ、8回のシリーズで日本健康増進財団の機関誌「いきいき健康だより」に掲載し、このようにまとめることができました。

多くの方々から研究協力をいただきました。鈴木賢二氏には共同研究者として最初から最後までお世話になり、日本人データを日系人データと比較できるように整理していただきました。シアトルではワシントン大学のエドワード・ペリン教授と故ロバート・ノップ教授の協力を得て、質的検査基準を満たしたラボでリピッドや血糖値を測定しました。アメリカでは眼底網膜写真から細動脈硬化を正確に診断できる専門家がいないため、シアトルの眼底写真を日本に送り、眼底写真を読影されている

日米国際比較研究にご協力して

令和2年（2020年）6月

一般財団法人日本健康増進財団前専務理事（現特別顧問）

鈴木　賢二

行方令博士には、1986年、当財団の理事でもある文部科学省統計数理研究所元所長故林知己夫博士が連れて来られて初めてお目にかかりました。

その際、アメリカ在住日系人の健康状態は日本在住日本人の10年後の健康状態を示しているのではないかと話され、シアトル在住日系人の健康調査を当財団の健診同様に行い、比較することでこれを明らかにできるのでないかと、そんな貴重な国際比較研究に、当財団が参画できることに大変興奮したことを記憶しています。その場で、常勤役員同席の元、ご協力すること、私が担当することを約しています。

その後、㈱フクダ電子や㈱キヤノンの協力が得られ、血管機能（動脈硬化）を測る大動脈脈波速度（PWV）計測装置と眼底細動脈が観察できる無散瞳眼底カメラを無料で提供してもらえるようになります。また、米国疾病予防研究センターから血液検査の質的管理を定期的に受けているワシントン大学リピッド・リサーチクリニック（シアトル）から血清検体を送ってもらい、シアトルでの測定値と当財団の測定値を比較し、相違のあるものは日本の検体検査センターにおいて種々調整を行い、再度血清検体を送ってもらい正確さを確保しています。ほかに、PWV検査は測定に熟練を要するため、当財団で健診に携わっていた故高橋美月臨床検査技師がシアトルに行くなど、健診をする準備が整い、検査の読影・判定には故長谷川元治博士（当時、東邦大学医学部生理機能学教授）や荒井親雄博士（同・助教授）、安部信行氏（同・中央検査部技師長）らの協力が得られ、1989～1994年の調査期間で1、466名の健康調査が実施されました。これに当財団の健診データを比較した解析が行われ、日米での学術活動（本文第1～5回）となります。さらに、当財団のCAVI（PWVを進化させ、血圧により依存しない動脈そのものの硬さ・しなやかさを測定）健診データを用いての研究（第6回）では白井厚治博士（当時、東邦大学医学部佐倉病院長）の協力が得られるなど研究が進められています。

こうして、シアトルでの日米国際比較研究の土台ができ、栄研化学の協力もあって、ピロリ菌の研究（第7、8回）に繋がっていきます。

この30有余年で素晴らしい研究成果が得られたものと確信しています し、これらの貴重な知見を日本の皆様やアメリカ在住日系人の皆様の健康管理、疾病予防にお役立ていただくために、分かりやすくご紹介できたと考えています。

日本人の健康に、アメリカからのメッセージ
シアトル日系人健康調査からの教訓
～見えてきた、将来の日本人の健康像～

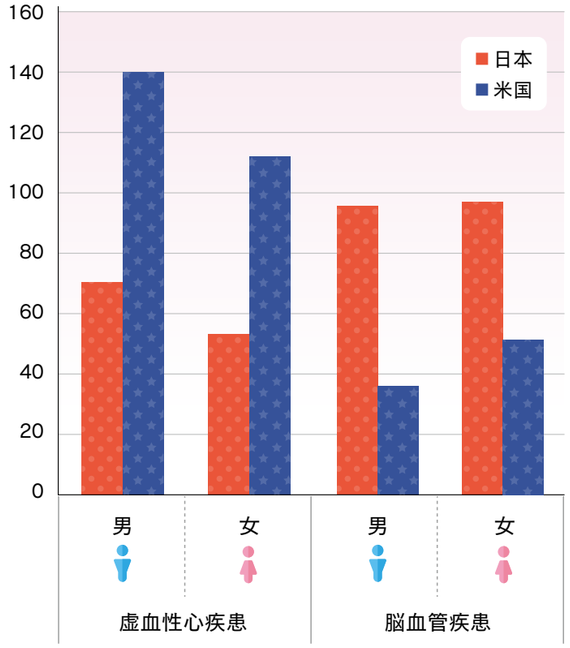
1971年8月以来アメリカで生活していて、多種多様な人種が共存し、自分自身が日本人であることから、外見は日本人と変わらない日系人の健康状態は日本人と変わらないのだろうかとの疑問をもっていました。日系人の人口は、白人やアフリカ系アメリカ人（黒人）と比べて極めて少なく、国の健康指標統計には記載されません。そこで、日系人を含むアメリカ人全体と日本人の死亡率を比較し、日系人の健康状態、ひいては日本人の健康問題を明らかにしようと試みました。ただし、ここで描き出されるのは単なる日米の健康状況の違いではありません。生活の多方面で欧米化が進む今日、「日系人の今の健康問題」は、近い将来の日本の姿なのかもしれないのです。

1 発端
～虚血性心疾患と脳血管疾患、その日米の違い

虚血性心疾患は、冠動脈が動脈硬化によって狭窄し、心臓の筋肉への酸素と栄養の供給が絶たれ、心臓が正常に機能しなくなる病気です。心筋梗塞を起こすと、最悪の場合、心臓が停止し、救急処置が遅れると死に至ります。最近の死亡統計（日本は2012年、米国は2010年）を比較すると、人口10万人に対して日本の男性は70・9人、アメリカの男性は139・8人と2倍、日本の女性は112・4人と、52・7人、アメリカの女性は1やはり2倍以上です。

脳血管疾患は、脳出血（29％）、くも膜下出血（11％）、脳梗塞（58％）などの総称です。脳出血は高血圧の人に起こりやすく、脳内血管の一部が破れて出血し、脳実質を圧迫、破壊し、片麻痺や意識障害などの重篤な症状が出現し、死亡に至ることが多い病気です。くも膜下出血は脳底部の動脈瘤が破裂して、脳を包んでいるくも膜下腔に出血するもので、突発的に起こり、突然死に至ることが多い。脳梗塞は脳動脈の動脈硬化が進行し、内径が狭くなり、血流が滞り、血栓ができて内腔が閉塞するか、脳以外から動脈硬化部の血栓が運ばれてきて細い脳動脈を塞ぐために片麻痺、意識障害、言語障害などの症状が現れ、脳血管疾患の中で最も死亡数が多く、60％近くを占めます。戦後日本中で行われた減塩運動のお蔭で高血圧患者が減少し、脳出血の死亡率が画期的に減少しましたが、まだ米国に比べて日本人の脳血管疾患死亡率は2倍です。なぜ日本人の脳血管疾患の死亡率がこれほど高いのか、血圧以外に日本人特有のリスク要因が存在するのではないかと考えてきました。

図1　心・脳血管疾患の死亡率の日米比較（人口10万対）

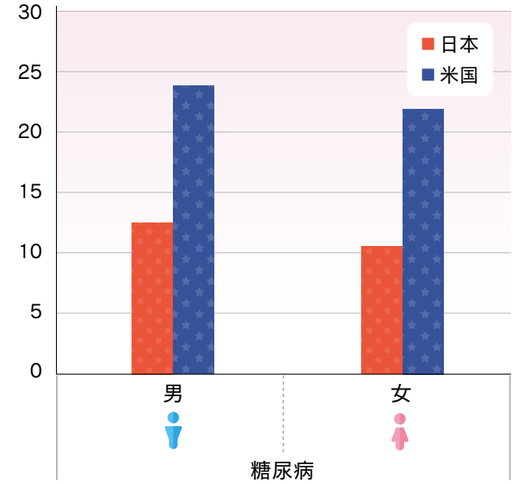


注）日本の死亡率は 2012 年、米国の死亡率は 2010 年であり、
国民衛生の動向 2014/2015 の第 17 表：死亡の国際比較から引用。

2 糖尿病や肺がん、胃がんにも有意な日米差が

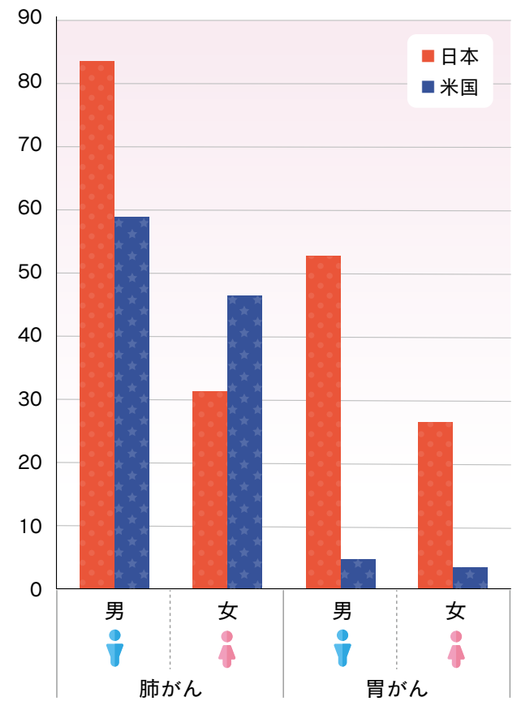
図2は糖尿病による死亡率の比較ですが、男女ともアメリカ人の死亡率が日本人の2倍です。糖尿病患者の大部分は成人に発病する2型ですし、食事とライフスタイルが大きく影響します。アメリカではカロリーの摂り過ぎと運動不足のため肥満となり、糖尿病にな

図2　糖尿病の死亡率の日米比較（人口10万人対）



注）日本の死亡率は 2012 年、米国の死亡率は 2010 年であり、
国民衛生の動向 2014/2015 の第 17 表：死亡の国際比較から引用。

図3　肺がんと胃がんの死亡率の日米比較（人口10万人対）



注）日本の死亡率は 2012 年、米国の死亡率は 2010 年であり、
国民衛生の動向 2014/2015 の第 17 表：死亡の国際比較から引用。

る人が多い。日本人も生活が欧米化するにつれて糖尿病が増えると予測されました。

図3は、日本人に多い肺がんと胃がんの死亡率を日米間で比較したものです。男性の肺がん死亡率は人口10万人に対して日本人が84人、アメリカ人が59人で、日本人男性の高い喫煙率の影響によります。女性はアメリカ人女性の高い喫煙率が影響して、その死亡率（46・1）は日本人女性（31・2）より高い。一方、胃がんの死亡率は男女とも日本人がアメリカ人より顕著に高い（男性52・5対4・5、女性26・2対3・1）。このような大きな違いは何故生じるのか、研究者として大変興味をそそられる疑問であり、日系人研究を通じてある程度解明できたと思っています。

なお、両国の死亡率の傾向は研究を始めた1980年代の後半から減少していますが、変わっていません。

3 シアトル在住の日系人との比較研究

シアトルの日系人研究を始める前に、日本人と他国の国民性を数10年にわたって調査研究してきた文部科学省統計数理研究所 所長・故林知己夫博士に1986年に相談したところ、すぐに日本労働文化協会（現日本健康増進財団）を紹介され、現在専務理事の鈴木賢二氏に面会、シアトルでの調査研究への協力を依頼したところ、全面的に協力する旨の承諾が得られました。

日本人とアメリカ人の死亡率の違いは、人種的（遺伝的）な差異と環境要因（食生活やライフスタイルを含む）の差異が考えられます。したがって、日本人集団とアメリカ人集団（白人や黒人を含む）を比べても、人種的な要因による影響を取り除くことはできません。日系人はアメリカに明治時代から移民した日本人を祖先とする二世・三世が大多数を占め、シアトルでの研究対象を日系人に絞れば、日本人と日系人の健康指標の違いは環境要因の違いに帰することができます。日本人の食事や生活が今後ますます欧米化することを考えると、日系人の研究結果を見ることによって、将来の日本人像が予測できることになります。

シアトルでの日系人と日本人の比較研究を始めるのに、次の疑問に答えられるよう設定しました。

(1) 日系人のコレステロールなどの脂質レベルはアメリカ人全体や日本人と比べて高いのか、低いのか。
(2) 日系人の大動脈の動脈硬化は日本人より年齢的に早く進行しているのか。
(3) 日系人の細動脈の動脈硬化は日本人より年齢的に早く進行しているのか。
(4) どのような要因が動脈硬化の進行に影響しているのか。
(5) 日系人の虚血性心疾患に影響している要因は何か。

4 日米間で検査結果の精度管理に

このような調査を行うには周到な準備が必要となります。

第一に、シアトル市とその周辺を含むキング郡に住む日系人を把握し、協力をお願いします。公表されている日系の団体会員の住所録と電話帳からその住所と電話番号を抜き出し、基本台帳を作成、全員に手紙を出し、研究対象となる方のお名前と連絡先、性・年齢を記入してもらい、研究対象者を無作為に抽出しました。

第二に、日本健康増進財団の健診データと比較するため、同じ検査機器を備えた健診施設を必要とします。健診施設はシアトル市で最初の日系女医である故ドクター・ルービー・イノウエ氏のクリニックを、健診ができるように改装しました。動脈硬化度を測る大動脈脈波速度（PWV）計測装置と眼底細動脈を観察できる無散瞳眼底カメラはそれぞれ㈱フクダ電子と㈱キヤノンから無料で提供していただくことができました。

第三に、血液検査によるコレステロールなど脂質測定値の質的管理を、日米間で如何にするかも難問でした。シアトルのワシントン大学リピッド・リサーチクリニックは米国疾病予防研究センター（国の機関）から脂質測定値の質的管理を定期的に受けているので、その正確さが保証されています。日系人の血液検査はそこで測定することができました。日本人の健診をしている日本健康増進財団の脂質測定が正確であることを確認するため、シアトルから血清検体を送って測定し、シアトルであらかじめ測っていた数値と比較、相異のある測定項目は財団側で検査方法の調整をし、再度血清検体を送って測定値が正確であることを確認しました。PWVの測定は熟練を要するため、財団で健診に数年携わってきた臨床検査技師をシアトルに呼び、その健診を担当してもらいました。

少し説明が長くなりましたが、このような手順を踏まないと信頼できる結果が得られないことを強調したかったからです。疫学研究で2集団を比較するには、同じ計測装置と測定方法を用いて同じ基準で測定し、はじめて比較が可能となります。シアトルでの研究に参加した日系人は男性724名（日系人人口の12・7％）、女性742名（日系人人口の10・3％）でした。

次回は、動脈硬化に影響する脂質の測定値を、日本人と日系人及びアメリカ人全体と比較した結果をご紹介します。

日本人の健康に、アメリカからのメッセージ

動脈硬化の原因といわれる血清脂質値を日米で比べると…？

研究を開始した時には、血清脂質についてシアトルの日系人と日本在住の日本人を比較するつもりでいましたが、日本人全体とアメリカ人全体を代表する調査データが存在し、すでに公表されていることが分かったため、これらのデータも加えて4集団を比較することにしました。

前回、血清脂質の測定値の精度チェックは、シアトルの日系人と日本健康増進財団の両方で実施したことにふれましたが、アメリカ人と日本人を代表する測定値も質的管理がなされており、その結果は信頼できることを確認しました。

表1は、4集団の調査期間と調査参加者数を示します。アメリカ人全体と日本人全体の意味は、無作為抽出によって選ばれ、アメリカ人と日本人を代表している集団だということです。

1 コレステロールと動脈硬化の関連

調査結果を示す前に、コレステロールと動脈硬化の関連を説明して、なぜ日系人と日本人の比較が重要なのか、理解の一助にしたいと思います。

人間の血液中には「脂質」と呼ばれる、水に溶けにくい物質があり、脂質の主なものには、コレステロール、中性脂肪（トリグリセライド、略してTG）、リン脂質、コレステロールエステル、遊離脂肪酸などがあります。水に溶けにくい脂質は血液中でリン脂質や遊離コレステロールと結合し、さらにたんぱく質を結合させて親水性（水に溶けやすい）のリポ蛋白複合体を作ります。リポ蛋白をつくっている蛋白質はアポリポ蛋白と呼び、ほとんどの脂質はアポリポ蛋白と結合し、リポ蛋白の形で血液に溶けて運ばれます。リポ蛋白のなかで低比重のものをLDLコレステロールと呼び、高比重のものをHDLコレステロールと呼びます。

コレステロールは細胞膜を形成するために不可欠な物質であり、コレステロールが体内にまったくなかったら、生存できないことになります。問題は余分のコレステロールを体内で適切に処理できるかどうかです。このコレステロールの処理能力に大きな個人差があり、体内にLDLコレステロールが過剰に蓄積されると、長い年月の間に動脈管壁に侵入して血管を狭くし、血液の通りを悪くする「動脈硬化」という状態を引き起こします。これが冠動脈で生じると、冠動脈に血液が流れにくくなり、一時的に心筋への血液供給が不足し、胸痛発作などの症状を呈する狭心症となります。心筋梗塞はプラークと呼ばれるコレステロールや細胞成分を含む柔らかい部分が血栓となり、狭くなった冠動脈を塞ぎ、心筋に酸素の供給が絶たれるために心筋が壊死する状態で、手当てが遅れると死に至ります。

表1　血清脂質の比較集団

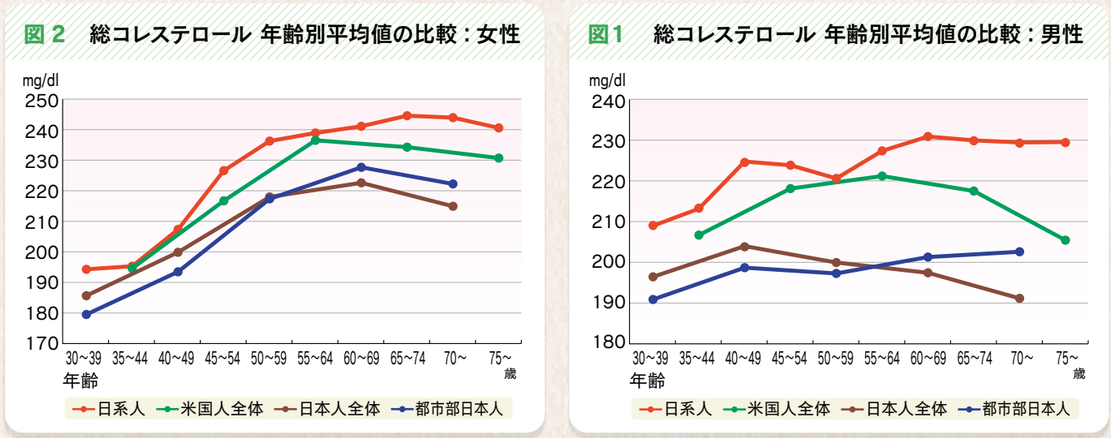
対象集団	調査期間	調査参加者数
シアトル日系人（パシフィック・リム疾病予防センターでの健診受診者）	1989～1994	1,466
アメリカ人全体（米国疾病予防センターの調査）	1988～1991	5,475
日本人全体（厚生労働省による調査）	1990	7,906
都市部日本人（日本健康増進財団での健診受診者）	1989	146,782

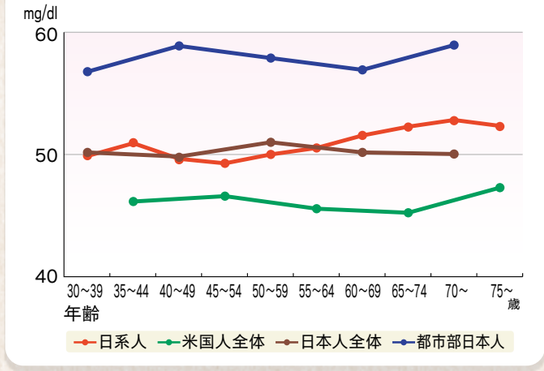
2 総コレステロールの比較

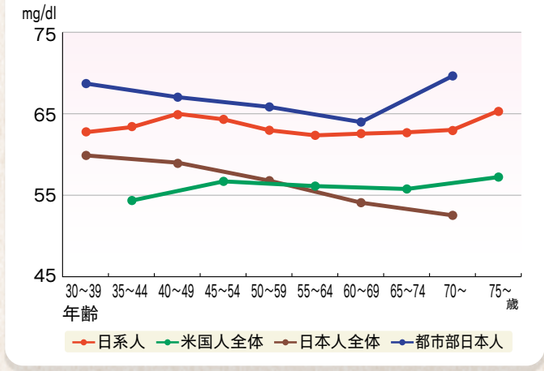
総コレステロールは、すべてのコレステロールの分子を含みますので、LDL、HDL、VLDLなどから成ります。高いほど動脈硬化を促進させると考えられています。**図1**は**表1**の4集団の男性総コレステロール平均値を年齢別に比較したものです。女性については**図2**をご覧ください。男女ともにシアトル日系人が最も高く、2番目にアメリカ人全体が高く、日本人全体と都市部日本人は最も低くなっています。この結果から、総コレステロール値は人種によって決定されるのではなく、住む環境、すなわち食生活やライフスタイルの影響に左右されることが分かります。日本人がアメリカに移住してアメリカの生活習慣になれて、食生活も肉食中心になった場合には、総コレステロール値がアメリカ人より高くなることを示しています。

男性においては、日系人と都市部日本人で加齢とともに総コレステロール値が上昇する傾向にありますが、米国人全体は凸型であり、日本人全体は40歳代以降加齢とともに下がる傾向にあります。一方、女性においては、すべての集団で総コレステロール値が加齢に伴って急上昇する傾向にあります。女性の場合、40歳代から女性ホルモンであるエストロジェンが減少し、50歳代から閉経し、エストロジェンがコレステロールの上昇を抑制する効果が薄れる結果、中高年からすべての集団において女性の総コレステロール値は男性より高くなっています。従って、女性は50歳以降動脈硬化関連疾患のリスクが徐々に高くなることを認識する必要があります。

米国コレステロール教育プログラムのガイドラインでは、総コレステロール値200㎎／dl以下を正常、201～239㎎／dlを境界線で要注意、240㎎／dl以上を異常としています。日本動脈硬化学会では、2017年4月に従来の血清脂質の診断基準を見直し、総コレステロールを診断基準から外しましたが、これは総コレステロール値だけを見てコレステロールを下げる薬を処方するのではなく、LDLとHDLコレステロール値や







3 中性脂肪の比較

中性脂肪値などの測定結果から判断して、治療薬を処方することを提案してのことです。総コレステロールの意義を無視している訳ではないことを強調しておきます。

図3は、男性の中性脂肪の年齢別平均値を4集団で比較した結果です。図4は、女性の結果を示します。男性においては、日系人、日本人全体、都市部日本人の中性脂肪値が40～49歳の年齢層でピークを示し、50歳以降減少傾向にありますが、米国人全体では45～54歳の年齢層でピークとなり、それ以降減少し、日系人より低くなっています。

女性は、日系人と米国人全体の中性脂肪における年齢別平均値のパターンが総コレステロール値のパターンと酷似しているのに対し、45歳以降日本人全体と都市部日本人の平均値は、日系人と米国人全体の平均値より一貫して低くなっています。特に注目されるのは、都市部日本人の年齢別平均値が日本人全体より20㎎／dl以上低いことです。これは都市部日本人の集団は都市部で働き、日本健康増進財団による健診の受診者であり、農村部等を含む日本人全体に比べて健康集団であることを反映しているものと考えられます。

4 HDLコレステロールの比較

図5と図6は、善玉コレステロールと呼ばれるHDLコレステロールの年齢別平均値を男女別に4集団間で比較したものです。HDLコレステロールが他の脂質と異なる特質は、加齢の影響を受けないことです。HDLコレステロールは、体内での余分の悪玉コレステロールを処理する重要な機能をもっているので、加齢とともに上昇してくれれば歳をとっても動脈硬化はそれほど進展せず、動脈硬化性疾患の発症も抑えられるのですが、現実はそうならず残念なことです。男性については、都市部日本人が最も高く60㎎／dl近くであり、最も低い集団は米国人全体で約45㎎／dlです。中間に日系人と日本人全体が位置し、50㎎／dl前後です。

女性については、各集団のHDLコレステロール平均値は、男性より5～10㎎／dl程度高くなっています。この男女差は、前回の図1で示した虚血性心疾患死亡率の男女差（男性が女性より高い）に反映されています。HDLコレステロール値が最も高いのは都市部日本人で64～70㎎／dlであり、2番目に高い集団は日系人女性で62～65㎎／dlです。最も低い集団は、日本人全体と米国人全体で53～60㎎／dlです。

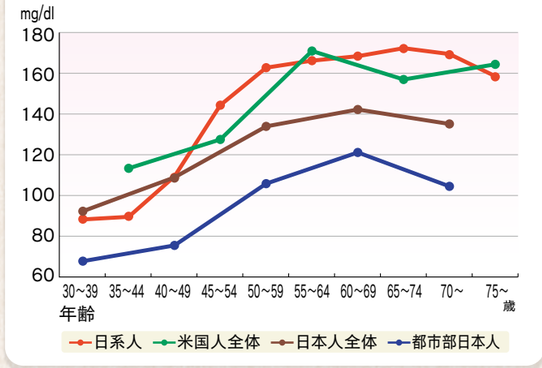
日本人を代表する日本人全体、3番目がシアトルの日系人、4番目がアメリカ人を代表する米国人全体と判断されます。シアトルの日系人女性については、総コレステロール値と中性脂肪値が4集団中最も高いのですが、善玉であるHDLコレステロール値が2番目に高く、すべての年齢層で65㎎／dlか、それに近いので、動脈硬化の程度は日本人全体に近いと推察されます。

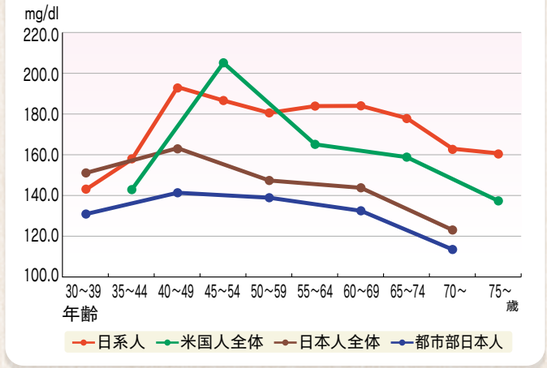
血清脂質に関しては、日本人が他の人種より遺伝的に優位であるわけではなく、住む環境、すなわち食生活とライフスタイルに大きく左右されます。日本人の食生活が欧米化し、車社会になり、運動不足になれば、総コレステロール値と中性脂肪値は上昇し、加えて善玉であるHDLコレステロール値が下がり、その結果動脈硬化が進展することになるので、上記のような欧米化を避けるなど、健康生活を維持するために十分注意してほしいと願っております。

次回は、具体的にどのような要因が血清脂質に影響しているのか、研究結果に基づいてお話します。

5 血清脂質の比較結果から、どの集団が最も健康といえるのか

これまでの血清脂質による比較結果から、最も健康な集団は都市部日本人、2番目は全国の





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どのような要因が血清脂質のレベルに影響しているのか

前回は血清脂質のレベルが日系人、アメリカ人全体、都市部の日本人、日本人全体で比べて、大きな差が見られたことを説明しました。日系人男性710名と女性728名、それに日本健康増進財団で健診を受けた都市部日本人男性3、833名を対象にして、それら集団の血清脂質レベルがどのような個人特性やライフスタイル要因によって影響を受けているのか、調べてみました。

1 統計解析方法

研究結果を理解していただくために、統計解析方法について大まかに説明いたします。用いた手法は重回帰分析といいます。総コレステロールを例にとると、総コレステロール値（Y）を推定する式は次のようになります。

$Y=b_1X_1+b_2X_2+b_3X_3\cdots+b_{10}X_{10}+b_0$

X_1～X_{10}は説明変数（独立変数）といいますが、私どもの研究ではX_1から順番に、年齢、BMI（体重kg÷［身長mの2乗］で算出される肥満の指標）、血圧降下剤の服用の有無（服用者は高血圧保持者）、飲酒習慣なしを基準にして週1ドリンク以下、週1～6ドリンク、1日1～2ドリンク、1日3～5ドリンク、5ドリンク以上（1ドリンクは純アルコールに換算して10gに相当する）、非喫煙を基準にして現喫煙、前喫煙の計10変数から目的変数（従属変数）である総コレステロール値Yを推定します。Xの前に付いているb_1～b_{10}を偏回帰係数といいますが、b_0は残差といい、これの2乗和を最小にする方法が採られます。日系人男性の総コレステロール値を推定する式は次のようになります。

$Y=0.419X_1+0.629X_2+5.730X_3-0.096X_4$
$+2.348X_5-7.710X_6+10.307X_7$
$+6.333X_8+8.648X_9-1571X_{10}+182.8$

疫学研究では、総コレステロール値Yがどの説明変数と有意な関連を示すのかに注目します。すなわち、b_1～b_{10}の偏回帰係数のどれが統計的に有意であるかを調べます。上の式で有意になったのはX_1の年齢とX_9の現喫煙です。日系人男性の総コレステロール値に関係しているのは説明変数のなかで加齢と現喫煙習慣であるといえます。なお、統計分析方法について興味がある方はインターネットで検索するなどして学習することができます。

以下、重回帰分析から得られた結果を各血清脂質ごとに説明します。

2 総コレステロール

総コレステロール値を予測する重回帰分析結果を**表1**にまとめました。3集団全てで加齢とともに総コレステロール値は増加することが分かります。肥満指数であるBMIの増加とともに日系人女性と日本人男性では総コレステロール値が増加しますが、日系人男性では有意にならず関連なしでした。血圧降下剤服用有無は総コレステロール値と無関係でした。全集団で、飲酒習慣は総コレステロール値と無関係であることが明白です。喫煙習慣については、日系人男性の喫煙者が総コレステロール値を高める方向に働きますが、日本人男性の喫煙者は逆に低める傾向にあるという相反する結果です。女性については関連なしでした。総コレステロールはLDLやHDLコレステロールも含みますが、それが高いから動脈硬化のリスクも高いとは必ずしもいえません。もし、HDLコレステロール値が高いため、総コレステロール値が高くなっているとすれば、その人の動脈硬化のリスクは高くなりません。日本人男性の喫煙者の偏回帰係数が負で有意ではありましたが、他の脂質の結果をみて実際に動脈硬化を軽減するように影響するかどうかを判断する必要があります。

表1　総コレステロール値に影響を及ぼす要因

説明変数（要因）	日系人男性	日系人女性	日本人男性
年齢	＋＋＋	＋＋＋	＋＋＋
BMI＝体重Kg÷（身長m）²	x	＋＋＋	＋＋＋
血圧降下剤：非服用者に比較して	x	x	x
飲酒習慣：非飲酒者に比較して			
週1ドリンク以下	x	x	x
週1～6ドリンク	x	x	x
日に1～2ドリンク	x	x	x
日に3～5ドリンク	x	x	x
日に5ドリンク以上	x	＊	x
喫煙習慣（非喫煙者に比較して）			
現喫煙者	＋	x	－
前喫煙者	x	x	x

注：＋は増加する方向で有意；＋5％水準、＋＋1％水準、＋＋＋0.1％水準
－は減少する方向で有意；－5％水準、－－1％水準、－－－0.1％水準
xは有意差なし（関連なし）
＊該当者1名のため意義ある結果なし

3 LDLコレステロール

LDLコレステロールは悪玉と呼ばれ、動脈硬化を促進すると考えられています。**表2**の結果から、年齢は3集団全てで正の関連を示し、BMIも日系人男性以外は正の関連を示しています。注目されるのは、飲酒習慣を持つものはLDLを下げる傾向にあることです。特に日本人男性においてその傾向は顕著に現れています。喫煙者は総コレステロー

表2　LDLコレステロール値に影響を及ぼす要因

説明変数（要因）	日系人男性	日系人女性	日本人男性
年齢	+++	+++	++
BMI＝体重Kg÷（身長m）²	x	+++	+++
血圧降下剤：非服用者に比較して	x	−	−
飲酒習慣：非飲酒に比較して			
週1ドリンク以下	x	x	x
週1〜6ドリンク	x	x	−−
日に1〜2ドリンク	−	−	−−
日に3〜5ドリンク	x	x	−−−
日に5ドリンク以上	x	*	−−−
喫煙習慣：非喫煙者に比較して			
現喫煙者	+	x	−
前喫煙者	x	x	x

注：＋は増加する方向で有意；＋5％水準、＋＋1％水準、＋＋＋0.1％水準
　　−は減少する方向で有意；−5％水準、−−1％水準、−−−0.1％水準
　　xは有意差なし（関連なし）
　　＊該当者1名のため意義ある結果なし

表3　HDLコレステロール値に影響を及ぼす要因

説明変数（要因）	日系人男性	日系人女性	日本人男性
年齢	x	x	+
BMI＝体重Kg÷（身長m）²	−−−	−−−	−−−
血圧降下剤：非服用者に比較して	x	−	−
飲酒習慣：非飲酒者に比較して			
週1ドリンク以下	x	x	++
週1〜6ドリンク	x	+++	+++
日に1〜2ドリンク	+++	+++	+++
日に3〜5ドリンク	+++	+++	+++
日に5ドリンク以上	++	*	+++
喫煙習慣：非喫煙者に比較して			
現喫煙者	−	−−	−−−
前喫煙者	x	x	x

注：＋は増加する方向で有意；＋5％水準、＋＋1％水準、＋＋＋0.1％水準
　　−は減少する方向で有意；−5％水準、−−1％水準、−−−0.1％水準
　　xは有意差なし（関連なし）
　　＊該当者1名のため意義ある結果なし

表4　中性脂肪値に影響を及ぼす要因

説明変数（要因）	日系人男性	日系人女性	日本人男性
年齢	x	+++	x
BMI＝体重Kg÷（身長m）²	+++	+++	+++
血圧降下剤：非服用者に比較して	x	+	+
飲酒習慣：非飲酒者に比較して			
週1ドリンク以下	x	−	x
週1〜6ドリンク	x	−	x
日に1〜2ドリンク	−	−	x
日に3〜5ドリンク	x	−	x
日に5ドリンク以上	x	*	+++
喫煙習慣：非喫煙者に比較して			
現喫煙者	+	+	+++
前喫煙者	x	x	+++

注：＋は増加する方向で有意；＋5％水準、＋＋1％水準、＋＋＋0.1％水準
　　−は減少する方向で有意；−5％水準、−−1％水準、−−−0.1％水準
　　xは有意差なし（関連なし）　　＊該当者1名のため意義ある結果なし

表5　TC／HDL比率に影響を及ぼす要因

説明変数（要因）	日系人男性	日系人女性	日本人男性
年齢	x	+++	x
BMI＝体重Kg÷（身長m）²	+++	+++	+++
血圧降下剤：非服用者に比較して	x	x	x
飲酒習慣：非飲酒者に比較して			
週1ドリンク以下	x	x	−−
週1〜6ドリンク	x	−−	−−−
日に1〜2ドリンク	−−−	−−	−−−
日に3〜5ドリンク	−−−	−	−−−
日に5ドリンク以上	−	*	−−−
喫煙習慣：非喫煙者に比較して			
現喫煙者	++	+	+++
前喫煙者	x	x	+++

注：＋は増加する方向で有意；＋5％水準、＋＋1％水準、＋＋＋0.1％水準
　　−は減少する方向で有意；％水準、−−1％水準、−−−0.1％水準、
　　−0.05％水準
　　xは有意差なし（関連なし）　　＊該当者1名のため意義ある結果なし

4 HDLコレステロール

HDLコレステロールは体内で余分のLDLコレステロールを処理する働きをしているので善玉と呼ばれ、その値が高いほど良いと考えられています。表3の結果から、年齢は日本人男性で正に関連していますが、日系人男女は年齢と無関係です。BMIは全ての集団で負の関連を示し、肥満はHDLコレステロールの結果と同様に日系人男性が正の関連を示し、日本人男性が負の関連を示しています。

5 中性脂肪

中性脂肪の血中濃度が高いと動脈硬化の一因となることから、150mg／dl以下に保つ必要があります。表4の結果から、年齢は日系人女性のみで正の関連を示し、BMIは全ての集団で正の関連を示し、肥満は中性脂肪値を増加させることを示しています。高血圧は日系人男性を除く集団で正の相関を示し、中性脂肪値を高める傾向にあります。飲酒習慣は日系人女性で負の関連を示し、中性脂肪を下げるように働きます。日本人男性でお酒を1日5ドリンク以上飲むと正の相関を示し、中性脂肪を高めます。飲み過ぎはよくないということでしょう。また、喫煙習慣は全ての集団で正の関連を示し、中性脂肪を高めるように影響します。

6 TC／HDL−C比率

総コレステロール（TC）をHDLコレステロール（HDL−C）で割った比率は虚血性心疾患あるいは心筋梗塞のリスク指標と考えられ、男性は4・5以上、女性は4・0以上が要注意とされます。表5の重回帰分析の結果から、TC／HDL−C比率と有意な関連を示す要因は、HDL−Cと有意な関連を示す要因と表裏一体であることがわかります。すなわち、HDL−Cの結果で負の関連（または正の関連）を示した要因はTC／HDL−C比率の結果で逆に正の関連（または負の関連）を示していることが分かります。表5の結果を見ると、BMIは正の関連を示し、体重増加がTC／HDL−C比率を高め、虚血性心疾患のリスクを上げることになります。逆に、飲酒習慣はTC／HDL−C比率を低め、虚血性心疾患のリスクを低めることになります。しかし、喫煙習慣は全ての集団で正の関連を示し、虚血性心疾患のリスクを高めることになります。

7 結語

以上の結果から、血清脂質全体に影響する要因には二通りあります。悪い影響を与える要因と良い影響を与える要因です。悪い影響を与える要因の第一は歳をとることですが、これは変えることができません。第二は肥満になることで、BMIを20〜24に保つことが大切です。日本人女性の中でBMIが18以下という極端な痩身の方が多くみられますが、骨粗鬆症のリスクが高く、健康体とは申せません。第三に喫煙習慣は悪玉であるLDLコレステロール値と中性脂肪値を高め、善玉であるHDLコレステロール値を低めますから、喫煙者は禁煙することをお勧めします。すぐに止めることが難しいようでしたら、ニコチンガムやニコチンパッチなどを使ってタバコを吸いたいという誘惑を断ち切ることができます。

血清脂質に良い影響を与える要因は、飲酒習慣です。私どもの研究結果で、あまりにはっきりと現れて、疫学研究のパワーに驚くほどです。飲酒習慣はLDLコレステロール値を高め、虚血性心疾患のリスク指標であるTC／HDL比率を効果的に下げます。特に日本人男性は少量のアルコール量でも有意に影響が現れています。他の研究者による研究結果においても同様な結果が報告されていますので、私どもの結果が覆ることはありません。このようにお酒は血清脂質に良い影響を与え、虚血性心疾患の予防にも貢献しますが、1日2〜3ドリンクまでが適量であり、それ以上の飲酒は肝臓に負担をかけ、アルコール依存症になりかねませんので、極力注意が必要です。

私どもが調べた要因以外に、血清脂質に影響する要因には運動習慣が挙げられます。毎日30分以上の軽い運動はHDLコレステロールを高めることが報告されています。当然、食生活も血清脂質のレベルに影響します。肉食をできるだけ避けて魚と菜食を中心にすることが理想的といえます。

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日本人の健康に、アメリカからのメッセージ

動脈硬化を促進する要因と予防する要因は何か

前回は、血清脂質のレベルがどのような個人特性やライフスタイル要因によって影響を受けているのか、について説明しました。

今回は、血清脂質が密接に関わって進展する動脈硬化についての研究結果をご紹介します。

1 PWV測定装置 実用化への経緯

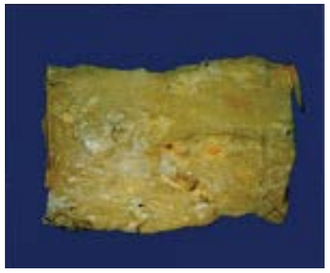
動脈硬化とは、動脈内壁にコレステロールや中性脂肪などが付着し、徐々に血管が細くなり、血管が弾力性や柔軟性を失ってゆく状態です。これが心臓の冠動脈に起こると、心臓に酸素と栄養を十分に供給できなくなるため狭心症の発作を起こし、最悪の場合は心筋梗塞を引き起こして死に至ることもあります。また、動脈硬化が脳動脈に起こると、脳梗塞のリスクが高まります。動脈硬化は若い時から徐々に進行しますので、それを推定する方法があれば脳・心血管疾患の発症予防に大いに役立ちます。その方法が日本健康増進財団で長年採用されてきた大動脈脈波測定法（今はその進化型であるCAVIが使われている）です。

大動脈脈波速度（pulse wave velocity、略してPWVと呼ぶ）は、心臓が収縮し血液が強い圧力（血圧）で大動脈に押し出される時に、弁口部に振動が発生し、動脈壁を伝播していきます。この伝播速度が動脈の柔らかさ・硬さと関連していることに気づいたイギリスの研究者が実験を開始しました。それが何と今から140年前です。日本が江戸時代から明治に変った頃です。その後、イギリスの研究者らがPWVの研究を続けましたが、戦後、PWVと動脈硬化との関連を究明し、PWVを測定する装置を開発したのが、慈恵医大の研究者らとフクダ電子㈱です。この装置では、PWVが心臓から右側の股動脈点まで伝播する速度を測定します。PWVは血管が柔らかいとゆっくり伝播し、硬いと速く伝播します。私は日本労働文化協会（今は日本健康増進財団と改名）に研究協力をお願いし、米国のシアトル日系人を対象にした研究を1989年に開始しました。PWVは拡張期血圧と密接に関係するため、研究で使用した測定装置は拡張期血圧が80mmHgでPWVの測定値が出せるように設定され、個人間での比較と集団間での比較が可能となりました。図1は、生前のPWV測定値と死後の大動脈内壁の写真を比較したものです。PWV値は速くなるほど動脈硬化が進展していることがわかります。

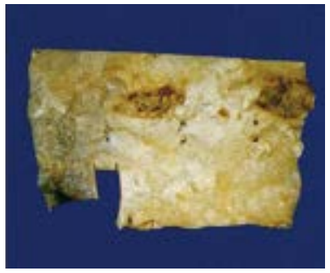
図1　生前のPWV値と死後の大動脈内壁の病理所見との関係

女性　22歳
PWV　6.4m/秒
病理所見　硬化所見なし

男性　56歳
PWV　8.3m/秒
病理所見　アテロームが20～30%を占めています。



女性　86歳
PWV　10.3m/秒
病理所見　アテローム、潰瘍、石灰化が80%を占めています。



男性　62歳
PWV　14.3m/秒
病理所見　内膜全域に硬化所見を認めています。

引用：鈴木賢二、他．大動脈脈波速度検査法のかいせつ．㈱フクダ電子 1988

2 統計解析方法

前回は重回帰分析方法について説明しましたが、この方法を採用すると従属変数であるPWVと年齢の相関が非常に高いため、他の説明変数とPWVの関連を正確に反映する

ことができません。PWVは6・0m／秒以下から15・0m／秒以上の間で表される連続変数です。どれ位までが正常値でどれ位以上が異常値なのかを示し、説明変数も層別化して、正常値に比べて異常値になるリスクはどれ位になるのかを推定できればわかりやすいと考えます。そのために多重ロジスティック回帰分析を採用しました。日本健康増進財団の22万人の健診データに基づく研究結果によると、60歳未満で8m／秒台、60歳以上では9m／秒台で、それぞれ動脈硬化性疾患の異常所見発現率が年齢別の平均発現率より有意に高くなることがわかりました。このことから年齢60歳未満でPWV8・0m／秒以上を異常、年齢60歳以上ではPWV9・0m／秒以上を異常と定義し、ロジスティック回帰分析を用いるために従属変数であるPWVの異常値の者を1、それ以外の者を0とする二項変数に変換しました。これによって各説明変数（リスク要因）におけるPWVの異常値出現リスクをオッズ比として算出できます。血圧を例にとると、血圧正常者のPWV異常値出現リスクを1とすると高血圧者のPWV異常値出現リスクはどれくらいになるのか推定することができます。

3 動脈硬化を促進させる要因は何か

シアトル市に在住の日系人を対象にして、どのような要因が動脈硬化を促進するのか、調べてみました。

図2は、動脈硬化の指標であるPWVの異常値出現リスクを動脈硬化関連要因ごとに多重ロジスティック回帰分析によって算出した結果です。この分析方法では基準グループを設定し、そのリスクを1として比較するグループのオッズ比を算出します。基準グループである60歳以下に比べて60歳以上になると、PWV異常値出現リスクを推定するオッズ比は3・6となり、動脈硬化に加齢が大きく影響していることがわかります。すなわち60歳以上の人の動脈硬化が異常に進むリスクは、60歳未満に比べて3・6倍ということです。

PWVの異常値出現リスク（動脈硬化が異常に促進されるリスク）については、

①正常血圧者に比べて高血圧者でのリスクは2倍

②健常者に比べて糖尿病の方のリスクは3・7倍

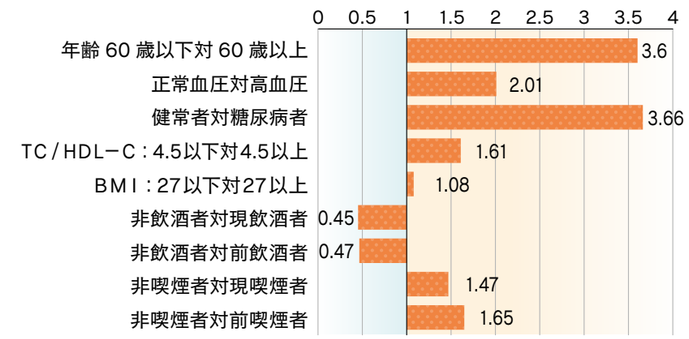
③虚血性心疾患のリスク指標であるTC／HDL－Cが4・5以下の方に比べて4・5以上の方のリスクは1・6倍

④肥満指標であるBMIが27以下の肥満でない方に比べて27以上で肥満者のリスクは1・08であり、1に近く、両者の間に有意差はなく、この集団で見る限りBMIは動脈硬化に影響していないとみられます。

⑤非飲酒者に比べて現飲酒者のリスクは0・45倍、すなわち動脈硬化のリスクが45％も低くなります。また、前飲酒者のリスクも47％低くなります。この結果は本誌第37号で紹介した脂質と飲酒習慣の結果と一致します。飲酒習慣は悪玉のLDLコレステロールを下げ、善玉のHDLコレステロールを上げ、虚血性心疾患のリスク指標であるTC／HDL比率を効果的に下げます。結果的に、飲酒習慣が動脈硬化を予防するように機能していることを、研究結果は示しています。

⑥非喫煙者に比べて現喫煙者と前喫煙者のリスクはそれぞれ1・47倍と1・65倍となり、喫煙習慣は動脈硬化を促進します。このことは前回の本誌で喫煙習慣が悪玉のLDLコレステロール値と中性脂肪値を上昇させ、善玉のHDLコレストロール値を下げると述べましたが、結果的には、喫煙は動脈硬化を促進することを示しています。

図2　シアトル日系人におけるPWV異常値出現リスクを推定するオッズ比

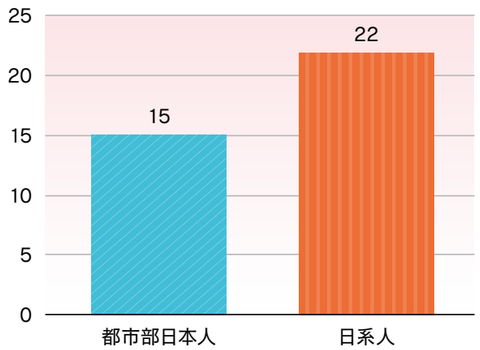


注）オッズ比はＢＭＩ以外が全て統計的に有意。

4 PWV異常値出現率をシアトル日系人と日本人で比較

図3は、年齢の影響を除いたPWV異常値出現率を表します。シアトル日系人が1000人に対して22、都市部日本人が15であり、この差は統計的に有意です。従って、動脈硬化は日系人の方が都市部日本人より進展しているといえます。この結果は、なぜアメリカ人の虚血性心疾患死亡率が日本人より高いのかという疑問に、ある程度答えてくれているものと思います。すなわち、冠動脈の動脈硬化が促進すると血栓が詰りやすくなり、虚血性心疾患が起こるリスクが高くなります。本研究に参加した日系人は88％がアメリカ生まれのアメリカ育ちであり、12％の一世もアメリカに永住している人達ですから、食生活も生活習慣もアメリカ人のそれと同じか、それに近いと考えられます。アメリカでの生活習慣は、日本における生活習慣よりも動脈硬化を早く促進させ、虚血性心疾患のリスクを高めるといえます

図3　PWV異常値出現率／1,000



5 結語

シアトル日系人を対象に、大動脈脈波速度（PWV）を用いて大動脈の動脈硬化がどのような要因の影響を受けているのか、調べました。動脈硬化を促進する要因は、加齢（特に60歳以上になると動脈硬化が急速に進みます）、高血圧、糖尿病、脂質異常症（TC／HDL－Cが4・5以上）、喫煙習慣（前喫煙者も含む）です。動脈硬化を防ぐ要因は、飲酒習慣（前飲酒者を含む）です。東京都監察医であった上野正彦氏は、飲酒と動脈硬化について次のように記しています。「あまりお酒を飲まない人たちが年をとると心臓は肥大気味になり、心筋は十分な栄養がとれなくなり、狭心症や心筋梗塞を起こしやすい危険な状態になる。とこころが……依存症といわれるほど酒を飲むと、血管壁に水分がたまって動脈硬化と同じように、心筋がだめになる。どちらにせよ極端はよくない」

生まれつきアセトアルデヒド脱水素酵素が少なく、お酒に弱い人は、無理して飲むべきではないと思いますが、お酒が飲める人は1日1合、グラス一杯のワイン、またはビール1缶くらいでしたら、動脈硬化を予防し、長生きに繋がる可能性があります。

日系人の動脈硬化が日本人より進んでいるのは、肉を多く食べるために脂質異常症の人が多く、日本人より運動量が少なく、飲酒習慣のある人が日本人より少ないことなどがあげられます。このことはアメリカ人全体に当てはまります。

次回は、眼底カメラ検査による細動脈の動脈硬化に関する研究結果をご紹介します。

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2. 行方　令、David Moore、鈴木賢二、旗野脩一、林　知己夫、森　誠、安倍信行、長谷川元治．シアトル日系アメリカ人における大動脈脈波速度と動脈硬化リスク要因との関連に関する研究．日本公衆衛生雑誌　1997；44(12): 942-951

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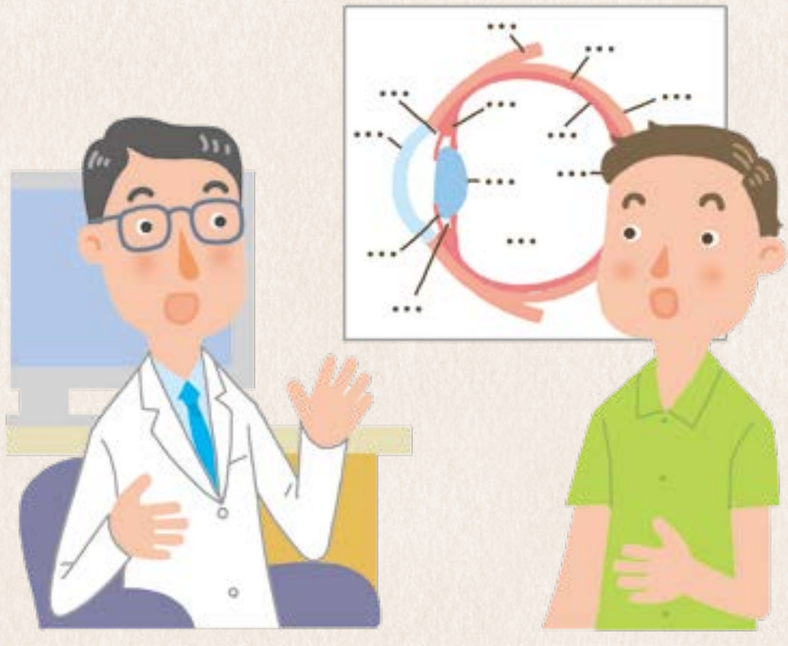
眼底細動脈の動脈硬化を促進する要因は何か



前回は、大動脈の動脈硬化がどのような個人特性やライフスタイル要因によって影響を受けているのかをお話しました。今回は、同じ遺伝子を持つ日本人と日系人において、細動脈の動脈硬化の頻度に違いがあるのか、動脈硬化の促進因子といわれる糖代謝異常や高血圧などの合併がどの程度の違いを生むのかなどについての研究成果をご紹介します。

1 日本での眼底検査導入の背景

大動脈の動脈硬化は大動脈脈波速度（pulse wave velocity, 略してPWV）によって推定できますが、細動脈の動脈硬化は無散瞳眼底カメラによって網膜の写真を撮り、細動脈と細静脈に異常がないかどうかを調べます。眼底の血管の変化を具体的に基準を作成して検査方法を確立したのは、アメリカの眼科医ハロルド・シャイエ博士で、それを1953年2月学術誌に発表されました。日本では、欧米諸国に比べて脳血管疾患死亡率が格段に高いことからシャイエ分類を日本循環器管理研究協議会が脳卒中を予防する手段として、1960年代の後半に取り入れ、集団検診で眼底検査を実施するようになりました。キヤノン社は無散瞳眼底カメラを開発し、私達が眼底写真を迅速に撮れるよう協力してくれました。世界中で眼底検査を集団検診で実施している国がなかったことを考えると、画期的なことだったと思います。

2 眼底検査の診断基準

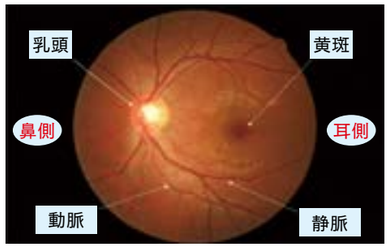
受診者の眼底写真を熟練された医師が観察し、シャイエ分類に従って、細動脈に異常がないかどうかをグレードⅠ（軽度の動脈硬化）～Ⅳ（重度の動脈硬化）として判定します。診断は高血圧性変化（S所見）と動脈硬化性変化（H所見）の二通りあり、前者が後者に先行すると考えられています。図1は、正常の眼底写真と細動脈変化がみられる例を示します。こうした眼底細動脈変化がある人は将来脳出血や脳梗塞を発症するリスクが高いことが過去の研究で報告されており、それ故に日本では、健診で眼底検査を実施して脳血管疾患の予防に力を入れているわけです。眼底検査の診断基準について詳しく知りたい方はインターネットで検索できます（https://www.jpm1960.org/exam/exam01/exam09.html）。

3 統計解析方法

対象は、シアトル日系人男性650名と日本人男性3、833名です。シャイエ分類でグレードⅡ以上を細動脈変化が異常に進んでいる者（以下、異常者とする）とし、グレー

図1 眼底写真の観察例（日本健康増進財団荒井親雄医師提供）

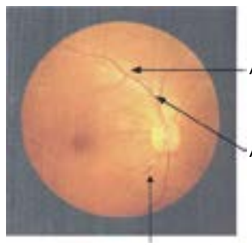
正常眼底（左目）



眼底写真観察例

Hemorrhage（bleeding）in The Retina

右眼

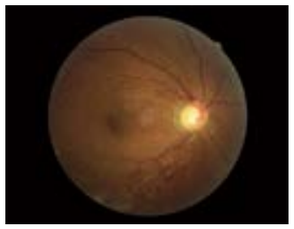


Arterial Crossing in Grade Ⅱ
グレードⅡ． 交叉現象

Arterial Reflex in Grade Ⅱ
グレードⅡ． 動脈壁反射

Hemorrhage or Bleeding グレードⅢ． 網膜出血

眼底写真観察例 右眼



グレードⅢの高血圧性変化(高度口径不同）やグレードⅣの動脈硬化性変化（銀線動脈といわれる動脈硬化が進行し細動脈が白く見える）その他眼科所見（出血、視神経乳頭辺縁部出血）が見られる。

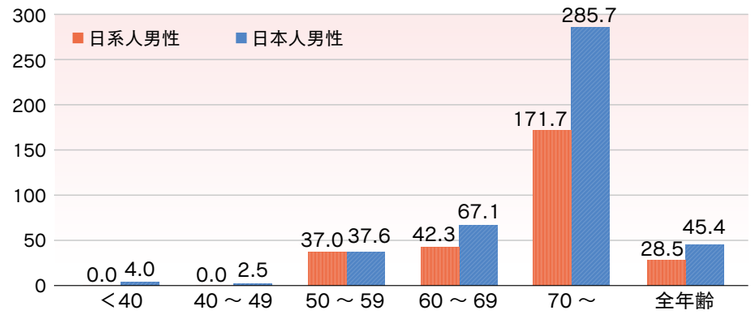
ドⅠ以下の者を正常者としました。まず異常者の年齢別頻度を両集団間で比較し、果たして遺伝的背景を日本人と同じくする日系人の細動脈変化の異常者の率が日本人と異なるのかどうかを調べました。

どのようなリスク要因が細動脈の変化に影響しているかを見るために、正常者を0、異常者を1とする二項変数にして、それを従属変数としました。説明変数(独立変数)は年齢、BMI、高血圧(収縮期血圧Ⅳ160mmHgまたは拡張期血圧Ⅳ100mmHg)、動脈硬化指標のTC／HDLコレステロールの率、糖代謝異常、飲酒習慣、喫煙習慣とし、ロジスティック回帰分析を採用しました。

4 結果

図2は、眼底細動脈変化の異常者の出現率を年齢別に、シアトル日系人男性と都市部日本人男性との間で比較したものです。両集団とも加齢と共にその異常者出現率は高くなっていますが、60歳を越すと日本人が日系人よりも高くなり、70歳以上では日本人の率は1,000人に対して285・7、日系人は171・7を示し、日本人の率が格段に高いことが明白です。全体で比較する際には、どちらかの集団で60歳以上の男性が多いと異常者出現率が高くなり、2集団を比較しても高齢者が多いためというように解釈される恐れがあります。そこで両集団の年齢構成が同じになるように調整して、両集団の異常者出現率を算出しました。その結果、年齢を調整(訂正)した上での率は日系人男性が1,000人に対し28・5であるのに比べ、日本人男性は45・4を示し、全体的に見て日本人が日系人より1・6倍高くなっています。

図2 シアトル日系人男性と都市部日本人男性における眼底細動脈変化異常者の出現率(1,000人対)の比較

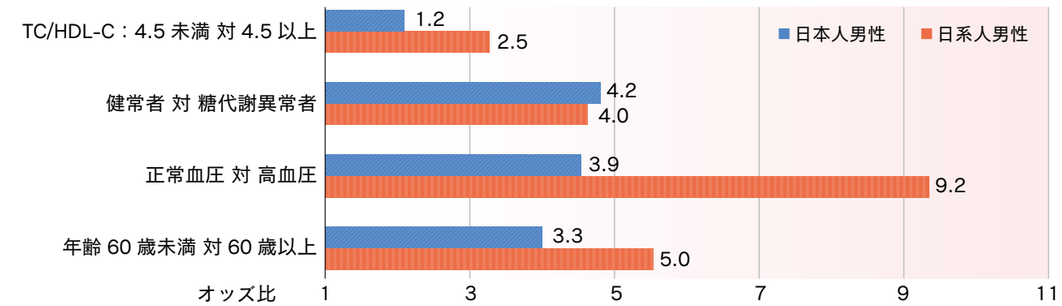


(注) 全年齢を含む総数の率はシアトル日系人人口を基に年齢訂正をした。

図3は、眼底細動脈変化に関連する要因をオッズ比で表したものです。この図に載せた要因以外に飲酒習慣と喫煙習慣もロジスティック回帰分析に加えたのですが、統計的に有意とならなかったため、図には示していません。この分析方法では、各要因ごとに基準群(対照群)のオッズ比を1・0としてリスクが高くなると考えられる群のオッズ比を比較します。動脈硬化指標であるTC／HDL−C4・5未満のオッズ比を1・0とすると、TC／HDL−C4・5以上では日本人男性のオッズ比が1・2となり、有意ではありませんが、日系人男性は2・5となり、有意でした。すなわち、日系人男性では眼底細動脈変化の異常となるリスクがTC／HDL−C4・5未満に比べて4・5以上では2・5倍になると推定されます。同様にして、以下のように説明できます。

- 眼底細動脈変化の異常となるリスクは、健常者に比べて糖代謝異常者は日本人男性で4・2倍、日系人男性で4・0倍です。
- 眼底細動脈変化の異常となるリスクは、正常血圧者に比べて高血圧者は日本人で3・9倍、日系人で9・2倍です。
- 眼底細動脈変化の異常となるリスクは、年齢60歳未満に比べて60歳以上の者は日本人で3・3倍、日系人で5倍です。
- 生活習慣要因であるBMI、飲酒習慣、喫煙習慣は有意に至らず、眼底細動脈変化との関連は薄いと考えられます。

図3 日系人及び日本人男性における眼底細動脈変化のリスクを推定するオッズ比



(注) 図中の日本人男性 TC/HDL-C 以外の要因は全て p<0.001 で有意。
飲酒習慣と喫煙習慣も解析に含めたが有意に至らなかった。

5 結語

昔から日本人は血圧が高いから脳卒中になる人が多いと思われてきましたが、我々のデータでは日本人男性の収縮期血圧の平均は130・4mmHg、日系人男性は132・4mmHgとなり、むしろ日系人男性の方が多少高くなっています。高血圧は脳血管疾患のリスクでありますが、それ以外に重大なリスク要因が存在することを日系人と日本人との比較が示しています。すなわち、日本人における脳血管疾患死亡率がアメリカ人に比べて男性で2・7倍、女性で1・9倍も高いという事実をある程度説明してくれています(『いきいき健康だより』第35号〔2017年夏号〕の拙者執筆第1回を参照)。日本人の細動脈(脳動脈を含める)は欧米に比べ、動脈硬化が60歳を過ぎると進行しやすく、そのため脳出血や脳梗塞が起こりやすくなるということです。これは生まれつき日本人であるからというわけでなく、食生活習慣や他の生活要因によると考えられます。一つの仮説として日本人の動物性たんぱく質の摂取量が日系人を含むアメリカ人より少なく、日本人の細動脈血管壁をアメリカ人より弱くしているのではないかということです。これは今後の研究課題として追究すべきだと考えています。

眼底細動脈変化のリスクについては、日系人男性と日本人男性の両方で有意となった要因が加齢(60歳以上になること)、高血圧や糖代謝異常であり、若い時から血圧をコントロールし、血糖値を100mg／dl以下に抑えて糖尿病にならないことが細動脈の動脈硬化の進行を遅らせることになります。それによって脳出血や脳梗塞を予防し、また虚血性心疾患をも予防することになります。

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2. T. Namekata, D. Hughes, C. Arai, D. Moore, K. Suzuki, M. Mori, S. Hatano, C. Hayashi, M. Hasegawa, R. Knopp. Arteriolar sclerotic or hypertensive changes in the retinal artery and atherosclerotic risk factors in Japanese Americans and native Japanese. Paper presented at the 14th International Scientific Meeting of the International Epidemiological Association in Nagoya, Japan, Aug.27-30, 1996.

日本人の健康に、アメリカからのメッセージ

心臓踝血管弾性指標（CAVI）は動脈硬化性疾患及びその危険因子に有意に関連するか

本シリーズ4回目で、大動脈脈波速度（略してPWV）と動脈硬化との関連についてご紹介しましたが、日本健康増進財団では、2005年9月からPWV測定装置に代わって心臓踝血管弾性指標（略してCAVI）測定装置を導入し、健診に適用しました。そのため、今回はPWVとCAVIとの関係に触れ、CAVIがどのように動脈硬化性疾患発症とそのリスク要因（危険因子）に関連しているのかを、研究結果に基づいてお話します。

1 CAVIとPWVとの関連

PWVは大動脈弁口部から股動脈拍動部の間の脈波伝播速度を示すのに対して、CAVI値は大動脈弁口部から足首または踝（くるぶし）までの動脈脈波（PWV）の伝播速度であり、それに血圧と血管弾性による補正調整を加えたもので、測定時の血圧の変動に左右されない、動脈そのものの硬化指標を示します（図1）。同一被検者のPWVとCAVIを測定すると、0・8以上（完全な一致は1・0）の高い相関係数が求められ、PWVもCAVIも動脈硬化を示す有効な指標であることがいくつも報告されています。CAVIは測定者の技術にあまり左右されず、また測定時の血圧に依存しないことから、CAVIの方が優れた動脈硬化指標であるといえます。

CAVI研究の第一人者である白井厚治先生が、本誌に2011年4月号から2012年1月号まで、CAVIについての解説を掲載されましたので、詳しくはそちらをご参照ください。

2 動脈硬化リスク要因の保持者は健常者よりCAVI値が高い

2004年から2006年までに日本健康増進財団での健診受診者3万2、627名を対象に、男女年齢別に脳心血管疾患のリスクを有する者（高リスク群）とリスクを有しない者（健常者群）に分け、CAVIの平均値を比較しました。高リスクとする基準は、収縮期血圧Ⅳ140mmHgまたは拡張期血圧Ⅳ90mmHg、脂質異常として総コレステロールⅣ240mg／dL、中性脂肪Ⅳ250mg／dLまたは善玉コレステロールHDL－CⅣ34mg／dL、糖代謝異常として血糖値Ⅳ110mg／dLまたは血中ヘモグロビンA1cⅣ5・9%、心電図に虚血性変化がみられる、眼底細動脈に異常がみられるなどです。

男性の結果をみると、図2に示したとおり、40歳以後高リスク群のCAVIの平均値が健常群より有意に高くなり、その差は加齢に伴って大きくなっています。女性についても同様な結果が得られ、脳心血管疾患のリスク

図1　CAVIの測定風景と測定部位の相違

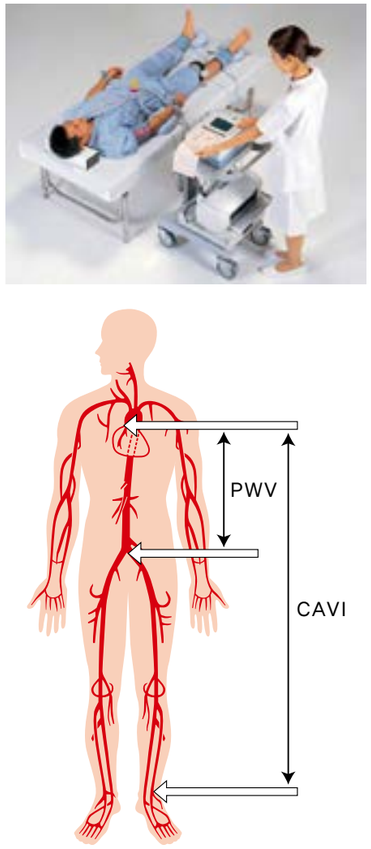
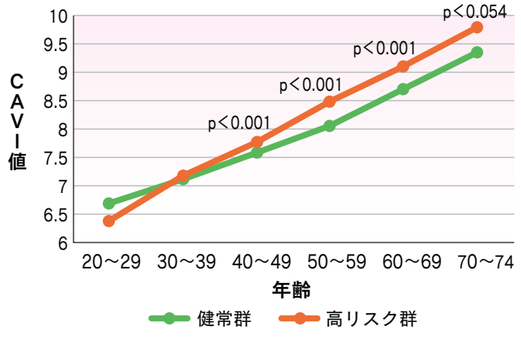


図2　健常群と高リスク群のCAVI平均値の比較



を有する者の動脈硬化が健常者よりも加齢に伴って進展し、虚血性心疾患や脳梗塞を発症するリスクが増大することが分かります。つまり、CAVIによって心筋梗塞や脳梗塞発症の危険度を知ることができるといえます。

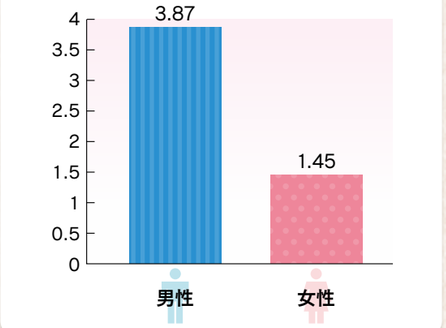
3 CAVI高値は虚血性心疾患発症のリスクを高めるか

私共研究チームはこの問いに答えるため、日本健康増進財団で受診した人たちのデータを基に、各要因のリスクを数値で表すことにしました。対象は2006年1月から2009年5月までに受診した男性9,881名、女性1万2,033名です。

まず、性年齢別にCAVIの平均値と標準偏差値を求め、次に既往歴と心電図から虚血性心疾患の者の頻度を性年齢別に求めました。CAVIの（平均値±1／2～1標準偏差値）の分布を調べ、虚血性心疾患の頻度が上昇する点（平均値＋1標準偏差値）以上をCAVI異常者、それ未満をCAVI正常者とし、対象者のCAVI値を二項変数に変換しました。また、虚血性心疾患の者を1、それ以外の者を0として従属変数にし、CAVIを含めた脳心血管疾患リスク要因を説明変数とし、多重ロジスティック回帰分析を行いました。この分析方法については本シリーズ4回目（2018年春／第38号）でも紹介しましたので参考にしてください。

CAVI異常値に対する虚血性心疾患が出現するリスクをオッズ比によって推定した結果は、図3に示したとおりです。CAVIが正常値である者に比べてCAVI異常値の者は、虚血性心疾患の出現するリスクが、男性は3・87倍であり、女性は1・45倍となりました。すなわち、動脈硬化が異常に進んでいる人は狭心症や心筋梗塞になる可能性が高いといえます。

図3 CAVI異常群における虚血性心疾患の出現リスクを推定するオッズ比

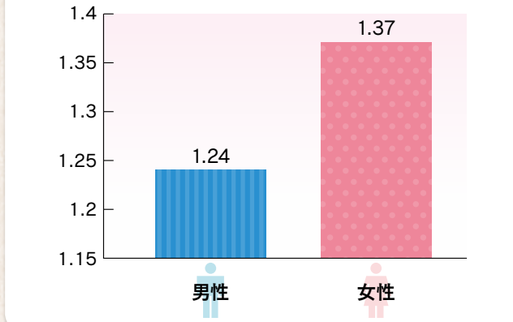


4 CAVIは眼底細動脈硬化と有意に関連する

本シリーズ5回目では、眼底細動脈の動脈硬化についてお話しましたが、では中大動脈の動脈硬化の指標であるCAVIと関連があるのでしょうか？　この研究データには眼底検査結果も含まれていますので、この問いに答えることができます。眼底写真を観察して異常を1、正常を0とし、それを従属変数とします。CAVIを含めた他のリスク要因を説明変数として、ロジスティック回帰分析を実施しました。図4がその結果です。眼底細動脈硬化が出現するリスクは、CAVI正常群に比べて、CAVI異常群では男性が1・24倍、女性が1・37倍です。このことは、中大動脈の動脈硬化が進行すると、眼底細動脈の動脈硬化も進む傾向があることを示しています。

眼底細動脈は脳動脈の先端に当たりますので、その動脈硬化の関連性は脳動脈にもいえることになります。

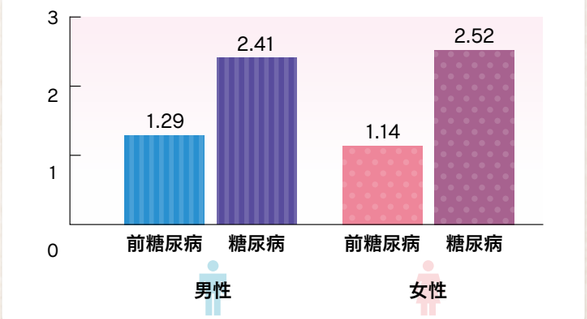
図4 CAVIに異常群における眼底細動脈硬化異常の出現リスクを推定するオッズ比



5 CAVIは糖代謝異常及び糖尿病と密接に関連する

白井厚治先生が「糖尿病は、動脈硬化を進める最大の要因であり、CAVIが顕著に高い値を示します」と述べていますように、私どもの研究結果でも、糖代謝が正常である者に比べて、糖代謝異常者（糖尿病患者を含む）のCAVI異常値出現リスクは男性10倍、女性8・4倍となり、糖代謝を正常に保つことの重要性が強調されます。前（プレ）糖尿病（糖尿病予備群）と糖尿病が出現するリスクは、CAVI正常群に比べてCAVI異常群でそれぞれ男性1・29倍と2・41倍、女性1・14倍と2・52倍となりました（図5）。ということは、CAVIの測定値が異常であれば、前糖尿病か糖尿病である可能性が高いといえます。CAVI測定値が異常に高い場合、血糖値を調べ、糖代謝異常がないかどうか確認する必要があります。

図5 CAVIに異常群における前糖尿病及び糖尿病の出現リスクを推定するオッズ比



6 結語

今回は、疫学研究者の立場から、CAVIと動脈硬化関連疾患及びリスク要因との関連を、今までの研究結果に基づいてお話しました。CAVI、血圧、コレステロールなどの測定値は連続変数ですが、これらを二項変数や層別化した変数に変換することで、関連疾患のリスクを数値化することが可能となりました。CAVIについての疫学や統計分析の新しい分野を開拓できたのではないかと思っています。

2017年の死亡統計を見ますと、心疾患と脳血管疾患による死亡者数は31万4,047人で、全死亡者数の23・4％を占め、がん死亡に次いで2番目に多い病気です。動脈硬化性疾患である虚血性心疾患や脳卒中はある程度防止できるものですし、効率的な予防にCAVIの活用が期待されます。白井厚治先生がいわれるように、CAVIは1年に1回だけでなく、3～6カ月ごとに測定し、CAVIが上昇した際には体重・糖尿病・血圧のコントロールやメタボリック症候群構成要因のコントロールをより強化するなど、CAVIを指標にした生活習慣病の指導を行うことによって、動脈硬化性疾患が予防できます。医師を初めとする医療関係者や健診に携わる方々の一層の努力に期待する次第です。

次回は、我々がシアトルで行った胃がんのリスク要因に関する疫学研究結果を中心にご紹介します。

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日本人の健康に、アメリカからのメッセージ

シアトル在住日系人における胃がんリスク要因の調査結果から日本人の健康を考える

シアトル市で胃がんのリスク要因を調査するきっかけとなったのは、1993年『厚生の指標』〔一財〕厚生労働統計協会刊〕に載った論文に遭遇したことです。そこには、血中ペプシノゲンを調べることで、胃がんの前駆症状である慢性萎縮性胃炎が診断できると書かれていました。同年9月に、オーストラリアのシドニーで開催された国際疫学会で研究発表した時、その論文の著者である稲葉裕教授（当時順天堂大学在職）に、シアトル市で日系人を対象にペプシノゲンを調べてみたいとお話したところ、次に東京に来る際、ペプシノゲン測定法を考案された三木一正先生をご紹介してくださるということになり、翌年東京で三木先生にお会いすることができ、シアトルでの調査研究が実現したという次第です。

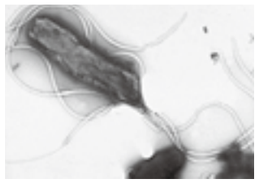
1 研究の背景

過去長い間、胃がんが発症する原因についてははっきりとしたことが解明できず、胃がんは特に日本人に多いことから日本人の食生活や生活習慣が胃がんの発症に関わっているのではないかと考えられてきました。日本人は漬物や味噌汁をよく摂取することから、塩分が原因だろうとか、焦げた魚や肉を食べることが原因であろうとか、あるいは日本人男性はよくタバコを吸うから喫煙が原因だろうとか、いろいろなことが原因として疑われてきました。

胃がんの発生メカニズムを解明するきっかけとなったのは、オーストラリアのウォレン博士とマーシャル博士が1982年に胃潰瘍患者の胃液からピロリ菌（Helicobacter pylori：図1）を発見したことによります。それまでは、酸性度の強い胃の中でバクテリアなどが生きられるはずがないと信じられていたのです。マーシャル博士がピロリ菌を発見したのは、胃潰瘍患者の胃液を培養しているとき、休日が挟まって取り出すのが1日遅れたために、ピロリ菌の培養が成功したと語っています。このような偶然が偉大な発見につながったことは、誠にラッキーです。ピロリ菌が発見されたことで、それを除菌する抗生物質が開発され、胃潰瘍はピロリ菌を除菌することで完治するようになりました。2005年にピロリ菌発見の功績が認められて、ウォレン博士とマーシャル博士はノーベル医学生理学賞を受賞しました。

ピロリ菌の発見に伴い、ピロリ菌は胃がんの発生機序に深く関与していることがわかり、多くの日本人がピロリ菌に、幼少時知らないうちに感染し、胃の中に住み着いて活発化すると、ピロリ菌が胃壁に炎症を起こし、胃潰瘍の原因になりますが、大部分の感染者は無症状です。何十年という長い時間をかけて、ピロリ菌は胃壁細胞をがん細胞に変えていきます。その前駆症状が慢性萎縮性胃炎であり、三木先生はこれを血液検査で診断するペプシノゲン測定法を開発され、その業績により2005年に朝日がん大賞を受賞されました。

図1 ピロリ菌 (Helicobacter pylori)



ピロリ菌は長さ約3μmで直径約0.5μmのバクテリア。

引用：Wikipedia, the free encyclopedia

2 シアトル市での日系人を対象にした胃がんリスク要因の調査

シアトル市で1994年に実施した健診参加日系人男性415名と女性361名を対象に、血液検査によるピロリ菌の感染の有無を、次にペプシノゲン法によって慢性萎縮性胃炎の有無を調べました。ペプシノゲンは蛋白質の分解酵素ペプシンの前駆体で、その99％は胃内腔に分泌されますが、1％は血液中に流入します。血中のペプシノゲン濃度は食事などの影響を受けず一定ですが、慢性萎縮性胃炎や胃がんを患うと、ペプシノゲンの分泌が阻害され、血中の濃度が減少します。減少の程度に基準を設けると慢性萎縮性胃炎の有無が診断できるわけです。

3 日系人のピロリ菌感染率と慢性萎縮性胃炎の有症率はどれくらいか

図2と図3は、日系人のピロリ菌感染率と慢性萎縮性胃炎有症率を年齢別に示しますが、男女ともに加齢にしたがって上昇します。男女のピロリ菌感染率と慢性萎縮性胃炎有症率は64歳までほぼ同じですが、65歳以上ではピロリ菌感染率は女性の方が男性より高くなっています。

では、ピロリ菌に感染している者がどれくらいの割合で慢性萎縮性胃炎になっているのでしょうか。それを示したのが図4です。64歳までは男女ともほぼ同じ割合ですが、65歳を過ぎると男女差が大きくなり、ピロリ菌感染者中で慢性萎縮性胃炎者の割合は65～74歳で男性77・5％、女性45・4％、75歳以上では男性85・7％、女性63・6％と、圧倒的に男性のほうが高い割合となります。このことは男性の胃がん死亡率が女性よりも高いとい

図2　日系人男性のピロリ菌感染率と慢性萎縮性胃炎有症率

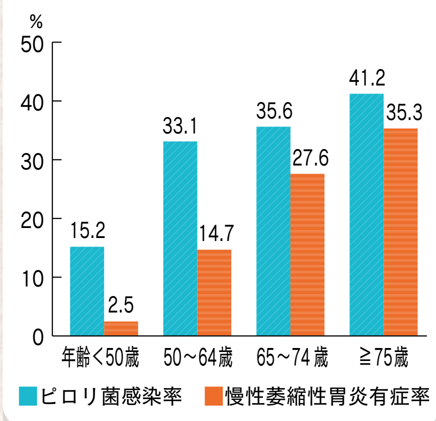


図3　日系人女性のピロリ菌感染率と慢性萎縮性胃炎有症率

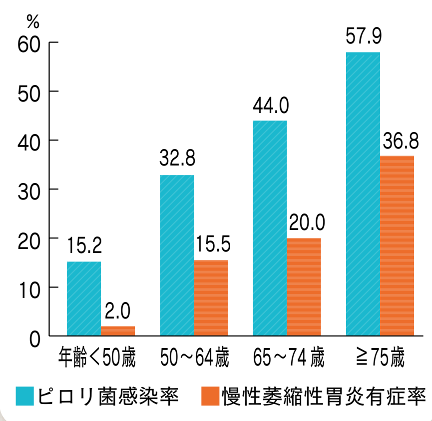
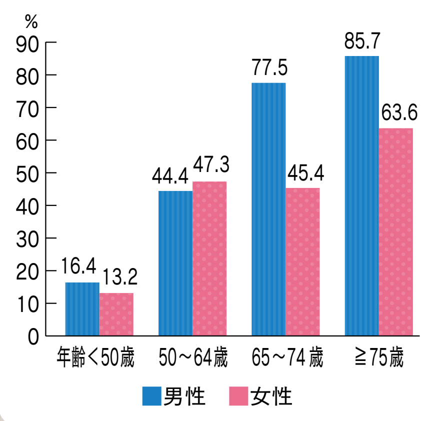


図4　ピロリ菌感染者中における慢性萎縮性胃炎有症者の割合（%）



う事実を裏付けるものと考えられます。

日系人の胃がん死亡統計はアメリカでは集計されていませんが、日本の国立がん研究センターによると、2016年の日本人の胃がん死亡率は人口10万人あたり男性49・0に対して女性は24・4です。男性の胃がん死亡率は女性の2倍です。

4 日系人と日本人を比べると……

日本からアメリカへ、100年以上前に移民して成り立った日系人集団のピロリ菌感染率と萎縮性胃炎率は、日本人とどれくらい違うのでしょうか。

京都府立医科大学の渡邊能行教授（当時）のご協力を得て、1987年に京都府K町で実施した健診参加者1、393名を比較対照集団とすることができました。まず、図5のピロリ菌感染率を比べてみましょう。ピロリ菌感染率は、日本人が50歳未満の65％から50～64歳の79％の間に位置するのに、日系人は50歳未満の15％から70歳以上の47％の間です。日本人のピロリ菌感染率が圧倒的に高いことは明らかです。

図6は、慢性萎縮性胃炎有症率の比較です。両集団とも加齢にしたがって有症率が上昇していますが、特に日系人はその傾向がピロリ菌感染率同様、顕著です。ピロリ菌の高い感染率を反映して日本人の慢性萎縮性胃炎有症率が各年齢層を通じて日系人より高くなっています。このような大きな違いは、日本人とアメリカ人の胃がん死亡率の大差を裏付けるものと考えられます。日本人の胃がん死亡率は人口10万人あたり男性49・0、女性24・4に対して、アメリカ人は男性4・5、女性3・1です。

図5　日系人と日本人のピロリ菌感染率（%）

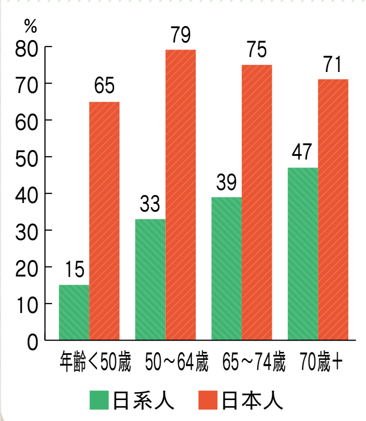
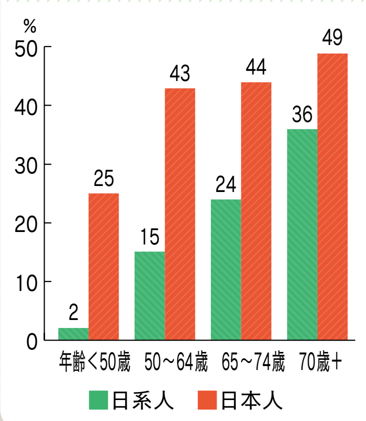


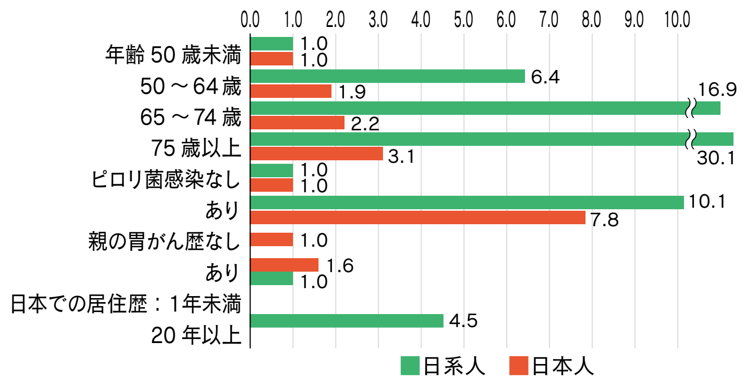
図6　日系人と日本人の慢性萎縮性胃炎有症率（%）



5 慢性萎縮性胃炎のリスクを高める要因は何か

慢性萎縮性胃炎のリスクを推定するために、シアトル日系人と京都府K町の住民を対象にして多重ロジスティック回帰分析を適用しました。この分析方法については本稿シリーズの4回目を参照ください。図7は、慢性萎縮性胃炎を従属変数として、そのリスクを推定したオッズ比を示します。シアトル日系人では、年齢50歳未満（オッズ比1・0）に比べて50歳以上の年齢層のリスクがそれぞれ6・4倍、16・9倍、30・1倍と大変高く現れていますが、これは50歳未満の慢性萎縮性胃炎有症者が極端に少ないためです。ピロリ菌より年齢が慢性萎縮性胃炎と胃がんのリスク要因として重要であるというわけではありません。京都府日本人の50歳以上の慢性萎縮性胃炎のリスクは50歳未満に比べて1・9倍、2・2倍、3・1倍となり、加齢とともにリスクが徐々に上昇する典型的なパターンです。

図7　シアトル在住日系人と京都府日本人における慢性萎縮性胃炎のリスクを推定するオッズ比



（注）親の胃がん歴あり（$p < 0.10$）以外のオッズ比は $p < 0.05$ で有意

京都府日本人のデータには親の胃がん歴の情報があり、親が胃がんに罹ったことがある場合、なしに比べて慢性萎縮性胃炎になるリスクが1・6倍です。これは親のがんになりやすい体質よりも同じ環境で育ったためにピロリ菌に感染し、子どもも成人してから慢性萎縮性胃炎になるためと考えられます。

シアトル日系人には、過去に日本でどれくらいの期間住んでいたかを質問しました。日本での居住歴1年未満に比べて20年以上の居住者の慢性萎縮性胃炎のリスクは4・5倍となり、日本で長く生活したことでピロリ菌に感染し、後年慢性萎縮性胃炎になるリスクが高くなることを示唆しています。

日系人の加齢のリスクを除くと、ピロリ菌感染者における慢性萎縮性胃炎のリスクは非感染者に比べて日本人が7・8倍、日系人が10・1倍となり、リスク要因の中では最も高いことが指摘されます。分析に喫煙習慣と飲酒習慣を加えましたが、慢性萎縮性胃炎との関連は見られませんでした。

6 結語

私共のシアトル日系人におけるピロリ菌と慢性萎縮性胃炎の研究が、アメリカ疫学誌（American Journal of Epidemiology）に発表されたのが2000年です。5年後の2005年にピロリ菌を発見したオーストラリアのウォレン博士とマーシャル博士にノーベル医学生理学賞が授与されました。私どもの研究はピロリ菌と慢性萎縮性胃炎との関連を疫学的に解析し、ピロリ菌の果たす役割の重要性に着目したことで、少しは学術的に貢献できたのではないかと思います。そして、日本健康増進財団の理事長である三木一正先生が2005年ペプシノゲン測定法の確立と普及の功績により、朝日がん大賞を受賞されたことは、三木先生にシアトルの研究を支援していただいただけに、誠に喜ばしいことと思っています。

本研究では、アメリカでのピロリ菌の感染率が低いことを反映して、シアトル日系人のピロリ菌感染率は日本人より相当低く、そのため慢性萎縮性胃炎有症率も日本人より格段に低いことが明らかになりました。慢性萎縮性胃炎のリスクは、第一にピロリ菌、それ以外に加齢、親の胃がん歴（日本人）、日本での長期居住（日系人）などがあげられます。

次回は、私どもがシアトルで日系人を含めたアジア系移民を対象として行ったピロリ菌と慢性萎縮性胃炎に関する疫学研究結果をご紹介します。

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日本人の健康に、アメリカからのメッセージ

米国シアトル市のアジア系移民における胃がんリスク要因の調査結果

1 はじめに

前回は胃がんのリスク要因について、シアトル市在住の日系人と日本人の間でどのような違いがあるのかをお話しました。今回は、シアトル市在住のアジア系移民（中国系、韓国系、フィリピン系、ベトナム系、日系）を対象に、胃がんのリスク要因を調査した結果をご紹介します。日系人以外のアジア系移民集団を対象に、ピロリ菌と慢性萎縮性胃炎について、アメリカで調査するのは初めてのことです。私どもの調査結果がこれらの移民集団に対して、今後の胃がん予防対策の指針となればと願っています。

2 どのように調査したの？

調査は、２００４年から２００５年にかけて、アジア系移民関連団体及び協会に呼びかけ、説明会を行い、協力をお願いしました。アメリカでは胃がん検診が行われていないことから割合関心が高く、男性３９６名・女性６０３名が調査に参加してくれました。年齢、性、出生地、世代、胃がんの家族歴、１世の場合は渡米年、生活習慣などを含む英語の質問票を作成し、日本語、中国語、韓国語、フィリピン語、ベトナム語に翻訳し、調査参加者の母国語に合わせて質問票に記入してもらいました。

慢性萎縮性胃炎を調べるペプシノゲン測定法がアメリカで確立されていないため、その検査をアメリカの検査機関に依頼することはできません。そこで東京に本社を置く栄研化学株式会社（略して栄研）に協力を依頼しました。栄研は濾紙に手指から4滴の血液を採取し、ピロリ菌と慢性萎縮性胃炎の有無を検査するキットと試薬を開発しており、この検査によって正確にピロリ菌感染の有無と慢性萎縮性胃炎を判定できるように精度管理を徹底していることから、私どもの研究に十分採用できるものと判断しました。

質問票の記入と採血については、参加者に各移民集団の都合に適した場所に来てもらい、あらかじめ訓練された数人のボランティアに役割分担をして実施しました。採血した濾紙はアイスパックと一緒に速達航空便で栄研のラボに届け、一週間以内に検査結果の報告を受けるようにしました。質問票の情報と血液検査の結果をコンピュータに入力し、統計解析を行いました。なお、日系移民については１９９４年に男性４８８人と女性３６５人を対象にして既に調査しており、その結果は前回説明してあります。今回は、その結果を他のアジア系移民集団に加えて説明させていただきました。

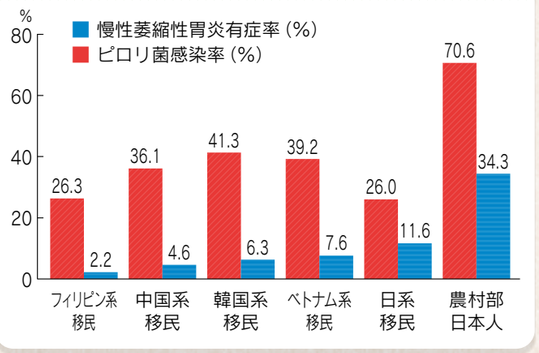
3 シアトル市のアジア系移民と日本人ではピロリ菌感染率や慢性萎縮性胃炎有症率がどのくらい違うの？

図1の赤グラフは、シアトル市とその周辺に住むアジア系移民における年齢を訂正したピロリ菌感染率を示します。

年齢を訂正する理由は比較する項目（この場合はピロリ菌感染率）が各集団の年齢構成によって影響を受けるし、高齢者が多いとピロリ菌感染率が高くなるため、すべての比較集団で年齢構成が同じになるように訂正して、ピロリ菌感染率を算出しました。日本人の比較集団としてシリーズ7回目で使用した京都府農村部の調査結果を引用しました。日系移民が最も低く26・0％、続いてフィリピン系移民26・3％、中国系移民36・1％、韓国系移民39・2％、ベトナム系移民41・3％となり、最も高いのが京都府農村部の70・6％です。アジア系移民集団のピロリ菌感染率の違いは、一つに世代の違いを反映していると考えられます。日系移民集団の8割以上はアメリカ生まれの2～4世であるのに対し、他は90％以上が母国生まれの1世で、ベトナム系移民はすべてが1世です。従って、日系を除くアジア系移民のピロリ菌感染率は母国の感染率を反映していると考えられます。アメリカでの以前の調査では、南部の黒人のピロリ菌感染率は農村部日本人並みに高いのに比べ、白人は極端に低く、日系移民はそれよりも低いことが分かっています。このことは他の移民集団の2世以降はピロリ菌感染率が急激に減少するものと推察されます。

図1の青グラフは、アジア系移民集団、農

図1　米国アジア系移民集団及び農村部日本人のピロリ菌感染率と慢性萎縮性胃炎有症率

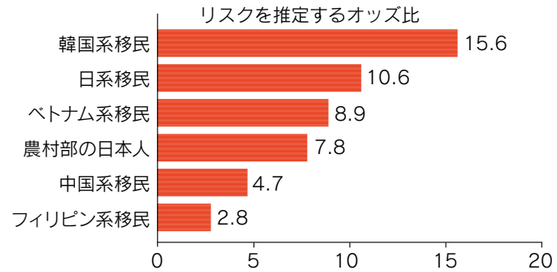


村部日本人の慢性萎縮性胃炎有症率の比較です。必ずしもピロリ菌感染率の順位と一致していないことがわかります。アジア系移民集団のなかで日系移民のピロリ菌感染率は最も低いにもかかわらず、慢性萎縮性胃炎有症率は最も高くなっています。これは過去に行われた研究結果から日本人と日系人のピロリ菌の株（strain）が特に強力で胃壁細胞を慢性萎縮性胃炎に変化させやすいためであると考えられます。都市部日本人（日本健康増進財団の健診データ）の慢性萎縮性胃炎有症率は22・1％ですが、これは農村部日本人34・3％の3分の2まで減少していることを示します。ピロリ菌は自然環境に普遍的に存在することから、都市部の衛生環境が改善されるに従って、その感染率も減少してきたものと考えられます。従って、それに伴い都市部日本人の慢性萎縮性胃炎有症率も農村部日本人に比べて激減したものと考えられます。

4 シアトル市のアジア系移民と農村部日本人のピロリ菌感染が慢性萎縮性胃炎になるリスクは？

図2は、各集団においてピロリ菌に感染していない人に比べ、感染している人の慢性萎縮性胃炎になるリスク（オッズ比）を推定したものです。なお、オッズ比は他の関連要因である年齢、性、喫煙習慣、飲酒習慣、胃潰瘍や他の消化器疾患の既往歴などの影響を補正して算出してあります。ピロリ菌非感染者のリスクを1・0とすると、ピロリ菌感染者のリスクは、韓国系移民が最も高く15・6倍、2番目が日系移民の10・6倍、3番目がベトナム系移民の8・9倍、4番目が農村部日本人の7・8倍、最後にフィリピン系移民2・8倍です。恐らく、韓国系移民に感染しているピロリ菌は、日本人及び日系人に感染しているピロリ菌同様に強力で、胃壁細胞を慢性萎縮性胃炎に変えやすいのではないかと思われます。これを裏付けるために胃がんの罹患率を調べてみました。

図2　シアトル市のアジア系移民と農村部日本人のピロリ菌感染者の慢性萎縮性胃炎になるリスクの推定

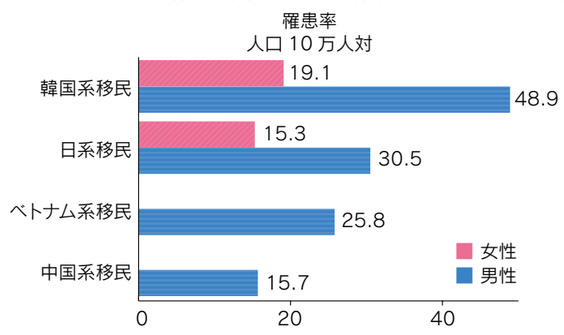


（注）オッズ比はピロリ菌非感染者のオッズ比を1.0としてピロリ菌感染者に対するオッズ比を算出した。上記のオッズ比は95％有意水準で全て有意である。なおオッズ比は他の関連要因（年齢、性、喫煙習慣、飲酒習慣、胃潰瘍や他の消化器疾患の既往歴）の影響を補正して算出してある。

5 アメリカにおけるアジア系移民の胃がん罹患率は？

アメリカでは、アジア系移民は極少民族であるため、詳細のがん統計は公表されることが少なく、最近のものは見つけられませんでした。20年前に公表されたパーカーらの論文を図3に引用しました。論文のなかで極少民族のがん罹患率の上位5番以内まで記載してあり、アジア系移民の胃がん罹患率の記載は図の4集団のみであり、女性では2集団の方々に厚くお礼申し上げます。研究協力とご指導を賜った元文部省数理統計研究所長の故林知己夫教授、京都府立医科大学の渡邊能行教授及び東邦大学の白井厚治教授らに心より謝意を表します。シアトル市では循環器疾患予防健診の検査技師として献身的に努力された故高橋美月女史、リピッド測定と研究を担当されたワシントン大学の故ロバート・ノップ教授、パシフィック・リム疾病予防センターの理事長を務められたワシントン大学の故フランク・ミヤモト名誉教授、同じく理事長を務められた日系人初の女性医師となられた故ルビー・イノウエ医師並びにケミー・ナカバヤシ医師らに心より感謝申し上げます。最後にシアトル市でのピロリ菌と慢性萎縮性胃炎の検査に全面的に協力された㈱栄研化学のスタッフの皆様に厚くお礼申し上げます。

図3　米国アジア系移民の胃がん罹患率



引用文献：Sheryl L. Parker et al. Cancer statistics by race and ethnicity, CA Cancer J.Clin 1998 ; 48 : 31 － 48

6 結語

本シリーズで2回にわたりピロリ菌、慢性萎縮性胃炎及び胃がんについてシアトルでの研究結果をまとめましたが、日本の胃がん死亡率は先進諸国中で最も高いことから、政府は胃がんの予防検診に積極的に取り組んできました。しかし、アメリカでは前述したようにあまり進んでいません。両国の施策の違いを反映する指標として、胃がんの5年相対生存率を見ると明らかです。これはがんと診断された場合に、治療でどれ位生命を救えるかみでした。この論文は、5年間に新たにがんと診断されたケースを集計して報告しています。男性の胃がん罹患率（10万人対）は韓国系移民48・9、日系移民30・5、ベトナム系移民25・8、中国系移民15・7であり、図2の慢性萎縮性胃炎になるリスクの順位と一致します。このことから、胃がんに罹るリスクをアジア系移民では共有していることがわかります。さらにパーカーらの論文で明らかになったことは、アジア系移民集団だけでなく他の少数民族集団でも、胃がんがん発生率の上位5番以内に入っているという事実です。すなわち、男性の胃がん罹患率（10万人対）はアラスカ系原住民27・2、ハワイ原住民20・5、アフリカ系アメリカ人（黒人）17・9、スペイン語系移民15・3と報告されています。ところがアメリカ人口の77％を占める白人の胃がん罹患率は2015年現在5・5と低く、そのために胃がんの予防対策は日本に比較して大変遅れているというのが現状です。

7 謝辞

30年以上にわたり日系人を中心に研究を続けられたことは、多くの方々のご支援とご協力があったからこそ実現できたと思っております。特に日本健康増進財団の理事長三木一正先生、専務理事 鈴木賢二氏及びスタッフの

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一般財団法人
日本健康増進財団
リサーチ・フェロー
行方　令
（なめかた　つかさ）

Profile

1966年 新潟大学教育学部卒業、同年東京大学大学院健康教育学科に移り、双生児集団による中高校生の身体発育と体力について遺伝的及び環境要因を研究。

1971年 米国イリノイ大学に留学、1974年に Ph.D. を取得、同大公衆衛生学部で環境疫学研究を担当。

1980年 シアトル市バテル記念研究所に移り、疫学研究を担当。

1983年 米国疫学学術院より上席研究フェローとして認定される。

1985年 東京大学医学部保健学科疫学教室より保健学博士を取得。

1989年 米国ワシントン州ワシントン大学公衆衛生学部臨床准教授兼任。

1989年～2016年
㈶パシフィック・リム疾病予防センターデレクターに就任し、日系人の健診と疫学調査を推進する。
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Abstract

Health Examination Surveys Conducted among Japanese Americans Living in Seattle and Japanese Living in Japan: Results of Study to answer the question "Are Japanese in Japan healthier than Japanese Americans in Seattle?"

The people of Japan are often considered to be a healthier population than are Americans. Japanese women on average live to 87 and Japanese men to 80, as compared to 81 years for American women and 76 for American men (OECD data). However, a comparison of cause-specific death rates indicates that the relative health status of the two populations is a more complicated matter. Mortality of coronary heart disease (CHD) in the US is two times higher than in Japan, while mortality of stroke in Japan is two times higher than in the US. Another extreme example is that mortality of stomach cancer in Japan is 11 times among men and 8 times among women higher than in the US. Why do such differences in mortality of these diseases exist between the two nations? Are the differences due to race (genetics) or due to the environment?

A strategic method for researching these intriguing questions suggested itself with the accessibility of Japanese Americans in the Seattle area as research subjects. This population is considered genetically very similar to the people of Japan, but as being substantially American in their nutritional and lifestyle background. Therefore, in 1989 we initiated the Seattle Nikkei Health Study to examine the health status of Japanese Americans in comparison to Japanese living in Japan (called native Japanese). First, we focused on cardiovascular disease and its risk factors, since CHD and stroke have been major contributors to mortality both in the U.S. and in Japan. We compared atherosclerotic indices and risk factors between Japanese Americans and native Japanese to detect effects due to the environment (changes in lifestyle and diet) and ultimately utilize our study outcomes for future prevention. Please see our research papers 1–4.

Then, we examined major risk factors of stomach cancer, *helicobacter pylori* infection and chronic atrophic gastritis, among Asian immigrants from Japan, China, South Korea, The Philippines and Vietnam. Please see our research papers 9 and 10 listed.

In our project, we used the measurement device of aortic pulse wave velocity (PWV) to estimate stiffness of aortic artery reflecting the extent of arteriosclerosis or atherosclerosis (see No. 3 on the list). Recently, with cooperation with Dr. Kohji Shirai at Toho University, Fukuda Denshi Company improved the original PWV measurement device and created a new device, VaSera VS-1000, to measure cardio-ankle vascular index (CAVI) expressing a

stiffness and arteriosclerosis indicator of thorax, abdomen, common iliac, femoral and tibial arteries. We made some research contributions to strengthening the justification for the use of CAVI in cardiovascular disease screening (see 5–8 on the list).

As a basic data-gathering mechanism, we adopted the cardiovascular screening program developed by the Epidemiological Arteriosclerosis Research Institute (EARI) in Japan Health Promotion Foundation which has been conducting cardiovascular disease prevention screening for company employees and their families throughout Japan. By doing so, EARI became a partner in our research providing us with data of native Japanese which we used in direct comparisons against our Seattle data. We began screening Japanese Americans in the Seattle Metropolitan Area in the fall of 1989 and continued to the fall of 1994. About 1,500 adults completed screening tests and questionnaires. The generational composition of our sample showed the following distribution: 12.3% Issei (first generation), 49.4% Nisei (second generation), 37.0% Sansei (third generation), and 1.3% Yonsei (fourth generation). This distribution is significant for our study, for 88% of the subjects were American-born persons who are quite Americanized in their habits, and therefore are largely Americans in their nurturance.

The study subjects in Japan consisted of 4,134 native Japanese males and females randomly selected from 31,068 people who underwent the disease prevention screening at the EARI. They were from prefectures of Tokyo, Kanagawa, Saitama, Chiba, Gunma, Ibaraki and Tochigi. More male workers underwent the screening than female workers, reflecting the current labor situation in which male workers greatly outnumber female workers in Japan.

Overall scope of our studies is presented in PowerPoint format in No. 11 on the list.

Lastly, I would like to express my sincere appreciation to Mr. Kenji Suzuki as a research partner for providing many suggestions and resources to conduct cardiovascular disease prevention screening in Seattle and for sharing the screening data from Japan Health Promotion Foundation enabling us to conduct comparative analyses between Seattle and Japan. Also, I thank many colleagues, Nikkei community and other Asian organizations, and many Japanese Americans for their wonderful support and collaboration. With much appreciation, I acknowledged the permissions to copy our research papers which were given by Journal of Atherosclerosis and Thrombosis, International Journal of Epidemiology, American Journal of Epidemiology, and Japanese Journal of Public Health (including permission of translation).

Tsukasa Namekata, Ph.D., Dr.H.Sc., F.A.C.E.
Project Director

Selected English publications and presentations related to Seattle Nikkei Health Study conducted by Tsukasa Namekata and co-investigators

1. **Cholesterol levels among Japanese Americans and other populations: Seattle Nikkei Health Study.**

2. **Biological and lifestyle factors, and lipid, and lipoprotein levels among Japanese Americans in Seattle and Japanese men in Japan.**

3. **A study of the association between the aortic pulse wave velocity and atherosclerotic risk factors among Japanese Americans in Seattle, U.S.A.**

4. **Association between Arteriolar Sclerotic and Hypertensive Changes in Retina and Cardiovascular Disease Risk Factors among Japanese Urban Workers and Their Families.**

5. **Establishing baseline criteria of cardio-ankle vascular index as a new indicator of arteriosclerosis: a cross-sectional study.**

6. **Association of cardio-ankle vascular index with cardiovascular disease risk factors and coronary heart disease among Japanese urban workers and their families.**

7. **Association of prediabetes and diabetes mellitus with cardiovascular disease risk factors among Japanese urban workers and their families: A cross- sectional study.**

8. **Estimating the extent of subclinical arteriosclerosis of persons with prediabetes and diabetes mellitus among Japanese urban workers and their families: a cross-sectional study.**

9. **Chronic atrophic gastritis and *Helicobacter pylori* infection among Japanese Americans in Seattle.**

10. ***Helicobacter Pylori* Infection and Chronic Atrophic Gastritis among Asian Immigrants in the Seattle Area, U.S.A.**

11. **Seattle Nikkei Health Study: Cross Cultural Surveys between Seattle and Japan.**

12. **Profile of Tsukasa Namekata**

Also, you can read the Japanese summary 「30 年間にわたる日系人と日本人の健康調査研究結果まとめ」and these publications and presentations from www.SeaNikkeiHlth.com.

Journal of Atherosclerosis and Thrombosis Vol. 3, No. 2

Original

Cholesterol Levels among Japanese Americans and Other Populations: Seattle Nikkei Health Study

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The purpose of this study was to compare average cholesterol levels between Seattle based Japanese Americans and three other populations: U.S. population, native Japanese population and native Japanese urban workers. A total of 1,466 Japanese Americans (724 men and 742 women) participated in cardiovascular disease screening in the Seattle area during 1989-94. Data sources for comparisons are from the Third National Health and Nutrition Examination Survey for 1988-91, the results of the National Cardiovascular Disease Examination Survey in Japan for 1990, and cardiovascular disease screening conducted by the Epidemiological Arteriosclerosis Research Institute in Japan for 1989. Total cholesterol and triglyceride levels of Seattle Japanese American men and women were highest among the four populations. Among men, high density lipoprotein cholesterol (HDL-C) levels for Seattle Japanese Americans and native Japanese were similar and fell between those of urban Japanese workers and the U.S. population. In women, the average HDL-C levels were highest in the Japanese urban workers, second highest in Seattle Japanese Americans, and lowest in both the U.S. population and native Japanese population. These differences in lipid levels may be caused by both genetic and environmental factors, which are now under investigation. ***J Atheroscler Thromb, 1996; 3: 105-113.***

Key words: Lipid, Lipoprotein, Triglycerides, Cross-cultural comparison

It is well known that Japan's coronary heart disease (CHD) (ICD 410-414) mortality rate is the lowest among the industrialized nations (41.4 per 100,000 persons in 1992) (1), while that of the U.S.A. remains high (188.2 per 100,000 persons in 1992) (2). To examine the causes of such a difference in CHD mortality between the two nations, the Ni-Hon-San (Nippon-Honolulu-San Francisco Japanese) study was initiated in 1965 and CHD prevalence was found to be lowest in native Japanese, intermediate in Japanese Americans in Honolulu and highest in Japanese Americans in San Francisco (SF) (3). The investigators also reported lowest total cholesterol levels in native Japanese, intermediate in Honolulu Japanese and highest in SF Japanese (4), although differences in CHD among the three populations could be caused by other multiple factors as well.

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Because major changes in nutrition and other risk factors (e.g., cigarette smoking, blood pressure) have occurred both in Japan and in the United States over the past three decades, it is important to examine the current status of CHD risk factors in both countries. We conducted cardiovascular disease prevention screening which included a survey among Japanese Americans in Seattle. Our paper compares cholesterol levels between our study sample and others from the U.S. population and Japanese populations in Japan.

Study Populations and Methods

Cardiovascular disease prevention screening was conducted among Japanese Americans in the Seattle area (King County) from the fall of 1989 to the fall of 1994. Participants were recruited through a media campaign, flyers and household contacts. A total of 1,466 persons aged 30 years or older participated in the program with completion of screening tests and questionnaires. Japanese Americans on the West coast originated from Southern prefectures in Japan including Hiroshima, Okayama, and Yamaguchi. Immigration began more than one century ago; it was abruptly halted in 1924 with the passage of the Immigration Act and resumed in 1965 when the act was repealed. The term Nikkei refers to persons of Japanese ancestry, so that the study in Seattle was named the Seattle Nikkei Health Study. The composition of our study sample according to generation was as follows: 12.3% Issei (first generation), 49.4% Nisei (second generation), 37.0% Sansei (third generation) and 1.3% Yonsei (fourth generation).

A comparison between the study sample and the Japanese American population in King County from the 1990 U.S. census is presented in Table 1 (5). Our sample represented 12.7% of the Japanese American men and 10.3% of Japanese American women in the Seattle area. To better define the characteristics of our study sample, we conducted an additional survey on household income levels among the participants in 1994 and compared their income distribution with that of Japanese American households in the 1990 census (Fig. 1) (6). The distribution of our screening participants is slightly shifted to higher-income categories. We will discuss the possible impact of such income differences on lipid levels later.

Our results were compared with those from three populations: the U.S. population, the native Japanese population and Japanese urban workers in Japan. U.S. results were from phase 1 of the Third National Health and Nutrition Examination Survey (NHANES III) conducted in 1988-1991 (7). The data consists of a representative sample of the civilian noninstitutionalized population and thus reflects the racial composition of the U.S. which is comprised of 74.8% white, 11.9% black, 9.5% Hispanic, 3.1% Asian and Pacific Islanders, and 0.7% American Indian, Eskimo and Aleut (8). The native Japanese population data used was based on the National Cardiovascular Disease Examination Survey (NCDES) performed in 1990 and its samples were drawn randomly from the entire Japanese population (9). The samples from the Japanese urban workers were based on cardiovascular disease prevention screening conducted by the Epidemiological Arteriosclerosis Research Institute (EARI) in major cities throughout Japan including Tokyo, Chiba, Osaka, Sapporo, and Kitakyushu in 1989. The sample size, survey period, and whether lipid evaluation was conducted according to CDC quality control standards is shown in Table 2. Because of differences in age-breakdowns between the U.S. and Japan data, we used two sets of age-breakdowns for the Seattle sample: (A) and

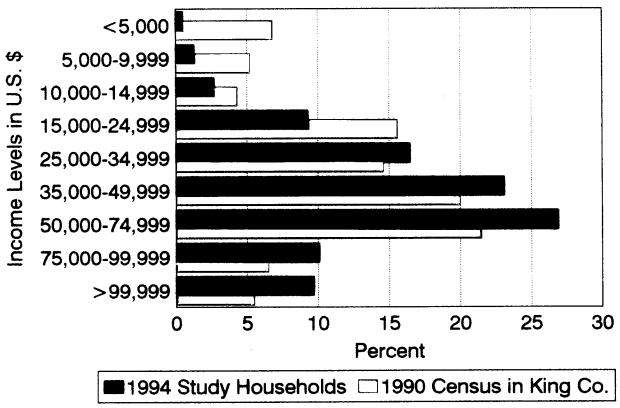

Fig. 1. Comparison of the distribution of annual household incomes of 636 study participants and that of Japanese Americans in King County as reported by the U.S. Department of Commerce, the Bureau of Census.

Table 1. Age and sex-specific distribution of screening participants in Seattle and the total Japanese American population in King County, Washington, U.S.A.

Age	Male Participants	Japanese Americans 1990 Census	Female Participants	Japanese Americans 1990 Census
30-49	238 (7.0%)	3405	248 (6.6%)	3785
50-69	355 (21.3%)	1667	380 (14.8%)	2562
70+	131 (20.1%)	651	114 (13.5%)	842
Total	724 (12.7%)	5723	742 (10.3%)	7189

Table 2. The four populations used for comparison of lipoprotein and lipid levels. The table shows the survey periods under which the analysis was conducted, sample size of each population and whether the blood analysis was conducted under the Centers for Disease Control and Prevention (CDC) and the National Heart, Lung, and Blood Institute's (NHBLI) lipid standardization program.

Population	Survey Period	Sample Size (≥30 yrs old)	Lipid Quality Control
Seattle Japanese Americans	1989-1994	1466	Yes, CDC/NHLBI Program
U.S. Population	1988-1991	5475*	Yes, CDC/NHLBI Program
Native Japanese	1990	7906	Yes, CDC/NHLBI Program
Japanese Urban Workers	1989	146782	Yes, before screening, quality control examination was conducted

Note : *Persons 35 years old or over.

Table 3. The sample size of four populations used for lipoprotein and lipid comparisons.

Age	Seattle Japanese Americans[1] (A)	Seattle Japanese Americans[1] (B)	U.S. Population[2]	Native Japanese[3]	Japanese Urban Workers[4]
Males					
30-39	99			620	27,681
35-44		128	303		
40-49	139			788	45,727
45-54		151	251		
50-59	149			758	24,608
55-64		163	253		
60-69	206			674	6,724
65-74		184	283		
70+	131			456	651
75+		61	229		
Females					
30-39	109			992	9,627
35-44		128	335		
40-49	139			1,124	15,150
45-54		138	229		
50-59	159			995	7,944
55-64		184	233		
60-69	221			870	1,794
65-74		195	219		
70+	114			629	172
75+		44	233		

Data sources used for comparison are from the following sources :

1) Seattle Japanese Americans from the surveys conducted by Nikkei Disease Prevention Center for 1989-1994
2) The representative sample of the U.S. population from the NHANES III (1989-1991)
3) The representative sample of the native Japanese population from the National Cardiovascular Disease Survey in Japan for 1990
4) Japanese urban workers from the 1989 screening data collected by the Epidemiological Arteriosclerosis Research Institute.

(B) as shown in Table 3.

At the screening conducted in Seattle, venous blood samples were obtained after a 12 hour fast. Analysis was conducted at the University of Washington Northwest Lipid Research Laboratory, which participates in the Centers for Disease Control and Prevention/National Heart Lung and Blood Institute's lipid standardization program. Total cholesterol (TC) and triglyceride (TG) levels were measured enzymatically by Abbott Spectrum analyzer, and high density lipoprotein cholesterol (HDL-C) levels were measured by the dextran sulfate magnesium precipitation method (10). Regarding quality control in lipid measurements, the other three surveys adopted the CDC/NHLBI program guidelines to some extent. According to the description of the study, NCDES did not require fasting prior to taking blood samples which may have had

some impact on the accuracy of certain lipid measurements, particularly TG. This is also true for the data from EARI. We conducted quality control examinations at EARI's lab by shipping frozen serum samples twice from Seattle to EARI prior to the screening. After adjustment was made at EARI's lab based on the measurement values from the first serum samples, all measurement values except a few from the second samples were within the acceptable ranges.

The data from NHANES III were weighted to produce nationally representative results and the standard errors were computed using SUDAAN to account for the complex sample survey design (11). A t-test was conducted to examine the difference in means of TC, HDL-C and TG

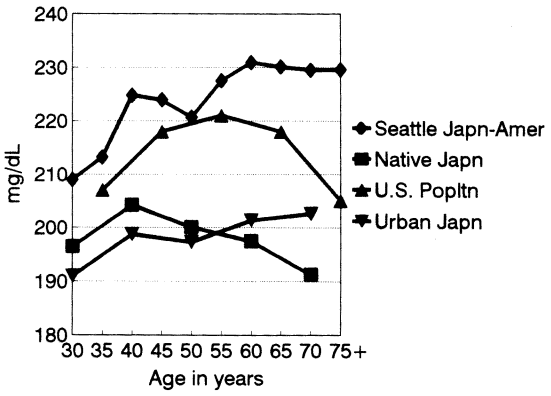

Fig. 2. Comparison of total cholesterol levels by age among four male populations : Seattle Japanese Americans, native Japanese population, Japanese urban workers and the U.S. population.

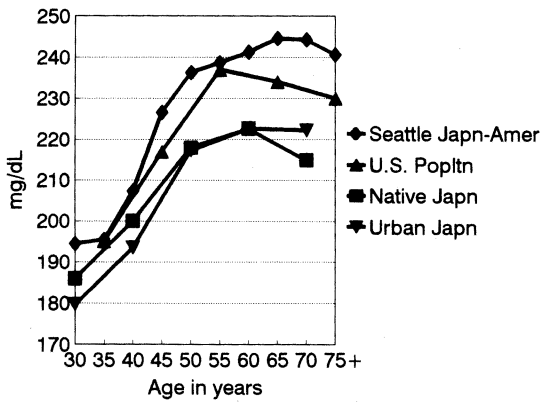

Fig. 3. Comparison of total cholesterol averages by age among four female populations : Seattle Japanese Americans, native Japanese population, Japanese urban workers and the U.S. population.

Table 4. The age-specific averages of total cholesterol levels in Seattle Japanese Americans, U.S. Population, native Japanese and Japanese urban workers.

Age	Seattle Japanese Americans		U.S. Population		Native Japanese		Japanese Urban Workers	
	Mean	SD	Mean	SE	Mean	SD	Mean	SD
Male								
30-39	209.0	33.9			196.4***	35.1	190.9***	33.0
35-44	213.2	33.8	206.7*	2.3				
40-49	224.8	37.9			204.2***	36.5	198.7***	34.8
45-54	223.9	38.8	218.1*	2.4				
50-59	220.7	36.3			200.0***	36.5	197.2***	33.3
55-64	227.5	37.4	221.3*	2.5				
60-69	230.9	40.2			197.4***	37.7	201.3***	31.6
65-74	230.1	39.7	217.7***	1.6				
70+	229.5	37.0			191.2***	36.6	202.6***	35.6
75+	229.6	39.2	205.4***	2.8				
Females								
30-39	194.4	31.4			185.9***	31.7	179.6***	28.4
35-44	195.4	29.8	194.7	1.4				
40-49	207.3	36.0			200.0***	34.5	193.4***	32.0
45-54	226.6	38.4	216.8***	2.8				
50-59	236.3	37.5			218.0***	36.8	217.3***	37.2
55-64	238.7	34.4	236.7	2.7				
60-69	241.2	37.9			222.6***	37.9	227.7***	35.2
65-74	244.5	41.2	234.3***	2.5				
70+	244.2	42.6			214.9***	41.9	222.2***	45.1
75+	240.6	44.0	230.5	3.2				

Note : SD=standard deviation, SE=standard error
The t-test was conducted between Seattle Japanese Americans and other populations.
Levels of significance are : *p<.10, **p<.05 and ***p<.01

between Seattle Japanese Americans and other populations by SPSS-PC 3.0 (12).

Results

A comparison of the average TC levels for men according to age-group was conducted among the four populations as shown in Fig. 2. TC levels were highest in Seattle Japanese Americans, second highest in the U.S. population and lowest in native Japanese and in Japanese urban workers. Average TC levels increased with age in all study populations except for native Japanese. As shown in Fig. 3, average TC levels for women indicate a similar trend regarding the order of TC levels among the populations. However, an increasing trend in TC levels with age was more pronounced in women than in men. Age-specific mean values of TC in the four populations are presented in Table 4. Significant differences in mean TC values between Seattle Japanese American and other populations are evident with the exception of U.S. women in the age groups 35-44, 55-64 and 75+ years old.

A comparison of HDL-C levels is shown in Fig. 4 for men and Fig. 5 for women. Age-specific mean values of HDL-C for both sexes and t-test results are shown in Table 5. Unlike TC levels, no consistent patterns in HDL-C levels with age were observed in the four populations in either sex. For men, the highest average HDL-C levels were observed in the urban Japanese workers and the lowest in the U.S. population. Both Seattle Japanese Americans and native Japanese came between the Japanese urban workers and the U.S. population. For women, the average HDL-C levels were highest in the Japanese urban workers, second highest in Seattle Japanese Americans and lowest in both the U.S. and native Japanese populations.

TG levels among the four populations are shown in Fig. 6 for males and in Fig. 7 for females. There is little difference between TG levels for men aged 30-39 and 35-44 years old. However, at the age of 40-49 years, TG levels are highest in Seattle Japanese Americans, second highest in the U.S. population, third in native Japanese, and lowest in Japanese urban workers, with the exception of the appearance of the highest peak in the 45-54 year age-group of the U.S. population. After 40-49 or 45-54 years of age, TG levels for men tend to decline as age advances, while TG levels for women increase with aging in all four populations. Both TG levels of the Seattle Japanese Americans and the U.S. population are highest, those of the native Japanese were higher than those of urban Japanese workers who were lowest in both sexes.

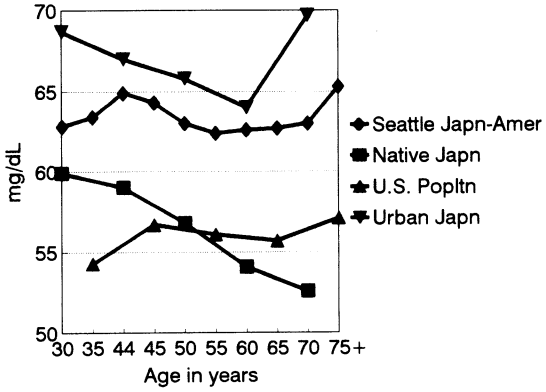

Fig. 5. Comparison of HDL-cholesterol averages by age among four female populations : Seattle Japanese Americans, native Japanese population, Japanese urban workers and the U.S. population.

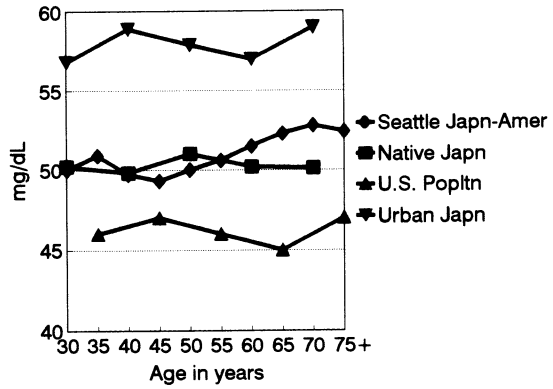

Fig. 4. Comparison of HDL-cholesterol averages by age among four male populations : Seattle Japanese Americans, native Japanese population, Japanese urban workers and the U.S. population.

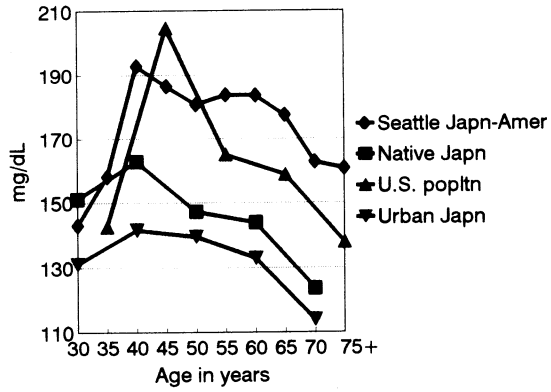

Fig. 6. Comparison of triglyceride averages by age among four male populations : Seattle Japanese Americans, native Japanese population, Japanese urban workers and the U.S. population.

Discussion

With regard to the representativeness of the Japanese American population in King county (the Seattle area), we compared the household income levels between the population in the 1990 Census (6) and our 1994 samples for which we conducted a follow-up survey. Out of 673 households of the study participants, 511 households (76%) have responded so far. As shown in Fig. 4, the distribution of our study sample, (annual median income: $46,000) is shifted towards a higher income level than the total population (annual median income: $37,244). The four-year gap between our survey and the census survey possibly contributed to slightly higher observed income levels in our study sample due to the time-related effects of inflation.

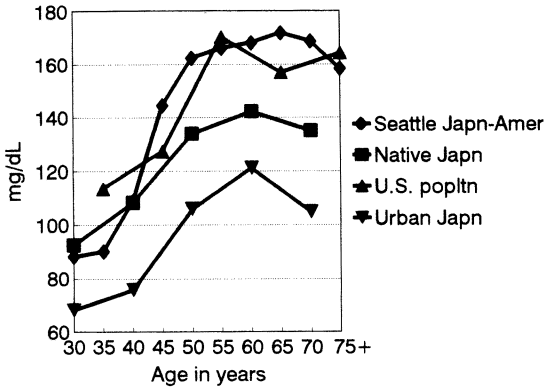

Fig. 7. Comparison of triglyceride averages by age among four female populations: Seattle Japanese Americans, native Japanese population, Japanese urban workers and the U.S. population.

Regarding differences in sample characteristics according to the year of participation, such differences might exist but are considered to be insignificant: the proportion of current drinkers was 63% for men and 42% for women among the participants screened between 1989-1992 vs. 65% for men and 46% for women among the 1989-1994 participants; and the proportion of current smokers was 15% for men and 10% for women among the 1989-1992 participants vs. 15% for men and 10% for women among the 1989-1994 participants.

Because the Seattle study participants were volunteers, we are concerned about response bias. At present we have no definitive method to ascertain whether our sample is biased, with the exception of comparing household incomes as described above. The Honolulu Heart Study

Table 5. The age-specific averages of HDL-cholesterol levels in Seattle Japanese Americans, U.S. population, native Japanese, and Japanese urban workers.

Age	Seattle Japanese Americans		U.S. Population		Native Japanese		Japanese Urban Workers	
	Mean	SD	Mean	SE	Mean	SD	Mean	SD
Male								
30-39	50.0	12.6			50.2	15.1	56.8***	13.4
35-44	50.9	13.0	46.3***	1.0				
40-49	49.7	14.1			49.8	14.2	58.9***	15.4
45-54	49.3	14.4	46.6*	0.8				
50-59	50.0	14.0			51.0	14.6	57.9***	14.5
55-64	50.6	13.3	45.6***	0.8				
60-69	51.5	13.2			50.2	16.0	57.0***	15.0
65-74	52.3	14.8	45.3***	0.8				
70+	52.8	15.8			50.1*	15.5	59.0***	16.1
75+	52.4	15.7	47.2**	0.8				
Females								
30-39	62.8	15.3			59.9**	14.1	68.7***	14.6
35-44	63.4	15.8	54.3***	0.9				
40-49	64.9	17.1			59.0***	15.0	67.0*	15.1
45-54	64.3	17.3	56.8***	0.8				
50-59	63.0	16.1			56.8***	15.5	65.8**	15.4
55-64	62.4	15.9	56.1***	0.9				
60-69	62.6	16.6			54.1***	14.3	64.0	16.2
65-74	62.7	17.7	55.7***	0.8				
70+	63.0	18.7			52.6***	15.2	69.7***	13.8
75+	65.3	19.5	57.1***	1.1				

Note: SD=standard deviation, SE=standard error
The t-test was conducted between Seattle Japanese Americans and other populations.
Levels of significance are: *$p<.10$, **$p<.05$ and ***$p<.01$

Table 6. The age-specific averages of triglycerides in Seattle Japanese Americans, U.S. population, native Japanese and Japanese urban workers

Age	Seattle Japanese Americans		U.S. Population		Native Japanese		Japanese Urban Workers	
	Mean	SD	Mean	SE	Mean	SD	Mean	SD
Male								
30-39	143.1	107.1			151.2	97.9	131.1	106.3
35-44	158.1	141.6	142.7***	7.3				
40-49	192.8	218.3			162.8**	122.3	141.6***	124.4
45-54	186.5	196.2	204.7	33.8				
50-59	180.7	138.6			147.2***	105.5	139.5***	93.0
55-64	183.7	136.2	165.0	8.9				
60-69	183.6	209.9			143.9***	98.4	132.9***	111.0
65-74	177.4	265.9	158.8*	8.4				
70+	162.7	214.1			123.6***	73.2	113.9***	81.6
75+	160.7	97.7	137.9	6.1				
Females								
30-39	88.2	49.3			92.5	56.0	68.2***	41.2
35-44	90.2	51.6	113.4	8.0				
40-49	108.8	122.2			108.2	78.1	75.8***	38.6
45-54	144.6	157.1	127.3	6.4				
50-59	162.4	145.9			133.8***	84.5	105.9***	64.3
55-64	166.0	131.9	170.3*	10.5				
60-69	168.1	115.9			142.2***	85.6	121.1***	79.9
65-74	171.8	114.4	156.9*	9.2				
70+	168.7	104.4			135.0***	78.5	104.8***	36.1
75+	158.3	77.5	164.2*	13.7				

Note : SD=standard deviation, SE=standard error
The t-test was conducted between Seattle Japanese Americans and other populations.
Levels of significance are : *p<.10, **p<.05 and ***p<.01

stated that the men who participated smoked less, had a slightly higher body mass index (BMI), a higher level of education, a lower percentage of non-married status and a lower coronary heart disease incidence rate than non-participants (13). Jones *et al*. reported that the participants in their screening program had a lower BMI, lower mean cholesterol level, lower mean systolic and diastolic blood pressure level and a higher education level than non-participants (14). If the findings from these studies are applied to our study, it is likely that non-participants of Seattle Japanese Americans would be less healthy in terms of cardiovascular health than our study participants. Thus, true values for mean lipid and lipoprotein levels among the Seattle Japanese American population may possibly be even less favorable than the observed values in our study.

Fasting requirements were different between the four populations used in our comparison. For native Japanese and native Japanese urban workers, fasting prior to blood collection was not required, whereas among Japanese Americans and the general U.S. populations, a 12 hour fasting requirement was imposed. Non-fasting status has been shown to influence TG levels. The NCDES report shows an inverse relationship between average TG levels and the number of fasting hours before blood sample collection : 141.0 mg/dl among those with less than 3-hours of fasting, 132.0 mg/dl among those with 3 to 6 hours of fasting and 116.2 mg/dl among those with more than 6 hours of fasting. The average TG of the entire sample was 132.1 mg/dl which is much higher than that for 6 or more hours of fasting (9). Thus, the age-specific average TG values of the native Japanese and Japanese urban workers used in our analysis are most likely to be overestimated as compared to fasting TG levels of Japanese Americans and the general U.S. population. In the United States, there has been a 15 mg/dl decline in total serum cholesterol for U.S. adults in the thirty years between the First National Health Examination Survey for 1960-1962 and the Third National Health Examination Survey for 1988-1991 (7). Possible factors that may have contributed to this decline are an extensive nutrition education (15), health promotion and disease prevention activities (16), decreased consumption of certain high-fat foods (17), increased use of lipid lowering diets and drugs (18), increased use of post-menopausal estrogen replacement therapy (19) and the development of lower-dose oral contraceptives (19), in addition to the extensive efforts of the National Cholesterol Education Program (NCEP) (20, 21).

In Japan, on the other hand, an increase in average

total cholesterol levels for both Japanese men and women was observed from 1980 to 1990 according to the National Survey : 12.2 mg/dl for men and 16.0 mg/dl for women 30 years old and over (9). This increase may be due to the westernization of the Japanese diet which includes higher amounts of animal fat and protein. Between 1980 and 1990, the consumption of animal protein in Japan rose from 39.2 grams per capita to 41.4 grams and the consumption of animal fat rose from 26.9 grams to 27.5 grams per capita (1).

Kitamura *et al*. conducted cardiovascular risk surveys among Japanese urban male workers in Osaka (22), showing similar trends in TC and HDL-C to those of the urban workers from EARI. Mean TC levels were 194.7 mg/dl for 40-44 years old, 199.7 mg/dl for 45-49 years old, 199.7 mg/dl for 50-54 years old and 205.1 mg/dl for 55-59 years old among Osaka male workers, compared with 198.7 mg/dl for 40-49 years old and 197.2 mg/dl for 50-59 years old among urban male workers fm EARI. Mean HDL-C levels were 56.5 mg/dl for 40-44 years old, 56.1 mg/dl for 45-49 years old, 58.1 mg/dl for 50-54 and 55.7 mg/dl for 55-59 years old among Osaka male workers, compared with 58.9 mg/dl for 40-49 years old and 57.9 mg/dl for 50-59 years old among urban male workers from EARI. Based on results from EARI and Kitamura *et al*., both male and female Japanese urban workers have lower mean TC levels and higher HDL-C levels than the average Japanese population, partly because company workers in Japan are a selected healthy group and partly because they might have a lifestyle which is more favorable concerning cardiovascular health.

There are striking differences between TC levels reported from the Ni-Hon-San study which examined three Japanese male populations between 1965-70 (4) and our findings. The average TC level of Hiroshima based Japanese men was less than 180 mg/dl twenty-five years ago, whereas the average TC level of native Japanese rose to between 191 and 204 mg/dl in 1990. It is also surprising that current TC levels of Seattle Japanese Americans are quite similar to that of San Francisco Japanese Americans 25 years ago ; both populations showed average cholesterol levels ranging from 220-230 mg/dl depending on age. This suggests that as the Japanese lifestyle and diet become increasingly westernized, the low risk status for CHD may be lost. We previously reported that Seattle Japanese Americans have a higher average BMI than native urban Japanese (23). Fujimoto *et al*. reported a higher prevalence of diabetes among Seattle Japanese Americans than U.S. whites or native urban Japanese (24). These factors may partly account for the observed differences in cholesterol levels. The association between environmental factors and lipid and lipoprotein levels in Japanese Americans and native Japanese are currently under our investigation.

It is interesting to note that consistent trends in cholesterol levels between the sexes were observed in all four study groups. TC and TG levels in women rose dramatically after ages 45-50 years at which time menopause typically begins. Average TC levels in premenopausal women were lower than in men, whereas postmenopausal women had higher average TC levels than men. Average TG levels for women remained lower than those of men for all age groups. Estrogen is considered to confer a protective benefit against cardiovascular disease which is mediated in part by its effects on lipoprotein metabolism (25). After menopause, risk factors have been shown to increase, Mathews *et al*. found HDL-C and LDL-C underwent greater menopause-related changes than those associated with aging in the absence of menopause (26).

It is impossible to predict if the incidence and mortality of CHD among Japanese would reach the rate of Americans as TC levels of native Japanese approach that of Americans. Such a question would be answered by future studies because the impact of cholesterol changes on CHD incidence or mortality in a population may take many years before any significant change is observed. Furthermore, there are multiple factors contributing to CHD which need to be examined as well.

As far as CHD mortality is concerned, there still exists a large gap between Japan and the United States (41.4 per 100,000 persons and 188.2 per 100,000 persons, respectively) (1, 2). Therefore, the risks for CHD in the United States need to be reduced. Despite the national campaign to lower cholesterol levels in the United States (20), Seattle Japanese Americans' TC levels were higher than those of the U.S. population. Thus, an investigation is needed to examine the cause of elevated TC levels among Seattle Japanese Americans, and further health promotion and education is essential to lower cardiovascular disease risks for this minority population.

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Biological and Lifestyle Factors, and Lipid and Lipoprotein Levels among Japanese Americans in Seattle and Japanese Men in Japan

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Namekata T (Nikkei Disease Prevention Center, 1605 South Washington, Suite 5, Seattle, WA 98144, USA), Moore D E, Suzuki K, Mori M, Knopp R H, Marcovina S M, Perrin E B, Hughes D A, Hatano S and Hayashi C. Biological and lifestyle factors, and lipid and lipoprotein levels among Japanese Americans in Seattle and Japanese men in Japan. *International Journal of Epidemiology* 1997; **26:** 1203–1213.

Background. It has been previously shown that Japanese Americans in Seattle have significantly higher cholesterol levels than native Japanese. The present study examines the association of biological and lifestyle factors with plasma lipid and lipoprotein levels among Japanese Americans (JA) and native Japanese (NJ) to determine if these associations are consistent between these high and low cholesterol populations.

Methods. Study samples consisted of 710 JA male and 728 JA female volunteers living in the Seattle area and a random sample of 3833 NJ male urban workers who participated in parallel cardiovascular disease screening and lifestyle surveys for 1989–1994. Multiple regression analysis was conducted to examine the association of lifestyle and biological factors with lipid and lipoprotein levels.

Results. Alcohol consumption was positively and linearly associated with high density lipoprotein cholesterol (HDL-C) levels and negatively associated with both low density lipoprotein cholesterol (LDL-C) levels and the ratio of total cholesterol (TC)/HDL-C ($P < 0.05$ to $P < 0.001$) among JA males and JA females and NJ males. Current smoking habit was observed to be negatively associated with HDL-C levels and positively with TC/HDL-C ratio and log TG levels (logarithmic transformation of triglyceride values) ($P < 0.05$ to $P < 0.001$) among all three groups. Body mass index (BMI) was negatively associated with HDL-C levels and positively associated with log TG and TC/HDL-C ratio among all three groups ($P < 0.05$ to $P < 0.001$). Moderate alcohol consumption was negatively associated with log TG levels among JA males and females ($P < 0.05$), whereas heavy alcohol consumption was positively associated with log TG levels in NJ males ($P < 0.001$). Smoking was positively associated with TC and LDL-C levels ($P < 0.05$) among JA males, whereas a negative association ($P < 0.05$) was observed in NJ males.

Conclusion. Overall, the fitted models were consistent between JA males and females and NJ males with the exception of smoking on TC and LDL-C. The results suggest that moderate alcohol consumption favourably influences lipid profiles in both high and low cholesterol populations. The results also indicate that light alcohol consumption is associated with decreased triglyceride levels, whereas heavy alcohol consumption is associated with increased triglyceride levels.

Keywords: alcohol, Japanese, Japanese Americans, lipids, lipoproteins, smoking

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It is well known that high serum total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C) levels are primary risk factors for coronary heart disease (CHD), and high serum levels of high density lipoprotein cholesterol (HDL-C) confer a protective benefit against its development.[1–3] Reducing TC levels has been shown to decrease the risk of CHD[4–6] and the National Cholesterol Education Program (NCEP) has identified LDL-C as the major atherogenic lipoprotein and the primary target of cholesterol lowering therapy.[7] Elevated triglyceride (TG) levels are also considered to increase the risk for CHD, partly because high TG levels are correlated with high levels of LDL-C[8] and low levels of

HDL-C.[9] In addition to constitutional determinants such as age, sex, ethnicity and genetic factors, other variables such as dietary fat and lifestyle factors including physical activity, alcohol consumption and smoking habit are known to affect serum lipid and lipoprotein levels.[10,11]

Compared with other industrialized nations, Japanese are known to be at a lower risk for CHD.[12] Annual CHD mortality rates per 100 000 population were 41.8 in Japan (1991),[13] 86.9 in France (1990),[14] 192.5 in the US (1991),[15] and 294.6 in England and Wales.[14] Cross-cultural epidemiological studies conducted more than two decades ago have shown that lipid levels and the prevalence of CHD was lowest among native Japanese in Japan, higher in Japanese Americans living in Hawaii and highest in Japanese Americans living in California.[16]

Over the past 25 years since the initiation of the Ni-Hon-San Study[16] there have been dramatic changes in health behaviours among Americans, including a decrease in the number of smokers, a decrease in the level of alcohol consumption and an increase in physical activity level.[17–19] Among native Japanese, there has been an increase in fat intake and alcohol consumption and a decline in smoking.[20] Despite these changes, current studies have shown that Seattle Japanese Americans have significantly higher TC levels and TG levels and lower HDL-C levels than native Japanese urban workers.[21] The present study examines the association between biological and lifestyle factors among Japanese Americans (JA) in Seattle and native Japanese (NJ) in Japan to examine if the associations are consistent between these low and high cholesterol groups. Such cross-cultural comparisons allow for minimization of the genetic components influencing lipid levels, and thus provide a better understanding of the impact of environmental factors including changes in lifestyle and constitutional factors on lipid and lipoprotein levels.

MATERIALS AND METHODS

Parallel cardiovascular disease screening was conducted by the Nikkei Disease Prevention Center in Seattle, Washington from 1989 to 1994 and the Epidemiological Arteriosclerosis Research Institute (EARI) in major cities in Japan in 1994. The study sample consisted of male and female JA residing in the greater Seattle area (King County) and NJ males from major metropolitan areas in Japan who participated in screening at EARI. Japanese American screening participants were respondents from a media and family registration campaign conducted by mail. A total of 1438 individuals (710 men and 728 females) who are of full Japanese ancestry aged 30–79 years participated in the study with complete clinical and lifestyle information. The composition of the study sample with respect to generation was as follows: 12.3% Issei (first generation), 49.4% Nisei (second generation), 37.0% Sansei (third generation) and 1.3% Yonsei (fourth generation). The study sample represented 12.7% of the JA men and 10.3% of JA women in the Seattle area according to an estimation of the JA population based on the 1990 US Census.[22]

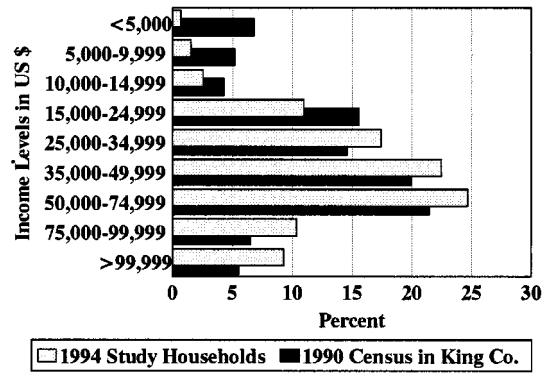

FIGURE 1 *Income distribution of 1175 study participants' households and the Japanese American households of the 1990 US census in King County*

Due to the fact that the study subjects in Seattle were voluntary participants, we conducted an additional survey on 1994 household income levels to better define our study sample characteristics and examine whether they were representative of the JA population in Seattle. We compared the household incomes from study participants with that of JA households in the 1990 census for King County.[23] Figure 1 shows that the income distribution of the screening participants is slightly higher than that reported for the JA population in King County for the 1990 census. We will later discuss possible response bias observed in the study results.

Native Japanese study subjects consisted of mostly urban white collar employees from major cities in Japan, including Tokyo, Chiba, Osaka, Sapporo, and Kitakyushu. A total of 3833 study subjects were randomly drawn from a pool of 28 635 male employees of various companies in Japan who had participated in cardiovascular disease screening conducted by EARI in 1994. Their occupations were classified as follows: 50.8% professionals, researchers, engineers and highly trained technicians, 35.7% administrators, accountants, salesmen and survey staff, and 13.5% others. In general, annual health screening is offered by the respective company as part of the employee's health benefits and participation is almost mandatory.

Venous blood samples were obtained after a 12-hour fast from JA study participants. Lipid analyses were conducted at the University of Washington Northwest Lipid Research Laboratories which participates in the Centers for Disease Control and Prevention/National Heart, Lung and Blood Institute's lipid standardization programme. Total cholesterol and TG levels were measured enzymatically on the Abbott Spectrum analyser using methods standardized to in-house reference methods and to the CDC's reference methods and in-house prepared reagent.[24] The HDL-C levels were measured by dextran sulphate magnesium precipitation method.[25] The LDL cholesterol was determined by the Friedewald algorithm: LDL-C = TC minus HDL-C minus TG/5.[26] Because LDL-C estimation becomes less accurate if the TG value >400 mg/dl, we excluded these few cases from statistical analysis involving LDL-C.[27]

Among the NJ screening participants, non-fasting venous blood samples were analysed by EARI's laboratory in Japan. Total cholesterol was measured by an enzymatic method which was described by Allain *et al.*[28] Serum TG levels were determined by a colorimetric method with lipoprotein lipase and glycerol dehydrogenase.[29] The HDL-C measurement was done by using the dextran sulphate magnesium method.[30] The LDL-C was determined by the Friedewald algorithm.[26]

Quality control (QC) examinations for EARI's laboratory were conducted by shipping frozen serum samples twice from Seattle to EARI prior to the screening. For each QC examination, nine standardized samples were used for TC measurements and six standardized samples were used for TG, LDL-C and HDL-C. After adjustments were made at EARI's laboratory based on the values obtained from the first measurements, all measured values in the second QC examination fell within 5% of the true value (10% range criteria was established for HDL-C), with the exception of a few samples. High correlation coefficients were obtained between true values and the second measurement values: r = 0.999 ($P < 0.01$) for TC, r = 0.969 ($P < 0.01$) for HDL-C, r = 0.910 ($P < 0.05$) for LDL-C and r = 0.999 ($P < 0.01$) for triglycerides.

Height and weight were measured with participants clothed in a hospital gown. Body mass index (BMI) was obtained by dividing weight in kilograms by the square of height in metres. Similar questionnaires were self-administered at the time of screening, which contained questions on personal and demographic background, disease history and lifestyle factors; one written in Japanese for NJ participants, and one in English for JA. Only those questions which could be considered comparable were used in our analysis. Average daily alcohol consumption was estimated based on responses to specific questions regarding frequency of drinking, size of serving and type of alcoholic beverage consumed. The estimated average amount of alcohol consumed was converted to pure alcohol equivalents. Then, one drink was defined as an equivalence of 10 g of pure alcohol. The study samples were stratified into six groups: non-drinkers, <1 drink/week, 1–6 drinks/week, 1–2 drinks/day, 3–5 drinks/day and >5 drinks/day and treated as dummy variables. Participants who had quit drinking less than one year ago were considered to be current drinkers.

Multiple regression models were constructed to explain differences in levels of lipids and lipoproteins by age, BMI, hypertensive medication, alcohol consumption and smoking status. Because TG values were highly skewed, logarithmic transformation of TG values was performed for normalization for regression analysis. All analyses were conducted separately by sex using IBM AT with SPSSPC + V3.0.[31]

RESULTS

Characteristics of the JA and NJ study samples are presented in Table 1. The average age for each of the three groups fell between 55 and 56 years. Higher averages of BMI, TC, LDL-C, TG and TC/HDL ratio were observed in JA males and females as compared to NJ males. The HDL-C average values were highest in JA females (63.2 mg/dl), lowest in JA males (51.0 mg/dl) and the average value for NJ males fell in the middle (55.4 mg/dl). There was a great difference in the amount of alcohol consumed between JA males and NJ males: NJ men consumed more than four times the amount consumed by JA men (27.3 versus 5.8 g/day). The percentage of current smokers was three times higher in NJ males than in JA males (46.0% versus 15.4%), while only 9% of JA women smoked. Current use of anti-hypertensive medication was more prevalent in both JA men and women than in NJ men. Overall, the lipid profiles of JA men and perhaps JA women (with the exception of high HDL-C averages) were worse than in NJ men despite less smoking and alcohol consumption among JA participants.

Table 2 summarizes the results of multiple regression analysis to explain differences in lipoprotein and lipid levels in JA and NJ male participants and JA female participants with age, BMI, level of alcohol consumption, smoking status and hypertensive medication as explanatory variables. The strength of the association, indicated by R^2, of lipids and lipoproteins with lifestyle and biological factors varied from 4.6% in the TC model to 19.7% in the HDL-C model among JA

TABLE 1 *Characteristics of Japanese Americans in Seattle, Washington, USA and native urban Japanese in Japan who participated in screening*

	Japanese American males n = 710		Japanese American females n = 728		Native Japanese males n = 3833	
	Mean	SD[a]	Mean	SD	Mean	SD
Age	56.4	13.7	55.9	13.6	55.6	7.7
BMI	25.7	3.2	24.0	3.8	23.8	2.7
TC[b] (mg/dl)	224.1	37.8	227.3	41.6	191.1	32.4
LDL-C[c] (mg/dl)	139.1	35.3	135.0	38.0	108.6	31.1
HDL-C[d] (mg/dl)	51.0	14.0	63.2	16.7	55.4	14.3
Triglycerides (mg/dl)	169.8	158.6	143.9	120.5	135.6	101.3
Log TG[e]	4.9	0.6	4.8	0.6	4.7	0.6
TC/HDL ratio	4.7	1.4	3.9	1.3	3.7	1.1
Alcohol (g/day)	5.8	11.9	1.3	4.6	27.3	22.2
	No.	%	No.	%	No.	%
Drinking habit						
Nondrinkers	257	36.2	389	53.4	686	17.9
<1 drink/week	157	22.1	212	29.1	378	9.9
1–6 drinks/week	157	22.1	98	13.5	621	16.2
1–2 drinks/day	89	12.5	24	3.3	516	13.5
3–5 drinks/day	44	6.2	4	0.5	1015	26.5
>5 drinks/day	6	0.8	1	0.1	617	16.1
Smoking						
Nonsmokers	265	37.3	512	70.3	1355	35.4
Current smokers	109	15.4	66	9.1	1762	46.0
Ex-smokers	336	47.3	150	20.6	716	18.7
Hypertensive medication	102	14.4	112	15.4	413	10.3

[a] SD = standard deviation.
[b] Total cholesterol.
[c] Low density lipoprotein cholesterol.
[d] High density lipoprotein cholesterol.
[e] Triglycerides.

males with the strongest association found in HDL-C. Among NJ males the strength of the association, R^2, varied from 4.2 in the TC model to 16.4 in the TC/HDL model. The R^2 in the regression models for JA females were high overall: from 15.4% in the HDL-C model to 26.9% in the log TG model. The appearance of significant regression coefficients varied somewhat between the three groups and between models. In the models predicting TC levels, there was a positive association with age in all three groups ($P < 0.001$) and BMI appeared positively significant in both JA females and NJ males ($P < 0.001$). Current smoking habit was observed to be positively associated with TC levels in JA males ($P < 0.05$), whereas in NJ males, a negative association was observed ($P < 0.05$).

Similar relationships were found for LDL-C levels as well; age was positively associated with LDL-C levels among all three groups ($P < 0.001$), and BMI was positively associated among NJ males and JA females ($P < 0.001$). Hypertensive medication was negatively associated with LDL-C in JA females ($P < 0.05$) and NJ males ($P < 0.01$). Among NJ males, LDL-C levels showed a negative association to levels of alcohol consumption in a dose dependant manner ($P < 0.01$ to $P < 0.001$). Alcohol consumption significantly reduced levels of LDL-C in JA males and females at one to two drinks per day ($P < 0.05$). Opposite associations were seen with current smoking status; a positive association was observed among JA males ($P < 0.05$), whereas in NJ males, smoking was negatively associated with LDL-C levels ($P < 0.05$).

The relationships observed between HDL-C and the explanatory variables were consistent between all three study groups. Overall, HDL-C was positively associated with alcohol consumption in a dose dependant manner ($P < 0.001$) and negatively associated with BMI ($P < 0.001$) and smoking ($P < 0.05$ to $P < 0.001$) in all three groups.

TABLE 2 *Multiple regression coefficients for examining the association between lipid and lipoprotein levels and biological and lifestyle factors*

Explanatory variables	Total cholesterol (mg/dl)			Low density lipoprotein cholesterol (mg/dl)			High density lipoprotein cholesterol (mg/dl)		
	JA[a] males	JA females	NJ[b] males	JA males	JA females	NJ males	JA males	JA females	NJ males
Age	0.419***	1.372***	0.243***	0.342**	0.956***	0.186**	0.029	0.048	0.057*
	(0.117)[c]	(0.112)	(0.069)	(0.104)	(0.104)	(0.065)	(0.040)	(0.047)	(0.028)
BMI	0.629	1.279***	2.166***	0.693	1.565***	1.966***	–1.203***	–1.387***	–1.567***
	(0.443)	(0.368)	(0.195)	(0.395)	(0.347)	(0.184)	(0.151)	(0.157)	(0.081)
Hypertensive	5.730	–4.355	–1.997	2.882	–8.536*	–4.476**	1.637	–0.314	0.099
medication	(4.120)	(4.045)	(1.709)	(3.797)	(3.813)	(1.616)	(1.428)	(1.677)	(0.705)
Drinking habit									
Nondrinkers (ref)									
<1 drink/week	–0.096	1.020	2.142	1.647	0.796	–0.097	–1.162	1.551	2.730**
	(3.860)	(3.291)	(2.048)	(3.432)	(3.078)	(1.936)	(1.311)	(1.364)	(0.845)
1–6 drinks/week	2.348	–1.498	0.227	2.946	–6.844	–4.713**	1.103	6.600***	4.632***
	(3.830)	(4.483)	(1.773)	(3.436)	(4.183)	(1.676)	(1.302)	(1.858)	(0.731)
1–2 drinks/day	–7.710	–3.902	–1.622	–10.179*	–16.367*	–5.568**	7.927***	12.682***	4.858***
	(4.650)	(7.922)	(1.858)	(4.109)	(7.287)	(1.757)	(1.581)	(3.284)	(0.767)
3–5 drinks/day	10.307	–3.859	0.494	–7.895	–20.436	–8.518***	15.348***	26.940***	9.565***
	(6.120)	(18.910)	(1.584)	(5.570)	(17.377)	(1.497)	(2.081)	(7.839)	(0.653)
>5 drinks/day[d]	6.333		1.451	–9.744		–16.244***	15.988**		11.051***
	(15.402)		(1.797)	(13.434)		(1.699)	(5.237)		(0.741)
Smoking habit									
Nonsmokers (ref)									
Smokers	8.648*	2.879	–2.495*	8.048*	6.615	–2.393*	–2.951*	–6.411**	–5.406***
	(4.358)	(5.104)	(1.173)	(3.957)	(4.650)	(1.109)	(1.482)	(2.079)	(0.484)
Ex-smokers	–1.571	–2.812	2.951	–0.586	0.550	1.476	–1.433	–2.226	–1.171
	(3.398)	(3.502)	(1.478)	(3.044)	(3.258)	(1.397)	(1.155)	(1.452)	(0.609)
Intercept	182.8	120.8	127.7	103.9	47.3	60.1	79.1	93.0	86.6
R^2(%)	4.6	21.1	4.2	4.7	16.3	6.5	19.7	15.4	16.0
F value	3.35***	19.15***	16.61***	3.30***	13.58***	26.53***	17.20***	13.10***	72.91***

continued overleaf

For TC/HDL-C ratio, consistent relationships were observed among all three groups as well; TC/HDL-C ratio was negatively associated with alcohol consumption in a dose-dependant manner ($P < 0.05$ to $P < 0.001$) and positively associated with BMI ($P < 0.001$) and current smoking habit ($P < 0.05$ to $P < 0.001$).

Triglyceride levels (log TG) appeared to be more strongly correlated with lifestyle and biological factors in JA females than in JA males. For JA females, all explanatory variables with the exception of two categories (ex-smokers and >5 drinks/day) showed a significant relationship to log TG; age ($P < 0.001$), BMI ($P < 0.001$) and medication for hypertension ($P < 0.05$) were positively associated and alcohol consumption was negatively associated ($P < 0.05$). Among JA males, log TG was positively associated with BMI ($P < 0.001$) and smoking status ($P < 0.05$) and negatively associated with a level of alcohol consumption of 1–2 drinks/day ($P < 0.05$). Among NJ males, log TG levels were positively associated with BMI ($P < 0.001$), hypertensive medication ($P < 0.05$), a level of alcohol consumption of ⩾5 drinks/day ($P < 0.001$), current smoking habit and ex-smoking habit ($P < 0.001$).

DISCUSSION

The observed relationships in the present study were fairly consistent between JA and NJ study participants for models predicting TC and HDL-C levels. Some differences were observed in the models predicting LDL-C and log TG levels. The analysis for each lipid component examined will be discussed separately.

Age and BMI were associated with a significant increase in TC levels among JA females and NJ males. Among JA males, age but not BMI was a significant predictor of TC levels. Other studies have shown that the association between TC and lifestyle factors was not strong.[32] The Honolulu Heart Study[11] showed no

TABLE 2 *Continued*

Explanatory variables	log Triglycerides (mg/dl)			Total cholesterol/High density lipoprotein cholesterol		
	JA males	JA females	NJ males	JA males	JA females	NJ males
Age	0.002	0.016***	0.001	0.006	0.020***	0.002
	(0.002)	(0.002)	(0.001)	(0.004)	(0.004)	(0.002)
BMI	0.050***	0.048***	0.068***	0.112***	0.104***	0.138***
	(0.007)	(0.005)	(0.003)	(0.016)	(0.012)	(0.006)
Hypertensive	0.054	0.120*	0.064*	0.022	0.012	–0.043
medication	(0.066)	(0.059)	(0.028)	(0.149)	(0.129)	(0.054)
Drinking habit						
Nondrinkers (ref)						
<1 drink/week	–0.008	–0.102*	–0.041	0.091	–0.128	–0.171**
	(0.061)	(0.048)	(0.038)	(0.137)	(0.104)	(0.065)
1–6 drinks/week	–0.042	–0.145*	0.008	–0.050	–0.382**	–0.353***
	(0.061)	(0.065)	(0.029)	(0.136)	(0.143)	(0.056)
1–2 drinks/day	–0.172*	–0.059*	–0.052	–0.837***	–0.721**	–0.397***
	(0.074)	(0.115)	(0.031)	(0.165)	(0.253)	(0.059)
3–5 drinks/day	0.099	–0.611*	–0.036	–0.986***	–1.356*	–0.645***
	(0.097)	(0.275)	(0.026)	(0.218)	(0.603)	(0.050)
>5 drinks/day[‡]	0.048		0.137***	–1.089*		–0.677***
	(0.244)		(0.030)	(0.548)		(0.057)
Smoking habit						
Nonsmokers (ref)						
Smokers	0.136*	0.168*	0.173***	0.512**	0.397*	0.341***
	(0.069)	(0.073)	(0.019)	(0.155)	(0.160)	(0.037)
Ex-smokers	–0.007	–0.043	0.096***	0.057	0.131	0.140***
	(0.054)	(0.051)	(0.024)	(0.121)	(0.112)	(0.047)
Intercept	3.5	2.8	3.0	1.5	0.3	0.5
R^2(%)	8.5	26.9	14.0	14.5	18.5	16.4
F value	6.49***	26.33***	62.20***	11.86***	16.32***	74.71***

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.
[a] Japanese American.
[b] Native Japanese.
[c] Standard error.
[d] No meaningful result for JA females could be obtained because only one person fell in this category.

strong association between lifestyle factors and TC in Japanese American men. Similarly, in the study examining Japanese white collar male workers,[33] age and BMI were significantly related to TC, but alcohol consumption was not. Total cholesterol is considered a crude indicator of lipid profile status, and factors such as alcohol may have opposite effects on TC components, LDL-C (negative) and HDL-C (positive), resulting in nonsignificant or spurious associations between lifestyle factors and TC.

Low density lipoprotein cholesterol has been labelled as the major atherogenic lipoprotein and has become the primary focus for cholesterol lowering therapy.[7] As observed in the model for TC, BMI was a significant predictor of LDL-C in JA females and for NJ males, but not among JA males. Similar to the Honolulu Heart Study[11] and other studies with native Japanese males[33] and American females,[34] alcohol consumption was significantly associated with reduced LDL-C levels in all three groups of our study. This effect was significant only at a consumption level of 1–2 drinks/day among JA subjects whereas among NJ it was significant for all levels of regular alcohol consumption. Sample size between study populations may account for such observed differences, in that the majority of JA study subjects were found to be non- or light to moderate drinkers with only a small percentage consuming ⩾3 drinks/day.

In accordance with numerous other epidemiological studies,[10,11,33,35,36] HDL-C levels were positively associated with alcohol consumption and inversely associated with BMI and smoking in both JA and NJ screening participants. Table 3 presents regression models for

TABLE 3 *Comparison of regression models for high density lipoprotein cholesterol among epidemiological studies*

Explanatory variables	Seattle Japanese Americans Seattle Nikkei Health Study		Native Japanese urban workers Seattle Nikkei Health Study	Hawaiian Japanese Americans Yano *et al.*[11]	US & Japan telephone company executives Ohara *et al.*[36]	Native Japanese white collar employees Choudhury *et al.*[33]
	Females	Males	Males	Males	Males	Males
Race (American versus Japanese)					–4.157***	
Age	NS[a]	NS	0.057*	NS	NS	0.132*
BMI	–1.387***	–1.203***	–1.567***	–1.351***	–0.726***	–1.408***
Medication for hypertension	NS	NS	NS	–1.589*		
Drinking habit						
Nondrinkers versus current drinker				0.544***		
<1 drink/week	NS	NS	2.730**			
1–6 drinks/week	6.600***	NS	4.632***			
1–2 drinks/day	12.682***	7.927***	4.858***			
3–5 drinks/day	26.940***	15.348***	9.565***			
>5 drinks/day		15.988***	11.051***			
<once/day					5.257***	
<30 cc/day					6.457***	
>30 cc/day					9.104***	
Alcohol (ml/day)						0.102***
Smoking habit						
Nonsmokers versus current smokers	–6.411**	–2.951*	–5.406***	NS	–4.004***	
ex-Smokers	NS	NS	NS			
no. of cigarettes/day						–0.164***
Physical activity				0.209*	1.806**	
Walking				NS		
Diastolic blood pressure				NS		
Haematocrit (%)				NS		
Serum uric acid (mg/dl)					–1.633***	
Intercept	92.97	79.11	86.6	65.10	73.60	not available
R^2 (%)	15.4	19.7	16.0	17.5	11.2	21.1
Sample size	728	710	3833	1363	1499	1010
Average age	56	56	56	68	46	47

*$P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.
[a] Not significant.

HDL-C obtained from the present study and other similar studies as follows JA males in the Honolulu Heart Study,[11] Japanese and American caucasian male telephone executives,[36] and NJ white collar workers in Japan.[33] The HDL-C levels were positively associated with alcohol and negatively with BMI in all four studies. A significant positive association between HDL-C levels and age was observed in NJ male subjects and in NJ white collar employees.[33] Smoking was consistently inversely associated with HDL-C levels with the exception of the Honolulu Heart Study. Many other studies have noted an inverse relationship between smoking and HDL-C levels,[10,37–42] which in conjunction to alteration of HDL-C's antiatherogenic properties,[43] is one mechanism proposed whereby smoking increases the risk of coronary atherosclerosis.

Similar to the LRC study[44] and others,[11,33] BMI was found to be positively associated with TG levels in all three groups. Alcohol consumption has also been reported to be positively associated with TG levels.[11,44,45] Among the NJ male study subjects, heavy alcohol consumption (>5 drinks/ day) was associated with a significant increase in TG levels, whereas alcohol consumption was negatively associated with TG levels in JA males who consumed 1–2 drinks/day and in JA women who consumed any amount. The difference in the fitted models for TG between JA males and NJ males might have been influenced by the difference in

alcohol consumption levels: JA male drinkers were predominantly light to moderate drinkers, whereas NJ male drinkers were predominantly moderate to heavy drinkers. A similar relationship was shown in NJ male subjects by Choudhury *et al.*;[33] light drinkers had significantly lower TG levels than heavy drinkers. Similarly, in British men[46] heavy drinking habit has a tendency to raise TG levels. However, log TG levels were significantly and negatively associated with more drinking levels in females than in either JA or NJ males despite the fact that JA females drink much less than JA and NJ males. This implies that even slight intake of alcohol might lower TG levels among females but not among males. In the future, this issue should be investigated in other female populations as well.

Anti-hypertensive medications, e.g. diuretics and selective and non-selective beta-blockers, have been shown to adversely affect blood lipids.[47] In our study, anti-hypertensive medication showed a negative association with LDL-C and a positive association with log TG in JA females and NJ males. The majority of study participants using anti-hypertensive medications were taking either diuretics, calcium channel blockers or adrenergic blockers, and a few of them were taking angiotensin converting enzyme inhibitors and vasodilators. Yano *et al.*[11] reported that anti-hypertensive medication (mainly thiazide diuretics) was associated with reduced HDL-C levels and increased TG levels independent of diastolic blood pressure, BMI and other confounding factors. In our study the sample size was too small to analyse the data by types of hypertensive medication.

Another observed difference between study groups was the effect of smoking on TC and LDL-C levels between JA and NJ males. Among JA males, a positive association between current smoking habit and TC or LDL-C levels was observed. This is consistent with other studies as reviewed by Craig *et al.*[48] In order to determine if the significant effects of smoking on lipid levels (TC, TC/HDL-C, HDL-C, LDL-C and log TG) depend on drinking habits, an effect for the interaction between smoking and drinking was estimated for each regression equation in the samples of Seattle JA. No significant interaction effects were found except for LDL-C among JA males ($F_{4,665} = 2.72$, $P < 0.05$). The results suggest that the effect of smoking on LDL-C is substantially greater for drinkers than for ex-drinkers and nondrinkers among JA males but not among JA females. Among NJ males the association of smoking with TC and LDL-C was found to be significant but negative. Choudhury *et al.* reported negative non-significant associations between the number of cigarettes smoked and TC or LDL-C levels among NJ male white collar male employees.[33] It is quite possible that other factors such as dietary intake might act as a confounding variable or interact with smoking to influence serum lipid levels among NJ men. Interactions between smoking and alcohol consumption with diet are currently under investigation in our study population.

The results of the present study need to be interpreted within the context of some limitations. One potential bias is that the sample was not randomly drawn from the JA population in the Seattle area and nonparticipants may have different characteristics and health status than participants. Other surveys have shown that non-participants have poorer health than participants,[49,50] and if this were the case in our survey, it would be possible that we might have observed a higher percentage of current smokers and drinkers among non-participants. In order to examine this issue further, we conducted an additional survey to determine the 1994 annual household income levels of our study sample and compared their income distribution with that of JA households in King County from the 1990 US census (which includes Seattle and the surrounding metropolitan area) (Figure 1).[23] Although our sample distribution is slightly shifted to higher income levels as compared to the census distribution, it is remarkably similar to that of JA in King County. The 4-year gap between our sample and the census population might have contributed to the slightly higher income levels observed in our study sample because of the rate of inflation in household income. Additionally, lipid levels were compared among JA men and women according to household income levels. No differences were found except for average HDL-C levels: 56.6 mg/dl for $<$ \$25 000, 57.6 mg/dl for \$25 000–\$49 999 and 52.9 mg/dl for $>$\$49 999; and thus, it may be considered that our Seattle JA sample reasonably represents the JA population in the area, although we must be cautious about possible selection bias in a comparison of health outcomes between populations.

Native Japanese screening participants represent urban white collar office workers from several major metropolitan areas in Japan. Overall, workers are considered to be healthier than the general population. In fact, comparison in TC and LDL-C between the two populations shows that urban workers had significantly lower averages than the general Japanese population.[21]

Fasting requirements were not imposed on NJ urban workers, whereas JA were required to fast 12 hours prior to blood drawing. Nonfasting status has been shown to influence TG levels. The National Cardiovascular Disease Examination Survey Report[51] shows an inverse relationship between average TG levels and the number of fasting hours before blood drawing: 141.0 mg/dl among those with $<$3 hours of fasting, 132.1 mg/dl among those

with 3–6 h of fasting and 116.2 mg.dl among those with >6 h of fasting. Despite the nonfasting requirements, NJ men had considerably lower TG values as compared with JA males: 135.6 mg/dl and 169.8 mg/dl, respectively. Also, nonfasting requirements might have influenced LDL-C values among native Japanese because LDL-C values were estimated based on the Friedewald equation, which includes TG. However, if any systematic bias were introduced due to nonfasting status, the deviation from true values of LDL-C would be quite small and almost negligible because TG values are divided by a factor of five in the estimation. Furthermore, the average LDL-C level of NJ males was much lower than that of JA males (108.6 mg/dl versus 139.1 mg/dl).

Nutrient intake was not included in the present analysis and may enhance predictive value of the current models or act as potential confounding factors to BMI, smoking and alcohol consumption. Some investigators have reported that calories from alcohol supplements normal energy intake,[52–54] whereas others have found that calories from alcohol replaces energy intake from other sources, especially in heavy drinkers.[55] Physical activity was also not included in the present analysis which has been shown to increase HDL-C levels.[11,36] In our previous investigation with Seattle JA males,[56] we observed no significant relationship between physical activity and HDL-C levels. This may have been due to the fact that the majority of Seattle JA males were found to be fairly sedentary, thus any associations may not be apparent in this group. We suspect that NJ urban workers are more physically active due to various factors such as limited use of automobiles, more commuting by public transportation, and thus more walking in metropolitan areas in Japan. Effects of dietary habits and physical activity on lipid levels are currently under investigation.

In conclusion, the observed associations between plasma lipid and lipoprotein levels and biological and lifestyle factors among the three study groups (Seattle JA males and females and NJ males) are consistent with findings from other studies. Recently, we have reported that Seattle JA males and females have significantly higher total serum cholesterol levels[21] and others have reported higher prevalence of diabetes[57] among Seattle JA than among NJ or the general American population. Thus, it is apparent that the current campaign by CDC for 'Healthy People 2000'[58] which includes lowering total cholesterol levels to an average of <200 mg/dl before year 2000 and changing lifestyle to promote cardiovascular health is quite relevant to Seattle JA. Although such general guidelines are quite useful, there is a growing appreciation for the interaction between environmental and genetic factors to the contribution of cardiovascular disease, and thus sensitivity to changes in environment and diet may vary significantly between ethnic groups. Current studies conducted with Seattle JA suggest that a westernized lifestyle may be more harmful to people of Japanese ancestry who may have a greater propensity for the development of various metabolic abnormalities such as diabetes[57] and hyperlipidaemia.[21] Further cross-cultural investigations of this nature which reduce the genetic variation between cohorts are important for providing a clearer picture of the mechanisms involved in these complex relationships.

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A study of the association between the aortic pulse wave velocity and atherosclerotic risk factors among Japanese Americans in Seattle, U.S.A.

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Abstract

Cardiovascular disease prevention screening was conducted among 1389 Japanese Americans in Seattle, Washington, U.S.A. from 1989 to 1994. The association between atherosclerotic risk factors and the aortic pulse wave velocity (PWV), an indicator of atherosclerosis, was examined by using multiple logistic regression method. Based on a study in 1996 by Suzuki et al. on the association between PWV and atherosclerotic indicators, abnormally high PWV was defined as 8.0 m/sec. and over for those less than 60 years of age and 9.0 m/sec. and over for those 60 years of age and older. Significant odds ratios to estimate the risk for the presence of abnormally high PWV were found in age >or= 60 years (4.31, $p < 0.001$), hypertension (2.00, $p < 0.001$), diabetes (5.65, $p < 0.001$), current drinker (0.44, $p < 0.001$), ex-drinker (0.49, $p < 0.05$), and ex-smoker (1.82, $p < 0.01$) among men. Women showed a similar association: age > or = 60 years (3.03, $p < 0.001$), hypertension (1.94, $p < 0.01$), diabetes (2.47, $p < 0.05$), TC/HDL-C >or= 4.5 (1.98, $p < 0.001$), current drinker (0.47, $p < 0.001$), and ex-drinker (0.45, $p < 0.05$). Our findings are almost identical to those from other studies showing the association between coronary heart disease and its risk factors. The question of whether PWV can be a predictor of atherosclerotic diseases, particularly coronary heart disease, remains to be answered by additional studies. However, PWV may serve as a simple and valuable indicator to estimate the extent and severity of asymptomatic atherosclerosis in the large artery.

I. Introduction

Some researchers have pointed out for a long time that pulse wave velocity (PWV) is closely related to modulus of elasticity of arterial wall[1,2]. Hasegawa and Otsuka established the experimental and theoretical rationale for aortic pulse wave velocity as a non-invasive and quantitative index reflecting atherosclerosis[3,4]. Morishita followed up the examinees of PWV measurement for one year and reported that the average PWV measurement of those who developed cerebrovascular and/or cardiovascular diseases (angina, AMI, cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage and transient ischemic attacks (TIA)) was significantly higher than that of those who did not[5]. Others reported that an average PWV

measurement is significantly higher in patients under treatment of hypertension, diabetes and hypercholesterolemia (60 years old and over) than in healthy normal controls[6~8]. If PWV serves as an index of atherosclerosis, it can be hypothesized that PWV is also significantly related to risk factors of atherosclerosis. In this study, we tested this hypothesis by applying it to health screening data of Japanese Americans in Seattle, U.S.A.

II. Methods

Participants were recruited by way of informal channels such as advertisements in local community newspapers, billboards in shopping centers and direct mails utilizing directories of the Japanese community compiled by NDPC (Nikkei Disease Prevention Center) soliciting participation in health examinations, because the U.S. has no official resident registry records like Japan. The study subjects thus recruited were 1,389 Japanese Americans aged 20 years old and older who voluntarily participated in preventive cardiovascular disease screening conducted by NDPC in Seattle, Washington, U.S.A. (Prior to 1992, subjects were voluntary participants (about 10%), but after 1993 subjects were randomly selected, about 90% of entire samples). Breakdowns of generation were, 12% for the first generation, 49% for the second generation, 37% for the third generation and 2% for the fourth and above.

Health examinations included PWV, electrocardiogram (EKG), observation of small artery changes in retina, serum lipid and lipoproteins, height, weight, pulmonary function tests and urinalysis. Participants were asked to fill out the self-administered questionnaire including occupation, past medical history, lifestyle and nutrition.

PWVs were measured by medical technicians (who were trained in Japan) using a PWV-200 device (Fukuda Denshi Co., Tokyo, Japan). As illustrated in Figure 1, the time difference between the upstarts of carotid and femoral pulse wave propagation(t) and the time difference between the upstart of the first component of the heart sound II and the notch on propagation of carotid pulse wave (tc) are measured. If the distance between the aortic valve and the pulsation point on femoral artery is denoted as D, then PWV is calculated as $[D \times 1.3/(t+tc)]_p$. Here, D x 1.3 reflects a correction factor considering anatomical structure. PWV values are adjusted at 80 mmHg of diastolic blood pressure (DBP) which is denoted as p because PWV values are highly correlated to DBP.

Lipids and lipoproteins were measured by the Northwest Lipid Research Laboratories of the University of Washington whose quality control is under strict surveillance by CDC. Total cholesterol was measured by the enzymic Abbot spectrum method, and high density lipoprotein cholesterol (HDL) was measured by the dextran sulfate-magnesium precipitation method.

Suzuki, et al. studied the relationship between PWV values and age-specific prevalence of atherosclerotic diseases based on the data involving more than 220,000 subjects[9]. According to his findings, prevalence of abnormal systolic blood pressure (SBP), arteriolar sclerotic changes of retinal artery and ischemic changes of EKG among those younger than 60 years old with PWV $\geq$8 m/sec and among those 60 years of age and over with $\geq$9 m/sec

became significantly elevated than that among all persons of the corresponding age groups with <8 m/sec for and <9 m/sec, respectively. Accordingly, the PWV value was used as a dependent variable and an abnormal PWV value was defined as the one >8 m/sec for those younger than 60 years of age and as the one >9 m/sec for those 60 years of age and older: coded “1” for abnormality and “0” for no abnormality. The following explanatory variables were also dichotomized as follows:

age (≥60:1, <60:0)

sex (male:1, female:0)

hypertension (present:1, not present:0): Hypertension is defined as either SBP≥160 mmHg or DBP≥95 mmHg plus anybody who is taking antihypertensive drugs.

diabetes (present:1, not present:0): History of diabetes is based on responses in self-administered questionnaires.

total cholesterol/HDL cholesterol (≥4.5:1, <4.5:0): Because an average ratio in American men is 4.5, we assumed that the ratio above this signifies an elevated risk of coronary heart disease[10].

Body Mass Index (BMI) (>27:1, ≤27:0): BMI=body weight (kg)/height(m)^2 and above 27 is defined as obesity.

Drinking habit was classified into three categories: non-drinkers, current drinkers, ex-drinkers, and an odds ratio was calculated with non-drinkers as controls. Likewise, smoking habit was classified into three categories and an odds ratio was calculated with non-smokers as controls.

The relationship between PWV and atherosclerotic risk factors was examined using multiple logistic regression analysis[11]. We did not adopt linear multiple regression analysis because the relationship between PWV values and atherosclerotic risk factors (e.g., hypertension and diabetes) is not linear and hence inappropriate for linear multiple regression analysis. Multiple logistic regression analysis is preferable for quantitatively estimating the magnitudes of individual risk factors regarding the abnormal PWV findings. All statistical analysis was conducted by using IBM/AT, SPSSPC+V3.0[12].

III Results

Table 1 shows characteristics of screening participants of Japanese Americans in Seattle. Their average age was 56 years old for both men and women. Average PWV values were 8.0 m/sec for men and 8.1 m/sec for women. Averages of BMI were 25.6 for men and 23.9 for women, indicating that men were slightly heavier than women. Average SBP was higher in men (133 mmHg) than in women (128 mmHg). Although average total cholesterol levels were almost the same for women and for men (226 vs 224 mg/dl), the average HDL cholesterol

level for women was higher by 12 mg/dl than for men, making the average of TC:HDL ratios 4.7 for men and 3.8 for women. The TC:HDL ratio for men was greater than 4.5, a threshold above which a risk of myocardial infarction becomes significantly elevated. The sex difference in drinking was large: while men consume 6.0 g of pure alcohol per day, women consume only 1.4 g. Proportion of current drinkers was 65% in men and 46% in women. Proportion of current smokers was 15% in men and 9% in women.

Table 2 indicates distribution patterns of PWV values by age. The distribution of PWV values becomes skewed toward higher age brackets with a wider variation particularly after 50 years old, indicating the increasing individual difference in PWV values as age advances.

Table 3 presents odds ratios (ORs)of abnormal PWV values calculated for each explanatory variable by multiple logistic regression analysis for both sexes combined. An odds ratio (OR) of each variable is adjusted for effects of other variables. ORs for all explanatory variables except BMI and current smokers were significant. The OR of abnormal PWV values for those over 60 years of age was three times that for those younger than 60. The OR for men was 35% less than that for women. OR for hypertension was 2 times that for non-hypertension and OR for diabetics became 3.7 times that for non-diabetics. The OR for those with high (>=4.5) TC/HDL ratios was 1.6 times that for those with low TC/HDL ratios. However, current drinkers had a 50% smaller OR than non-drinkers, and also the OR for former drinkers was almost 50% smaller than that for non-drinkers. On the other hand, the OR for former smokers was elevated by 1.6 times that for nonsmokers.

Table 4 displays ORs for men. The results are similar to the results for both sexes combined in Table 3 except that the risk of elevated TC/HDL was reduced from 1.61 to 1.32 making it insignificant. Table 5 displays ORs for women. It differs from those for men in that the OR for elevated TC/HDL ratios became 1.98 making it significant at $p<0.001$. The reduced risk observed in current and ex-drinkers was held good for women too, with ORs being 0.47 for current drinkers ($p<0.001$) and 0.45 for ex-drinkers ($p<0.05$). However, the slightly elevated ORs observed in current and ex-smokers of women failed to reach statistical significance.

IV. **Discussion**

Since Japanese Americans are an ethnic minority and there is no resident registry as seen in Japan, it was impossible to conduct a random sampling (based on the census). Study subjects were partially voluntary participants (about 10%) and mostly random-sampled participants in health examinations casting doubt on whether the sample actually represents the Japanese American population residing in and around the Seattle area (King County).In the United States the National Census has been conducted every ten years and its results are published 2-3 years later, which include a distribution of annual household income levels of Japanese Americans in King county. To verify the representativeness of the study sample, we conducted a survey using household income as a proxy variable. We mailed out anonymous questionnaires asking their annual household income in 1994 to be compared with the income reported in the census. A total of 1,117 households (80% of study participants) responded.

Figure 2 compares the distribution of annual household income levels of the study participants with those of the Japanese American population in King county[13]. Although the distribution of the study participants is slightly skewed to higher income brackets, both distribution patterns resemble each other. Considering 5.4% of an annual growth rate in household income during the five-year interval between the census year (1989) and our survey year(1994)[14], the mean household income, $49,000, of the study participants corresponds well to $50,000 of the estimated household income of the Japanese American population in 1994. With these findings, the study participants may well be deemed to represent the Japanese American population at least in terms of their income.

Participants during 1989-92 and those in 1994 did not differ significantly in terms of their characteristics (% of current drinkers: male 63% (1989-1992) vs. 65% (1989-94), female 42% vs. 46%, percent of current smokers: male15% vs.15%, female 10% vs. 9%). Hence it was considered that combining the data from the two periods is appropriate to increase statistical power. For 60 participants who participated in the health examinations in both periods, the first data were included for analysis.

Since the study participants in this study were recruited from volunteers, it might be questioned whether the study participants differ from non-participants in terms of their health status. Unfortunately, we are unable to provide an answer. In this respect, the Honolulu Heart Study conducted in Hawaii investigated the difference between participants and non-participants and revealed that total mortality and CHD incidence were higher in non-participants than in participants[15]. If this finding is also applicable to our study, one may well assume that nonparticipants would be less healthy than participants.

What characterizes Japanese Americans in Seattle can be examined in comparison with the American general population and the Japanese general population. With regards to BMI, the average BMI of Japanese American males (25.6) is close to American men and that of females is close to Japanese women (23.9). The average BMI of American general population (20-74 years old) was 26.3 for men and 26.3 for women[16], and the age-specific average BMI of Japanese general population (20-80 years or over) ranges from 21.0 to 23.2 for men and 21 to 23.4 for women[17]. In this study, obesity was dichotomized as above or below 27[16] to be used as an explanatory variable but failed to demonstrate any significant association with PVW abnormalities in men and demonstrated 1.28, only a slightly elevated non-significant odds ratio in women.

The second characteristics of Japanese Americans in Seattle is that they have a higher average total cholesterol level than American and Japanese general populations: 224.3 mg/dl for men and 226.0 mg/dl for women as compared to the averages of 202 mg/dl for American men and 200 mg/dl for American women[18], 198.6 mg/dl for Japanese men and 207.1 mg/dl for Japanese women[19]. In this study, TC/HDL-C ratio was dichotomized as above or below 4.5 to be used as an explanatory variable and demonstrated a significantly elevated odds ratio of 1.61 for both sexes combined and 1.98 for women but proved to be non-significant in men (1.32) suggesting a gender discriminatory effect of cholesterol on PWV.

Morishita reported that average PWV values in the hypertensives were higher than in controls in every age group[6]. Also, our results showed that the association between hypertension and prevalence of PWV abnormalities as shown by significant odds ratios of 2.0 for men and 1.94 for women, suggesting strong effects of hypertension on development of atherosclerosis.

Diabetes is a known atherosclerotic risk factor[20,21] and our study shows highly elevated odds ratios in men (5.7) and women (2.5) of the prevalence of abnormal PWV values for diabetics as compared to non-diabetics. This finding is consistent with the findings by Hasegawa and Morishita that PWV for diabetics is more accelerated than PWV for non-diabetics[22,23].

Smoking is another known atherosclerotic risk factor[24,25] but the odds ratios of abnormal PWV values for current smokers were not significant: 1.56 for men and 1.32 for women. As for ex-smokers, the odds ratios were 1.82 ($p<0.01$) for men and 1.38 (NS) for women. It is possible, however, that an extremely low rate of smokers among Japanese Americans in Seattle (15.3% for men and 8.9% for women), in comparison to rates in American general population (27.7% for men and 22.5% for women[26]) and in native Japanese (59.8% for men and 13.8% for women[27]), might have weakened the statistical power to reach significance in an odds ratio of abnormally high PWV values for current smokers.

Alcohol consumption among Japanese Americans in Seattle (3.7 g/day/person in pure alcohol in Table 1) was also extremely lower (only one-fifth of) than among Americans and among native Japanese living in Japan (19.9g and 17.9g/day/person, respectively, calculated from published reports[27,28] in both countries).

Moore and Pearson reported that they had identified studies demonstrating the negative relationship between alcohol consumption and atherosclerosis but no studies showing the positive association after their careful review of pathological studies[29]. Barboriak[30], Gruchow[31] and Pearson[32] also reported that alcohol consumption and coronary occlusions were inversely correlated. We found that the odds ratio of abnormal PWV values for current drinkers was 50% smaller than that for non-drinkers in both sexes, and such findings are consistent with findings of other previous studies suggesting protective effects of drinking on atherosclerosis. Furthermore, the negative odds ratio observed for ex-drinkers suggests anti-atherosclerotic effects of drinking persists even after drinking cessation. The inverse relationship between coronary heart disease (CHD) and alcohol consumption has been reiterated by numerous studies[29, 33-37] warranting further investigation in Japanese Americans in Seattle.

Prevalence of abnormal PWV values was 25.8% in men and 28.8% in women. Logistic regression analysis demonstrated that the male-sex factor reduces the risk of abnormal PWV values by 35% (Table 3). Hasegawa reported that the average PWV value was higher in women than in men after 50 years of age based on his age- and sex-specific PWV measurement on healthy Japanese population and attributed such a sex difference to

hormonal changes in women passing 50 years of age and healthy survivors' effect (attrition due to atherosclerotic deaths) in men[38]. Such effects may be particularly strong in Japanese Americans in Seattle. The sex ratio (men/women) of Japanese Americans in King county including the City of Seattle over 55 years old was 0.67[39], lower than that of native Japanese of the same age group, 0.8[27]. Although no ready explanation is given to a sharp drop in the male population after 55 years of age in Seattle, the healthy survivors' effects cannot be ruled out as a possible explanation of the low prevalence of PWV abnormalities in men, which may lead to further research.

It is generally accepted that atherosclerotic changes in coronary arteries advance faster in men than in women as evidenced by a sharp sex difference in age-specific CHD mortality below age 70, but our findings suggest that atherosclerotic changes in large arteries differ from coronary atherosclerosis. Current research indicates that atherosclerosis of large arteries precedes that of cerebral and coronary arteries[40~42]. Also, the presence of atherosclerosis in large arteries and coronary arteries does not necessarily translate into the onset of CHD, suggesting that causes of CHD are affected by a complexity of other risk factors. Such complex issues may be partly answered by comparing PWV values with EKG readings[43].

In 1984 Hara, et al. reported that the age-specific means of PWV values in Japanese Americans in Hawaii islands were significantly ($p<0.001$) higher than in native Japanese after age 50s[44]. If the findings in Japanese Americans in Hawaii applies to Japanese Americans in Seattle (i.e., their PWV values are higher than those of native Japanese after their 50s), the relationship between PWV and atherosclerotic risk factors could have been overestimated among Japanese Americans leading to statistical significance. We are planning to pursue this hypothesis by comparing our results in Seattle with native Japanese.

The findings obtained from this study in addition to our other studies are summarized as follows: 1) age-specific averages of total cholesterol, LDL cholesterol and triglycerides in Japanese Americans were significantly higher than those of both American and Japanese general populations[45]; 2) age-adjusted prevalence of high PWV abnormalities in Japanese American men is significantly higher than male urban workers in Japan[46]; 3) age-adjusted prevalence of abnormal changes in retinal arteries in Japanese American men was significantly lower than that in male urban workers in Japan[47]; 4) prevalence of coronary heart disease in Japanese American men and women was significantly higher than that in male urban workers in Japan[48]. These observations reflect differences in progress of atherosclerosis and prevalence of related diseases resulting from differences in eating habits, life style and environmental factors between the United States and Japan. Comparative studies of Japanese Americans and native Japanese continue to play an important role in elucidating how environmental factors affect the onset of diseases.

PWV reflects the anatomical severity of atherosclerotic changes in aorta. However, whether or not PWV predicts the onset of atherosclerotic diseases particularly coronary heart disease warrants further investigation. PWV is an effective tool to measure the severity of

atherosclerotic changes in a quick and easy manner and to keep patients well informed of their severity of atherosclerotic changes.

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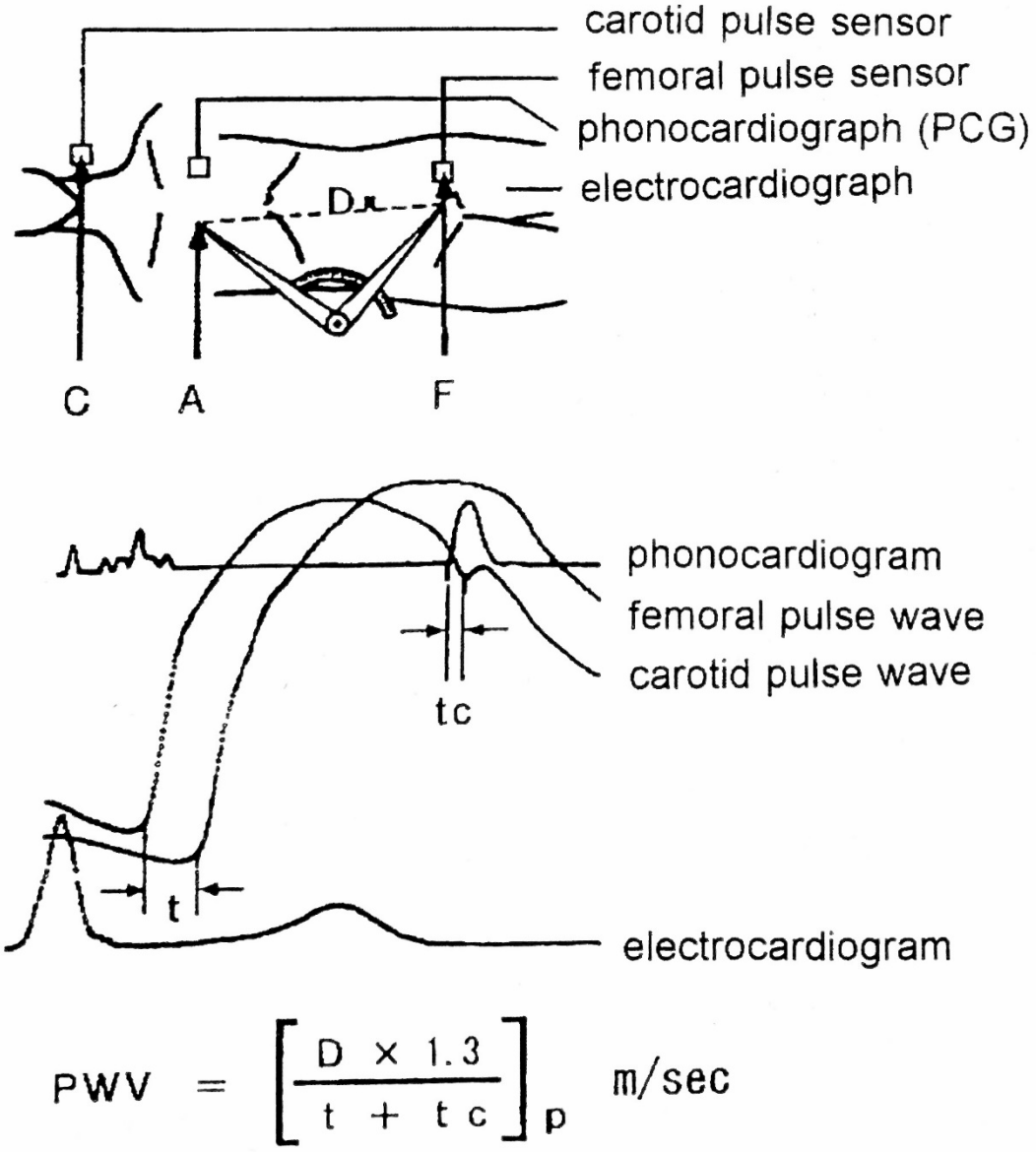
(Translated by Tsukasa Namekata)

Figure 1 Method for measuring the aortic pulse wave velocity (PWV)



$$PWV = \left[\frac{D \times 1.3}{t + tc}\right]_p \quad m/sec$$

Figure 2 Comparison between 1994 household income of Japanese American (JA) screening participants and 1989 household income of JA population in King County, Washington, U.S.A.

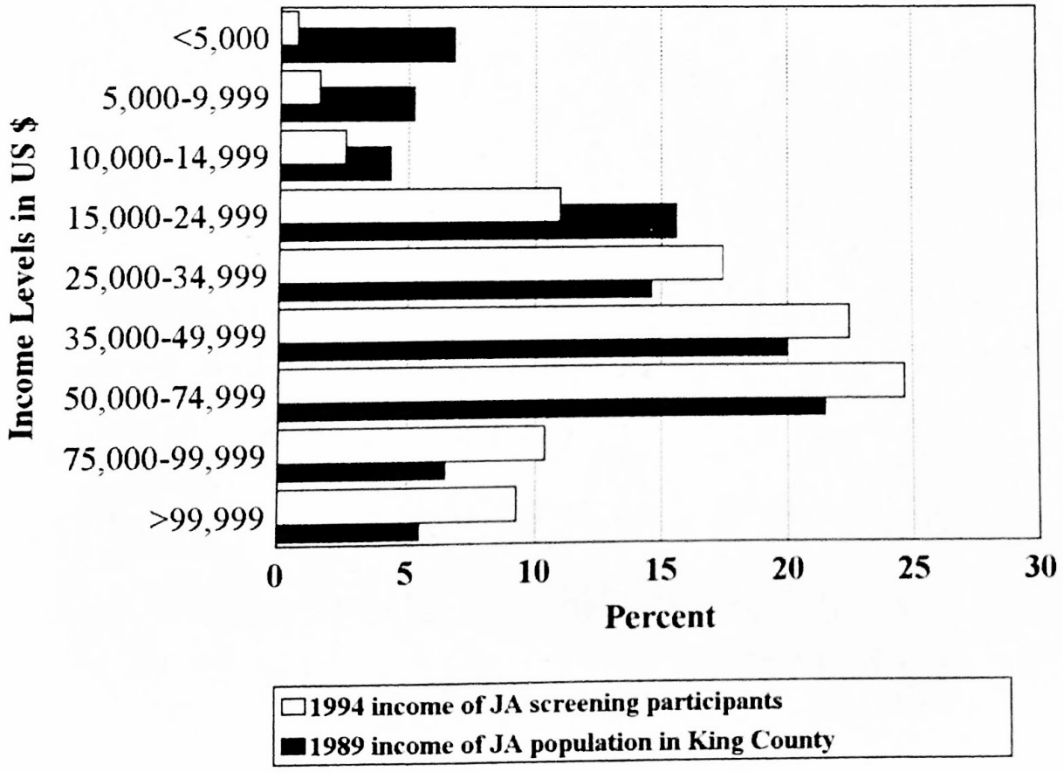


Table 1 Characteristics of study participants in Seattle, U.S.A.

Variables	Total (n=1,389)		Males (n=681)		Females (n=708)	
	Mean	SD	Mean	SD	Mean	SD
Age	56.0	13.7	56.1	13.7	55.9	13.7
PWV (m/sec)	8.0	1.5	8.0	1.5	8.1	1.5
Body mass index	24.8	3.6	25.6	3.3	23.9	3.7
Systolic BP (mmHg)	130.5	18.5	133.1	17.5	128.0	19.1
Total cholesterol (mg/dl)	225.6	40.0	224.3	38.0	226.0	41.8
HDL cholesterol (mg/dl)	57.4	16.6	51.2	14.0	63.4	16.7
TC/HDL ratio	4.2	1.4	4.7	1.5	3.8	1.3
Daily alcohol consumption (grams)	3.7	10.1	6.0	12.7	1.4	6.0
	Number	Percent	Number	Percent	Number	Percent
Current drinkers	767	55.2	441	64.8	326	46.0
Ex-drinkers	189	13.6	115	16.9	74	10.5
Non-drinkers	433	31.2	125	18.3	308	43.5
Current smokers	167	12.0	104	15.3	63	8.9
Ex-smokers	468	33.7	319	46.8	149	21.0
Non-smokers	754	54.3	258	37.9	496	70.1

Table 2 Distribution of persons by age and aortic pulse wave velocity among Japanese Americans in Seattle, U.S.A.: males and females combined

PWV (m/sec)	Age in Years					
	<40	40-49	50-59	60-69	≥70	all ages
<6.0	48(22.9%)	15(5.7%)	4(1.4%)			67(4.8%)
6.0- 6.9	116(55.2%)	121(46.4%)	50(17.4%)	17(4.2%)	1(0.4%)	305(22.0%)
7.0- 7.9	40(19.0%)	106(40.6%)	129(44.8%)	84(20.8%)	14(6.2%)	373(26.9%)
8.0- 8.9	6(2.9%)	19(7.3%)	77(26.7%)	142(35.2%)	45(19.8%)	289(20.8%)
9.0- 9.9			26(9.0%)	96(23.8%)	80(35.2%)	202(14.5%)
10.0-10.9			2(0.7%)	41(10.2%)	54(23.8%)	97(7.0%)
11.0-11.9				18(4.5%)	19(8.4%)	37(2.7%)
≥12.0				5(1.2%)	14(6.2%)	19(1.3%)
total	210(100%)	261(100%)	288(100%)	403(100%)	227(100%)	1,389(100%)

Table 3 Adjusted odds ratio for presence of abnormally high PWV values among Japanese Americans in Seattle, U.S.A.: males and females combined

Variable		Persons at risk	Adjusted odds ratio†	Significance
Sex:	females	708	1.00	
	males	681	0.65	<0.01
Age:	<60 years	759	1.00	
	≥60 years	630	3.60	<0.001
Hypertension:	no	1,093	1.00	
	yes	296	2.01	<0.001
Diabetes:	no	1,311	1.00	
	yes	78	3.66	<0.001
TC/HDL-C:	<4.5	857	1.00	
	≥4.5	532	1.61	<0.001
BMI:	≤27	1,053	1.00	
	>27	336	1.08	NS‡
Alcohol:	non-drinkers	433	1.00	
	current drinkers	767	0.45	<0.001
	ex-drinkers	189	0.47	<0.001
Smoking:	non-smokers	754	1.00	
	current smokers	167	1.47	<0.10
	ex-smokers	468	1.65	<0.01

† Odds ratios were simultaneously adjusted for all variables included in the model.
‡ NS=not significant

Table 4 Adjusted odds ratio for presence of abnormally high PWV values among Japanese Americans in Seattle, U.S.A.: males

Variable		Persons at risk	Adjusted odds ratio†	Significance
Age:	<60 years	369	1.00	
	≥60 years	312	4.31	<0.001
Hypertension:	no	524	1.00	
	yes	157	2.00	<0.001
Diabetes:	no	639	1.00	
	yes	42	5.65	<0.001
TC/HDL-C:	<4.5	329	1.00	
	≥4.5	352	1.32	NS‡
BMI:	≤27	474	1.00	
	>27	207	0.93	NS‡
Alcohol:	non-drinkers	125	1.00	
	current drinkers	441	0.44	<0.001
	ex-drinkers	115	0.49	<0.05
Smoking:	non-smokers	258	1.00	
	current smokers	104	1.56	NS‡
	ex-smokers	319	1.82	<0.01

† Odds ratios were simultaneously adjusted for all variables included in the model.
‡ NS=not significant

Table 5 Adjusted odds ratio for presence of abnormally high PWV values among Japanese Americans in Seattle, U.S.A.: females

Variable		Persons at risk	Adjusted odds ratio†	Significance
Age:	<60 years	390	1.00	
	≥60 years	318	3.03	<0.001
Hypertension:	no	563	1.00	
	yes	139	1.94	<0.01
Diabetes:	no	672	1.00	
	yes	36	2.47	<0.05
TC/HDL-C:	<4.5	528	1.00	
	≥4.5	180	1.98	<0.001
BMI:	≤27	579	1.00	
	>27	129	1.28	NS‡
Alcohol:	non drinkers	308	1.00	
	current drinkers	326	0.47	<0.001
	ex-drinkers	74	0.45	<0.05
Smoking:	non-smokers	496	1.00	
	current smokers	63	1.32	NS‡
	ex-smokers	149	1.38	NS‡

† Odds ratios were simultaneously adjusted for all variables included in the model.

‡ NS=not significant

Association between Arteriolar Sclerotic and Hypertensive Changes in Retina and Cardiovascular Disease Risk Factors among Japanese Urban Workers and Their Families

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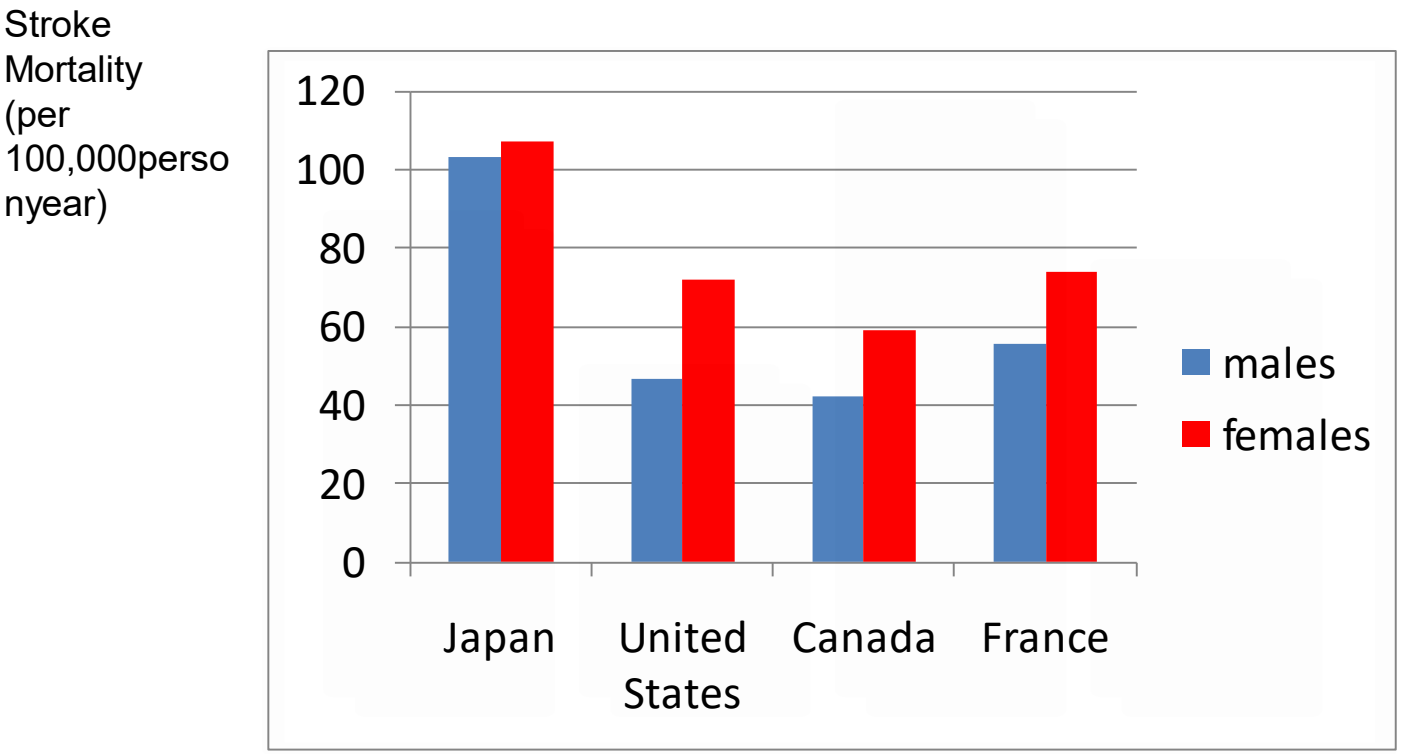
BACKGROUND

Having a high mortality of stroke, Japanese citizens has been encouraged to take annual cardiovascular medical checkup including ophthalmoscopy since 1960s.

Fig1. Mortality of Stroke Among Countries



OBJECTIVE

The purpose of the study is to examine the association of arteriolar sclerotic and hypertensive (ASH) changes in retinal arteries with cardiovascular disease (CVD) risk factors.

METHODS(1)

Subjects

Subjects were 7,272 employees and families (4,431 men and 2,841 women) recruited from those who participated in CVD screening in major cities in Japan for 2006-2007.

METHODS(2)

Measurements of CAVI

- Measurement of CAVI, a stiffness indicator of arteries is measured by VaSera VS-1000 manufactured by Fukuda-Denshi Company (Tokyo, Japan).

- The average CAVI score of healthy people was used as threshold, and abnormally high CAVI scores were determined as those exceeding (mean score + standard deviation) of the age-specific healthy group. All CAVI scores were converted to the binary variable.

METHODS(3)

- Blood was drawn from the subjects after 12 hour-fasting.
- The criterion for defining diabetes;

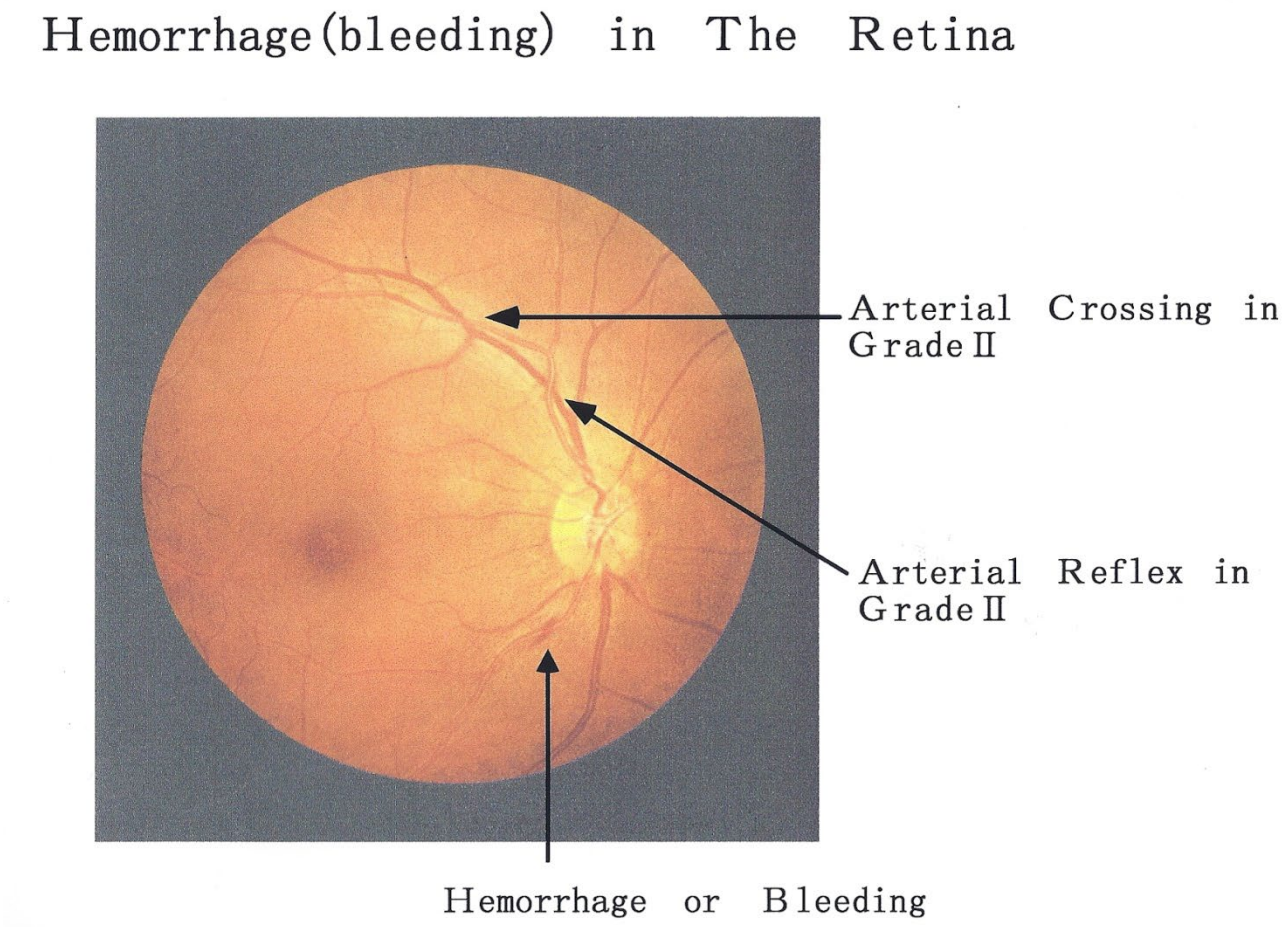
  ≥126mg/dl of fasting plasma glucose concentration
- The criterion for hypertension：

  SBP ≥ 160mmHg and/or DBP ≥ 100mmHg.
- Self-administered questionnaires on lifestyle were filled out by subjects at the time of screening.

METHODS(4)

- Retinal photographs of the right eye were taken by non-mydriatic retinal camera (Canon Co., Tokyo, Japan) to identify subjects with abnormal changes in retinal arteries by using Scheie's classification method.
- ASH changes in retinal arteries were transformed to the binary table: 0 for score 0 as normal and 1 for scores I –IV as abnormal.

Fig 2 Example of ASH changes using Scheie's classification method



METHODS(5)

Statistical Method

Multiple logistic regression analysis was conducted using ASH changes in retinal arteries as a dependent variable and CVD risk factors as covariates.

SPSS vs.16 was used for statistical analysis.

RESULTS(1)

Age

*p<0.05
**p<0.01
***p<0.001

	Males			Females		
Risk factors	% in all subjects	ORs (95%CI)	p-value	% in all subjects	ORs (95%CI)	p-value
20-39 (reference)	**33**	**1.00**		**39**	**1.00**	
40-59	**56**	**2.30 (1.61-3.29)**	***	**55**	**10.09 (2.80-36.31)**	***
≥60	**11**	**7.70 (5.07-11.69)**	***	**6**	**49.41 (12.43-194.27)**	***

RESULTS(2)

*p<0.05
**p<0.01
***p<0.001

BMI

	Males			Females		
Risk factors	% in all subjects	ORs (95%CI)	p-value	% in all subjects	ORs (95%CI)	p-value
≤19.9	10	1.03 (0.62-1.73)		38	0.58 (0.24-1.44)	
20-22.9	33	0.82 (0.58-1.14)		38	0.98 (0.46-2.09)	
23-24.9 (reference)	26	1.00		13	1.00	
25-26.9	17	1.30 (0.91-1.84)		6	1.34 (0.50-3.62)	
≥27	14	1.53 (1.05-2.23)	*	5	1.39 (0.51-3.78)	

RESULTS(3)

*p<0.05
**p<0.01
***p<0.001

Hypertension

	Males			Females		
Risk factors	% in all subjects	ORs (95%CI)	p-value	% in all subjects	ORs (95%CI)	p-value
No (reference)	**94**	**1.00**		**98**	**1.00**	
Yes	**6**	**17.10 (12.97-22.54)**	***	**2**	**28.52 (15.02-54.17)**	***

RESULTS(4)

Hyperglycemia

*p<0.05
**p<0.01
***p<0.001

	Males			Females		
Risk factors	% in all subjects	ORs (95%CI)	p-value	% in all subjects	ORs (95%CI)	p-value
No (reference)	**96**	**1.00**		**99**	**1.00**	
Yes	**4**	**6.59 (4.80-9.06)**	***	**1**	**33.95 (12.78-90.15)**	***

RESULTS(5)

HDL

*p<0.05
**p<0.01
***p<0.001

	Males			Females		
Risk factors	% in all subjects	ORs (95%CI)	p-value	% in all subjects	ORs (95%CI)	p-value
<40 (reference)	**7**	**1.00**		**1**	**1.00**	
40-59	**47**	**0.38 (0.25-0.56)**	***	**17**	**0.29 (0.07-1.26)**	
≥60	**46**	**0.40 (0.26-0.61)**	***	**82**	**0.30 (0.08-1.20)**	

RESULTS(6)

CAVI

*p<0.05
**p<0.01
***p<0.001

	Males			Females		
Risk factors	% in all subjects	ORs (95%CI)	p-value	% in all subjects	ORs (95%CI)	p-value
Normal (reference)	**81**	**1.00**		**80**	**1.00**	
High	**19**	**1.88 (1.44-2.47)**	***	**20**	**2.49 (1.42-4.39)**	**

RESULTS(7)

*p<0.05
**p<0.01
***p<0.001

Drinking

	Males			Females		
Risk factors	% in all subjects	ORs (95%CI)	p-value	% in all subjects	ORs (95%CI)	p-value
none (reference)	**23**	**1.00**		**57**	**1.00**	
Current drinkers	**77**	**0.95 (0.71-1.27)**		**43**	**0.89 (0.50-1.59)**	

RESULTS(8)

Smoking

*p<0.05
**p<0.01
***p<0.001

	Males			Females		
Risk factors	% in all subjects	ORs (95%CI)	p-value	% in all subjects	ORs (95%CI)	p-value
none (reference)	**29**	**1.00**		**75**	**1.00**	
ex-smokers	**26**	**1.15 (0.85-1.56)**		**9**	**1.04 (0.32-3.38)**	
smokers	**45**	**0.68 (0.50-0.92)**	**	**16**	**2.34 (1.13-4.81)**	*

DISCUSSION(1)

- **Our study shows the strong association between ASH changes in retinal arteries and some cardiovascular risk factors such as hypertension, hyperglycemia and arterial stiffness in major arteries predicted by Cardio Ankle Vascular Index (CAVI).**

DISCUSSION(2)

- **There was a strong association between age (40years and older) and ASH changes in retinal arteries.**

DISCUSSION(3)

- As for dyslipidemia, we saw the negative associations between HDL-cholesterol and ASH changes in retinal arteries in males. Although we could not reach the statistically significance in females, this is probably due to the small number of female dyslipidemia subjects (24people).
-

DISCUSSION(4)

- **There was a positive association for obese (BMI>27) and ASH changes in retinal arteries independent of hypertension in males.**

DISCUSSION(5)

Regarding to the association between smoking and ASH changes in retinal arteries, we saw the different pattern between genders. Compared to the male current smokers who had negative association between ASH changes in retinal arteries, female current smokers had statistically significant high odds ratios. We can at least say that this might imply the characteristic difference between gender among Japanese smoking population.

DISCUSSION(6)

- **We saw no statistically significant association between drinking and ASH changes in retinal arteries.**

Thank you.

BMC Cardiovascular Disorders

RESEARCH ARTICLE Open Access

Establishing baseline criteria of cardio-ankle vascular index as a new indicator of arteriosclerosis: a cross-sectional study

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Abstract

Background: A cardio-ankle vascular index (CAVI) has been developed to represent the extent of arteriosclerosis throughout the aorta, femoral artery and tibial artery independent of blood pressure. To practically use CAVI as a diagnostic tool for determining the extent of arteriosclerosis, our study objectives were (1) to establish the baseline CAVI scores by age and gender among cardiovascular disease (CVD) risk-free persons, (2) to compare CAVI scores between genders to test the hypothesis that the extent of arteriosclerosis in men is greater than in women, and (3) to compare CAVI scores between the CVD risk-free group and the CVD high-risk group in order to test the hypothesis that the extent of arteriosclerosis in the CVD high-risk group is greater than in the CVD risk-free group.

Methods: Study subjects were 32,627 urban residents 20-74 years of age who participated in CVD screening in Japan during 2004-2006. A new device (model VaSera VS-1000) was used to measure CAVI scores. At the time of screening, CVD high-risk persons were defined as those having any clinical abnormalities of CVD, and CVD risk-free persons were defined as those without any clinical abnormalities of CVD. Age-specific average CAVI scores were compared between genders and between the CVD risk-free group and the CVD high-risk group. Student's t-test using two independent samples was applied to a comparison of means between two groups.

Results: Average age-specific baseline scores of CAVI in the CVD risk-free group linearly increased in both genders as their age increased. Average age-specific baseline scores of CAVI in the CVD risk-free group were significantly greater among men than among women. Average age-specific baseline scores of CAVI in the CVD risk-free group were significantly smaller than those in the CVD high-risk group in both genders after 40 years of age.

Conclusions: The baseline CAVI scores from the CVD risk-free group are useful for future studies as control values. The CAVI method is a useful tool to screen persons with moderate to advanced levels of arteriosclerosis.

Background

One leading cause of premature deaths in industrialized nations is cardiovascular disease including coronary heart disease (CHD), an atherosclerosis-related disease. In 2005, the CHD death rates (per 100,000 persons) were 159.0 for US males, which was 2.3 times higher than for Japanese males (68.1), and 142.0 for US females, which was 2.7 times higher than for Japanese females (53.5) [1,2]. Thus, there is a great need to prevent CHD incidence as well as mortality in the US. One approach is to identify persons with moderately advanced state of arteriosclerosis and provide recommendations for improving their lifestyle and diet. Japan has been taking such an approach for the past few decades and successfully kept CHD mortality low [2].

One method to quantitatively estimate the extent of arteriosclerosis is the use of the pulse wave velocity (PWV). The idea on the association of PWV with arteriosclerosis is traced back to an experiment using artificial blood vessels conducted by Moens in 1878 [3]. Then, Bramwell and colleagues showed that PWV depends on the modulus of arterial volume elasticity by experiments in 1922-23 [3-7]. Their experimental results have been a basis for the development of the measurement device PWV-200 (Fukuda-Denshi Co., Tokyo)

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which measures PWV propagating through the aorta (thorax, abdomen, and part of common iliac artery) from the aortic valve to the femoral pulsation point, as described by Hasegawa in 1970 [8]. Because PWV is highly correlated with diastolic blood pressure, Hasegawa developed a nomogram showing the association between diastolic blood pressure and PWV. He proposed an adjustment to any measured PWV values at 80 mmHg. As a result, such an adjustment was built into the PWV-200 machine. This is an important step allowing clinicians and researchers to compare PWV values between individuals and between populations. Namekata et al. conducted cardiovascular disease prevention screening in Seattle and found that PWV was positively and significantly associated with aging (≥ 60 years of age), hypertension, diabetes, the ratio of total cholesterol to high density lipoprotein cholesterol, ex-smokers and negatively and significantly with alcohol consumption among Japanese Americans [9]. In addition, they had similar findings among Japanese urban workers [10].

To overcome some problems associated with PWV-200 (i.e., technical difficulty in the method for measuring PWV), the cardio-ankle vascular index (CAVI) was developed as a new indicator of arteriosclerosis in 2004 [11]. CAVI quantitatively reflects arteriosclerosis of the aorta, femoral and tibial arteries based on Bramwell-Hill's equation [3] and stiffness parameter [12] which is allowed to be converted from PWV propagating from the aortic valve to ankle. Some researchers proposed to use CAVI scores as an indicator of atherosclerosis. Nakamura et al. found a strong association of CAVI with the presence of severity of coronary atherosclerosis based on their ordinal logistic regression analysis [13]. Kadota et al. suggested the use of CAVI as a screening tool for atherosclerosis based on their findings from the general population study of 1,014 adults showing strong significant associations of CAVI scores with carotid intima-media thickness and with homocysteine after adjustment for age and sex [14]. Thus, it is considered that CAVI scores reflect arterial stiffness, atherosclerosis and arteriosclerosis of which conditions are overlapping and inseparable. We use CAVI to represent the extent of arteriosclerosis in this paper but it is inclusive of arterial stiffness and atherosclerosis.

To practically use CAVI as a diagnostic tool for determining the extent of arteriosclerosis, our study objectives are (1) to establish the baseline CAVI scores by age and gender among cardiovascular disease (CVD) risk-free persons, (2) to compare CAVI scores between genders to test the hypothesis that the extent of arteriosclerosis in men is greater than in women, and (3) to compare CAVI scores between the CVD risk-free group and the CVD high-risk group to test the hypothesis that the extent of arteriosclerosis in the CVD high-risk group is greater than in the CVD risk-free group.

Methods

Study Subjects

Subjects for the study were recruited through the screening program at Japan Health Promotion Foundation which has been conducting cardiovascular disease and cancer screening throughout major cities of Japan. Subjects were company employees and their family members: 16,661 men and 15,966 women between 20 and 74 years of age (see Table 1) after excluding persons with history of heart disease, hypertension, stroke, diabetes, nephritis, and gout. The proportion of CVD risk-free subjects to all subjects decreases as age advances (both genders combined): 45.4% for 20-29 years of age, 30.1% for 30-39 years of age, 18.7% for 40-49 years of age, 9.7% for 50-59 years of age, 6.9% for 60-69 years of age, and 3.7% (or only 36 CVD risk-free subjects out of 979 subjects) for 70-74 years of age.

The study was approved by the Institutional Review Board and all subjects gave their consent to participate in the study.

Measuring Cardio-Ankle Vascular Index

CAVI, a stiffness and arteriosclerosis indicator of thorax, abdomen, common iliac, femoral and tibial arteries, is measured by VaSera VS-1000 manufactured by Fukuda-Denshi Company, LTD (Tokyo, Japan), as shown in Figure 1. This device is a new version of PWV-200. It is significantly improved as it achieved 3.8% of the average coefficient of variation among five repeated measurements of CAVI for each of the 22 subjects [11] showing that its operation is less dependent on a technician's skill. Furthermore, CAVI scores were not changed but brachial-ankle PWV values were significantly changed when both systolic and diastolic blood pressure of 12 healthy volunteer men was significantly changed after metoprolol (80 mg) was administered [15]. This suggests that CAVI is not affected by blood pressure at the time of measuring.

The method to measure CAVI is illustrated in Figure 2. A subject is placed in supine position and

Table 1 Subjects by age and sex

	All subjects		CVD risk-free subjects	
Age	Males	Females	Males	Females
20-29	1214	949	455	526
30-39	4008	3243	877	1307
40-49	3880	4111	421	1077
50-59	4619	5653	306	690
60-69	2319	1654	155	119
70-74	623	356	25	11
Total	16661	15966	2239	3730

Figure 1 Demonstration of CAVI measurement by VaSera VS-1000.

electrocardiogram and heart sound are monitored. PWV between heart and ankle is obtained by L/T where L is the distance from the aortic valve to the ankle, and T is the time during which PWV propagates from the aortic valve to the ankle (or the sum of tb and tba in place of t'b and tba, because t'b and tb are theoretically equal: tba is the time between the rise of the brachial pulse wave and the rise of the ankle pulse wave, tb is the time between the aortic valve's closing sound and the notch of the brachial pulse wave, and t'b is the time between the aortic valve's opening sound and the rise of the brachial pulse wave) [11].

The scale conversion from PWV to CAVI is performed by the following formula:

$$\mathrm{CAVI} = a\left\{\left(2\rho/\Delta P\right) \times \ln\left(P_s/P_d\right) PWV^2\right\} + b$$

where P_s and P_d are systolic and diastolic blood pressure values, respectively, PWV is the pulse wave velocity between heart and ankle, ΔP is P_s-P_d, ρ is blood density, and a and b are constants. This equation was derived from Bramwell-Hill's equation [3] and stiffness parameter [12]. Scale conversion constants are determined so as to match CAVI with PWV by Hasegawa's method [8]. All these measurements and calculations are automatically made in VaSera VS-1000. More theoretical details of CAVI method are available elsewhere [11].

Clinical Criteria for Selecting CVD Risk-Free Persons and CVD High-Risk Persons

Blood was drawn from the subjects after a 12 hour-fast. The following measurements were made: total cholesterol (TC), triglycerides (TG), creatinine (Cre) by enzymatic

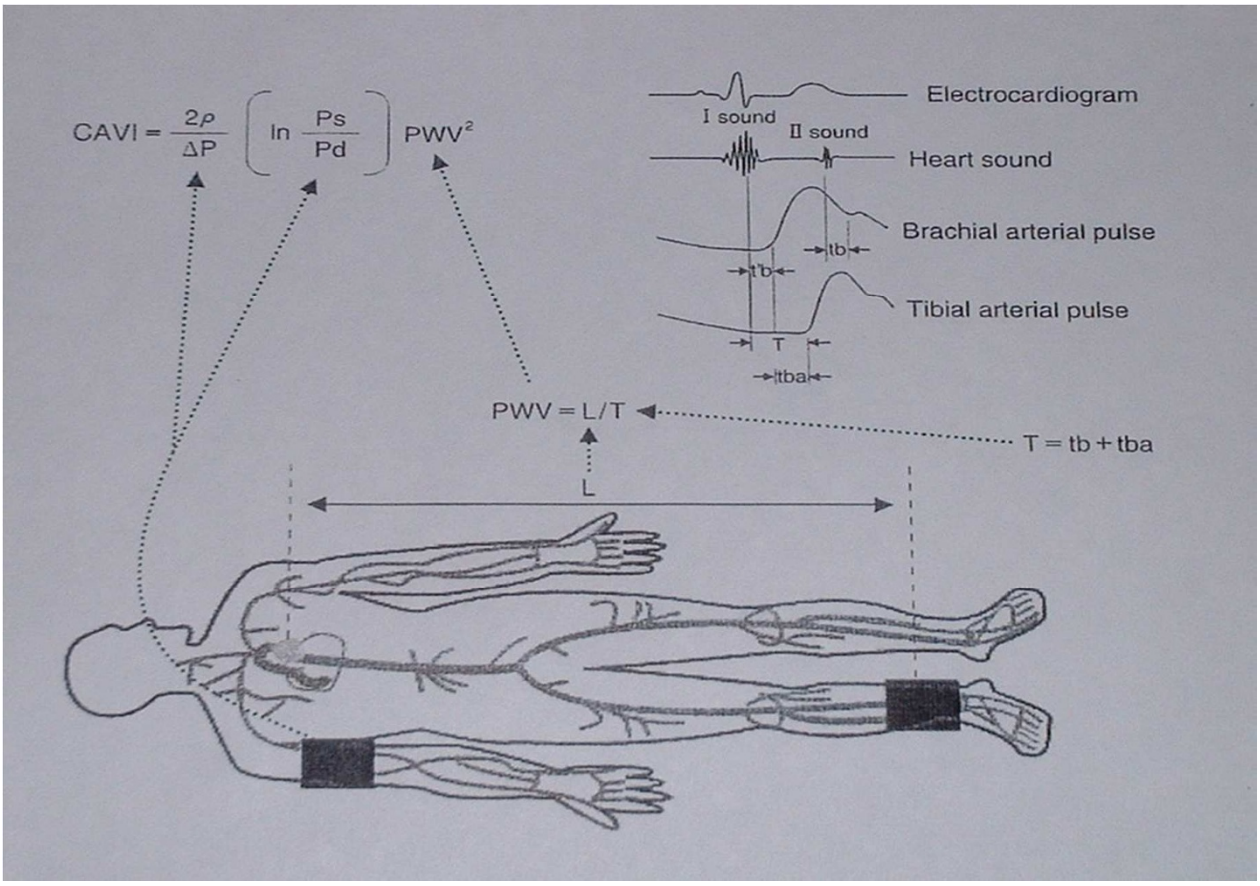

Figure 2 Illustration of CAVI measurement.

assay; high density lipoprotein cholesterol (HDL-C) by modified enzymatic method; uric acid by uricase peroxides method, glucose by hexokinase glucose-6-phosphate dehydrogenate assay, glyco-hemoglobin A1c (HbA1c) by latex agglutination, and white blood cells (WBC) by direct current detection method. To identify subjects with ischemic changes, outputs from electrocardiogram were classified by Minnesota code [16] which has been internationally and uniformly used in the epidemiology setting. Retinal photographs of the right eye were taken by non-mydriatic retinal camera (Canon Co., Tokyo, Japan) to identify subjects with abnormal changes in retinal arteries by using Scheie's classification method [17].

The criteria to select subjects for the CVD risk-free group and for the CVD high-risk group were based on the guidelines established by Japan Atherosclerosis Society and Japan Society of Hypertension [18-21]. The CVD risk-free persons were defined as those meeting the following clinical criteria at the time of screening:

- blood pressure: systolic blood pressure(SBP) ≤ 139 mmHg and diastolic blood pressure (DBP) ≤ 89 mmHg;
- serum lipids: TC ≤ 219 mg/dL, HDL-C = 40-99 mg/dL and TG ≤ 149 mg/dL;
- serum glucose: glucose ≤ 109 mg/dL and HbA1c ≤ 5.8%;
- renal function: creatinine: male ≤ 1.10 mg/dL, female ≤ 0.80 mg/dL and uric-acid ≤ 7.0 mg/dL for both genders;
- white blood cells: 3.2-8.5 × 10^3/μL;
- electrocardiogram: excluding persons with 1-1-1 to1-3-6, 3-1 to 3-3, 4-1 to 4-4, 5-1 to 5-5, and 9-2; and
- retinal artery changes: no arteriolar sclerotic change and no hypertensive change.

The CVD high-risk persons were defined as those who fall in one or more following groups of clinical abnormalities at the time of screening:

- borderline hypertension group: SBP:140-159 mmHg, and/or DBP:90-99 mmHg;
- hypertension group: SBP ≥ 160 mmHg, and/or DBP ≥ 100 mmHg;
- abnormal lipid metabolism group: TC ≥ 240 mg/dL, TG ≥ 250 mg/dL, and/or HDL-C ≤ 34 mg/dL;

- borderline high-glucose group: serum glucose 110-125 mg/dL and/or HbA1c 5.9-6.1%;
- hyperglycemia group: serum glucose ≥ 126 mg/dL and/or HbA1c ≥ 6.2%;
- ischemic change group: 1-1-1 to 1-1-3 (abnormal Q wave), and/or 4-1 to 4-3 (ischemic change); and
- arteriolar sclerotic change group: sclerotic change ≥ II in Scheie's method.

Statistics Methods

In addition to the use of descriptive statistics, Student's t-test using two independent samples was applied to a comparison of means between two groups and $p < 0.05$ was considered statistically significant. Statistical Packages for Social Sciences version 16 was used for data analysis.

Results

As shown in Table 1, there were 2,239 men and 3,730 women who were free from clinical CVD abnormalities. Table 2 represents age-specific means and standard deviations of the baseline CAVI scores from the CVD risk-free group by age and gender. Age-specific average CAVI scores became higher in both genders as their age advanced and 0.22-0.66 of increment was added to the average CAVI score as the age increased to every 10 years.

Figure 3 shows a comparison of age-specific average CAVI scores between genders. It is observed that average CAVI scores at each age-interval were significantly greater for men than for women with a borderline significance for 70-74 years of age ($p = 0.071$), and that men's CAVI scores were about 5 years ahead of women's between 30 and 60 years of age and even 10 years ahead of women's after 60 years of age.

Tables 3 and 4 show a comparison of average CAVI scores between the CVD risk-free group and each CVD high-risk group by age among men and among women, respectively. There were not enough cases of all CVD high-risk groups under 30 years of age for comparisons and of some CVD high-risk groups 30-39 years of age. Most average CAVI scores from each of the CVD high-risk groups were significantly higher than those from the CVD risk-free groups with one exception: the average CAVI score (6.95) of the hypercholesterolemia and hypertriglyceridemia group for men 30-39 years of age was significantly smaller than that (7.12) of the CVD risk-free group for the same gender and age-bracket ($p = 0.021$). On one hand, age-specific average CAVI scores of the hypertension group were significantly greater than those of the CVD risk-free group after 30 years of age among men but after 40 years of age among women. On the other hand, age-specific average CAVI scores of the hypercholesterolemia and hypertriglyceridemia group, the hyperglycemia group, the ischemic changes group, and the retinal artery changes group were significantly greater for both men and women after 40 years of age compared to those of the CVD risk-free group with exceptions of non-significance in the hypercholesterolemia and hypertriglyceridemia group of men 70-74 years of age ($p = 0.106$), in the hyperglycemia group of women 40-49 years of age ($p = 0.093$), and in the ischemic changes group and the retinal artery changes group of women 70-74 years of age ($p = 0.052$ and $p = 0.071$, respectively).

Figures 4 and 5 show differences in average CAVI scores by age between the CVD risk-free group and all CVD high-risk groups combined for men and for women, respectively. After 40 years of age, the difference in age-specific average CAVI scores became statistically significant between the two groups, with borderline significance in men 70-74 years of age ($p = 0.054$), and also became wider as age advanced both for men and for women.

Table 2 Comparison of average cardio-ankle vascular index (CAVI) scores of CVD risk-free subjects by age and gender

	Males		Females		t-value	p-value
Age	Mean	SD	Mean	SD		
20-29	6.69	0.70	6.57	0.66	2.89	$p = 0.005$
30-39	7.12	0.68	6.79	0.63	5.23	$p < 0.001$
40-49	7.59	0.70	7.29	0.66	7.82	$p < 0.001$
50-59	8.07	0.76	7.82	0.70	4.97	$p < 0.001$
60-69	8.73	0.81	8.26	0.72	4.95	$p < 0.001$
70-74	9.35	1.00	8.71	0.75	1.88	$p = 0.071$

Note: SD indicates standard deviation.

Discussion

As shown in Table 2, we have established the baseline CAVI scores based on 5,969 CVD risk-free persons selected out of 32,627 persons 20-74 years of age. It is shown that there exists a linear association between CAVI scores and age in both genders confirming that aging is an independent risk factor of atherosclerosis and cardiovascular disease as described in western [22,23] and Japanese studies [24]. Table 2 and Figure 3 show a biological aging of major arteries among CVD risk-free persons. We found that age-specific average CAVI scores among men were significantly greater than among women. Such a finding is consistent with the fact that men have a higher risk for coronary heart disease (of which one major risk factor is arteriosclerosis) than women [1,2]. Based on these findings, we need to evaluate an individual's CAVI scores according to his/her age and gender when we conduct screening.

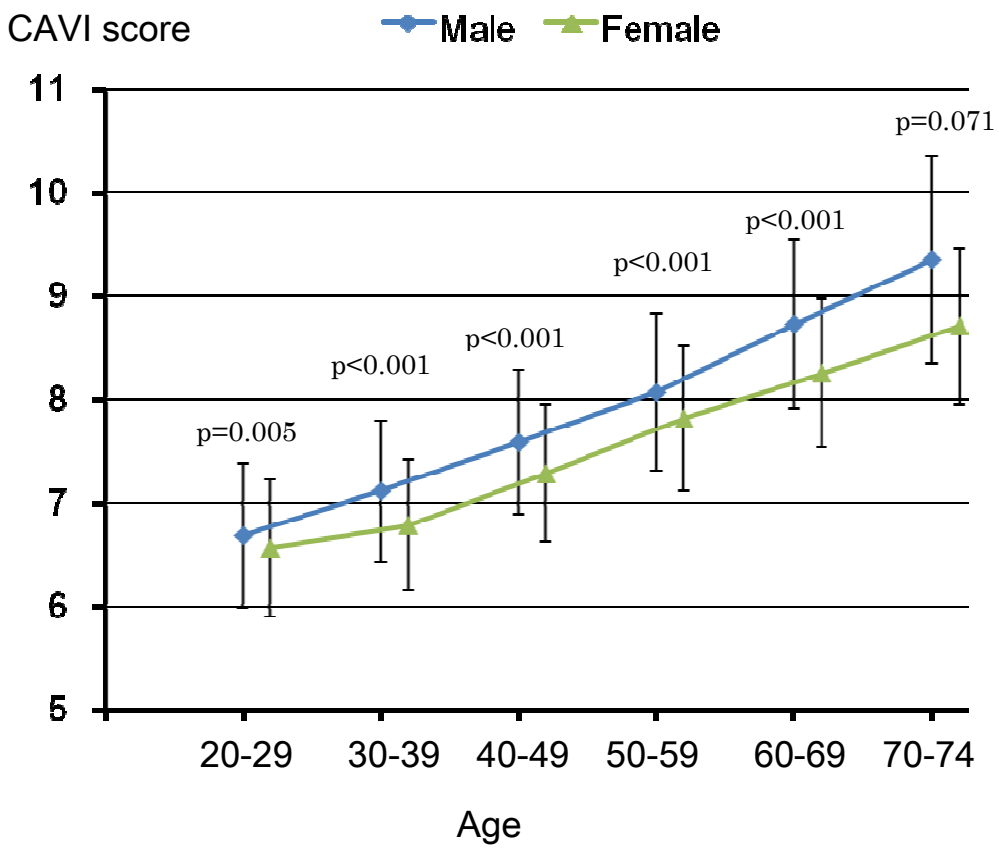

Figure 3 Differences in average CAVI scores by age between males (blue line) and females (green line) among CVD risk-free individuals based on results shown in Table 2 (Vertical bars indicate standard deviation.).

As established by Framingham studies and others [25-27], hypertension is a risk factor of cardiovascular disease. Hypertension is also significantly associated with PWV [9,10,28]. High PWV values are found to be an independent predictive factor of cardiovascular disease [29]. Since our results indicate that age-specific average CAVI scores in the hypertension group were significantly higher than those from the CVD risk-free group (Tables 3, 4), it is implied that hypertension is a risk factor of arteriosclerosis.

The association between serum lipid levels and atherosclerotic disease, namely coronary heart disease, has been established through the findings from several epidemiological studies such as the Seven Countries Study [30], the Multiple Risk Factor Intervention Trial Study [31], and Klag et al's follow-up study [32]. Namekata et al. reported that abnormally high PWV was significantly associated with 4.5 or greater value of the ratio of total cholesterol to high density lipoprotein (HDL) cholesterol implying that abnormal lipid imbalance is a risk factor of arterial stiffness and arteriosclerosis [9]. Our results support such an association by showing that age-specific average CAVI scores among persons with hypercholesterolemia and hypertriglyceridemia of ages 40 and over were significantly greater than those among CVD risk-free persons for the same age-specific groups (Tables 3, 4).

Diabetes mellitus is proven to be a risk factor for cardiovascular disease [33,34]. It is reported that CVD risk among diabetics was 2-6 times higher than among non-diabetics and PWV values were associated with fasting glucose levels among diabetics [35,36]. An odds ratio for having abnormally high PWV among diabetics is also reported to be 3.66 ($p < 0.001$) as compared to non-diabetics [9]. Our results are consistent with these findings by showing significantly higher average age-specific CAVI scores among persons with hyperglycemia after 40 years of age than those among CVD risk-free persons (Tables 3, 4).

Ischemic changes in ECG and arteriolar changes in retina are considered as surrogate markers of arterial stiffness and arteriosclerosis in the coronary arteries and retinal arteries, respectively. It is also shown that atherosclerotic lesions in the aorta proceeds onset of CVD [37-39], as an increase in PWV values proceeds ischemic changes in ECG and arterial changes in retina appear

Table 3 Comparison of average CAVI scores between CVD risk-free group and CVD high-risk groups for males

Age	20-29	30-39	40-49	50-59	60-69	70-75
			CVD risk-free group			
Mean	6.69	7.12	7.59	8.06	8.73	9.35
SD	0.70	0.68	0.70	0.76	0.81	1.00
			Hypertension group			
Mean	-	7.43	7.86	8.47	9.12	9.84
SD		0.86	0.87	1.01	1.12	1.15
t-value		4.24	4.75	6.51	4.06	2.07
p-value		p < 0.001	p < 0.001	p < 0.001	p < 0.001	p = 0.041
			Hypercholesterolemia & Hypertriglyceridemia group			
Mean	-	6.95	7.74	8.42	8.97	9.71
SD		0.84	0.86	0.95	0.91	0.82
t-value		-2.39	2.33	5.05	2.34	1.62
p-value		p = 0.021	p = 0.023	p < 0.001	p = 0.022	P = 0.106
			Hyperglycemia group			
Mean	-	7.25	7.76	8.68	9.41	10.01
SD		0.88	0.82	0.98	1.65	1.40
t-value		1.14	2.31	8.80	6.94	2.19
p-value		p = 0.123	p = 0.034	p < 0.001	p < 0.001	p = 0.042
			Ischemic changes group			
Mean	-	-	7.81	8.79	9.29	9.97
SD			0.70	1.12	0.87	1.31
t-value			2.29	8.36	5.43	2.14
p-value			p = 0.033	p < 0.001	p < 0.001	p = 0.043
			Retinal artery changes group			
Mean	-	-	8.09	8.77	9.16	9.97
SD			0.77	1.25	1.10	1.14
t-value			2.60	6.69	3.77	2.38
p-value			p = 0.014	p < 0.001	p < 0.001	p = 0.022
			All high-risk groups combined			
Mean	6.39	7.18	7.79	8.49	9.12	9.80
SD	0.69	0.85	0.85	0.98	1.05	1.14
t-value	-1.87	1.26	3.96	7.20	4.48	1.93
p-value	p = 0.061	p = 0.209	p < 0.001	p < 0.001	p < 0.001	p = 0.054

Note: SD is standard deviation and - indicates that the number of cases was too small to obtain any meaningful results.

Table 4 Comparison of average CAVI scores between CVD risk-free group and CVD high-risk groups for females

Age	20-29	30-39	40-49	50-59	60-69	70-75
			CVD risk-free group			
Mean	6.57	6.97	7.29	7.82	8.26	8.71
SD	0.66	0.63	0.66	0.70	0.72	0.74
			Hypertension group			
Mean	-	7.02	7.73	8.16	8.89	9.46
SD		0.74	1.02	0.84	0.96	1.02
t-value		0.40	6.85	8.22	6.44	2.38
p-value		p = 0.346	p < 0.001	p < 0.001	p < 0.001	p = 0.023
			Hypercholesterolemia & Hypertriglyceridemia group			
Mean	-	6.97	7.68	8.00	8.77	9.26
SD		0.78	1.21	0.78	0.90	0.74
t-value		-0.03	4.12	3.82	5.06	2.28
p-value		p = 0.914	p < 0.001	p < 0.001	p < 0.001	p = 0.034
			Hyperglycemia group			
Mean	-	-	7.47	8.16	9.09	9.77
SD			0.86	0.74	1.04	0.79
t-value			1.74	5.23	6.57	3.69
p-value			p = 0.093	p < 0.001	p < 0.001	p < 0.001
			Ischemic changes group			
Mean	-	-	7.49	8.10	8.75	9.39
SD			0.82	0.82	0.88	1.02
t-value			2.95	5.71	4.69	2.07
p-value			p = 0.004	p < 0.001	p < 0.001	p = 0.052
			Retinal artery changes group			
Mean	-	-	8.03	8.34	9.36	9.32
SD			0.89	0.86	1.11	0.87
t-value			3.97	5.24	7.37	1.92
p-value			p < 0.001	p < 0.001	p < 0.001	p = 0.071
			All high-risk groups combined			
Mean	6.88	6.93	7.58	8.12	8.81	9.34
SD	0.42	0.76	0.91	0.81	0.96	0.99
t-value	1.48	-0.56	6.25	8.05	5.96	2.09
p-value	p = 0.138	p = 0.578	p < 0.001	p < 0.001	p < 0.001	p = 0.038

Note: SD is standard deviation and - indicates that the number of cases was too small to obtain any meaningful results.

[40]. We have shown that the age-specific average CAVI scores of the ischemic changes group and of the retinal artery changes group were significantly greater than those of the CVD risk-free group (Tables 3, 4). This implies that CAVI scores reflect the extent of arteriosclerotic changes not only in medium-size and large-size arteries but also in small-size arteries.

We have shown that age-specific average CAVI scores of all CVD high-risk persons combined were significantly higher than those of the CVD risk-free group after 40 years of age (Tables 3, 4), indicating that the overall arteriosclerosis status of the CVD high-risk group was significantly worse than that of the CVD risk-free group. Because no difference in average CAVI scores between the two groups was detected before 40 years of age, effective CAVI screening might be recommended for people age 40 and over.

With regard to the validity to use CAVI scores as an indicator of arteriosclerosis, Otsuka examined 72 deceased patients' ante-mortem PWV (which is a basis for deriving CAVI scores) and pathological changes measured by the diffuse fibrotic thickening, formation of atheroma and calcification in the wall of their aorta. He reported multiple regression coefficient R = 0.810 between PWV and scores of those pathological changes [41]. In addition, other researchers reported that CAVI scores were significantly associated with coronary

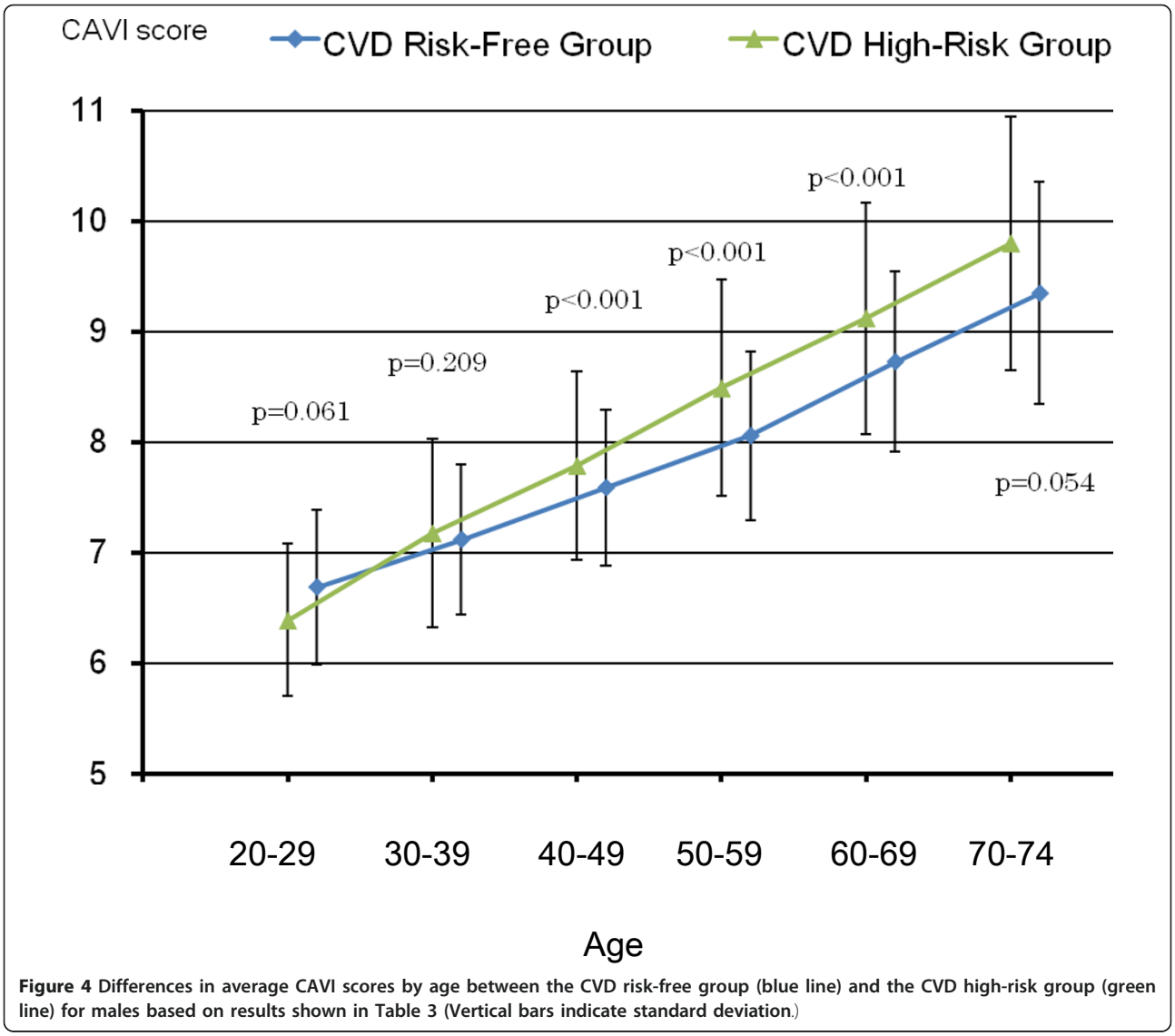

Figure 4 Differences in average CAVI scores by age between the CVD risk-free group (blue line) and the CVD high-risk group (green line) for males based on results shown in Table 3 (Vertical bars indicate standard deviation.)

atherosclerosis [13], with carotid intima-media thickness and with homocysteine [14]. Thus, the use of CAVI scores derived from PWV values is valid to estimate the extent of arteriosclerosis.

VaSera VS-1000, which was used in our study, was designed to measure CAVI scores independent of blood pressure and CAVI scores represent the extent of arteriosclerosis between the aortic valve and the ankle. We have shown biological aging of the major artery by measuring CAVI scores in the CVD risk-free group and disease-related pathological aging of the major artery in the CVD high-risk group. CAVI scores allow us to evaluate the extent of arteriosclerosis in the major arteries between the aortic valve and the ankle, to screen persons with subclinical stage of CVD, and provide an opportunity to modify diet and lifestyle to improve CAVI scores as reported by Satoh et al [42]. Thus, the use of CAVI scores potentially leads to savings on high treatment costs and to prolonging many productive lives.

There are some limitations in our study. First, the study design was cross-sectional and results were based on our observations at the time of screening. Secondly, our data did not include behavioral and lifestyle factors, although we consider that effects of such factors were reflected on clinical measurements related to CVD which we included. Currently we are examining the association between CAVI scores and lifestyle factors such as smoking, alcohol consumption, and body mass index, and will report results in the near future.

Conclusions

Our results imply that advancement of arteriosclerosis among men is greater in every age group than among

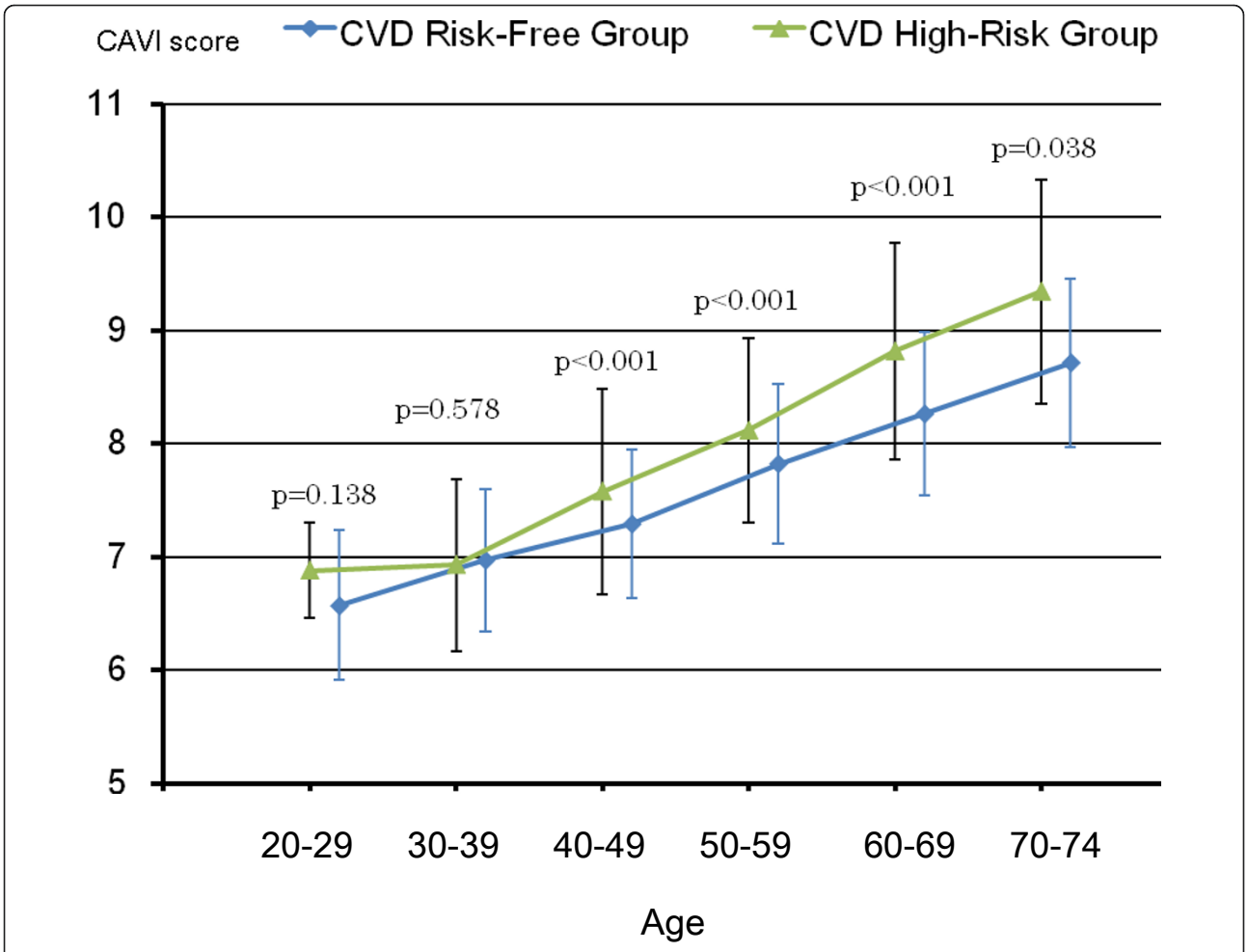

Figure 5 Differences in average CAVI scores by age between the CVD risk-free group (blue line) and the CVD high-risk group (green line) for females based on results shown in Table 4 (Vertical bars indicate standard deviation.)

women. It is also implied that arteriosclerosis of the CVD high-risk group advances faster than that of the CVD risk-free group after 40 years of age. The baseline CAVI scores from the CVD risk-free group are useful for future studies as control values. The CAVI method is a useful tool to screen persons with moderate to advanced levels of arteriosclerosis.

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Authors' contributions
TN, KS and KS conceived and designed the study. KS and NI acquired the data. TN and KS performed statistical analyses. TN and KS drafted the manuscript, all other authors revised critically and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

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Research Article Open Access

Association of Cardio-Ankle Vascular Index with Cardiovascular Disease Risk Factors and Coronary Heart Disease among Japanese Urban Workers and their Families

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Abstract

Purpose: Recently the cardio-ankle vascular index (CAVI) has been developed to represent the extent of arteriosclerosis in the artery from the aortic valve to the ankle. The aim of the study is to examine the association of CAVI scores with the established cardiovascular disease (CVD) risk factors and coronary heart disease (CHD).

Methods: Subjects were 9,881 men and 12,033 women of company employees and their families between 20 and 70 years of age and over who participated in CVD screening in Japan. The screening included measurements of CAVI, electrocardiogram, blood pressure, lipids, serum glucose, hemoglobin A1c, height, weight, and questions on smoking and drinking status. Persons having CHD were defined as those having history of CHD and/or having abnormal Q wave and/or ischemic change in ECG. After converting CAVI scores to binary variables (normal or abnormally high CAVI scores), logistic regression analysis was conducted.

Results: After adjusting for age, significant odds ratios (ORs) of abnormally high CAVI scores among men were found with diabetes mellitus (10.02, $p<0.001$), hypertension (8.37, $p<0.001$), triglycerides (2.76, $p<0.001$, for 150-199mg/dL and 2.85, $p<0.001$, for ≥200mg/dL, as reference:<150mg/dL), high density lipoprotein cholesterol (0.19, $p<0.001$, for 40-59mg/dL and 0.20, $p<0.001$ for ≥60mg/dL, as reference: <40mg/dL), body mass index (2.04, $p<0.001$, for <20, 2.31, $p<0.001$, for 28-29.9 and 3.37, $p<0.001$, for ≥30 as reference:20-22.9), and ex-smokers (1.20, $p<0.01$, as reference: non-smokers). Almost identical results were found among women, except a significant OR with current smokers (2.25, $p<0.001$). The significant association between CHD and abnormally high CAVI scores was found: OR=3.87, $p<0.001$ for men and 1.45, $p<0.01$ for women after adjusting for CVD risk factors.

Conclusions: Our results confirmed that CAVI scores are a reliable indicator of arteriosclerosis reflecting the extent of arterial stiffness and atherosclerosis in the major artery between the aortic valve and the ankle.

Keywords: Cardio-ankle vascular index; Arteriosclerosis; Arterial stiffness; Pulse wave velocity; Hypertension; Diabetes mellitus; Coronary heart disease

Abbreviations: CAVI: Cardio-Ankle Vascular Index; CVD: Cardiovascular Disease; CHD: Coronary Heart Disease; ORs: Odds Ratios; PWV: Pulse Wave Velocity; SD: Standard Deviation; TC: Total Cholesterol; TG: Triglycerides; HDL-C: High Density Lipoprotein Cholesterol; HbA1c: Glyco-Hemoglobin A1c; ECG: Electrocardiogram; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; BMI: Body Mass Index; CI: Confidence Interval

Introduction

Several methods have been designed to assess arterial stiffness and arteriosclerosis. Among them, pulse wave velocity (PWV) [1-7], augmentation index [8], the stiffness parameter β [9,10], and carotid-femoral PWV [11] have been proposed as markers of arterial stiffness. In 2002, brachial-ankle PWV was proposed as a marker of vascular damage [12], and was reported to be a predictive factor of coronary artery disease [13]. However, PWV is known to depend on blood pressure at the time of measurement [14]. To overcome such a problem the cardio-ankle vascular index (CAVI) was developed with the objective to obtain an arterial stiffness index that is not affected by blood pressure at the time of measurement, and which reflects the stiffness or arteriosclerosis of a long artery from the aortic valve to the ankle [15].

Some researchers proposed to use CAVI scores as an indicator of atherosclerosis. Nakamura et al. found a strong association of CAVI with the presence of severity of coronary atherosclerosis based on their ordinal logistic regression analysis [16]. Kadota et al. suggested the use of CAVI as a screening tool for atherosclerosis based on their findings from the general population study of 1,014 adults showing strong significant associations of CAVI scores with carotid intima-media thickness and with homocysteine after adjustment for age and sex [17]. Thus, it is considered that CAVI scores reflect arterial stiffness, atherosclerosis and arteriosclerosis of which conditions are overlapping and inseparable. We use CAVI to represent the extent of arteriosclerosis in this paper but it is inclusive of arterial stiffness and atherosclerosis.

To practically use CAVI as a diagnostic tool for determining the

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extent of arteriosclerosis, Namekata et al. have recently published the baseline CAVI scores by age and gender among cardiovascular disease (CVD) risk-free persons, and then have found that the age- and sex-specific average CAVI scores were significantly greater among CVD high-risk persons than among CVD risk-free persons [18]. It implies that the extent of arteriosclerosis is more advanced among persons with CVD risk factors than among persons without such risk factors.

In our present study all CAVI scores were converted to categorical scores based on the baseline CAVI scores of the CVD risk-free persons in our previous study [18]. Such conversion enabled us to examine the association of CAVI categorical scores with CVD risk factors and with coronary heart disease (CHD) among Japanese urban workers and their families.

Methods

Study subjects

Subjects for the study were recruited from January 2006 to May 2009 through the screening program at Japan Health Promotion Foundation which has been conducting cardiovascular disease and cancer screening throughout major cities in Japan. Subjects were company employees and their family members: 9,881 men and 12,033 women between 20 and 70 years of age and over (Table 1). The study was approved by the Institutional Review Board and all subjects gave their consent to participate in the study.

Measuring cardio-ankle vascular index

CAVI, a stiffness and arteriosclerosis indicator of thorax, abdomen, common iliac, femoral and tibial arteries, is measured by VaSera VS-1000 manufactured by Fukuda-Denshi Company, LTD (Tokyo, Japan).

Figure 1 illustrates how PWV is measured [19]. The scale conversion from PWV to CAVI is performed by the following formula:

$$CAVI=a\{(2\rho/\Delta P) \times \ln(P_s/P_d)PWV^2\} + b$$

where P_s and P_d are systolic and diastolic blood pressure values, respectively, PWV is the pulse wave velocity between heart and ankle, ΔP is P_s-P_d, ρ is blood density, and a and b are constants. This equation was derived from Bramwell-Hill's equation [20] and stiffness parameter [21]. Scale conversion constants are determined so as to match CAVI with PWV by Hasegawa's method [22]. All these measurements and calculations are automatically made in VaSera VS-1000. More theoretical details of CAVI method are available elsewhere [15,19].

To examine the association of CAVI with CVD risk factors and CHD, CAVI scores of screening participants were stratified according to Table 2. These were constructed based on means and standard deviations in "Table 2 - Comparison of average cardio-ankle vascular index (CAVI) scores of CVD risk-free subjects by age and gender" from the paper by Namekata et al. [18]. All CAVI scores were converted to 1 for scores less than (mean – one standard deviation (SD)), 2 for scores between (mean – 1SD) and (mean - ½SD), 3 for scores between (mean - ½SD) and mean, 4 for scores between mean and (mean + ½SD), 5 for scores between (mean+ ½SD) and (mean + 1SD), and 6 for scores greater than (mean + 1SD). Based on distribution of CAVI scores by CHD status, there was a substantial increase in CHD cases from CAVI scores ≤5 to 6: prevalence of CHD corresponding to codes 1,2,3,4, 5 and 6 was 1.9%, 1.2%, 1.8%, 2.8%, 2.7% and 4.6%, respectively, among men and was 2.1%, 2.8%, 2.6%, 3.8%, 2.7% and 4.7%, respectively, among women.Thus, we coded CAVI scores as a binary variable: 1 for codes 1-5 combined and 2 for code 6 as abnormally high CAVI scores in order to conduct logistic regression analysis.

Clinical measurements

The methods to measure other clinical indicators were adopted based on the guidelines established by Japan Atherosclerosis Society, Japan Diabetes Society and Japan Society of Hypertension [23-25]. Blood was drawn from the subjects after a 12 hour-fast. The following measurements were made: total cholesterol (TC) and triglycerides (TG) by enzymatic assay; high density lipoprotein cholesterol (HDL-C) by modified enzymatic method; glucose by hexokinase glucose-6-phosphate dehydrogenate assay; and glyco-hemoglobin A1c (HbA1c) by latex agglutination. To identify subjects with ischemic changes, outputs from electrocardiogram (ECG) were classified by Minnesota code [26] which has been internationally and uniformly used in the epidemiology setting. Persons having CHD were defined as those having history of angina pectoris and/or myocardial infarction and/or as those who showed ECG codes: 1-1-1 to 1-1-3 (abnormal Q wave), and/or 4-1 to 4-3 (ischemic change). Persons having high blood pressure were defined as those taking hypertension drugs and/or as those whose systolic blood pressure (SBP) was higher than 160mmHg and/or diastolic blood pressure (DBP) was higher than 100mmHg. Persons with diabetes mellitus were defined as those who were previously diagnosed with diabetes mellitus, as those taking diabetes

Age in year	Males		Females	
	Number	Per cent	Number	Per cent
≤29	1066	10.8	905	7.5
30-39	2659	26.9	3089	25.7
40-49	2396	24.2	3127	26.0
50-59	2236	22.6	3578	29.7
60-69	1247	12.6	1148	9.5
≥70	277	2.8	186	1.5
Total	9881	100.0	12033	100.0

Table 1: Study participants by age and sex.

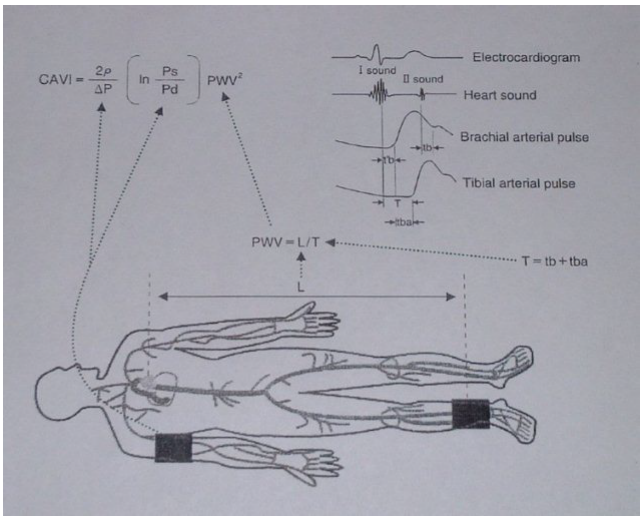

Figure 1: Illustration of CAVI measurement. A subject is placed in supine position and electrocardiogram and heart sound are monitored. PWV between heart and ankle is obtained by L/T where L is the distance from the aortic valve to the ankle, and T is the time during which PWV propagates from the aortic valve to the ankle (or the sum of tb and tba in place of t'b and tba, because t'b and tb are theoretically equal: tba is the time between the rise of the brachial pulse wave and the rise of the ankle pulse wave, tb is the time between the aortic valve's closing sound and the notch of the brachial pulse wave, and t'b is the time between the aortic valve's opening sound and the rise of the brachial pulse wave).

mellitus medication and/or as those whose serum glucose were higher than 126mg/dL and/or those whose HbA1c were higher than 6.2% in Japan Diabetes Society value. It is approximately equivalent to 6.6% in National Glycohemoglobin Standardization Program (NGSP) value.

Questionnaire

A short self-administered questionnaire was filled out by each subject during the screening. It contains questions on medical history and lifestyle factors such as smoking habit (non-smokers, ex-smokers, and current smokers) and frequency of alcohol consumption (not drinking, 1-2 times/week, 3-4 times/week, 5-6 times/week, and every day).

Statistical methods

In addition to the use of descriptive statistics, logistic regression method was used to examine the association of CAVI scores with CVD risk factors and CHD. Statistical Packages for Social Sciences version 18 was used for data analysis.

Results

Characteristics of study participants are shown in Table 3 for males and Table 4 for females. Means of CAVI scores among men increased from 6.38 for 29 years of age and younger to 9.43 for 70 years of age and older, while scores among women increased from 6.21 for 29 years of age and younger to 9.10 for 70 years of age and older. Differences in CAVI scores between genders ranged from 0.17 for 29 years of age and younger to 0.33 for 70 years of age and older, indicating that the average of CAVI scores for men advanced about five years faster than for women. It is observed that the means for both systolic and diastolic blood pressure linearly increased as ages advanced among women, while the same trend is seen for systolic blood pressure but not for diastolic blood pressure among men. Such an increasing trend with age was not observed in lipids, serum glucose and body mass index (BMI) among men, while an increasing trend in TC, TG, and serum glucose levels was observed among women as ages advanced. We observed that prevalence of CHD and diabetes linearly increased with advancing ages in both genders. We also observed that prevalence of abnormally high CAVI scores increased with advancing ages in women, while the highest prevalence of abnormally high CAVI scores (24.7%) appeared in 50-59 years of ages among men. Greater prevalence of drinkers and smokers was observed in men than in women. (Table 3, 4)

Table 5 shows odds ratios (ORs) of abnormally high CAVI scores for each CVD risk factor after making adjustment for age among men. Significantly high ORs were found in persons having hypertension, 8.37 (confidence interval: 7.32-9.56), and in persons with diabetes mellitus, 10.02 (CI: 8.74-11.49). All other CVD risk factors have significant ORs ranging 1.20 (CI: 1.05-1.36) in ex-smokers to 3.37 (CI: 2.72-4.18) in BMI≥30. Only HDL-C shows negative or protective ORs: 0.19 (CI: 0.17-0.23) for persons with 40-59mg/dL and 0.20 (CI: 0.17-0.24) in persons with ≥60mg/dL, as compared with the reference category of HDL-C<40mg/dL.

age		Mean(M)	SD	M-1SD	M-0.5SD	M+0.5SD	M+1SD
20-29	Males	6.69	0.70	5.99	6.34	7.04	7.39
	Females	6.57	0.66	5.91	6.24	6.90	7.23
30-39	Males	7.12	0.68	6.44	6.78	7.46	7.80
	Females	6.79	0.63	6.16	6.48	7.11	7.42
40-49	Males	7.59	0.70	6.89	7.24	7.94	8.29
	Females	7.29	0.66	6.63	6.96	7.62	7.95
50-59	Males	8.07	0.76	7.31	7.69	8.45	8.83
	Females	7.82	0.70	7.12	7.47	8.17	8.52
60-69	Males	8.73	0.81	7.92	8.33	9.14	9.54
	Females	8.26	0.72	7.54	7.90	8.62	8.98
70+	Males	9.35	1.00	8.35	8.85	9.85	10.35
	Females	8.71	0.75	7.96	8.34	9.09	9.46

Table 2: Baseline values of CAVI scores.

Variables	Age	≤29	30-39	40-49	50-59	60-69	≥70
CAVI scores	mean±SD	6.38±0.64	7.00±0.64	7.53±0.67	8.19±0.78	8.71±0.81	9.43±0.85
Systolic Blood Pressure	mean±SD	119±11	122±13	126±14	132±16	133±17	136±16
Diastolic Blood Pressure	mean±SD	69±9	74±10	79±11	83±11	81±10	79±11
Total Cholesterol(mg/dL)*	mean±SD	186±33	204±34	214±36	213±34	211±32	209±34
HDL-C(mg/dL)	mean±SD	62±15	59±16	60±17	61±18	63±18	62±18
Triglycerides(mg/dL)	mean±SD	95±77	135±103	158±169	147±113	126±72	122±81
Body Mass Index(kg/m^2)	mean±SD	22.3±3.5	24.0±3.7	24.2±3.2	24.0±2.9	23.7±2.8	23.5±3.0
Serum Glucose(mg/dL)*	mean±SD	84.6±12.6	87.7±13.2	92.4±20.8	99.3±27.5	99.1±24.7	99.9±25.1
Coronary Heart Disease	prevalence (%)	0.2	0.5	1.2	3.5	6.9	12.3
Diabetes Mellitus	prevalence (%)	0.2	1.7	4.0	9.5	12.0	15.2
Abnormally High CAVI	prevalence (%)	6.1	11.4	14.0	24.7	16.1	13.7
Drinkers	prevalence (%)	61.8	73.4	77.9	79.3	77.4	66.8
Ex-smokers	prevalence (%)	11.2	18.7	25.4	31.6	35.9	37.2
Smokers	prevalence (%)	55.4	51.9	48.4	41.2	28.5	18.1

Note: Number of persons having total cholesterol measurements was 5193 and number of persons having serum glucose measurements was 8705. Abnormally high CAVI scores were defined as CAVI scores greater than (mean + 1SD)

Table 3: Characteristics of study participants: Males.

Variables	Age	≤29	30-39	40-49	50-59	60-69	≥70
CAVI scores	mean±SD	6.21±0.57	6.74±0.60	7.21±0.64	7.87±0.71	8.41±0.77	9.10±0.80
Systolic Blood Pressure	mean±SD	109±10	113±12	119±14	127±16	130±16	135±16
Diastolic Blood Pressure	mean±SD	63±8	66±9	71±10	75±11	76±10	77±10
Total Cholesterol (mg/dL)*	mean±SD	180±28	194±32	209±34	233±36	236±35	233±42
HDL-C (mg/dL)	mean±SD	76±15	76±17	77±18	76±19	75±19	73±17
Triglycerides (mg/dL)	mean±SD	59±31	70±57	79±49	96±55	105±55	108±54
Body Mass Index (kg/m^2)	mean±SD	20.4±3.0	20.9±3.1	21.7±3.2	22.2±3.2	22.3±3.0	22.9±3.6
Serum Glucose (mg/dL)*	mean±SD	82.2±7.6	83.2±7.4	86.1±9.9	88.9±15.1	90.4±15.9	91.0±12.0
Coronary Heart Disease	prevalence (%)	0.4	1.2	1.9	5.0	6.4	14.5
Diabetes Mellitus	prevalence (%)	0.2	0.4	1.3	3.1	4.4	6.5
Abnormally High CAVI	prevalence (%)	5.9	15.0	12.0	21.3	24.5	33.9
Drinkers	prevalence (%)	50.4	45.5	43.4	36.2	33.4	28.0
Ex-smokers	prevalence (%)	10.4	13.3	9.1	5.8	6.1	4.8
Smokers	prevalence (%)	22.8	15.6	11.7	8.5	5.7	3.8

Note: Number of persons having total cholesterol measurements was 9706 and number of persons having serum glucose measurements was 5955. Abnormally high CAVI scores were defined as CAVI scores greater than (mean + 1SD)

Table 4: Characteristics of study participants: Females.

CVD risk factors	Reference	Covariates	persons at risk	Odds ratio		lower CI	upper CI
Hypertension	No	Yes	755	8.37	***	7.32	9.56
Diabetes Mellitus	No	Yes	548	10.02	***	8.74	11.49
Total cholesterol	<200mg/dL	200-239	2128	1.01		0.87	1.18
		≥240	862	1.88	***	1.56	2.26
HDL-C	<40mg/dL	40-59	4859	0.19	***	0.17	0.23
		≥60	4369	0.20	***	0.17	0.24
Triglycerides	<150mg/dL	150-199	1319	2.76	***	2.43	3.14
		≥200	1609	2.85	***	2.53	3.22
Body Mass Index	20-22.9	<20	1012	2.04	***	1.72	2.41
		23-24.9	2453	0.94		0.82	1.08
		25-27.9	2205	0.90		0.78	1.04
		28-29.9	563	2.31	***	1.89	2.83
		≥30	429	3.37	***	2.72	4.18
Drinking	Non-drinkers	1-2 times/week	2151	1.12		0.96	1.31
		3-4 times/week	1183	1.81	***	1.53	2.14
		5-6 times/week	1216	1.87	***	1.58	2.21
		every day	2852	1.22	**	1.06	1.40
Smoking	Non-smokers	Current smokers	4457	1.05		0.94	1.19
		Ex-smokers	2481	1.20	**	1.05	1.36

Note: * p<0.05, **p<0.01, ***p<0.001, CI: Confidence Interval
Total number of persons at risk for total cholesterol is 5193

Table 5: Estimated risk for having abnormally high CAVI scores after making adjustment for age: Males.

Almost the same trend among females was found as shown in Table 6, except that significantly high ORs in both current smokers, 2.25 (CI: 1.98-2.56) and ex-smokers, 2.42 (CI: 2.11-2.79) when non-smokers were used as reference.

Table 7 shows crude and adjusted odds ratios (ORs) of coronary heart disease in association with abnormally high CAVI scores. We observed 26.79 of crude OR, 10.47 of OR adjusted for age and 3.87 of OR when making adjustment for other CVD risk factors including diabetes mellitus, hypertension, HDL-C, BMI, drinking and smoking among men, while women's ORs were 20.25 for crude, 3.70 for age-adjusted, and 1.45 for making other CVD risk factors adjusted. Because age is confounded with both CHD and CAVI scores, OR drastically decreased after age was included in logistic regression analysis. Adjusting for other CVD risk factors further made OR smaller, but it retained significance.

Discussion

In order to accept CAVI as a good indicator of arteriosclerosis, we need to achieve three objectives: (1) showing that age-sex-specific average CAVI scores are significantly higher in the CVD high-risk group than in the CVD risk-free group; (2) showing that CAVI scores are significantly associated with most of the established CVD risk factors; and (3) showing that CAVI scores are significantly associated with arteriosclerotic or atherosclerotic disease. We accomplished the first objective in the previous study [18] in which average CAVI scores in each of CVD high-risk groups (hypertension, hypercholesterolemia and hypertriglyceridemia, hyperglycemia, ischemic changes in ECG, retinal artery changes, and all high risk groups combined) were significantly higher than the baseline CAVI scores from the CVD risk-free group after 40 years of age in both genders. The second and third objectives were achieved by our present study and were shown in Tables 5, 6 and 7, respectively.

CVD risk factors	Reference	Covariates	persons at risk	Odds ratio		lower CI	upper CI
Hypertension	No	Yes	477	6.57	***	5.67	7.61
Diabetes	No	Yes	229	8.42	***	7.22	9.81
Total cholesterol	<200mg/dL	200-239	3793	1.13		0.99	1.29
		≥240	2276	1.33	***	1.15	1.54
HDL-C	<50	50-59	1667	0.47	***	0.38	0.57
		≥60	9722	0.33	***	0.28	0.39
Triglycerides	<150mg/dL	150-199	608	2.89	***	2.46	3.40
		≥200	402	4.30	***	3.60	5.14
Body Mass Index	20-22.9	<20	3992	1.43	***	1.28	1.60
		23-24.9	1677	1.17	*	1.01	1.35
		25-27.9	1091	0.98		0.82	1.17
		28-29.9	274	2.60	***	2.01	3.38
		≥30	272	2.45	***	1.87	3.20
Drinking	Non-drinkers	1-2 times/week	2473	1.05		0.93	1.19
		3-4 times/week	940	1.81	***	1.54	2.13
		5-6 times/week	654	2.50	***	2.10	2.99
		every day	884	2.06	***	1.75	2.41
Smoking	Non-smokers	Current smokers	1430	2.25	***	1.98	2.56
		Ex-smokers	1080	2.42	***	2.11	2.79

Note: * p<0.05, **p<0.01, ***p<0.001, CI: Confidence Interval
Total number of persons at risk for total cholesterol is 9706

Table 6: Estimated risk for having abnormally high CAVI scores after making adjustment for age: Females.

	Males				Females			
	odds ratio		confidence interval		odds ratio		confidence interval	
			lower	upper			lower	upper
(1) Crude	26.79	***	24.07	29.81	20.25	***	18.45	22.21
(2) Adjusted for age	10.47	***	8.93	12.27	3.70	***	3.18	4.31
(3) Adjusted for CVD risk factors	3.87	***	3.06	4.91	1.45	**	1.16	1.82

Note: (1) Only abnormally high CAVI scores were included as a covariate in logistic regression analysis.
(2) Age breakdowns (<50, 50-59, 60-69, ≥70 years of age) were added to logistic regression analysis.
(3) Other CVD risk factors (diabetes, hypertension, HDL-C, BMI, drinking, and smoking) were further added to logistic regression analysis.
* p<0.05, **p<0.01, ***p<0.001

Table 7: Crude and adjusted odds ratios of coronary heart disease in association with abnormally high CAVI scores among Japanese urban workers and their families.

Compared with non-diabetics, estimated risk of having abnormally high CAVI scores was 10 times higher among male diabetics and 8 times higher among female diabetics. The findings are consistent with significantly higher CAVI scores observed among diabetics [18,27] and significantly high odds ratios of abnormally high PWV values (5.65 among men and 2.47 among women) in association with diabetes mellitus reported by Namekata et al. [28].

Our results show that estimated risks of having abnormally high CAVI scores were 8 times higher among hypertensive men and 6.5 times higher among hypertensive women than among non-hypertensive persons. This is consistent with significant odds ratios of abnormally high PWV values (2.0 among men and 1.94 among women) in association with hypertension reported by Namekata et al. [28].

Hyperlipidemia per se does not immediately increase the stiffness of arterial wall. After accumulation of cholesterol in the lipid pool, oxidative stress generates oxysterol, which is strongly toxic and enhances inflammation, followed by the onset of atherosclerosis [19]. Our results show that higher concentrations of triglycerides (≥150mg/dL) were positively associated with abnormally high CAVI scores in both genders, while higher HDL-C levels (≥40mg/dL for men and ≥50mg/dL for women) were negatively associated with abnormally high CAVI scores, indicating that high HDL-C levels prevent advancement of arteriosclerosis. Namekata et al. reported that TC/HDL-C ratio ≥4.5 increased an estimated risk of having abnormally high PWV values to 1.32 among men and 1.98 among women [28]. Thus, persons with lipid abnormality possibly advance the extent of arteriosclerosis.

Visceral fat accumulation has been suggested to induce glucose intolerance, hypertension, and dyslipidemia such as low HDL-cholesterol and hypertriglyceridemia [29]. These conditions are believed to be due to insulin resistance. High CAVI scores are associated with obesity and metabolic syndrome [30]. Our study results show that the association between BMI and abnormally high CAVI scores was not linear but U-shape curve when 20-22.9 of BMI was used as the reference category. There is no doubt that the persons with BMI ≥28 have an elevated risk of having abnormally high CAVI scores in both genders, but it is important to recognize that the extremely slim persons (BMI <20) have significantly higher risk of having abnormally high CAVI scores in both genders of Japanese urban workers and their families. The impact of the slim population on cardiovascular disease cannot be ignored in Japan, because 10% of men and 30% of women fall in the slim category in our study sample.

Kubozono et al. [31] reported that CAVI was high in smoking subjects. Noike et al. [32] reported that smoking increases CAVI. Despite high prevalence of Japanese male smokers (45.1% in our study

sample), odds ratio of abnormally high CAVI scores was not significant among male current smokers (OR=1.05) but was significant among ex-smokers (OR=1.20). Our results for women showed significantly high odds ratios of abnormally high CAVI scores in both current smokers (OR=2.25) and ex-smokers (OR=2.42). There might be gender difference in terms of effects of smoking on the cardiovascular system in the Japanese population.

Namekata et al. found significantly reduced odds ratios of having abnormally high PWV values for current drinkers and ex-drinkers of both genders, as compared to non-drinkers among Japanese Americans [28]. However, our present results showed elevated odds ratios of having abnormally high CAVI scores for persons drinking more than 3-4 times per week in both genders. The difference in such study results might be partly caused by the difference in length of artery measured between PWV method by Hasegawa [22] and CAVI method [15,19].

As seen in Table 7, we have shown that abnormally high CAVI scores were significantly associated with coronary heart disease, one of the atherosclerotic or arteriosclerotic diseases. Our findings are supported by Nakamura et al. report [16] that CAVI scores increases as the number of vessels with stenosis (>75%) increases. They also found that a stepwise ordinal logistic regression analysis including mean intima-media thickness, maximum intima-media thickness, plaque score and CAVI as independent variables identified only CAVI as the one significantly associated with the severity of coronary atherosclerosis.

A limitation of this study is that it is an observational and cross-sectional study. The strengths of this study are having the large sample size and including many clinical and behavioral factors as independent variables with enough statistical power.

In conclusion, our results show that CAVI scores were significantly associated with the established CVD risk factors and coronary heart disease, one of the arteriosclerotic diseases. We confirmed that CAVI scores are a reliable indicator of arteriosclerosis reflecting the extent of arterial stiffness and atherosclerosis in the major artery from the aortic valve to the ankle.

Authors' Contributions

TN, K. Suzuki and K. Shirai conceived and designed the study. K. Suzuki and NI acquired the data. TN and MN performed statistical analyses. TN drafted the manuscript, and all other authors revised critically and approved the final manuscript.

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Research Article Open Access

Association of Prediabetes and Diabetes Mellitus with Cardiovascular Disease Risk Factors among Japanese Urban Workers and their Families: A Cross-Sectional Study

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Abstract

Purpose: The purposes of the study were to examine prevalence of prediabetes and diabetes mellitus (here after called diabetes) and to examine the association of prediabetes and diabetes with cardiovascular disease (CVD) risk factors among Japanese urban workers and their families.

Methods: Subjects were 9881 men and 12033 women of company employees and their families between 17 and 87 years of age who participated in cardiovascular disease screening in major cities, Japan. Persons having diabetes were defined as those taking medication of diabetes and/or having medical history of diabetes and/or whose fasting plasma glucose was equal to or higher than 126 mg/dl and/or whose hemoglobinA1c was equal to or higher than 6.5%. Persons with prediabetes were defined as those whose fasting plasma glucose was from 100 mg/dl to 125 mg/dl and/or whose hemoglobinA1c was from 5.7% to 6.4% excluding persons defined as having diabetes. In addition to descriptive analysis, logistic regression method was applied to examine the association of prediabetes and diabetes with CVD risk factors.

Results: There were 2001 (20.3%) men and 2756 (22.9%) women with prediabetes, whereas 678 (6.9%) men and 330 (2.7%) women were identified as having diabetes. Significant odds ratios (ORs) of prediabetes and diabetes were observed in association with age, hypertension, triglycerides ≥200 mg/dl and BMI ≥25 in both genders. Significant ORs of prediabetes and diabetes appeared in low HDL-C (<40 mg/dl), ex-smokers and smokers among men but not among women, except significant OR of diabetes in ex-smokers. Among women negatively significant ORs of prediabetes and diabetes were found in drinkers≤4 times/week but not among men except 0.73 of OR for those with diabetes drinking ≥5 times/week.

Conclusions: Our results confirmed that prevalence of prediabetes and diabetes increased with advancing age and that prediabetes and diabetes share almost the same CVD risk factors.

Keywords: Diabetes mellitus; Prediabetes; Body mass index; Smoking; Alcohol consumption; Japanese population; Cardiovascular disease risk factors

Abbreviations:

DM: Diabetes Mellitus; ORs: Odds Ratios; CVD: Cardiovascular Disease; ADA: American Diabetes Association; IFG: Impaired Fasting Glucose; FPG: Fasting Plasma Glucose; HbA1c: Glycol-hemoglobin A1c; NGSP: National Glycol-Hemoglobin Standardization Program; TG: Triglycerides; HDL-C: High Density Lipoprotein Cholesterol; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HP: Hypertension; PWV: Aortic Pulse Wave Velocity; CAVI: Cardio- Ankle Vascular Index

Introduction

Diabetes mellitus (hereafter called diabetes) is a chronic illness which requires continuous medical care, and its prevalence continues to rise among developed countries. Shaw et al. estimated that the prevalence of diabetes among adults (aged 20-79 years) was 6.4% of the world population affecting 285 million adults in 2010, and will increase to 7.7%, 439 million adults by 2030 [1]. This diabetes epidemic places financial burden on most industrial nations. The direct medical cost of diabetes in the United States was estimated to be $116 billion in 2007 [2]. Thus, it is crucial to prevent onset of diabetes before it requires substantial medical resources because of its complications.

Recently, a group of individuals whose glucose levels, although not meeting the criteria of diabetes, are too high to be considered as normal are defined as having prediabetes [3]. Zhang et al. found that prediabetes is a strong predictor to progress to diabetes in the future

[4]. Using the Stern and Framingham risk estimates, Ackermann et al. estimated that the probabilities for incident of type 2 diabetes (over 7.5 years) and cardiovascular disease (CVD, over 10 years) were 33.5% and 10.7% respectively among adults meeting the 2003 American Diabetes Association (ADA) definition for prediabetes [5]. Perreault et al. pointed out that reversion to normal glucose regulation from prediabetes is significantly associated with a reduced risk of future diabetes [6]. Also, Pour et al. confirmed that lifestyle intervention (e.g., diet and exercise) for prediabetes can significantly reduce the incidence of type 2 diabetes [7].

To target persons with prediabetes and make an effective plan for prevention of diabetes, we need to answer the following questions: (1) Does prevalence of prediabetes and diabetes increase as age advances? (2) Are prediabetes and diabetes associated significantly with CVD risk factors? (3) If yes, is the risk of diabetes in association with CVD risk factors higher than the risk of prediabetes?"

To provide answers to the above questions we analyzed a large data set based on CVD screening conducted for urban workers and their families in Japan.

Materials and Methods

Subjects

Subjects for the study were recruited from January 2006 to May 2009 through the screening program at Japan Health Promotion Foundation which has been conducting cardiovascular disease and cancer screening throughout major cities in Japan. Subjects were employees and their family members in companies of major cities in Japan: 9,881 men and 12,033 women between 17 and 87 years of age (Table 1). The study was approved by the Institutional Review Board and all subjects gave their consent to participate in the study.

Males	**Age**	**≤29**	**30-39**	**40-49**	**50-59**	**60-69**	**≥70**	**Total**
Normal	Number	1042	2338	1731	1235	704	152	7202
	Percent	97.7%	87.9%	72.2%	55.2%	56.5%	54.9%	72.9%
Prediabetes	Number	22	270	555	738	350	66	2001
	Percent	2.1%	10.2%	23.2%	33.0%	28.1%	23.8%	20.3%
Diabetes	Number	2	51	110	263	193	59	678
	Percent	0.2%	1.9%	4.6%	11.8%	15.5%	21.3%	6.9%
Total	Number	1066	2659	2396	2236	1247	277	9881
	Percent	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
Females	**Age**	**≤29**	**30-39**	**40-49**	**50-59**	**60-69**	**≥70**	**Total**
Normal	Number	892	2657	2340	2235	711	112	8947
	Percent	98.6%	86.0%	74.8%	62.5%	61.9%	60.2%	74.4%
Prediabetes	Number	11	413	728	1184	361	59	2756
	Percent	1.2%	13.4%	23.3%	33.1%	31.4%	31.7%	22.9%
Diabetes	Number	2	19	59	159	76	15	330
	Percent	0.2%	0.6%	1.9%	0.5%	6.6%	8.1%	2.7%
Total	Number	905	3089	3127	3578	1148	186	12033
	Percent	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

Note: Diabetes: FPG>=126 mg/dl or HbA1c>=6.5% or diabetes medication use or medical history of diabetes mellitus, and prediabetes: FPG 100-125 mg/dl or HbA1c 5.7-6.4%

Table 1: Study participants according to status of normal, prediabetes and diabetes mellitus by age and gender

Definition of prediabetes and diabetes

In 2003, ADA has proposed the criterion for prediabetes as those having Impaired Fasting Glucose (IFG), between 100 mg/dl and 125 mg/dl in Fasting Plasma Glucose (FPG). Also, ADA classified persons whose Glycol-hemoglobin A1c (HbA1c) is between 5.7 to 6.4% as having high risk for future diabetes [3]. Japan Diabetes Society defines people whose FPG is between 100 mg/dl and 110 mg/dl as high- normal FPG, and states that this group has higher prevalence of impaired glucose tolerance than those whose FPG is normal [8]. In our present study persons having diabetes were defined as those taking medication for diabetes and/or having history of diabetes and /or those whose fasting plasma glucose was equal to or higher than 126 mg/dl and/or whose HbA1c was equal to or higher than 6.5% in value of the National Glycol-hemoglobin Standardization Program (NGSP). Persons with prediabetes were defined as those whose fasting plasma glucose was from 100 mg/dl to 125 mg/dl and/or whose HbA1c was from 5.7% to 6.4% in NGSP value except those defined as having diabetes.

Clinical measurements

Blood was drawn from subjects after a 12 hour fast. The following measurements were made: total cholesterol and triglycerides (TG) by enzymatic assay; high density lipoprotein cholesterol (HDL-C) by modified enzymatic method; glucose by hexokinase glucose-6- phosphate dehydrogenate assay; and HbA1c by latex agglutination.

Persons having hypertension were defined as those taking hypertension drugs and/or having medical history of hypertension and/or as those whose systolic blood pressure (SBP) was equal to or higher than 140 mmHg and/or diastolic blood pressure (DBP) was equal to or higher than 90 mmHg. Persons with the state of borderline hypertension were defined as those whose SBP was from 120 mmHg to 139 mmHg and/or DBP was from 80 mmHg to 89 mmHg except those defined as having hypertension, following the guideline by American Heart Association in 2007 [9].

Questionnaire

During the screening, a short self-administered questionnaire was filled out by each subject. It contains questions on medical history and lifestyle factors such as smoking habit and alcohol consumption.

Statistical methods

In addition to the use of descriptive statistics, logistic regression method was used to examine the association of prediabetes and diabetes with cardiovascular disease risk factors. Statistical Packages for Social Sciences version 17 was used for data analysis.

Results

Distribution of study participants is shown according to age, gender, and status of prediabetes or diabetes in Table 1. There were 2001 (20.3%) men and 2756 (22.9%) women with prediabetes, whereas 678 (6.9%) men and 330 (2.7%) women were identified as having diabetes. Prevalence of prediabetes and diabetes increased with advancing age. Prevalence of prediabetes sharply increased until reaching 50-59 years of age in both genders: from 2.1% for ≤29 years of age to 33.0% for 50-59 years of age among men and from 1.2% for ≤29 years of age to 33.1% for 50-59 years of age among women. Regarding prevalence of diabetes, on the other hand, the rate of increase in men was more than double the rate of increase in women: 0.2% for ≤29 years of age to 21.3% for ≥70 years of age among men and 0.2% for ≤29 years of age to 8.1% for ≥70 years of age among women.

mean ± SD	Age	≤29	30-39	40-49	50-59	60-69	≥70
Systolic blood pressure	Males	119 ± 11	122 ± 13	126 ± 14	132 ± 16	133 ± 17	136 ± 16
	Females	109 ± 10	113 ± 12	119 ± 14	127 ± 16	130 ± 16	135 ± 16
Diastolic blood pressure	Males	69 ± 9	74 ± 10	79 ± 11	83 ± 11	81 ± 10	78 ± 11
	Females	63 ± 8	66 ± 9	71 ± 10	75 ± 11	76 ± 10	77 ± 10
Total cholesterol (mg/dl)	Males	186 ± 33	204 ± 34	214 ± 36	213 ± 34	211 ± 32	209 ± 34
	Females	180 ± 28	194 ± 32	209 ± 34	233 ± 36	236 ± 35	233 ± 42
HDL-C (mg/dl)	Males	62 ± 15	59 ± 16	60 ± 17	61 ± 18	63 ± 18	62 ± 18
	Females	76 ± 15	76 ± 17	77 ± 18	76 ± 19	75 ± 19	73 ± 17
Triglycerides (mg/dl)	Males	95 ± 77	135 ± 103	158 ± 169	147 ± 113	126 ± 72	122 ± 81
	Females	59 ± 31	70 ± 57	79 ± 49	96 ± 55	105 ± 55	108 ± 54
Body Mass Index (kg/m^2)	Males	22.3 ± 3.5	23.9 ± 3.7	24.2 ± 3.2	24.1 ± 2.9	23.7 ± 2.8	23.5 ± 3.0
	Females	20.4 ± 3.0	20.9 ± 3.1	21.7 ± 3.2	22.2 ± 3.2	22.3 ± 3.0	22.9 ± 3.6
Prevalence (%)	**Age**	**≤29**	**30-39**	**40-49**	**50-59**	**60-69**	**≥70**
Drinkers	Males	61.8	73.4	77.9	79.3	77.4	66.8
	Females	50.4	45.5	43.4	36.2	33.4	27.0
Ex-smokers	Males	11.2	18.7	25.4	31.6	35.9	37.2
	Females	10.4	13.3	9.1	5.8	6.1	4.8
Smokers	Males	55.4	51.9	48.4	41.2	28.5	18.1
	Females	22.8	15.6	11.7	8.5	5.7	3.8

Table 2: Characteristics of study participants

Characteristics of study participants are shown in Table 2. It was observed that the averages for both systolic and diastolic blood pressure linearly increased with advancing age in both genders with an exception of men's diastolic blood pressure after 60 years of age of which average slightly decreased. Almost all averages of clinical indicators increased until 60 years of age except HDL-C of which averages were constantly at the same level in both genders. Striking differences in averages of clinical indicators between genders were observed and were unfavorable for men in terms of cardiovascular disease risk. BMI averages ranged from 22.3 to 24.2 among men and from 20.4 to 22.9 among women. Greater prevalence of drinkers and smokers was observed among men than among women. Also, greater prevalence of drinkers and smokers was observed among younger women than among older women.

Tables 3 and 4 show odds ratios (ORs) of prediabetes and diabetes associated with CVD risk factors among men and women, respectively. Crude ORs are shown to be compared with adjusted ORs which were taken as final results. Significant ORs of prediabetes and diabetes were observed in association with age, hypertension, triglycerides ≥200 mg/dl and BMI ≥25 in both genders. Significant ORs of prediabetes and diabetes appeared in low HDL-C (<40 mg/dl), ex-smokers and smokers among men but not among women, except significant OR of diabetes for ex-smokers. Among women negatively significant ORs of prediabetes and diabetes were found in drinkers ≤4 and ≥5 times/week but not among men except 0.73 of OR for those with diabetes drinking ≥5 times/week. In addition, we examined the association of prediabetes and diabetes with quantity of alcohol consumption (not shown in tables): comparing with non-drinkers, significant negative ORs of prediabetes in women drinking 1-3 drinks (1 drink=23 g ethanol) per occasion ≤4 times/week (OR=0.62, 95% CI: 0.49-0.80) and ≥5 times/week (OR=0.73, CI: 0.57-0.93), significant negative ORs of diabetes in men drinking 1-3 drinks per occasion ≤4 times/week (OR=0.73, CI: 0.54-0.99) and ≥5 times/week (OR=0.68, CI: 0.54-0.87), and significant negative ORs of diabetes in women drinking <1 drink (OR=0.59, CI: 0.43-0.82) and 1-3 drinks (OR=0.43, CI: 0.20-0.94) per occasion ≤4 times/week and <1 drink per occasion ≥5 times/week (OR=0.30, CI: 0.16-0.58).

Covariates		Prediabetes			Diabetes		
		Crude Odds Ratio	Adjusted Odds Ratio	95%CI	Crude Odds Ratio	Adjusted Odds Ratio	95%CI
Age (Ref: <40)	40-49	3.71	3.34	2.85 - 3.92***	4.05	3.75	2.66 - 5.27***
	50-59	6.92	6.11	5.20 - 7.18***	13.58	13.20	9.55 - 18.25***
	60-69	5.76	5.28	4.37 - 6.38***	17.48	18.37	13.04 - 25.89***
	≥70	5.03	4.56	3.29 - 6.33***	24.75	24.25	15.66 - 37.56***
Hypertension (HP) (Ref: normal)	Borderline HP	1.58	1.18	1.03 - 1.36*	1.80	1.15	0.89 - 1.50
	HP	3.24	1.45	1.24 - 1.70***	6.24	1.92	1.46 - 2.51***
HDL-C (Ref: ≥ 40 mg/dl)	<40 mg/dl	1.50	1.24	1.00 - 1.54*	2.02	1.39	1.02 - 1.90*
Triglycerides (Ref: <150 mg/dl)	150-199	1.43	1.08	0.92 - 1.25	1.13	1.01	0.78 - 1.30
	≥200	1.70	1.25	1.07 - 1.45**	2.37	1.75	1.40 - 2.19***
BMI (Ref: 20-22.9)	<18.5	0.44	0.58	0.36 - 0.91*	0.92	1.20	0.67 - 2.14
	18.5-19.9	0.69	0.88	0.68 - 1.13	0.56	0.83	0.52 - 1.32
	23-24.9	1.46	1.21	1.05 - 1.39**	1.25	0.96	0.75 - 1.23
	25-27.9	1.98	1.58	1.37 - 1.83***	2.02	1.40	1.11 - 1.78**
	≥28	2.07	2.13	1.75 - 2.59***	3.43	3.60	2.70 - 4.78***
Drinking (Ref: Non-drinkers)	≤4 times/week	0.70	1.01	0.87 - 1.16	0.74	0.83	0.65 - 1.04
	≥5 times/week	0.70	1.04	0.90 - 1.19	1.09	0.73	0.59 - 0.91**
Smoking (Ref: Non-smokers)	Ex-smokers	1.42	1.17	1.01 - 1.34*	1.56	1.26	1.01 - 1.58*
	Current smokers	1.05	1.20	1.05 - 1.37**	1.03	1.40	1.13 - 1.74**

Note: Ref = reference category; *p<0.05, **p<0.01, ***p<0.001; CI = Confidence Interval of adjusted odds ratio

Table 3: Odds ratios to estimate risks of prediabetes and diabetes mellitus in association with CVD risk factors: Males

Covariates		Prediabetes			Diabetes		
		Crude Odds Ratio	Adjusted Odds Ratio	95%CI	Crude Odds Ratio	Adjusted Odds Ratio	95%CI
Age (Ref: <40)	40-49	2.60	2.26	1.98 - 2.59***	4.26	3.23	1.94 - 5.38***
	50-59	4.43	3.47	3.04 - 3.96***	12.02	7.27	4.49 - 11.77***
	60-69	4.25	3.16	2.65 - 3.76***	18.07	9.70	5.75 - 16.37***
	≥70	4.41	2.97	2.11 - 4.20***	22.63	10.59	5.07 - 22.15***
Hypertension (HP) (Ref: normal)	Borderline HP	2.21	1.55	1.40 - 1.72***	3.17	1.57	1.15 - 2.14**
	HP	2.92	1.44	1.25 - 1.69***	8.29	2.12	1.50 - 2.99***
HDL-C (ref: ≥50 mg/dl)	<50 mg/dl	1.46	0.98	0.80 - 1.20	2.47	1.11	0.73 - 1.68
Triglycerides (Ref:<150 mg/dl)	150-199	1.91	1.20	0.99 - 1.45	3.20	1.33	0.90 - 1.98
	≥200	2.28	1.43	1.12 - 1.81**	5.84	2.40	1.58 - 3.64***
BMI (Ref: 20-22.9)	<18.5	0.62	0.83	0.71 - 0.98*	0.50	0.81	0.47 - 1.39
	18.5-19.9	0.71	0.86	0.76 - 0.98*	0.59	0.81	0.53 - 1.24
	23-24.9	1.26	1.06	0.93 - 1.21	2.17	1.59	1.14 - 2.23**
	25-27.9	1.82	1.46	1.25 - 1.70***	4.78	3.15	2.26 - 4.39***
	≥28	2.62	2.20	1.80 - 2.70***	7.30	5.15	3.47 - 7.65***
Drinking (Ref: Non-drinkers)	≤4 times/week	1.26	0.89	0.80 - 0.99*	0.41	0.56	0.41 - 0.77***
	≥5 times/week	0.96	0.83	0.72 - 0.96*	0.37	0.42	0.27 - 0.66***
Smoking (Ref: Non-smokers)	Ex-smokers	0.76	1.01	0.86 - 1.20	0.90	1.59	1.05 - 2.42*
	Current smokers	0.69	0.92	0.79 - 1.08	0.50	0.97	0.62 - 1.53

Note: Ref = reference category; *p<0.05, **p<0.01, ***p<0.001; CI = Confidence Interval of adjusted odds ratio

Table 4: Odds ratios to estimate risks of prediabetes and diabetes mellitus in association with CVD risk factors: Females

Discussion

Regarding the association between prediabetes or diabetes and increase in age, we observed an increasing trend in prevalence of prediabetes and diabetes in both genders as age advanced (Table 1): from 2.1% of prediabetes and 0.2% of diabetes for 29 years of age and younger to 23.8% of prediabetes and 21.3% of diabetes for 70 years of age and older, respectively, among men; and from 1.2% of prediabetes and 0.2% of diabetes for 29 years of age and younger to 31.7% of prediabetes and 8.1% of diabetes for 70 years of age and older, respectively, among women. That is, about 45% of men and 40% of women from our study population fell in either prediabetes or diabetes after reaching 70 years of age, as compared with 41% of men and 35% of women, respectively, in the 2007 National Health and Nutrition Survey in Japan [10].

In this paper, we conducted the logistic regression analysis to assess the association of CVD risk factors with either prediabetes or diabetes to confirm the hypothesis that prediabetes and diabetes share the same risk factors. First, age is a substantial risk factor for diabetes and prediabetes, as ORs increased significantly with ages (Tables 3 and 4). Persons 70 years of age and over had more than 24 times greater estimated risk among men and 11 times greater estimated risk among women for having diabetes than those younger than 40 years of age, whereas the same trend was observed in ORs of prediabetes with a less dramatic increase: 5 times greater estimated risk among men and 3 times greater estimated risk among women.

We found that hypertension was significantly associated with prediabetes and diabetes in both genders as observed in other studies [11,12], whereas borderline hypertension was significantly associated both with prediabetes and diabetes among women and with prediabetes among men.

De Fronzo et al. find that among individuals with prediabetes and type 2 diabetes, the incidence of small, dense LDL particles (phenotype B) markedly increases and represents a major risk factor for accelerated atherogenesis [13]. Our results support their implication, since lower HDL-C (<40 mg/dl) among men and higher triglycerides (≥200 mg/dl) in both genders were significantly associated with prediabetes and diabetes.

We found a linear association between BMI and prediabetes and diabetes in both genders, implying that prevalence of prediabetes and

diabetes increases as BMI becomes higher in our study population. In comparison with 20-22.9 of BMI, ORs of prediabetes for BMI<18.5 (that is considered to be very slim) were 0.58 among men and 0.83 among women, implying that prevalence of prediabetes is much further decreased as BMI becomes smaller. Then, do we recommend that people maintain their BMI less than 18.5? Our answer is "no" because extremely slim persons are susceptible to certain diseases. Chen et al. examined the association between BMI and cardiovascular disease mortality in the data from the Asia Cohort Consortium and their results show a U shaped association between BMI and overall CVD mortality in East Asians including Japanese: elevated risk of death was observed for overall CVD at BMI value 25 and above and at BMI value 17.4 and below, compared with reference range of 22.5-24.9 [14].

Cullmann et al. show that high alcohol consumption and binge drinking increases the risk of prediabetes and type 2 diabetes in men, while low alcohol consumption lowers the risk of type 2 diabetes in women in Swedish population [15]. Our women's results are consistent with Cullmann's findings: estimated risk of both prediabetes and diabetes were significantly lowered in less frequent drinkers as well as frequent drinkers, compared with non-drinkers, while estimated risk of diabetes became significantly low in frequent male drinkers. Our results are consistent with the trend in lowering risk for the development of diabetes with an increase in frequency of alcohol intake among Japanese men followed up for about 10 years by Heianza et al. [16]. Our findings and theirs imply that alcohol possibly works protectively toward both prediabetes and diabetes, as in the same way that alcohol lowers the risk of coronary heart disease [17].

We found that the estimated risk of prediabetes and diabetes was significantly elevated in both male current smokers and ex-smokers, while the estimated risk of diabetes was raised in female ex-smokers, compared with non-smokers. Our results are consistent with Shi et al.'s findings showing that smoking was positively associated with type 2 diabetes mellitus among middle-age and elderly Chinese men [18].

Overall, both prediabetes and diabetes were associated with all of the CVD risk factors included in our analysis except HDL-C among women and implying persons with both conditions are more advanced in atherosclerosis or arteriosclerosis. Namekata et al. show significant odds ratios of the abnormally high aortic pulse wave velocity (PWV, an indicator of arteriosclerosis reflecting stiffness of artery and atherosclerosis) in an association with diabetes mellitus among Japanese Americans and among native Japanese (3.66 and 2.43, respectively) [19]. Recently, Namekata et al. have developed criteria of cardio-ankle vascular index (CAVI), a new indicator of arteriosclerosis reflecting both stiffness of artery and atherosclerosis in the arteries from heart to ankle which is converted from PWV, and observe that ORs of having abnormally high CAVI scores after making adjustment for ages among persons with diabetes mellitus are 10.02 for men and 8.42 for women, compared with those without diabetes [20,21]. Their results estimate much faster advancement of arteriosclerosis among persons with diabetes than in the group without diabetes.

A limitation of this study is that it is an observational and cross-sectional study. The strength of this study is having the large sample size and including several clinical and behavioral factors as covariates with enough statistical power.

In conclusion, (1) prevalence of prediabetes and diabetes increased as age became higher; (2) prediabetes and diabetes were significantly associated with the established CVD risk factors; and (3) the estimated risk of diabetes in association with CVD risk factors was higher than that of prediabetes. As the American Diabetes Association's guideline recommends [3], it is important to introduce an early intervention of lifestyle and diet modification to persons with prediabetes to prevent them from onset of diabetes.

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Estimating the extent of subclinical arteriosclerosis of persons with prediabetes and diabetes mellitus among Japanese urban workers and their families: a cross-sectional study

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Abstract

Background: Diabetes mellitus (hereafter called diabetes) is considered to accelerate arteriosclerosis leading to coronary heart disease and stroke. Thus, it is important to quantitatively estimate the extent of subclinical arteriosclerosis. A new method called cardio-ankle vascular index (CAVI) is developed to reflect arterial stiffness independently from blood pressure at the time of measurement. Then, we examined if CAVI scores could discriminate the extent of arteriosclerosis between persons with prediabetes (or borderline diabetes) and with diabetes among Japanese urban workers and their families.

Methods: Subjects were 9881 men and 12033 women of company employees and their families who participated in cardiovascular disease screening in Japan. Persons having diabetes and prediabetes were defined based on the criteria set by American Diabetes Association. CAVI scores were measured by VaSera VS-1000. We applied the established age-sex specific cutoff points of CAVI scores above which were determined to be abnormally high or advanced level of arteriosclerosis. To examine the association of prediabetes and diabetes with CAVI scores, CAVI scores of screening participants were converted to a binary variable: 1 for less than cutoff points and 2 for equal or greater than cutoff points or abnormally high CAVI scores. Logistic regression method was used to examine the association of prediabetes and diabetes with CAVI scores after adjusting for major cardiovascular disease (CVD) risk factors.

Results: Prevalence of abnormally high CAVI scores was significantly higher after 40 years of age among persons with diabetes than either among persons with prediabetes or among normal persons in both genders. Significantly elevated odds ratios (ORs) of abnormally high CAVI scores appeared among persons with prediabetes: 1.29 (95 % confidence interval (CI), 1.11-1.48) for men and 1.14 (CI, 1.01-1.28) for women, and among persons with diabetes: 2.41 (CI, 1.97-2.95) for men and 2.52 (CI, 1.94-3.28) for women.

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Conclusions: The extent of subclinical arteriosclerosis (including arterial stiffness and atherosclerosis) was moderately enhanced among persons with prediabetes and was further advanced among persons with diabetes. Thus, it is important to introduce earlier interventions for changing lifestyle and diet of persons with prediabetes in order to prevent them from developing diabetes and further advancing arteriosclerosis.

Keywords: Cardio-ankle vascular index (CAVI), Diabetes mellitus, Prediabetes, Arteriosclerosis, Epidemiology, Japanese population

Background

One of the most serious complications among person with diabetes is the deterioration of arterial system or the acceleration of arteriosclerosis which could not be easily measured in the past. One method to quantitatively estimate the extent of arteriosclerosis is the use of the pulse wave velocity (PWV). The idea on the association of PWV with arteriosclerosis is traced back to an experiment using artificial blood vessels conducted by Moens in 1878 [1]. Then, Bramwell and colleagues showed that PWV depends on the modulus of arterial volume elasticity by experiments in 1922-23 [1–5]. Their experimental results have been a basis for the development of the measurement device PWV-200 (Fukuda-Denshi Co., Tokyo) which measures PWV propagating through the aorta (thorax, abdomen, and part of common iliac artery) from the aortic valve to the femoral pulsation point, as described by Hasegawa in 1970 [6]. Because PWV is highly correlated with diastolic blood pressure, Hasegawa developed a nomogram showing the association between diastolic blood pressure and PWV. He proposed an adjustment to any measured PWV values at 80 mmHg. As a result, such an adjustment was built into the PWV-200 machine. This is an important step allowing clinicians and researchers to compare PWV values between individuals and between populations. Namekata et al. conducted cardiovascular disease prevention screening in Seattle and found that PWV was positively and significantly associated with aging (≥60 years of age), hypertension, diabetes, the ratio of total cholesterol to high density lipoprotein cholesterol, ex-smokers and negatively and significantly with alcohol consumption among Japanese Americans [7]. In addition, they had similar findings among Japanese urban workers [8].

To overcome some technical difficulty for measuring PWV, the cardio-ankle vascular index (CAVI) was developed as a new indicator of arteriosclerosis in 2004 [9]. CAVI scores quantitatively reflect arteriosclerosis of the aorta, femoral and tibial arteries based on Bramwell-Hill's equation [1] and stiffness parameter [10] which is allowed to be converted from PWV propagating from the aortic valve to ankle. Some researchers proposed to use CAVI scores as an indicator of atherosclerosis. Nakamura et al. found a strong association of CAVI with the presence of severity of coronary atherosclerosis based on their ordinal logistic regression analysis [11]. Kadota et al. suggested the use of CAVI as a screening tool for atherosclerosis based on their findings from the general population study of 1,014 adults showing strong significant associations of CAVI scores with carotid intima-media thickness and with homocysteine after adjustment for age and sex [12]. Thus, it is considered that CAVI scores reflect arterial stiffness, atherosclerosis and arteriosclerosis of which conditions are overlapping and inseparable. We use CAVI scores to represent the extent of subclinical arteriosclerosis in this paper but it is inclusive of arterial stiffness and atherosclerosis.

To practically use CAVI as a diagnostic tool for determining the extent of arteriosclerosis, our previous study established the baseline CAVI scores by age and gender among cardiovascular disease (CVD) risk-free persons [13]. In our present study we measured CAVI scores and identified persons with abnormally high CAVI scores in Japanese urban workers and their families based on the criteria developed by our studies [13, 14], and then examined the extent of subclinical arteriosclerosis among persons with prediabetes and among persons with diabetes mellitus after making adjustment for major cardiovascular disease (CVD) risk factors.

Methods

Subjects

Subjects for the study were recruited from January 2006 to May 2009 through the screening program at Japan Health Promotion Foundation which has been conducting cardiovascular disease and cancer screening throughout major cities in Japan. Subjects were company employees and their family members: 9,881 men and 12,033 women between 17 and 87 years of age. Following Japan's Personal Information Protection Law, the use of anonymized screening data for research purpose was approved by the board of Japan Health Promotion Foundation. The study was approved by the board of Pacific Rim Disease Prevention Center.

Definition of prediabetes and diabetes mellitus

Following the recommendation from American Diabetes Association [15], persons having diabetes were defined as those having medical history of diabetes and/or taking medication of diabetes and/or whose fasting plasma glucose were equal to or higher than 126 mg/dl and/or whose hemoglobinA1c (HbA1c) were equal to or higher than 6.5 % in NGSP value (48 mmol/mol in IFCC). Persons with the state of prediabetes were defined as those whose fasting plasma glucose was from 100 mg/dl to 125 mg/dl and/or whose HbA1c was from 5.7 % to 6.4 % in NGSP value (39 mmol/mol to 47 mmol/mol in IFCC). Persons defined as "normal" were those without diabetes and prediabetes.

Clinical measurements

Blood was drawn from subjects after a 12 h fast. The following measurements were made: total cholesterol (TC) and triglycerides (TG) by enzymatic assay; high density lipoprotein cholesterol (HDL-C) by modified enzymatic method; glucose by hexokinase glucose-6-phosphate dehydrogenate assay; and glyco-hemoglobin A1c (HbA1c) by latex agglutination.

Following the guideline released by American Heart Association in 2007 [16], persons having hypertension were defined as those having medical history of hypertension and/or taking hypertension drugs and/or whose systolic blood pressure (SBP) was equal to or higher than 140 mmHg and/or whose diastolic blood pressure (DBP) was equal to or higher than 90 mmHg.

Cardio-ankle vascular index

CAVI, a stiffness and arteriosclerosis indicator of thorax, abdomen, common iliac, femoral and tibial arteries, was measured by VaSera VS-1000 manufactured by Fukuda-Denshi Company, LTD (Tokyo, Japan).

As illustrated by Shirai et al. [9], the scale conversion from PWV to CAVI is performed by the following formula:

$$\mathrm{CAVI} = \mathrm{a}\left\{(2\rho/\Delta\mathrm{P})\ \mathrm{x}\ \ln(\mathrm{Ps}/\mathrm{Pd})\mathrm{PWV}^2\right\}\ +\ \mathrm{b}$$

where Ps and Pd are systolic and diastolic blood pressure values, respectively, PWV is the pulse wave velocity between heart and ankle, ΔP is Ps-Pd, ρ is blood density, and a and b are constants. This equation was derived from Bramwell-Hill's equation [1] and stiffness parameter [10]. Scale conversion constants are determined so as to match CAVI with PWV by Hasegawa's method [6]. These measurements and calculations are automatically made in VaSera VS-1000.

In the previous study we established the age-sex specific cutoff points of CAVI scores above which were determined to be abnormally high or advanced level of arteriosclerosis [14]. The cutoff points are (mean of CAVI + one standard deviation) among CVD risk-free subjects: 7.39 for 20-29 years of age, 7.80 for 30-39 years of age, 8.29 for 40-49 years of age, 8.83 for 50-59 years of age, 9.54 for 60-69 years of age, and 10.35 for 70 years of age and over among men; and 7.23 for 20-29 years of age, 7.42 for 30-39 years of age, 7.95 for 40-49 years of age, 8.52 for 50-59 years of age, 8.98 for 60-69 years of age, and 9.46 for 70 years of age and over among women. To apply the logistic regression method for examining the association of prediabetes and diabetes with CAVI scores, CAVI scores of screening participants were converted to a binary variable: 1 for less than cutoff points and 2 for equal or greater than cutoff points or abnormally high CAVI scores.

Questionnaire

A short self-administered questionnaire was filled out by each subject during the screening. It contains questions on medical history and lifestyle factors such as smoking habit and alcohol consumption.

Statistical methods

All statistical analyses were performed gender-specifically. To examine characteristics of study participants by diabetes status, Student's t-tests and chi-square tests were conducted for detecting significant differences in means and in prevalence, respectively, between persons with normal status and persons with prediabetes and diabetes. Cochran-Armitage test for linear trend was applied to evaluate the dose-dependent association between the degree of glycemic status and the prevalence of abnormally high CAVI scores. Crude, age-adjusted and multivariable-adjusted odds ratios (OR) and the 95 % confidence intervals (CI) of abnormally high CAVI scores according to diabetic status were calculated in logistic regression models, with normal persons who were treated as the reference category. In the age-adjusted model, age was entered as a variable of 10-year interval categories (50-59, 60-69, 70+ vs. <50). The multivariable model was further adjusted for major CVD risk factors including hypertension (yes vs. no), HDL-C (≥40 mg/dl vs. <40 mg/dl for males, ≥50 mg/dl vs. <50 mg/dl for females), triglycerides (150-199 mg/dl, ≥200 mg/dl vs. <150 mg/dl), BMI (20-22.9, 23-24.9, 25-27.9, 28-29.9, 30+ vs. <20), drinking habit (≤4 times/week, ≥5 times/week vs. non-drinkers), and smoking habit (ex-smokers, current smokers vs. non-smokers).

Results

Characteristics of study participants by age and gender were described in our previous paper [14]. We briefly summarize those here. It is observed that the averages for both systolic and diastolic blood pressure and CAVI

scores linearly increased as ages advanced in both genders with an exception of men's diastolic blood pressure after 60 years of age of which averages slightly decreased. Almost all averages of clinical indicators increased until 60 years of age except HDL-C of which averages were at the same level in both genders. Striking differences in averages of clinical indicators between genders are observed and are unfavorable for men in terms of cardiovascular disease risk. BMI averages ranged from 22.3 to 24.2 among men and from 20.4 to 22.9 among women. Greater prevalence of drinkers and smokers was observed in men than in women. Prevalence of drinkers and smokers was greater in younger women than in older women.

Table 1 shows characteristics of study participants by diabetes status. Averages of all variables in both genders were lowest in normal, highest in diabetes, and middle in prediabetes, except averages of HDL-C which were in the reverse order. Prevalence of abnormally high CAVI scores was lowest in normal, highest in diabetes, and middle in prediabetes.

Prevalence of abnormally high CAVI scores is shown according to the status of prediabetes and diabetes by age and gender in Table 2. It is observed that such prevalence was higher after 40 years of age among persons with diabetes than either among persons with prediabetes or among normal persons in both genders.

Table 3 shows odds ratios (ORs) of abnormally high CAVI scores in association with prediabetes and diabetes as compared with the reference of normal CAVI scores: (1) without an adjustment for confounding factors (crude ORs); (2) age breakdowns were added to logistic

Table 1 Characteristics of study participants by diabetes status

		Normal	Prediabetes	Diabetes
Sample size	Men	7,202	2,001	678
	Women	8,947	2,756	330
		mean ± SD (t-value)		
Age	Men	43 ± 13	51 ± 10 (t = 28.11***)	56 ± 10 (t = 26.72***)
	Women	44 ± 12	51 ± 9 (t = 27.54***)	55 ± 9 (t = 16.60***)
Systolic blood pressure	Men	125 ± 14	131 ± 15 (t = 15.12***)	136 ± 18 (t = 18.53***)
	Women	118 ± 15	125 ± 15 (t = 21.58***)	132 ± 18 (t = 16.43***)
Diastolic blood pressure	Men	76 ± 11	81 ± 11 (t = 17.26***)	82 ± 11 (t = 14.03***)
	Women	70 ± 10	73 ± 11 (t = 14.32***)	77 ± 12 (t = 11.19***)
Total cholesterol (mg/dl)	Men	205 ± 35	215 ± 35 (t = 8.07***)	214 ± 37 (t = 4.54***)
	Women	209 ± 37	225 ± 38 (t = 18.34***)	230 ± 40 (t = 9.21***)
HDL-C (mg/dl)	Men	61 ± 17	60 ± 17 (t = 3.90***)	57 ± 18 (t = 5.81***)
	Women	77 ± 18	75 ± 19 (t = 3.63***)	70 ± 18 (t = 6.66***)
Triglycerides (mg/dl)	Men	129 ± 112	156 ± 139 (t = 8.96***)	170 ± 133 (t = 8.82***)
	Women	78 ± 52	95 ± 56 (t = 14.18***)	121 ± 80 (t = 14.30***)
CAVI	Men	7.43 ± 0.99	7.97 ± 0.96 (t = 21.28***)	8.49 ± 1.11 (t = 26.08***)
	Women	7.24 ± 0.92	7.62 ± 0.89 (t = 18.93***)	8.09 ± 1.02 (t = 16.38***)
Body Mass Index (kg/m^2)	Men	23.5 ± 3.2	24.6 ± 3.3 (t = 13.56***)	25.1 ± 3.9 (t = 12.46***)
	Women	21.3 ± 3.0	22.5 ± 3.6 (t = 17.79***)	24.3 ± 4.2 (t = 17.53***)
		Prevalence (%) (chi-square statistics)		
Abnormally high CAVI score	Men	12.8	18.5 (χ^2 = 43.41***)	30.4 (χ^2 = 157.25***)
	Women	15.2	18.9 (χ^2 = 21.01***)	34.2 (χ^2 = 85.95***)
Drinkers	Men	74.3	77.9 (χ^2 = 10.62**)	72.7 (χ^2 = 0.81)
	Women	43.1	36.9 (χ^2 = 34.05***)	23.0 (χ^2 = 52.65***)
Ex-smokers	Men	23.3	29.5 (χ^2 = 33.23***)	31.7 (χ^2 = 24.29***)
	Women	9.4	7.6 (χ^2 = 35.23***)	9.1 (χ^2 = 10.24**)
Smokers	Men	46.0	43.1 (χ^2 = 33.23***)	41.4 (χ^2 = 24.29***)
	Women	12.8	9.4 (χ^2 = 35.23***)	7.0 (χ^2 = 10.24**)

Note: Student's t-tests and chi-square tests were conducted by comparing means and prevalence respectively between persons with normal status and persons with prediabetes or persons with diabetes
p-value: *< 0.05, **< 0.01, ***< 0.001

Table 2 Prevalence (%) of abnormally high CAVI scores by status of prediabetes and diabetes mellitus

	Age	≤29	30-39	40-49	50-59	60-69	70+
Men							
Normal	prevalence	6.0	10.9	13.2	21.5	12.8	11.8
	persons at risk	1042	2338	1731	1235	704	152
Prediabetes							
	prevalence	9.1	16.3	15.5	23.3	16.9	12.1
	persons at risk	22	270	555	738	350	66
Diabetes							
	prevalence	—	11.8	19.1	43.7	26.9	20.3
	persons at risk	2	51	110	263	193	59
χ^2value for linear trend (*p*-value)		—	4.25 (0.039)	4.31 (0.038)	39.9 (0.000)	21.16 (0.000)	2.14 (0.144)
Women							
Normal	prevalence	5.9	14.8	11.6	19.8	23.2	33.9
	persons at risk	892	2657	2340	2235	711	112
Prediabetes							
	prevalence	—	16.9	12.4	21.9	23.3	30.5
	persons at risk	11	413	728	1184	361	59
Diabetes							
	prevalence	—	—	20.3	37.7	42.1	—
	persons at risk	2	19	59	159	76	15
χ^2value for linear trend (*p*-value)		—	—	2.12 (0.145)	17.53 (0.000)	6.24 (0.012)	—

Note: — indicates that the sample size was too small to obtain meaningful prevalence

regression analysis; and (3) other CVD risk factors were further added to logistic regression analysis. As more confounding factors were adjusted, odds ratios decreased in both prediabetes and diabetes mellitus except ORs of prediabetes in women indicating that ORs after adjusting for ages and for CVD risk factors were almost identical and lower than crude OR. After adjusting for major CVD risk factors, significantly elevated ORs appeared among persons with prediabetes: 1.29 (95 % confidence interval (CI), 1.11-1.48) for men and 1.14 (CI, 1.01-1.28) for women, and among persons with diabetes: 2.41 (CI, 1.97-2.95) for men and 2.52 (CI, 1.94-3.28) for women.

Discussion

In the present cross-sectional study of Japanese urban workers and their families, prevalence of abnormally high CAVI scores were dose-dependently elevated along with

Table 3 Estimated risk of having abnormally high CAVI scores in association with prediabetes and diabetes mellitus among Japanese urban workers and their families

	Prediabetes				Diabetes mellitus			
	OR		95 % CI		OR		95 % CI	
			lower	upper			lower	upper
Men								
(1) Crude	1.56	***	1.36	1.78	2.98	***	2.50	3.56
(2) Adjusted for age	1.32	***	1.15	1.51	2.38	***	1.97	2.88
(3) Adjusted for CVD risk factors	1.29	**	1.11	1.48	2.41	***	1.97	2.95
Women								
(1) Crude	1.30	***	1.16	1.45	2.90	***	2.29	3.66
(2) Adjusted for age	1.12		0.99	1.25	2.19	***	1.72	2.78
(3) Adjusted for CVD risk factors	1.14	*	1.01	1.28	2.52	***	1.94	3.28

Note: *OR* Odds ratio, *CI* Confidence interval; *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$; (1) Prediabetes or diabetes was included alone as a covariate in logistic regression analysis. (2) Age breakdowns (<50, 50-59, 60-69, ≥70 years of age) were added to logistic regression analysis. (3) Other CVD risk factors (hypertension, HDL-C, TG, BMI, drinking, and smoking) were further added to logistic regression analysis

the advancing degree of diabetic status both in men and in women. Compared with normal persons, significantly elevated odds ratios of abnormally high CAVI scores were observed not only in persons with diabetes but also in those with prediabetes.

With regard to the validity to use CAVI scores as an indicator of arteriosclerosis, Otsuka examined 72 deceased patients' antemortem PWV (which is a basis for deriving CAVI scores) and pathological changes measured by the diffuse fibrotic thickening, formation of atheroma and calcification in the wall of their aorta. He reported multiple regression coefficient R = 0.810 between PWV and scores of those pathological changes [17]. In addition, other researchers reported that CAVI scores were significantly associated with coronary atherosclerosis [11], with carotid intima-media thickness and with homocysteine [12]. Thus, the use of CAVI scores derived from PWV values is valid to estimate the extent of arteriosclerosis.

VaSera VS-1000, which was used in our study, was designed to measure CAVI scores independent of blood pressure at the time of CAVI score measurement and CAVI scores represent the extent of arteriosclerosis between the aortic valve and the ankle. We have shown biological aging of the major artery by measuring CAVI scores in the CVD risk-free group and disease-related pathological aging of the major artery in the CVD high-risk group [13]. CAVI scores allow us to evaluate the extent of arteriosclerosis in the major arteries between the aortic valve and the ankle, to screen persons with subclinical stage of CVD, and provide an opportunity to modify diet and lifestyle to improve CAVI scores as reported by Satoh et al [18]. Thus, the use of CAVI scores potentially leads to savings on high treatment costs and to prolonging many productive lives.

Namekata et al. showed significant odds ratios of the abnormally high aortic pulse wave velocity (PWV, an indicator of arteriosclerosis reflecting stiffness of artery and atherosclerosis) in an association with diabetes among Japanese Americans and among native Japanese (3.66 and 2.43, respectively) [8]. Namekata et al. observed that odds ratios of abnormally high CAVI scores in an association with diabetes after making adjustment for ages were 10.02 for men and 8.42 for women, compared with those who did not have diabetes [14]. In our recent study significant ORs of prediabetes and diabetes were observed in association with most CVD risk factors including age, hypertension, triglycerides ≥ 200 mg/dl and BMI ≥ 25 in both genders [19]. Our results imply much faster advancement of arteriosclerosis among persons both with prediabetes and with diabetes than in the normal persons.

In our present study it is shown that prevalence of abnormally high CAVI scores has an increasing trend with an age increase in all three groups of non-diabetes normal persons, prediabetes and diabetes (Table 2). Our results show that comparing with persons with normal CAVI scores, estimated risks of abnormally high CAVI scores in association with prediabetes and with diabetes were 1.29 times higher and 2.41 times higher, respectively, in men and were 1.14 times higher and 2.52 times higher, respectively, among women (Table 3). Our study results have confirmed the association between prediabetes and arteriosclerosis and the much stronger association between diabetes and arteriosclerosis estimated by CAVI scores.

A limitation of this study is that it is an observational and cross-sectional study. Thus, we cannot tell how many persons with prediabetes will develop diabetes or will return to normal in their blood glucose levels or/and HbA1c levels. The strengths of this study are having the large sample size and being able to adjust for many CVD risk factors with enough statistical power to examine the association of CAVI scores with prediabetes and diabetes mellitus.

Conclusion

In conclusion, both prediabetes and diabetes mellitus were significantly associated with CAVI scores. It is implied that the extent of arteriosclerosis (including arterial stiffness and atherosclerosis) was moderately enhanced among persons with prediabetes and was further advanced among persons with diabetes. Thus, it is important to introduce earlier interventions for changing lifestyle and diet of persons with prediabetes in order to prevent them from developing diabetes and further advancing arteriosclerosis.

Abbreviations

BMI: Body mass index; CAVI: Cardio-ankle vascular index; CHD: Coronary heart disease; CI: Confidence interval; CVD: Cardiovascular disease; DBP: Diastolic blood pressure; Diabetes: Diabetes mellitus; HbA1c: Glycohemoglobin A1c; HDL-C: High density lipoprotein cholesterol; ORs: Odds ratios; PWV: Pulse wave velocity; SBP: Systolic blood pressure; SD: Standard deviation; TC: Total cholesterol; TG: Triglycerides.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

TN, KoS, KeS, NT, and KM participated in the design of the study. KeS, CA, and NI managed the CVD prevention screening and organized the data set. TN and MN performed statistical analyses. TN drafted the manuscript and revised based on other authors' comments. All other authors reviewed critically and approved the final manuscript.

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Chronic Atrophic Gastritis and *Helicobacter pylori* Infection among Japanese Americans in Seattle

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Gastric cancer is still a major cause of mortality due to cancer worldwide. The most common type of gastric cancer is intestinal type carcinoma, which usually occurs in stomachs containing chronic atrophic gastritis. Individuals with chronic atrophic gastritis are considered to be at increased risk for developing intestinal type carcinoma of the stomach. To examine the association between chronic atrophic gastritis and other gastric cancer risk factors, a cross-sectional study was conducted using serum samples and questionnaire information collected from 776 persons of full Japanese ancestry in the greater Seattle area in 1994. The presence of chronic atrophic gastritis and *Helicobacter pylori* infection was determined by measurement of serum pepsinogen levels and *H. pylori* antibodies, respectively. Based on multiple logistic regression, the significant predictors of chronic atrophic gastritis were age over 50 years, *H. pylori* infection, and 20 years or more lived in Japan. Alcohol consumption, smoking, prior peptic ulcer, and history of gastric cancer in parents were not significantly associated with chronic atrophic gastritis. The results imply that *H. pylori* infection since earlier life and other unknown exposure factors in Japan might have played an important role in the development of chronic atrophic gastritis. *Am J Epidemiol* 2000;151:820–30.

gastritis, atrophic; *Helicobacter pylori*; life style; pepsinogens; smoking

Despite the recent decline in the incidence of gastric cancer, it remains a major cause of cancer mortality worldwide (1), with one of the highest rates found in Japan and one of the lowest in the United States (2). The decline in gastric cancer rates can be attributed mainly to a decrease in the incidence of intestinal type carcinoma, whereas there has been little, if any, decrease in diffuse type carcinoma (3–5). Numerous studies have indicated that intestinal type carcinoma is strongly influenced by environmental factors, and the shifts that have occurred are thought to be a consequence of changes in dietary and environmental factors that contribute to carcinogenesis (6). In addition to age, the two most contributory factors to the development of intestinal type carcinoma are considered to be a diet that is high in salt and low in fresh fruits and vegetables and chronic infection with *Helicobacter pylori* (6, 7).

As first hypothesized by Correa (8), chronic atrophic gastritis is considered to be a preceding condition in the sequential histopathologic changes that lead to intestinal type gastric carcinoma. Therefore, persons with chronic atrophic gastritis are considered to have a higher risk for developing gastric cancer than those without such a condition. With the development of radioimmunoassay for pepsinogen I (PG I) and pepsinogen II (PG II), it has been reported that the PG I/PG II ratio in combination with the level of PG I predicted the presence of atrophic gastritis (9–11), and thus the method has been used in Japan as a serum marker to screen individuals at high risk for gastric cancer who are then recommended for endoscopic examination (12–14).

Since the first reports on gastric colonization by *H. pylori* in the early 1980s (15, 16), it has been established that *H. pylori* infection is strongly associated with peptic ulcer disease (17–20) and chronic atrophic gastritis and intestinal metaplasia (21–23). *H. pylori* strains possessing the cytotoxin-associated gene A

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Abbreviations: CI, confidence interval; OR, odds ratio; PG I, pepsinogen I; PG II, pepsinogen II.

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(*cagA*) are considered to enhance induction of acute inflammation leading to the development of atrophic gastritis and gastric cancer (21). Early life acquisition of *H. pylori* has been considered to increase the risk of developing both gastric cancer and gastric ulcer (20). A growing body of research suggests a link between *H. pylori* infection and gastric carcinoma (21–26). Furthermore, ecologic studies show a significant relation between the prevalence of *H. pylori* infection and gastric cancer incidence and mortality (27) and an association between the prevalence of chronic atrophic gastritis and the standard mortality ratio for gastric cancer (28). There must be additional risk factors that play an important role in the causation of gastric cancer, since only a small proportion of persons infected with *H. pylori* develop gastric carcinoma.

The investigators hope to shed some light on the role of *H. pylori* in the development of gastric cancer by examining the relation between chronic atrophic gastritis and *H. pylori* infection among Japanese Americans. This is an important population to study because they share a common genetic background with native Japanese, who suffer one of the highest gastric cancer mortality rates of all populations, but live in the nation where gastric cancer mortality is the lowest in the world (2).

The present study estimated the prevalence of chronic atrophic gastritis by using the serum pepsinogen method and the presence of immunoglobulin G antibodies to *H. pylori* infection among Japanese Americans in Seattle, Washington. The associations of possible risk factors with *H. pylori* infection and chronic atrophic gastritis were also examined.

TABLE 1. Study sample characteristics of Japanese Americans, Seattle, Washington, 1994

	Males, *n* = 415 (%)	Females, *n* = 361 (%)
Age (years)		
<50	38.1	41.8
50–64	32.8	32.1
65–74	21.0	20.8
≥75	8.2	5.3
Generation in United States		
First	9.4	16.9
Second	44.8	37.4
Third	43.9	44.3
Fourth	1.9	1.4
Lived in Japan (years)		
<1	70.1	65.4
1–9	13.0	13.6
10–19	7.5	5.5
≥20	9.4	15.5
Alcohol drinking		
Nondrinkers	12.0	28.0
Former drinkers	20.5	17.7
Current drinkers	67.5	54.3
Smoking		
Nonsmokers	41.0	70.1
Former smokers	46.0	21.9
Current smokers	13.0	8.0
History of peptic ulcer	10.4	6.1
Parental history of gastric cancer	3.1	4.4
Helicobacter pylori infection	27.5	29.1

MATERIALS AND METHODS

The study sample consisted of male and female Japanese Americans residing in the greater Seattle area (King County) who participated in cardiovascular disease screening conducted by the Pacific Rim Disease Prevention Center in 1994. The screening participants were respondents from a media and family registration campaign. Completed clinical and survey information was collected from a total of 415 males and 361 females of full Japanese ancestry between the ages of 20 and 86 years. The composition of the study sample with respect to generation was as follows: 12.9 percent Issei (first generation), 41.4 percent Nisei (second generation), 44.1 percent Sansei (third generation), and 1.7 percent Yonsei (fourth generation), as shown in table 1.

Due to the fact that the study subjects were voluntary participants, an additional survey on 1994 household income levels was conducted to better define our study sample characteristics and examine whether they were representative of the Japanese American population in the Seattle area. Of the 776 study participants, 82.0 percent responded to the survey. The household incomes from the study participants were compared with those of Japanese American households in the 1990 census for King County (29). Figure 1 shows that the income distribution of the screening participants was slightly higher than that reported for the Japanese American population in King County for the 1990 census.

Venous blood samples were obtained after a 12-hour fast from study participants in 1994. Two ml of sera were stored at −70°C. Serum samples were thawed and divided into two aliquots for analysis of serum pepsinogen levels and *H. pylori* antibodies. Serum PG I and PG II levels were measured using Riabead kits (Dainabot Co., Tokyo, Japan) (30), and subjects with chronic atrophic gastritis were defined as those with a PG I level of <70 μg/liter and a PG I/PG II ratio of <3.0. The presence of *H. pylori* antibodies was determined using an immunoglobulin G enzyme-linked

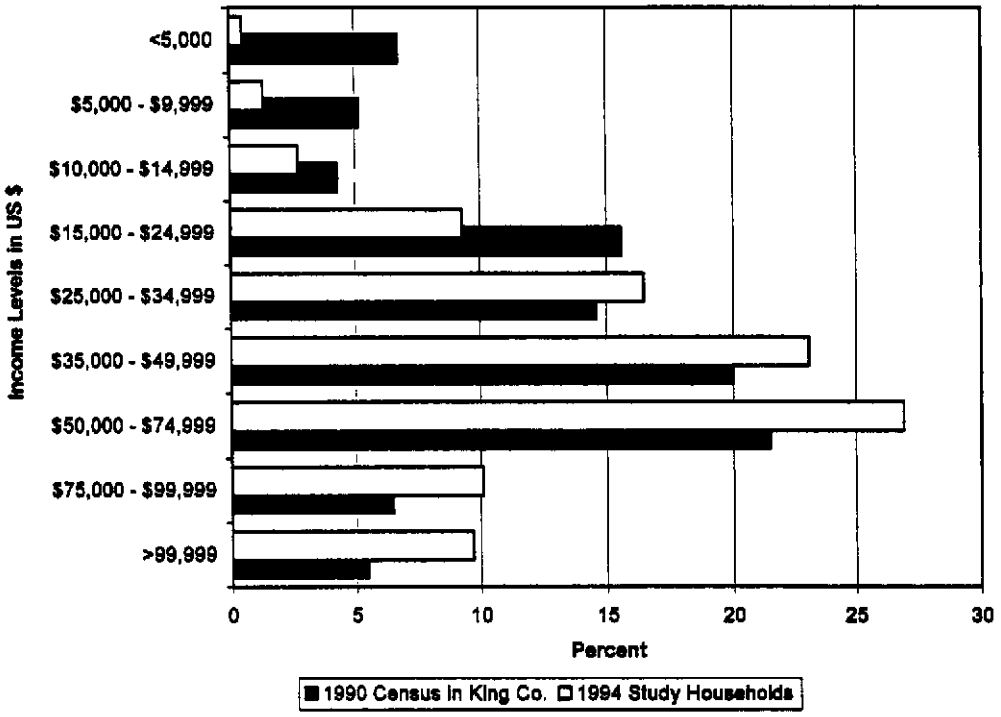

FIGURE 1. Comparison of income distributions of Japanese Americans between the 636 households that participated in the study in 1994 and the 8,518 households in King County, Washington, from the 1990 US census.

immunosorbent assay for *H. pylori* (Bio-Rad Laboratories, Anaheim, California) (31, 32). Specimens tested having greater than 12.5 units/ml for immunoglobulin G antibodies were considered to be positive for *H. pylori* infection.

Surveys, self-administered at the time of screening, contained questions on personal and demographic background, medical history, and lifestyle habits such as alcohol consumption and smoking. Those who had never or rarely (less than once per month) consumed alcoholic beverages were classified as nondrinkers.

Two analyses with multiple logistic regression were conducted: to predict seropositivity of *H. pylori* infection by age, years lived in Japan, alcohol consumption, smoking status, history of ulcer, and family history of gastric cancer; and to predict the presence of chronic atrophic gastritis as determined with low serum pepsinogen levels by the same factors as above and *H. pylori* infection. Analyses were conducted separately by sex and generation using SPSS/PC+ V8.0 software (SPSS, Inc., Chicago, Illinois) (33).

RESULTS

Characteristics of the study subjects are presented in table 1. More than 60 percent of the subjects were older than 50 years old. The majority of the study sample had never lived in or had spent less than 1 year in Japan (70 percent of men and 65 percent of women). Seropositivity for *H. pylori* infection was found to be 27.5 percent for men and 29.1 percent for women. The prevalences of *H. pylori* infection and chronic atrophic gastritis were similar between men and women and increased steadily with age (table 2).

The results of multiple logistic regression analysis to predict seropositivity of *H. pylori* with age, years lived in Japan, alcohol consumption, smoking, history of ulcer, and parental death due to gastric cancer are presented in table 3. No great discrepancy is observed between crude and adjusted odds ratios. Significant odds ratios were observed in both men and women for increasing age (with the exception of men over the age of 75 years), having lived in Japan for more than 20 years for men (odds ratio (OR) = 5.12, 95 percent confidence interval (CI): 2.44, 10.69) and for women (OR = 2.80, 95 percent CI: 1.45, 5.39), and past history of peptic ulcer for men (OR = 2.88, 95 percent CI: 1.42, 5.83) and for women (OR = 4.30, 95 percent CI: 1.54, 12.03). Current smoking habit and past smoking habit were associated with an increased risk for *H. pylori* infection in men only (OR = 2.39, 95 percent CI: 1.14, 5.03; and OR = 1.77, 95 percent CI: 1.00, 3.14, respectively). Alcohol consumption and family history (death of either parent due to gastric

TABLE 2. Prevalence of *Helicobacter pylori* infection and chronic atrophic gastritis among Japanese Americans, Seattle, Washington, 1994

	H. pylori seropositive				Chronic atrophic gastritis			
	Males		Females		Males		Females	
	No. of cases	%	No. of cases	%	No. of cases	%	No. of cases	%
Age (years)								
<50	24	15.2	23	15.2	4	2.5	3	2.0
50–64	45	33.1	38	32.8	20	14.7	18	15.5
65–74	31	35.6	33	44.0	24	27.6	15	20.0
≥75	14	41.2	11	57.9	12	35.3	7	36.8
Chi-square test for trend	$p < 0.0001$		$p < 0.0001$		$p < 0.0001$		$p < 0.0001$	

cancer) were not found to be associated with *H. pylori* infection.

To examine the difference in the association of *H. pylori* infection with biologic and lifestyle factors between the first generation and the second to fourth generation of Japanese Americans, we computed the odds ratios again for the two groups (table 4). Only having the past diagnosis of peptic ulcer was significantly associated with *H. pylori* infection (OR = 16.62, 95 percent CI: 1.84, 150.05) in the first gener-

TABLE 3. Odds ratios for *Helicobacter pylori* infection by sex among Japanese Americans, Seattle, Washington, 1994

	Males				Females			
	No. of cases of *H. pylori* infection	Crude OR*	Adjusted OR†	95% CI*	No. of cases of *H. pylori* infection	Crude OR	Adjusted OR†	95% CI
Age (years)								
<50	24	1.00	1.00		23	1.00	1.00	
50–64	45	2.76	1.93	1.03, 3.60	38	2.71	2.42	1.27, 4.57
65–74	31	3.09	2.16	1.06, 4.40	33	4.37	3.73	1.82, 7.68
≥75	14	3.91	2.55	0.98, 6.61	11	7.65	8.33	2.74, 25.31
Lived in Japan (years)								
<1	62	1.00	1.00		62	1.00	1.00	
1–9	16	1.56	1.13	0.56, 2.29	11	0.81	0.77	0.34, 1.72
10–19	13	2.67	2.09	0.93, 4.71	5	0.94	0.88	0.28, 2.75
≥20	23	5.31	5.12	2.44, 10.69	27	2.61	2.80	1.45, 5.39
Drinking status								
Nondrinkers	15	1.00	1.00		36	1.00	1.00	
Former drinkers	23	0.87	0.98	0.41, 2.34	13	0.46	0.95	0.42, 2.20
Current drinkers	76	0.87	1.05	0.50, 2.24	56	0.72	1.47	0.80, 2.73
Smoking status								
Nonsmokers	29	1.00	1.00		76	1.00	1.00	
Former smokers	65	2.51	1.77	1.00, 3.14	24	1.02	0.93	0.50, 1.75
Current smokers	20	2.86	2.39	1.14, 5.03	5	0.49	0.36	0.12, 1.08
History of peptic ulcer								
No	91	1.00	1.00		90	1.00	1.00	
Yes	23	3.55	2.88	1.42, 5.83	15	5.93	4.30	1.54, 12.03
Parental history of gastric cancer								
No	107	1.00	1.00		96	1.00	1.00	
Yes	7	3.22	1.93	0.58, 6.42	9	3.33	1.69	0.54, 5.30

* OR, odds ratio; CI, confidence interval.

† Adjusted odds ratios obtained from a multiple logistic regression that included age (years), years lived in Japan, drinking status, smoking status, history of peptic ulcer, and parental history of gastric cancer.

TABLE 4. Odds ratios for *Helicobacter pylori* by generation among Japanese Americans, Seattle, Washington, 1994

	First generation				Second to fourth generation			
	No. of cases of *H. pylori* infection	Crude OR*	Adjusted OR†	95% CI*	No. of cases of *H. pylori* infection	Crude OR	Adjusted OR†	95% CI
Female								
No	22	1.00	1.00		92	1.00	1.00	
Yes	28	0.66	0.61	0.23, 1.67	77	1.07	1.30	0.87, 1.95
Age (years)								
<50	14	1.00	1.00		33	1.00	1.00	
50–64	28	2.63	2.31	0.84, 6.31	55	2.63	2.28	1.37, 3.78
≥65	8	2.38	2.12	0.49, 9.20	81	4.85	3.89	2.32, 6.50
Lived in Japan (years)								
<10	2	1.00	1.00		149	1.00	1.00	
10–19	7	1.31	0.48	0.05, 4.93	11	1.41	1.12	0.52, 2.39
≥20	41	1.58	0.86	0.12, 6.23	9	4.79	3.65	1.22, 10.94
Smoking status								
Nonsmokers	28	1.00	1.00		77	1.00	1.00	
Former smokers	17	1.26	0.86	0.30, 2.51	72	1.62	1.29	0.83, 2.01
Current smokers	5	0.48	0.35	0.09, 1.41	20	1.57	1.57	0.83, 2.97
Drinking status								
Nondrinkers	13	1.00	1.00		38	1.00	1.00	
Former drinkers	6	0.92	1.06	0.22, 5.23	30	0.64	0.88	0.47, 1.64
Current drinkers	31	1.15	0.99	0.32, 3.01	101	0.73	1.11	0.67, 1.86
History of peptic ulcer								
No	39	1.00	1.00		142	1.00	1.00	
Yes	11	13.82	16.62	1.84, 150.05	27	3.52	2.40	1.30, 4.43
Parental history of gastric cancer								
No	47	1.00	1.00		156	1.00	1.00	
Yes	3	3.13	2.40	0.20, 28.3	13	3.44	1.76	0.74, 4.16

* OR, odds ratio; CI, confidence interval.
† Adjusted odds ratios obtained from a multiple logistic regression that included age (years), years lived in Japan, drinking status, smoking status, history of peptic ulcer, and parental history of gastric cancer.

ation group. For the second to fourth generation group, on the other hand, odds ratios were significantly elevated in ages greater than 50 years: 50–64 years (OR = 2.28, 95 percent CI: 1.37, 3.78) and 65 years and over (OR = 3.89, 95 percent CI: 2.32, 6.50), living in Japan for 20 years and longer (OR = 3.65, 95 percent CI: 1.22, 10.94), and having the past diagnosis of peptic ulcer (OR = 2.40, 95 percent CI: 1.30, 4.43).

Table 5 presents the results of multiple logistic regression analysis to predict the presence of chronic atrophic gastritis. The risk of chronic atrophic gastritis increased steadily with age for both men and women. Significant odds ratios were also observed for living in Japan for 1–9 years for men (OR = 2.98, 95 percent CI: 1.22, 7.26) and living in Japan for more than 20 years for men (OR = 8.30, 95 percent CI: 3.13, 21.76) and for women (OR = 3.32, 95 percent CI: 1.32, 8.34) and *H. pylori* infection for men (OR = 9.63, 95 percent CI: 4.55, 20.18) and for women (OR = 16.31, 95 percent CI: 6.18, 42.87). Current or past smoking and drinking habits and history of peptic ulcer were not associated with chronic atrophic gastritis. Similarly, death due to gastric cancer of either parent was not found to be associated with chronic atrophic gastritis. When multiple logistic regression analysis was done by generation (table 6), the results are almost the same as those in table 5, except that the longer duration lived in Japan was not significantly associated with chronic atrophic gastritis in the first generation, while it remained significant in the second to fourth generation (20 years or more lived in Japan: OR = 6.96, 95 percent CI: 1.69, 28.65).

To examine the possibility that the areas of severe atrophy and intestinal metaplasia can be hostile to *H.*

TABLE 5. Odds ratios for chronic atrophic gastritis by sex among Japanese Americans, Seattle, Washington, 1994

	Males				Females			
	No. of cases of chronic atrophic gastritis	Crude OR*	Adjusted OR†	95% CI*	No. of cases of chronic atrophic gastritis	Crude OR	Adjusted OR†	95% CI
Age (years)								
<50	4	1.00	1.00		3	1.00	1.00	
50–64	20	6.64	5.67	1.61, 19.95	18	9.06	6.05	1.47, 24.42
65–74	24	14.67	14.88	4.10, 54.04	15	12.33	7.80	1.72, 35.00
≥75	12	21.00	26.62	5.95, 119.27	7	28.78	18.12	3.05, 108.16
Lived in Japan (years)								
<1	23	1.00	1.00		23	1.00	1.00	
1–9	14	4.08	2.98	1.22, 7.26	1	0.19	0.15	0.02, 1.23
10–19	5	2.24	1.36	0.41, 4.50	2	1.03	0.78	0.12, 4.89
≥20	18	9.99	8.30	3.13, 21.76	17	4.04	3.32	1.32, 8.34
Drinking status								
Nondrinkers	10	1.00	1.00		20	1.00	1.00	
Former drinkers	12	0.66	1.46	0.45, 4.71	4	0.27	0.73	0.18, 3.02
Current drinkers	38	0.63	0.61	0.47, 3.62	19	0.43	0.73	0.31, 1.76
Smoking status								
Nonsmokers	16	1.00	1.00		32	1.00	1.00	
Former smokers	36	2.24	0.76	0.32, 1.80	9	0.89	1.18	0.19, 6.04
Current smokers	8	1.67	0.76	0.24, 2.42	2	0.51	1.06	0.43, 3.26
History of peptic ulcer								
No	52	1.00	1.00		37	1.00	1.00	
Yes	8	1.41	0.47	0.17, 1.31	6	3.06	1.03	0.30, 3.46
Parental history of gastric cancer								
No	56	1.00	1.00		40	1.00	1.00	
Yes	4	2.75	0.69	0.15, 3.23	3	1.76	0.69	0.00, 0.03
Helicobacter pylori infection								
No	16	1.00	1.00		6	1.00	1.00	
Yes	44	11.20	9.63	4.55, 20.18	37	22.67	16.31	6.18, 42.87

* OR, odds ratio; CI, confidence interval.
† Adjusted odds ratios obtained from a multiple logistic regression that included age (years), years lived in Japan, drinking status, smoking status, history of peptic ulcer, parental history of gastric cancer, and *H. pylori* infection.

pylori colonization (34–36), we explored further the analysis of the level of PG I and the PG I/PG II ratios in relation to *H. pylori* status in the 103 subjects with chronic atrophic gastritis. In this group, 22 were seronegative for *H. pylori* and 81 subjects were seropositive. The mean PG I/PG II ratio in subjects with chronic atrophic gastritis and seronegative for *H. pylori* (mean = 1.30) was significantly lower than the mean PG I/PG II ratio among seropositive subjects (mean = 2.00) ($p < 0.0001$). Similarly, the mean level of PG I in subjects with chronic atrophic gastritis and seronegative for *H. pylori* (mean = 18.5 ng/liter) was significantly lower than the mean PG I level among seropositive subjects (mean = 39.0 ng/liter) ($p < 0.0001$).

DISCUSSION

One potential bias in the present study is that the sample was not randomly drawn from the Japanese American population in the Seattle area, and nonparticipants may have different characteristics and health status from those of the participants. Other surveys have shown that nonparticipants had poorer health than did participants (37). In order to examine this issue further, we conducted an additional survey to determine the 1994 annual household income levels of our study sample and compared their income distribution with that of Japanese American households in King County from the 1990 US census (which includes Seattle and the surrounding metropolitan

TABLE 6. Odds ratios for chronic atrophic gastritis by generation among Japanese Americans, Seattle, Washington, 1994

	First generation				Second to fourth generation			
	No. of cases of chronic atrophic gastritis	Crude OR*	Adjusted OR†	95% CI*	No. of cases of chronic atrophic gastritis	Crude OR	Adjusted OR†	95% CI
Female								
No	11	1.00	1.00		49	1.00	1.00	
Yes	18	1.07	1.33	0.32, 5.60	25	0.61	0.43	0.21, 0.87
Age (years)								
<50	4	1.00	1.00		3	1.00	1.00	
50–64	17	4.96	5.12	0.90, 29.21	21	10.16	7.57	2.09, 27.45
≥65	8	11.67	29.67	2.36, 373.35	50	29.47	17.97	5.09, 63.49
Lived in Japan (years)								
<10	2	1.00	1.00		59	1.00	1.00	
10–19	1	0.11	0.01	0.00, 0.67	6	1.92	1.04	0.35, 3.03
≥20	26	0.72	0.10	0.00, 3.95	9	14.39	6.96	1.69, 28.65
Smoking status								
Nonsmokers	16	1.00	1.00		32	1.00	1.00	
Former smokers	11	1.41	1.31	0.30, 5.81	34	1.73	0.81	0.39, 1.70
Current smokers	2	0.38	0.49	0.04, 6.06	8	1.40	1.04	0.36, 3.02
Drinking status								
Nondrinkers	7	1.00	1.00		23	1.00	1.00	
Former drinkers	2	0.52	1.64	0.13, 20.15	14	0.50	0.81	0.33, 1.98
Current drinkers	20	1.43	3.94	0.70, 22.52	37	0.43	0.58	0.28, 1.21
History of peptic ulcer								
No	22	1.00	1.00		67	1.00	1.00	
Yes	7	4.20	3.91	0.59, 26.11	7	1.26	0.41	0.16, 1.07
Parental history of gastric cancer								
No	26	1.00	1.00		70	1.00	1.00	
Yes	3	8.08	1.80	0.11, 29.50	4	1.58	0.68	0.20, 2.36
Helicobacter pylori infection								
No	2	1.00	1.00		20	1.00	1.00	
Yes	27	28.17	34.88	5.25, 231.66	54	11.43	9.34	5.04, 17.30

* OR, odds ratio; CI, confidence interval.
† Adjusted odds ratios obtained from a multiple logistic regression that included age (years), years lived in Japan, drinking status, smoking status, history of peptic ulcer, parental history of gastric cancer, and *H. pylori* infection.

area) (figure 1). Although our sample distribution is slightly shifted to higher income levels as compared with the census distribution, it is remarkably similar to that of Japanese Americans in King County. The 5-year gap between our sample and the census population might have contributed to the slightly higher income levels observed in our study sample because of the rate of inflation in household income between 1990 and 1994. Thus, it is considered that our Seattle Japanese-American sample reasonably represents the Japanese-American population in the area, although we must be cautious about possible selection bias when a comparison of health outcomes is made between populations.

One of the important questions in the study was if the rate of *H. pylori* infection in Japanese Americans in Seattle is different from those of other populations. Figure 2 shows that the age-specific infection rates of Japanese Americans are consistently lower than those of native Japanese in Hokkaido (38) and African Americans and European Americans in Houston, Texas (39), although caution must be taken because of differences in sampling methods and sample size among the four populations. It is interesting to observe the equivalent prevalence of *H. pylori* infection in African Americans and native Japanese. If *H. pylori* infection were a dominant factor to elevate the gastric cancer risk, mortality for gastric cancer in African

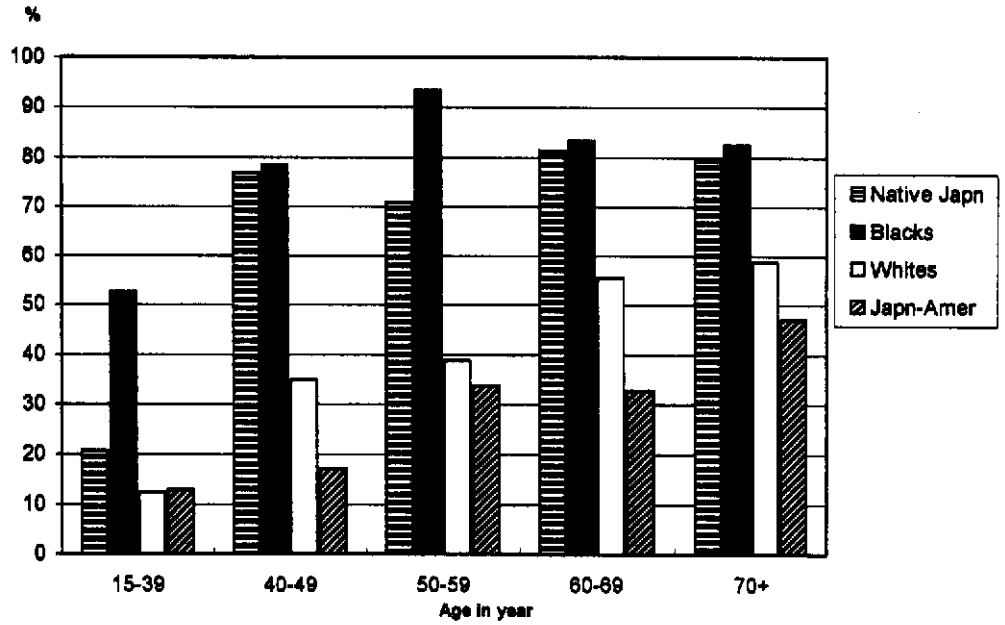

FIGURE 2. Comparison of seroprevalence of *Helicobacter pylori* infection among four populations: native Japanese (native Japn) in Japan, 1990; Blacks and Whites in Houston, Texas, 1989–1990; and Japanese Americans (Japn-Amer) in King County, Washington, 1994. Sources: for native Japanese, M. Asaka et al. Figure 2 in Gastroenterology 1992;102:760-6; for Blacks and Whites, D. Graham et al. Figure 1 in Gastroenterology 1991;100:1495-501, and additional information from D. Y. Graham.

Americans would be close to that in native Japanese. However, the actual mortality of African Americans was one fourth of that of native Japanese (9.8 vs. 40.8/100,000 persons for 1983–1987) (2), implying that other risk factors unique to Japanese may play a significant role in the etiology of gastric cancer.

Another important question was whether the prevalence of chronic atrophic gastritis in Japanese Americans in Seattle differs from that in native Japanese in Japan. The data from Seattle were compared with those from 25,415 persons in urban areas in Japan (40), as shown in figure 3. The prevalence of

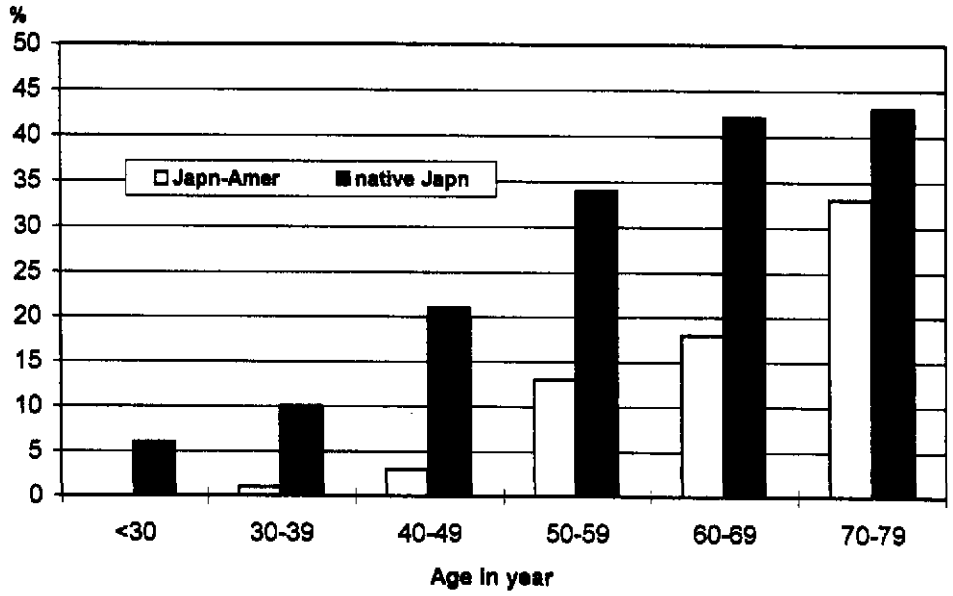

FIGURE 3. Comparison of prevalence of chronic atrophic gastritis between Japanese Americans (Japn-Amer) in Seattle, Washington, 1994, and native Japanese (native Japn) in urban areas of Japan, 1991–1995. Source: for native Japanese, K. Miki. Jpn J Electroph 1996;40:295–8.

chronic atrophic gastritis is clearly age dependent in both populations. For each age group, a higher prevalence of chronic atrophic gastritis is observed in native Japanese than in Japanese Americans, which coincides with trends in *H. pylori* prevalence compared between the two populations (figure 2). The questions on the incidence of gastric cancer in the two populations remain to be answered in the future.

The prevalence of chronic atrophic gastritis was not found to be associated with alcohol consumption, smoking status, or history of death of either parent due to gastric cancer in the present study. In a similar study conducted by Tsugane et al. (41), there was no association between alcohol consumption and chronic atrophic gastritis in Japanese men aged 40–49 years. This is consistent with the fact that there is no strong evidence that alcohol plays an etiologic role in stomach cancer (6). Smoking status was not associated with the prevalence of chronic atrophic gastritis in the present study, but Tsugane et al. (41) reported a negative association between smoking and chronic atrophic gastritis. However, a study among Japanese workers reported a dose-dependent positive association between smoking and PG I levels and the PG I/PG II ratio (42). As reviewed by the US Surgeon General (43), epidemiologic studies have shown an association between smoking and stomach cancer, although its association is weak in comparison with those found between smoking and other cancers. Tsugane et al. (41) also reported a positive association between chronic atrophic gastritis and family history of gastric cancer in either parent or any sibling, whereas no such association was found in the present study.

Unlike the second to fourth generation Japanese Americans, the first generation did not show an association between the years lived in Japan and the presence of chronic atrophic gastritis. This is possibly due to the small number of individuals ($n = 5$) in this group who lived in Japan for less than 10 years but who had a high prevalence (40 percent) of chronic atrophic gastritis, as compared with its prevalence in persons who lived in Japan for 10–19 years (7 percent) and in persons who lived there for >20 years (32.5 percent). As an increased risk for chronic atrophic gastritis was found in persons who lived in Japan for 20 years and longer among the second to fourth generation Japanese (table 6) and in both sexes (table 5), it is likely that long-term residence in Japan (or long-term exposure to the Japanese environment) is a risk factor for chronic atrophic gastritis, in addition to age and *H. pylori* infection. Possible risk factors associated with the Japanese environment include a high consumption of rice and salted foods (salted fish and pickles) (6), which had been a main source of food in rural areas in Japan during the winter until around 1970 because of the lack of refrigeration. Most Japanese Americans who lived in Japan for many years had possibly consumed rice and salted foods every day prior to 1970 and might have continued these eating habits even after immigrating or returning to the United States. This should be clarified in a future study.

The finding that PG I levels and PG I/PG II ratios were significantly less in subjects with chronic atrophic gastritis who were *H. pylori* seronegative is interesting. Since the absolute level of PG I and PG I/PG II ratios correlates with the degree of atrophic gastritis (10), subjects with more gastric atrophy are more likely to be *H. pylori* seronegative. This is consistent with other observations that *H. pylori* do not thrive in atrophic gastric mucosa (34–36). Furthermore, since antibodies to *H. pylori* persist for several years after elimination of the bacteria, it is likely that these seronegative individuals with chronic atrophic gastritis have had atrophic mucosa for some time and perhaps are at the highest risk for cancer development.

The next phase of the study will involve upper endoscopic examination to confirm histologically the presence of intestinal metaplasia in individuals with a low PG I level and PG I/PG II ratio. Because individuals with chronic atrophic gastritis are considered to have a higher risk for gastric cancer, the endoscopic examination will also serve the purpose of screening for early tumors.

At present, screening for gastric cancer has not been recommended by either the National Cancer Institute or the American Cancer Society. However, such screening should be considered for the following reasons. 1) The pepsinogen test as a first screening of persons with chronic atrophic gastritis and endoscopy as a second screening are technically feasible (9–14, 44). 2) The estimated number of deaths due to gastric cancer in 1997 is 14,000, which is comparable to 8,300 deaths due to rectal cancer, 12,400 deaths due to liver cancer, 9,490 deaths due to skin cancer, 14,200 deaths due to ovarian cancer, or more than 4,800 deaths due to cancer of the cervix uteri and 6,000 deaths due to cancer of the corpus uteri (45). Thus, gastric cancer is not a rare disease in the United States. 3) Gastric cancer is one of the five most frequently diagnosed cancers in some ethnic populations in the United States, including Koreans, Japanese, Vietnamese, Hawaiians, Alaska natives, African Americans, Chinese, and Hispanics. Their annual average incidence rates ranged from 13.0 per 100,000 persons in Hawaiian females to 48.9 per 100,000 persons in Korean males for 1988–1992 (45). 4) The 5-year survival rate of gastric cancer in Osaka, Japan, where gastric cancer screening is conducted, is

34.1 percent (46), a much higher proportion than that in Detroit, Michigan, where its screening has not been promoted (11.3–14.5 percent depending on income levels) (47). Unlike cancers of the lung, liver, and pancreas, gastric cancers are potentially curable if they are diagnosed at early stages. Thus, the screening of gastric cancer in the United States should be available to persons who are considered to be at high risk for this disease.

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Chapter 5

Helicobacter Pylori Infection and Chronic Atrophic Gastritis among Asian Immigrants in the Seattle Area, U.S.A.

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Abstract

Helicobacter pylori (*H. pylori*) is considered to play an important role in gastric carcinogenesis, since chronic atrophic gastritis, a precursor of gastric carcinoma, is caused by *H. pylori*. We previously examined the role of *H. pylori* for gastric cancer by examining the relationship between chronic atrophic gastritis and *H. pylori* infection among Japanese Americans in Seattle and found that chronic atrophic gastritis was significantly associated with age over 50 years, *H. pylori* infection, and greater than 20 year residence in Japan. In this study, we extended these observations by examining prevalence of *H. pylori* infection and chronic atrophic gastritis among Asian immigrants from China, South Korea, Philippine and Vietnam. Age-adjusted prevalence of *H. pylori* infection ranged from the lowest in Japanese immigrants (26.0%) to the highest in Vietnam immigrants (43.3%), as compared to 70.6% in rural

residents in Japan. Age-adjusted prevalence of chronic atrophic gastritis was found to be the lowest in Filipino immigrants (2.2%) and the highest in Japanese immigrants (11.6%), as compared to 34.3% in rural residents in Japan. Multiple logistic regression analysis was conducted to estimate the risk of chronic atrophic gastritis associated with other factors. It was found that having *H. pylori* infection significantly elevated the risk for chronic atrophic gastritis (5.856, $p<0.001$). At present, the screening of gastric cancer has not been recommended by either the National Cancer Institute or the American Cancer Society. However, such screening should be considered in high risk groups because the pepsinogen test to detect chronic atrophic gastritis with follow-up is technically feasible and may lead to the detection of gastric cancer in the United States.

Key words: gastric cancer; gastric cancer screening; *Helicobacter pylori*; pepsinogen; chronic atrophic gastritis; Asian American immigrants; cancer epidemiology; high risk populations for gastric cancer

Abbreviations: ELISA, enzyme-linked immunosorbent assay; *H. pylori, Helicobacter pylori*; IgG, immunoglobulins G; 95% CI, 95 percent confidence interval; PG I, pepsinogen I; PG II, pepsinogen II; the U.S., the United States of America

1. Introduction

Although gastric cancer mortality has declined over the past several decades, it is the second highest cause of male cancer deaths and 4th highest cause of female cancer deaths worldwide [1]. One of the highest rates is found in Japan (53.9 per 100,000 persons for males and 27.0 per 100,000 persons for females in 2007) and one of the lowest is present in the United States (4.6 per 100,000 persons for males and 3.2 per 100,000 persons for females in 2005) [2]. Because of Japan's high gastric cancer incidence screening program for gastric cancer has been carried out in Japan for all residents aged 40 years and over since 1983, whereas gastric cancer screening program is not practiced in the U.S. Such policy differences are responsible for better 5-year survival rates in Japan (62.1%) than in the U.S. (25.7%) [3].

Chronic atrophic gastritis precedes the development of intestinal type gastric carcinoma [4-5]. Thus, persons with chronic atrophic gastritis are considered to be at a higher risk for having or developing gastric cancer. With the development of radioimmunoassay for pepsinogen I (PG I) and pepsinogen II (PG II), it has been reported that the PG I/PG II ratio in combination with the level of PG I predicts the presence of atrophic gastritis [6-8]. This method has been used in Japan as a screening test to detect individuals at high risk for gastric cancer and subsequent upper endoscopic examination [9-11]. Since the first reports on gastric infection with *H. pylori* in the early 1980's [12,13], it has been established that *H. pylori* infection is strongly associated with peptic ulcer disease [14-17], and chronic atrophic gastritis and intestinal metaplasia [18-20].

H. pylori strains possessing cytotoxin associated gene A (cagA) are considered to enhance induction of acute inflammation leading to the development of atrophic gastritis and gastric cancer [18]. Early life acquisition of *H. pylori* has been considered to increase the risk of developing both gastric cancer and gastric ulcer [17]. A growing body of research suggests a link between *H. pylori* infection and gastric carcinoma [18-23]. Furthermore, ecological studies show a significant relation between the prevalence of *H. pylori* infection and gastric cancer incidence and mortality [24] and an association between prevalence of chronic atrophic gastritis and the standard mortality ratio for gastric cancer [25]. There must be additional risk factors which play an important role in the causation of gastric cancer, since only a small proportion of persons infected with *H. pylori* develop gastric carcinoma. However, *H. pylori* plays an important role in gastric carcinogenesis, since almost all gastric cancer including both intestinal type and diffuse type arise from the mucosa infected by *H. pylori,* and the results of four cohort studies suggest that *H. pylori* eradication reduces gastric cancer incidence.

Namekata et al. examined the role of *H. pylori* in gastric cancer by examining the relationship between chronic atrophic gastritis and *H. pylori* infection among Japanese Americans who share a common genetic background with native Japanese who suffer one of the highest gastric cancer mortality of all populations, but Japanese Americans live in the nation where gastric cancer mortality is the lowest in the world [26]. They found that chronic atrophic gastritis was significantly associated with age over 50 years, *H. pylori* infection, and greater than 20-year residence in Japan. This suggests that *H. pylori* infection earlier in life and other unknown exposure factors in Japan might have played an important role in the development of chronic atrophic gastritis and then gastric cancer [26].

They also observed that *H. pylori* infection rates increased from 18% for 40-49 years old to 47% for 70 years old and over among Japanese Americans (comprising of 12.9% 1st, 41.2% 2nd, 44.2% 3rd, and 1.7% 4th generations) while Asaka et al. reported that its rates among Japanese in Japan were consistently high, 70-80% after 40 years old [27]. The rates of chronic atrophic gastritis among Japanese Americans were found to be linearly increased with age from 1% for 30-39 years old to 33% for 70-79 years old, as compared with 10% for 30-39 years old to 43% for 70-79 years old among Japanese in Japan [28]. By migrating from Japan to the U.S. both the prevalence of *H. pylori* infection and the prevalence of chronic atrophic gastritis among Japanese Americans significantly decreased from the level of Japanese in Japan.

Now our question is if the prevalence of chronic atrophic gastritis is proportionate to the prevalence of *H. pylori* infection in other Asian immigrants in the U.S. To answer this question, we conducted screening and surveys among immigrants from Korea, China, Vietnam, and Philippine in the Seattle area. We also examined the association of *H. pylori* infection and chronic atrophic gastritis with possible risk factors.

2. Materials and Method

The study sample consisted of male and female Asian immigrants residing in the greater Seattle area (King County). Study participants were recruited through churches and community centers. Completed clinical and survey information was collected from a total of 298 males and 505 females in 2004-2005, as shown in **Table 1**.

Table 1: Study subjects

Immigrants	Both genders	Males	Females
Koreans	207	79	128
Chinese	223	76	147
Vietnamese	199	84	115
Filipinos	174	59	115
Total	803	298	505

The study protocol and the consent form were approved by the human subject committee at the Pacific Rim Disease Prevention Center. The consent form was translated into Korean, Chinese, Vietnamese and Filipino for those who cannot read English. Screening was conducted at churches and community centers. All subjects signed on the consent form before their participation in the study. Four drops of blood were taken from a finger of each subject and collected on a filtered paper (Eiken Chemical Co., Tokyo). The collected filters were shipped with ice packs to the Eiken Chemical Company's laboratory by overnight freight service. Temperature monitoring confirmed all specimen were kept below 25°C. *H. pylori* antibody was tested by "E plate 'Eiken' Disk *H. Pylori* Antibody" (Eiken Chemical Co., Tokyo) and pepsinogen I and II levels were measured by ELISA using "E plate 'Eiken' Disk PGI or II" (Eiken Chemical Co., Tokyo).

Subjects with chronic atrophic gastritis were defined as those with PG I $\leq$ 70 μg/liter and PG I/PG II ratio $\leq$ 3.0. Specimens having greater than 12.5 units/ml for IgG antibodies were considered to be positive for *H. pylori* infection.

The questionnaire was translated in each language of Korean, Chinese, Vietnamese and Filipino for those who cannot read English. Surveys were conducted with help from volunteers at the time of screening contained questions on personal and demographic background, medical history, and lifestyle habits such as alcohol consumption and smoking. Those who had never or rarely (less than once per month) consumed alcoholic beverages were classified as non-drinkers.

Two analyses with multiple logistic regression were conducted: to predict seropositivity of *H. pylori* infection by age, alcohol consumption, smoking status, history of digestive disease, and family history of gastric cancer; and to predict the presence of chronic atrophic gastritis by

the same factors as those in analysis for *H. pylori* infection. Analyses were conducted by using SPSS 11.5 (SPSS Inc., Chicago, Illinois) [29].

3. Results

Characteristics of the study subjects are presented in **Table 2**. More women participated in the study than men: ranging from 58.1% for Vietnamese women to 67.1% for Chinese women. More young Koreans and Vietnamese participated in the study than Chinese and Filipinos. Almost all subjects were the 1st generation with few exceptions. According to median income based on zip code of subjects' residences, about 70% of Korean subjects lived in the areas with the median income of $50, 000 or more, while only 25-35% of Chinese, Vietnamese and Filipinos lived in such medium-high income area. Rates of current drinkers ranged from 25% of Koreans to 57% of Vietnamese. Current smokers were extremely few in all immigrants: 2.7% of Chinese to 9.7% of Vietnamese. Having family history of gastric cancer appeared highest in Koreans, 16.6%, and lowest in Filipinos, 5.2%. Vietnamese had highest prevalence of digestive disease, 18.7%, whereas Filipinos had lowest prevalence, 11.0%.

Table 2: Characteristics of Asian Immigrant subjects in the Seattle area

	Chinese	**Koreans**	**Vietnamese**	**Filipinos**
	n=222	n=207	n=198	n=173
	(%)	(%)	(%)	(%)
Sex: males	32.9	37.7	41.9	33.5
females	67.1	62.3	58.1	66.5
Age: ≥49	23.8	46.3	49.0	19.1
50-64	34.7	37.7	36.9	26.6
65-74	28.4	12.1	10.6	26.6
≥75	13.1	3.9	3.5	27.7
Generation: 1st	91.4	96.6	100.0	96.5
2nd	7.7	3.4		3.5
3rd	0.9	0.0		
Income: ≤$29K	13.1	1.0	3.0	4.2
$30K-$49K	52.6	30.7	71.7	60.4
$50K-$69K	21.2	60.8	24.8	32.4
≥$70K	13.1	7.5	0.5	3.0
Alcohol: non-drinkers	65.6	75.3	42.8	67.1
current drinkers	34.4	24.7	57.2	32.9
Smoking: nonsmokers	90.1	82.2	81.5	80.9
ex-smokers	7.2	11.2	8.8	14.5
current smokers	2.7	6.6	9.7	4.6
Family history of gastric cancer	12.0	16.6	6.1	5.2
Having digestive disease	16.2	14.4	18.7	11.0

Figure 1 shows age-adjusted prevalence rates of *H. pylori* infection and chronic atrophic gastritis among Asian immigrants in addition to Japanese immigrants [26] and Japanese in a rural area in Japan [30] from the previous surveys. *H. pylori* infection rates were the lowest in Japanese immigrants, 26.0%, and in Filipino immigrants, 26.3%, and the highest in Japanese in rural Japan, 70.6%. On the other hand, prevalence rates of chronic atrophic gastritis are 2.2%, the lowest in Filipino immigrants, 4.6% in Chinese immigrants, 6.3% in Vietnamese immigrants, 7.6% in Korean immigrants, 11.6 % in Japanese immigrants and 34.3%, the highest in Japanese living in rural Japan. The order of *H. pylori* infection is not the same as the order of chronic atrophic gastritis rates.

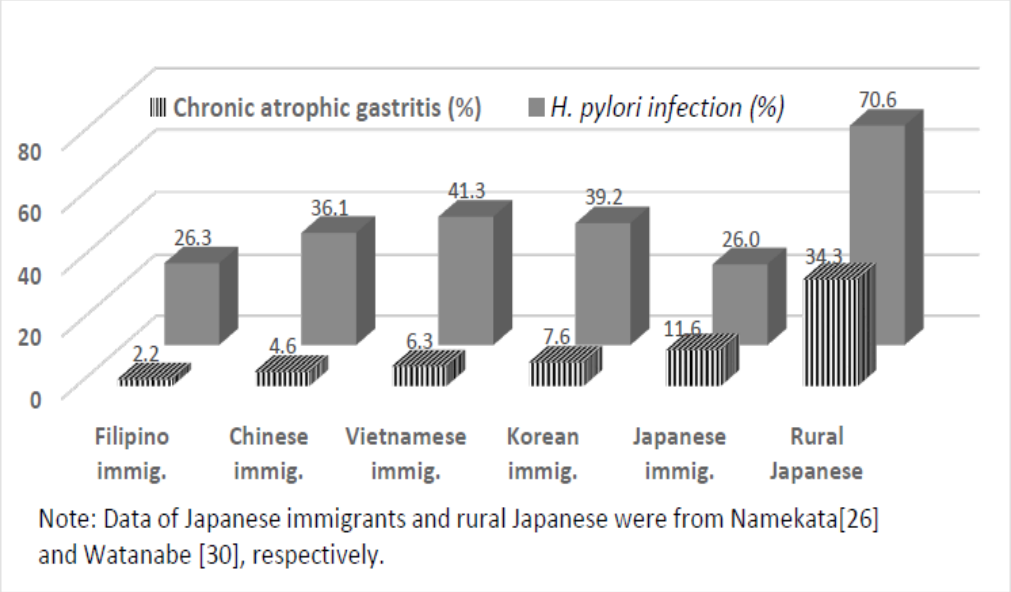

Figure 1: Age-adjusted prevalence of *H. pylori* infection and chronic atrophic gastritis among Asian immigrants in Seattle and among rural Japanese in Japan

The results of multiple logistic regression analysis to predict seropositivity of *H. pylori* with age, sex, race, drinking, smoking, having digestive disease, and family history of gastric cancer are presented in **Table 3**. Significant odds ratios were observed for being females (0.725, $p<0.05$) when setting males as a reference variable, increasing age from ≤49 years old to 65-74 years old (1.579, $p<0.05$), Vietnamese as compared to Chinese (1.615, $p<0.05$), family history of gastric cancer (1.658, $p<0.01$), and drinking habit (0.696, $p<0.05$).

Table 4 presents the results of multiple logistic regression analysis to predict the presence of chronic atrophic gastritis. The odds ratio of chronic atrophic gastritis among women was one-third lower than among men (0.326, $p<0.001$). Odds ratios for persons 65-74 years old and 75 years old and over were significantly and marginally higher (2.441, $p<0.05$ and 2.177, $p<0.10$, respectively), as compared with that for persons younger than 50 years old. When making Chinese as a reference group, only the odds ratio for Vietnamese was significant (2.472, $p<0.017$) and those for Koreans and Filipinos were not significant. Having family history of gastric cancer and having digestive disease showed an increased risk for chronic

atrophic gastritis (7.914, p<0.001 and 6.193, p<0.001, respectively). Having *H. pylori* infection significantly elevated the risk for chronic atrophic gastritis (5.856, p<0.001). Current drinking habit and current or past smoking habits were significantly and negatively associated with chronic atrophic gastritis (0.204, p<0.001 and 0.071, p<0.001, respectively).

Table 3: Adjusted odds ratios for *H. pylori* infection in four immigrant groups combined in Seattle

Explanatory variables	Odds ratio	95% CI	P-value	
Sex				
Males	1.000			
Females	0.725	0.527-0.997	0.048	*
Age in year				
≤49	1.000			
50-64	1.057	0.741-1.507	0.759	
65-74	1.579	1.019-2.449	0.041	*
≥75	1.113	0.652-1.901	0.694	
Race				
Chinese	1.000			
Vietnamese	1.615	1.065-2.447	0.024	*
Koreans	1.246	0.819-1.894	0.304	
Filipinos	0.767	0.494-1.173	0.217	
Family history of gastric cancer				
No	1.000			
Yes	1.658	1.127-2.440	0.010	**
Having digestive disease				
No	1.000			
Yes	0.853	0.583-1.247	0.412	
Drinking habit				
No	1.000			
Yes	0.696	0.513-0.943	0.019	*
Smoking habit				
No	1.000			
Yes (current & ex-smokers)	0.856	0.643-1.141	0.290	

Note: Significance level indicates * p <0.05 and ** p <0.01.

Table 4: Adjusted odds ratios for chronic atrophic gastritis in four immigrant groups combined in Seattle

Explanatory variables	Odds ratio	95% CI	P-value	
Sex				
Males	1.000			
Females	0.326	0.189-0.561	0.000	***
Age in year				
≤49	1.000			
50-64	1.067	0.546-2.083	0.850	
65-74	2.441	1.167-5.108	0.018	*
≥75	2.177	0.884-5.361	0.090	
Race				
Chinese	1.000			
Vietnamese	2.472	1.174-5.204	0.017	*
Koreans	1.151	0.553-2.397	0.706	
Filipinos	1.158	0.512-2.618	0.724	
Family history of gastric cancer				
No	1.000			
Yes	7.914	4.466-14.023	0.000	***
Having digestive disease				
No	1.000			
Yes	6.193	3.481-11.018	0.000	***
H. pylori infection				
No	1.000			
Yes	5.856	3.318-10.336	0.000	***
Drinking habit				
No	1.000			
Yes	0.204	0.109-0.380	0.000	***
Smoking habit				
No	1.000			
Yes (current & ex-smokers)	0.071	0.021-0.248	0.000	***

Note: Significance level indicates * <0.05, ** <0.01, and *** <0.001.

4. Discussion

One of the important questions in the study was if the rates of *H. pylori* infection and those of chronic atrophic gastritis among the four Asian immigrant groups in Seattle are different from those of Japanese Americans in Seattle and of Japanese in Japan. **Figure 1** compares age-adjusted rates of *H. pylori* infection and those of chronic atrophic gastritis among the four Asian immigrant groups from the present study, Japanese immigrant group in Seattle and rural Japanese group in Kyoto Prefecture of Japan from our previous studies [26,30]. There

is no linear relationship between *H. pylori* infection rates and chronic atrophic gastritis rates: *H. pylori* infection rate of Japanese Americans was lowest (26.0%) but their chronic atrophic gastritis rate was the second highest among the six population groups and both rates of Japanese in Kyoto Prefecture were highest, 70.6% for *H. pylori* and 34.3% for chronic atrophic gastritis. This implies that other risk factors which are unique to Japanese may play a significant role in etiology of gastric cancer.

Based on adjusted odds ratios in Table 4, the risk for chronic atrophic gastritis is reduced to nearly 70% as being females, to 80% as being drinkers and to 93% as being smokers or ex-smokers. On the other hand, the risk for chronic atrophic gastritis is increased to 2.4 times among seniors as compared with persons younger than 50 years old, to 2.5 times among Vietnamese immigrants as compared with Chinese immigrants, to 7.9 times for persons with family history of gastric cancer, to 6.2 times for persons having digestive disease, and to 5.9 times for persons infected with *H. pylori*. In the similar study conducted by Tsugane et al., there was no association between alcohol consumption and chronic atrophic gastritis in Japanese men aged 40 to 49 years [31]. Although there has been no strong evidence that alcohol plays an etiological role in gastric cancer [32], our results imply that drinking habits among Asian immigrants might prevent persons from developing chronic atrophic gastritis.

With regard to smoking status, our result is consistent with Tsugane et al. [31] reporting a negative association between smoking and chronic atrophic gastritis. However, a study among Japanese workers reported a dose-dependent positive association between smoking and PGI levels and PGI/PGII ratio [33]. As reviewed by the U.S. Surgeon General [34] epidemiological studies have shown an association between smoking and stomach cancer, although its association is weak in comparison with those found between smoking and other cancers. Also, our result supports the findings by Tsugane et al. showing a positive association between chronic atrophic gastritis and family history of gastric cancer in either parent or any sibling [31].

At present, the gastric cancer screening has not been recommended by either the National Cancer Institute or the American Cancer Society. However, such screening should be considered in high risk groups for the following reasons: (i) The serum pepsinogen test as a first screening of persons with chronic atrophic gastritis and endoscopy as a secondary screening are technically feasible [6-11,35]; (ii) Estimated deaths due to gastric cancer in 2019 in the U.S. is 11,140, which is comparable to 13,980 deaths due to ovarian cancer, 4,250 deaths due to uterine cervix cancer and 12,160 deaths due to uterine corpus cancer [36]. Thus, gastric cancer is not a rare disease in the U.S.; (iii) Gastric cancer is one of the five most frequently diagnosed cancers in some ethnic populations in the U.S. including Koreans, Japanese, Vietnamese, Hawaiians, Alaska natives, African Americans, Chinese and Hispanics. The average incidence rates in men ranged from 15.3 per 100,000 in Hispanics to 48.9 per 100,000 in Koreans for 1988-92

[37]; (iv) The five year survival rates of gastric cancer in Japan, where gastric cancer screening has been conducted, is 60.3 percent for both genders combined, a much higher proportion than that in the U.S., where its screening has not been promoted (33.1 percent for both genders combined) [38]. Unlike cancers of the lung, liver and pancreas, gastric cancers are potentially curable if they are diagnosed at early stages. Thus, the screening of gastric cancer in the U.S. should be considered for persons at high risk for this disease including Asian immigrants, Hawaiians, Alaska natives, African Americans, and Hispanics.

Since gastric cancer prevention screening has been conducted in Japan, it is recommended to adopt their method and criteria in the U.S. as well as in other countries. Screening participants are classified according to the results of the two serologic tests, anti-*Hp* IgG antibody titers and the PG I and II levels: Group A [*Hp*(-)PG(-)], infection free subjects who are not required for endoscopic follow-up examinations; Group B [*Hp*(+)PG(-)], chronic atrophic gastritis free or mild who are required to eradicate *H. pylori*; Group C [*Hp*(+)PG(+)], chronic atrophic gastritis who are required to eradicate *H. pylori* and to have continuous endoscopic follow-up examinations and ; Group D [*Hp*(-)PG(+)], severe chronic atrophic gastritis with extensive intestinal metaplasia who are required for continuous endoscopic follow-up examinations [39].

5. Note

Parts of this work were presented at the following meetings:

- The 67th Annual Meeting of American College of Gastroenterology in Seattle, Washington, October 20-22, 2002
- Digestive Disease Week Japan 2005, Kobe, Japan, October 5-8, 2005.
- Congress of Epidemiology 2006, Seattle, Washington, June 21-24,2006.

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Seattle Nikkei Health Study: Cross Cultural Surveys between Seattle and Japan

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in Tokyo, Japan on July 9-13, 2007.

Background of the Study

Effects of environmental changes on cardiovascular health can be examined by comparing factors between the same race who live in different environment conditions. Thus, Japanese Americans are ideal subjects to be compared with native Japanese, because both have the same genetic background but live in drastically different environment. We hope that our study outcome can contribute to further understanding of disease etiology and cardiovascular disease prevention.

Objectives

Compare the following indicators between Japanese Americans and native Japanese:

- **Lipids and lipoproteins**
- **Aortic pulse wave velocity (PWV)**
- **Coronary heart disease (CHD)**
- **Retinal artery changes**

Study Sample

Seattle Japanese Americans

Base population: 12,507
Age 30 - 79

Screening participants:
1,389 (11%)
For all analyses

Nutrition survey participants:
830:

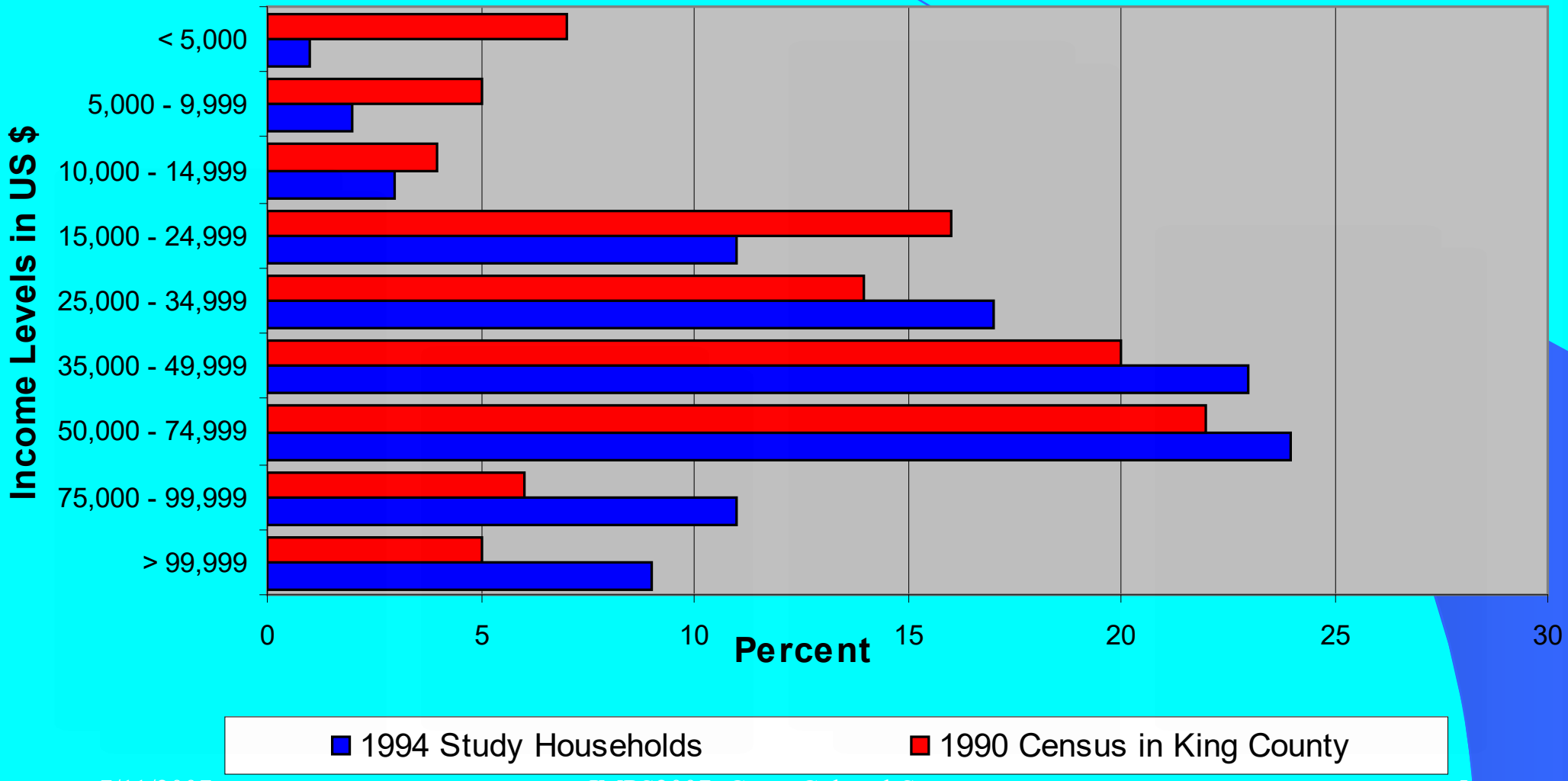
Native Japanese in Japan

Base population: 28,745
Age 30 – 79 (screening participants)
For cholesterol analysis

4,134 randomly selected
For all other analyses

Nutrition survey participants:
1841

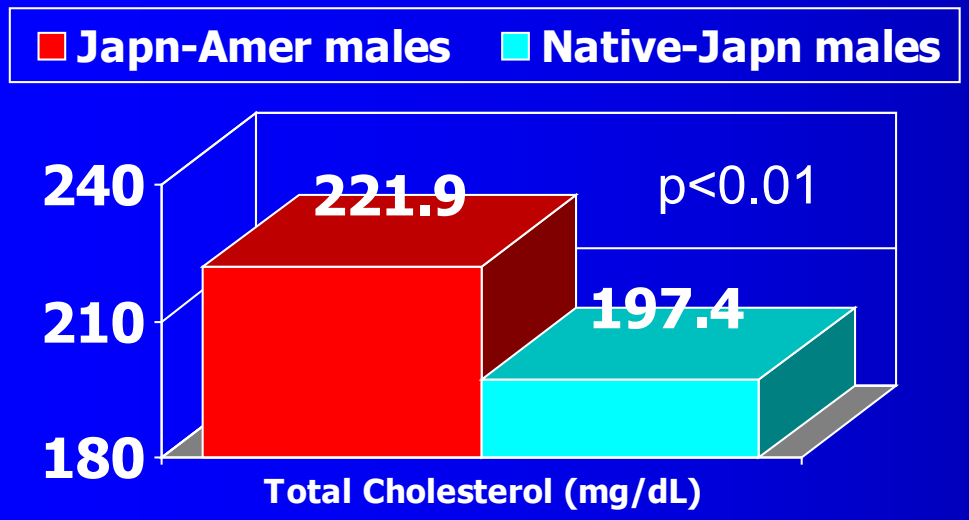
Comparison of household income distribution between King County census population and study participants of Japanese Americans

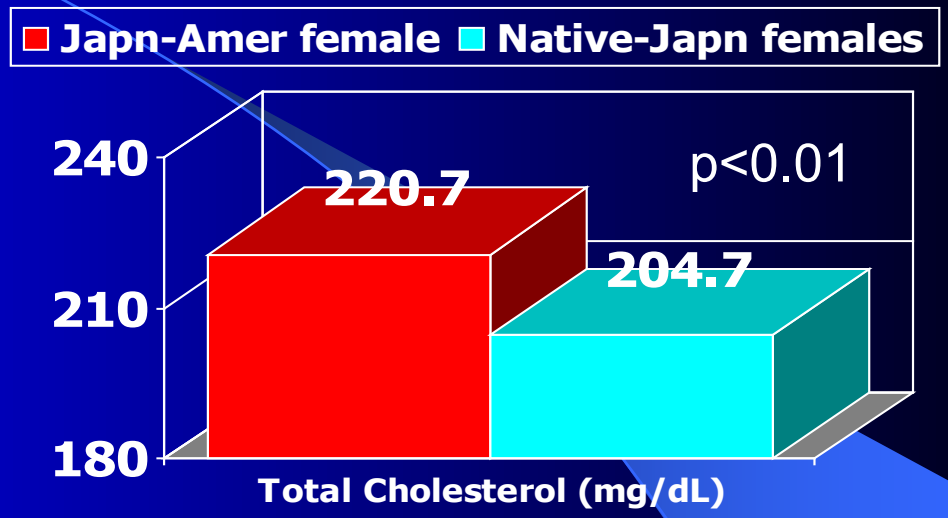


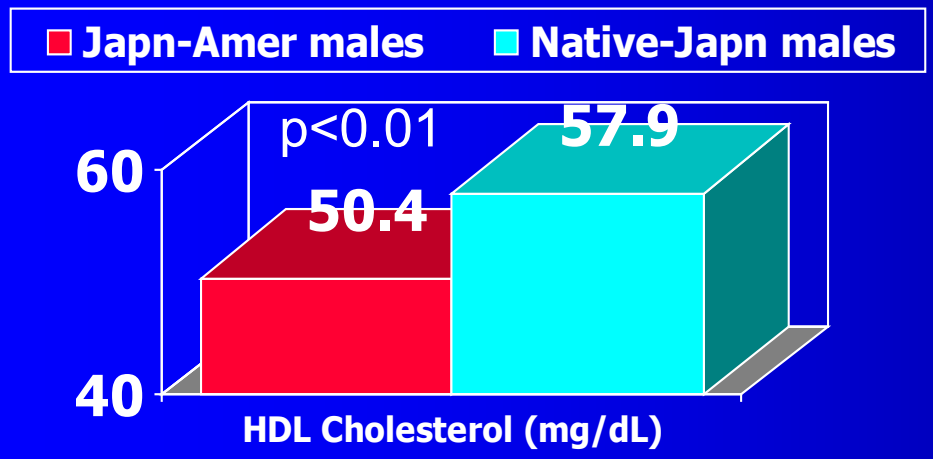
Methods

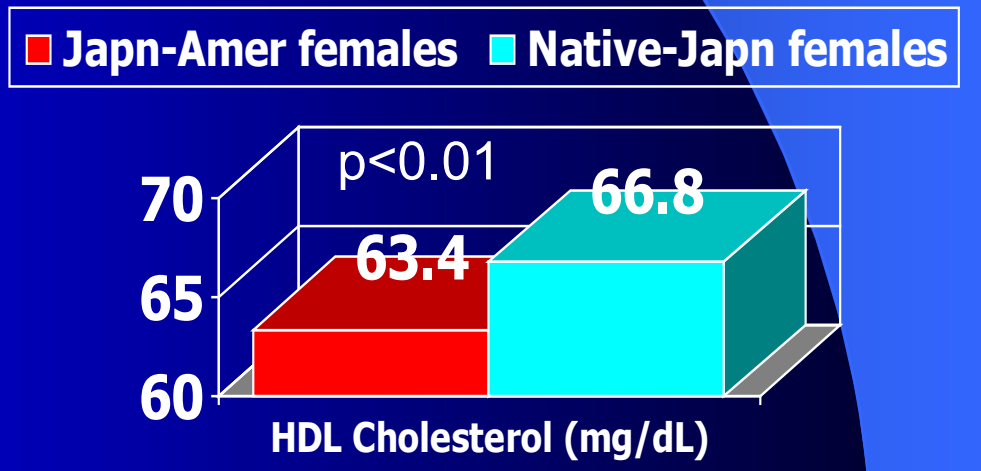
- Clinical examinations: Lipid profiles, glucose, blood pressure, PWV, ECG, retinal photos, lung function test
- Self-administered questionnaire survey (disease history, lifestyle, diet, etc.)
- Criteria for definite CHD
  - Abnormal Q or QS pattern by Minnesota codes
  - And/or self-reported history of angina pectoris and/or myocardial infarction
- Statistical analyses: descriptive statistics, multiple regression analysis, multiple logistic regression analysis

Comparison of age-adjusted average cholesterol levels between Japanese Americans and native Japanese









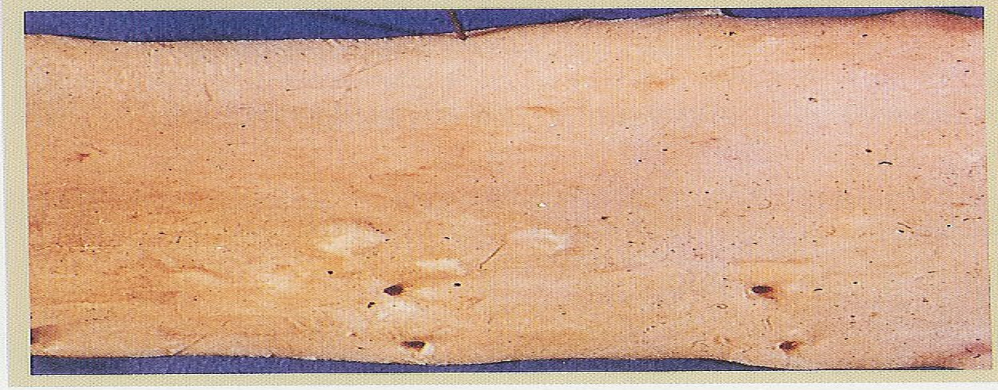
Selected Characteristics of Study Samples: Males

Selected Characteristics	Japn-Amer	Native-Japan
Mean		
BMI	25.7**	23.8
Daily alcohol consump(g)	5.8**	27.3
Percent		
Current smokers	15.4%**	46.0%

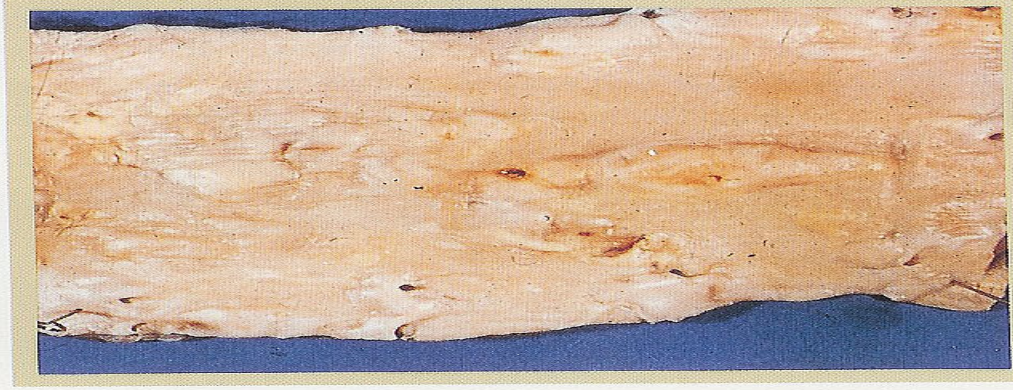
* p<0.05 **p<0.01

肉眼的内膜病理所見と生前大動脈脈波速度の関係

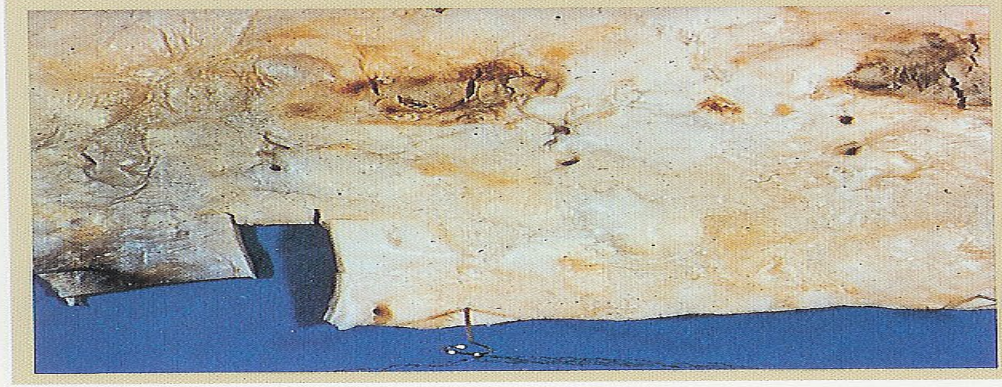
女性　22歳
PWV：6.4m/sec
病理所見：硬化所見なし



男性　56歳
PWV：8.3m/sec
病理所見：アテローマが20－30%を占めています。



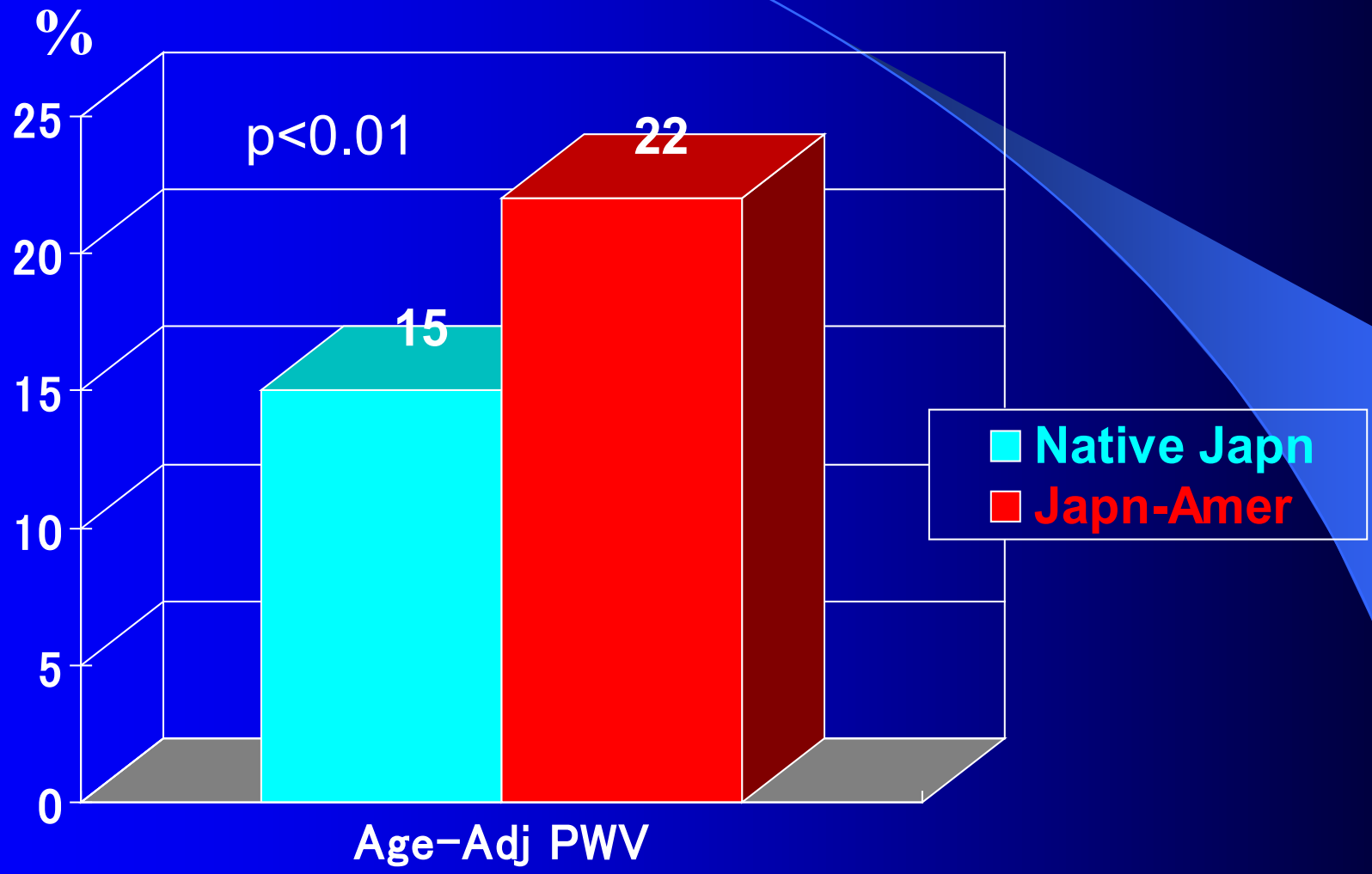
女性　86歳
PWV：10.3m/sec
病理所見：アテローム、潰瘍、石灰化が80%を占めています。



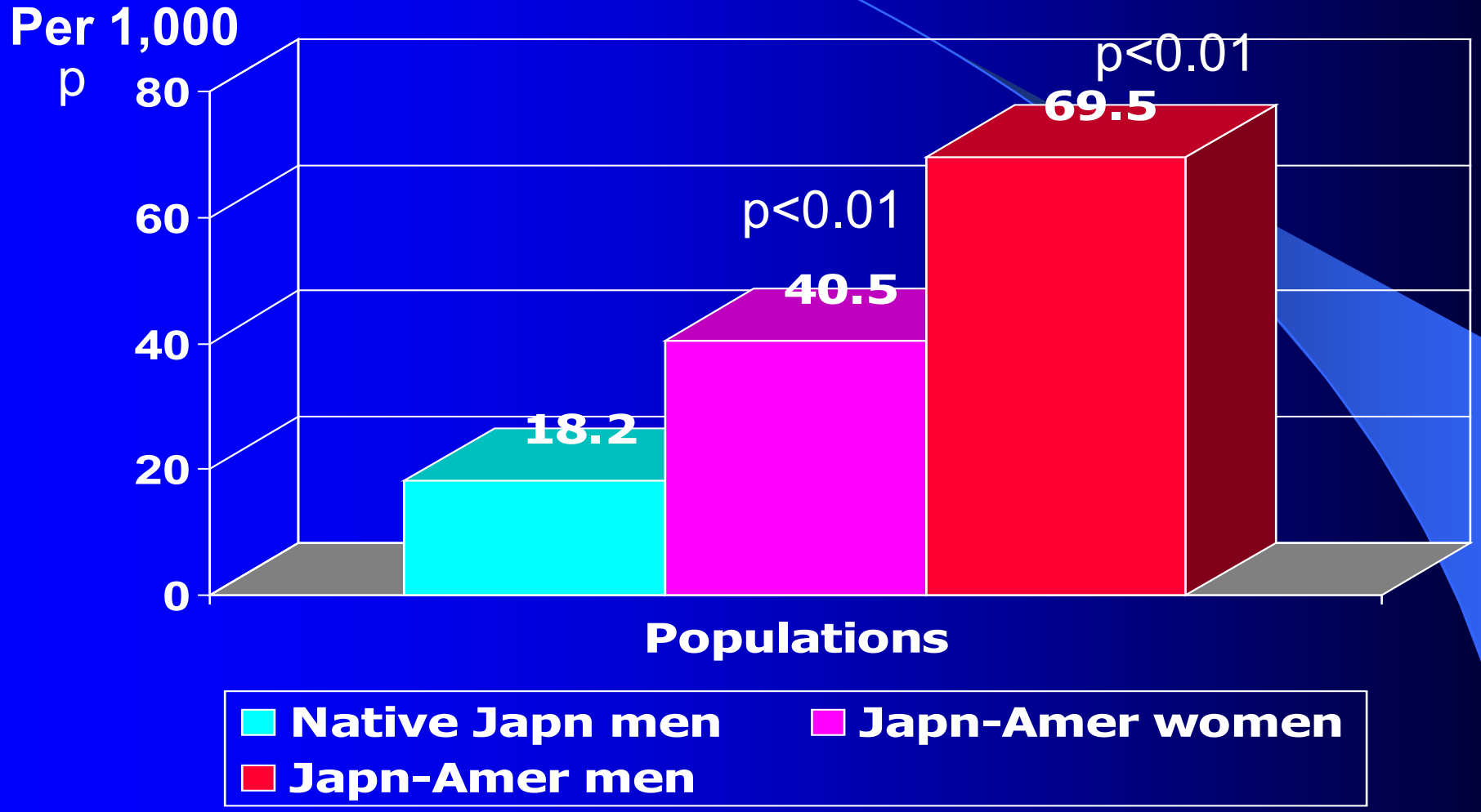
男性　62歳
PWV：14.3m/sec
病理所見：内膜全域に硬化所見を認めています。

(1) 東邦大学医学部臨床生理機能学、同第1内科、衣部省統計数理研究所：糖尿病と動脈硬化、糖尿病学の進歩、17：81－97、1983.

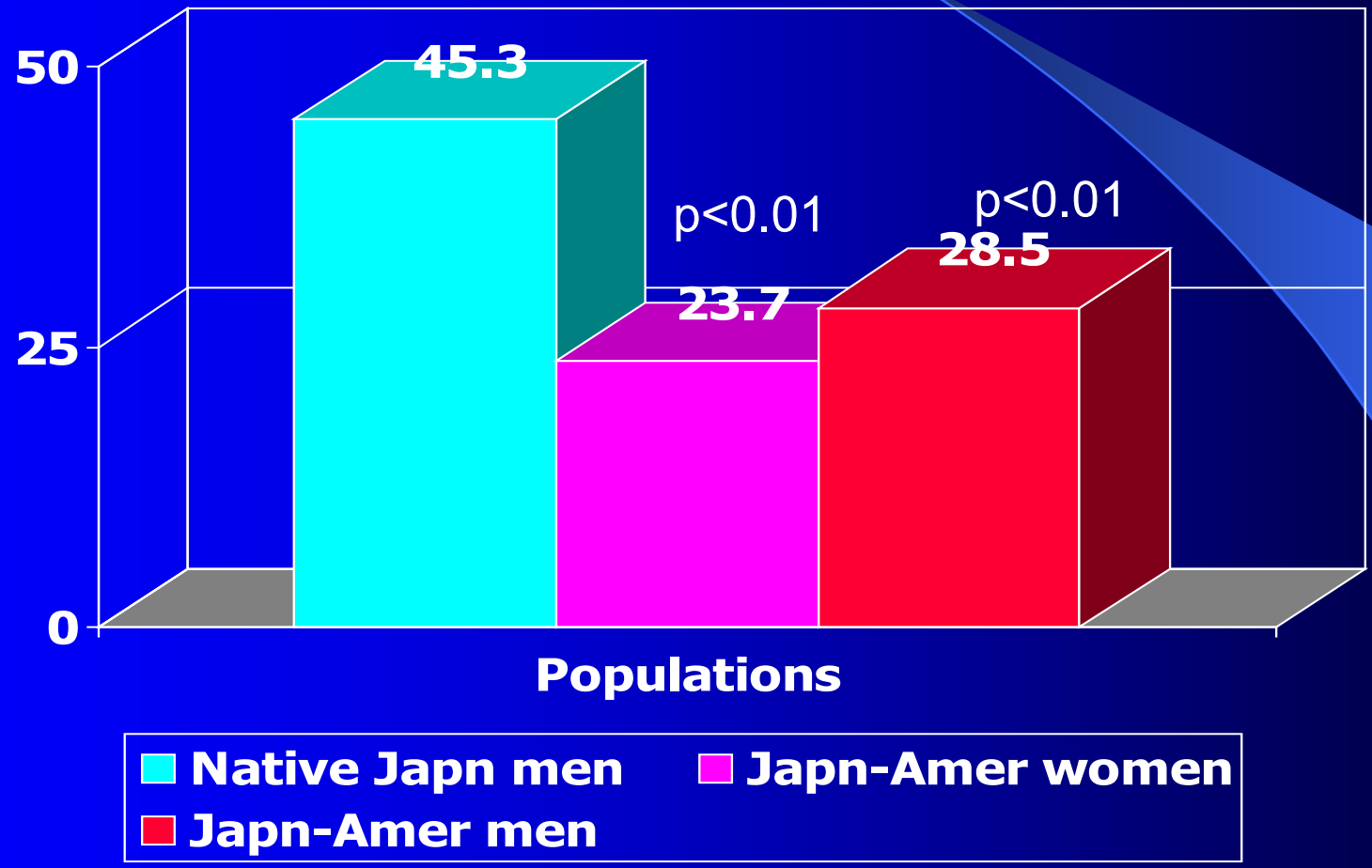
Age-adjusted prevalence of abnormally high PWV among Japanese Americans and native Japanese



Age-adjusted prevalence of coronary heart disease among Japanese American men and women and native Japanese men

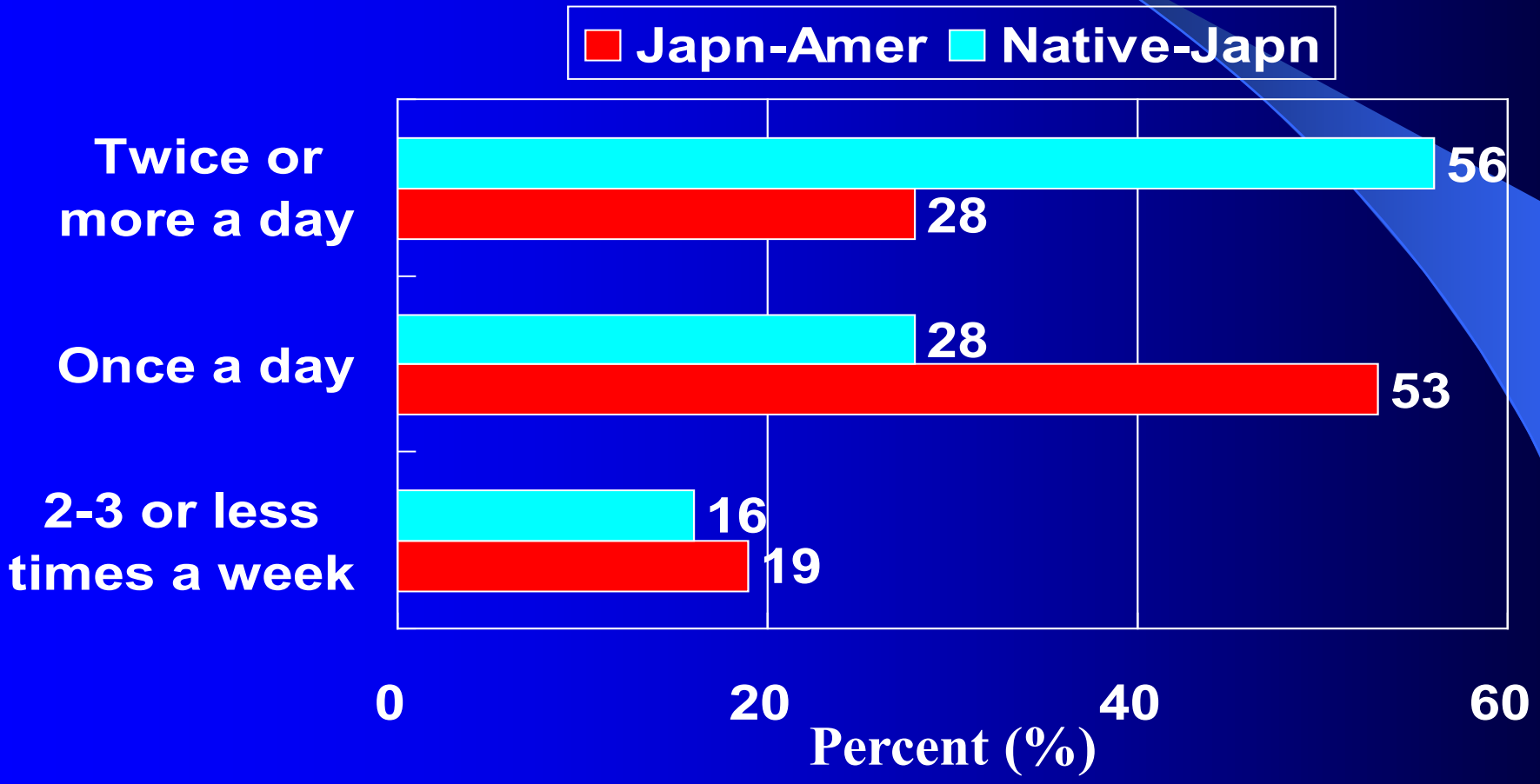


Age-adjusted prevalence of abnormal changes in retinal artery among Japanese American men and women and native Japanese men



Comparison of vegetable consumption between Japanese Americans and native Japanese

How often do you eat vegetable?



Adjusted odds ratios for presence of abnormally high PWV Among Japanese Americans and native Japanese

Variables	Reference (OR=1.00)	Japn-Amer	Native Japn
BMI	<27	1.08	1.34**
Hypertension	No	2.01***	2.76***
TC/HDL-ratio	<4.5	1.61***	1.28**
Diabetes	No	3.66***	2.43***
Current drinkers	No	0.45***	0.85 (p<.06)
Ex-drinkers	No	0.47***	1.07
Current smokers	No	1.47***	1.02
Ex-smokers	No	1.65**	1.05

Discussion and Conclusion

◆The result of PWV analysis implied that atherosclerosis among Japanese Americans advances much earlier for their age than among native Japanese , leading to higher risk for developing CHD among Japanese Americans.

◆It is considered that one of the factors to have higher prevalence of abnormally high PWV values and CHD among Japanese Americans is due to much less consumption of vegetables among Japanese Americans than among native Japanese.

◆As our results shows, Japanese are not superior to other races in terms of their health. As Japanese lifestyle and diet is westernized, an increase in incidence of diabetes and CHD may be predicted in the future.

We've been greatly appreciated to late Prof. Chikio Hayashi for his invaluable advice and contribution and to late Miss Mizuki Takahashi for conducting cardiovascular screening in Seattle, U.S.A.

Profile

of

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EDUCATION

B.S.	1966	Health Education/Mathematics, University of Niigata, Japan
M.S.	1968	Health Education/Public Health, University of Tokyo, Japan
Ph.D.	1974	Health Education/ Health Statistics (minor), University of Illinois
	1975	Post Doctoral Training in Public Health, University of Illinois, U.S.A.
Dr.H.Sc.	1985	Epidemiology, University of Tokyo School of Health Sciences, Japan

PROFESSIONAL EXPERIENCE

2014-Present	Research Fellow, Japan Health Promotion Foundation
1989-2014	Clinical Associate Professor, School of Public Health, University of Washington, Seattle, Washington
1992-2014	Director, Pacific Rim (former Nikkei) Disease Prevention Center, Seattle, Washington
2000-2001	Visiting Director, Department of Epidemiology, The Hope Heart Institute, Seattle, Washington
1997	Visiting Professor at Dept. of Public Health, School of Medicine, Niigata University, Japan

1980-1992	Research Scientist, Health and Population Research Center, Battelle Memorial Institute, Seattle, Washington
1982	Visiting Scientist, Department of Epidemiology, School of Health Sciences, University of Tokyo, Tokyo, Japan
1976-1979	Assistant Professor, Department of Environmental and Occupational Health Sciences, School of Public Health, University of Illinois Medical Center, Chicago, Illinois
1974-1975	Research Associate, Occupational and Environmental Medicine Program, School of Public Health, University of Illinois Medical Center, Chicago, Illinois
1971-1973	Teaching Assistant, Rehabilitation-Education Center, College of Applied Life Science, University of Illinois, Urbana-Champaign, Illinois

PROFESSIONAL MEMBERSHIPS

American College of Epidemiology (Fellow) Japan Epidemiological Association

AWARDS

1973 Graduate Student Research Award, University of Illinois Graduate School
1997 NIH/JSPS Short-term Fellowship Award in Biomedical and Behavioral Research conducting research at Dept. of Public Health, University of Niigata, Japan

予防医学広報事業団（青木平八郎・國雄記念）について

青木國雄の長兄平八郎は遺産の一部を予防医学教育振興のために使うようにと遺言しましたので、担当弁護士と相談し、青木平八郎記念予防医学広報事業団を組織し、予防医学教育振興事業を始めました。本事業団の役員は東海地域の疫学研究会の会員に依頼して承諾を得、田島和雄博士（三重大学客員教授、元愛知県がんセンター研究所長）に編集発行委員会委員長をお願いしました。青木平八郎が三重県在住であり、できれば三重県で始めてほしいとの内意があったからです。

この事業団の目的は予防医学に関する一般啓発書、卒後教育用の参考資料などの出版としましたが、従来の書籍・発刊物ではなく、電子ブックとして発刊しました。書籍の保存が難しい時代になりつつあり、また啓発書や発刊物では頒布数が限られ、頒布された資料も多くの人に回し読みされる機会が乏しい現状がありました。医学関連発刊物ではまだ電子ブックは十分普及していませんでしたが、次第に若い年代で利用者が増加しております。電子ブックは意外にも読みやすく、情報交換に優れており、長く保存され、検索も容易です。やがて医学会でも中心的な情報伝達のメディアになるかと予想したからです。

本事業団としては、田島編集委員長のもと、すでに表記のように 11 巻が発行され、かなりに評価をいただいており、ありがたく思っております。しかし、2019 年、田島委員長が三重大学を退職されましたので、一時活動を中止せねばならなくなりました。関係者相談いたし、弁護士のご意見もいただき、若干改変した組織：予防医学広報事業団（青木平八郎・國雄記念）として、継続することになりました。新しい役員は別表のごとくです。

2019 年 5 月には日本医学史学会が名古屋で山内一信名大名誉教授のもと、開催されるのを機に、予防医学教育に関連の深い当地方の医学活動や先哲の業績録を第 11 巻として発刊し、関係者に配布しました。

なお、第 1 巻から 10 巻および別巻は、三重大学医学部付属病院疫学のホームページ
http://www.hosp.mie-u.ac.jp/epidemiology/
で公開しています。

第 11 巻は名古屋大学学術機関リポジトリのホームページ
https://nagoya.repo.nii.ac.jp
と名古屋大学附属図書館医学部分館ホームページ
https://www.med.nagoya-u.ac.jp/medlib/
で公開しています。

第 12 巻は自治医科大学公衆衛生学部門のホームページ
https://www.jichi.ac.jp/dph/
で公開しています。

第 13 巻は HUSCAP：北海道大学学術成果コレクション
https://eprints.lib.hokudai.ac.jp
で公開しています。

第 14 巻は名古屋大学大学院医学系研究科予防医学のホームページ
https://www.med.nagoya-u.ac.jp/yobo/
で公開しています。

第 15 巻は名古屋大学大学院医学系研究科予防医学のホームページ
https://www.med.nagoya-u.ac.jp/yobo/
で公開を予定しています。

予防医学広報事業団（青木平八郎・國雄記念）
編集発行委員会幹事　　黒石哲生

発刊ＤＶＤ

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第６巻　田島和雄 編集　　日本の国際的がん特別調査研究の歩み（II）
文部科学省がん特別研究・がんの疫学研究領域報告書（1999-2009 年）を中心に

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名古屋医史談話会の歩み、シジホスの会、知られざる国際的業績に輝く４先哲　第 120 回日本医史学会総会・学術大会 2019

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学際的研究と疫学の役割

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―日本人はアメリカ日系人より健康か？―
シアトル市パシフックリム疾病予防センターと日本健康増進財団の共同研究

予防医学広報事業団（青木平八郎・國雄記念）

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３０年にわたる日系人と日本人の健康調査研究結果のまとめ

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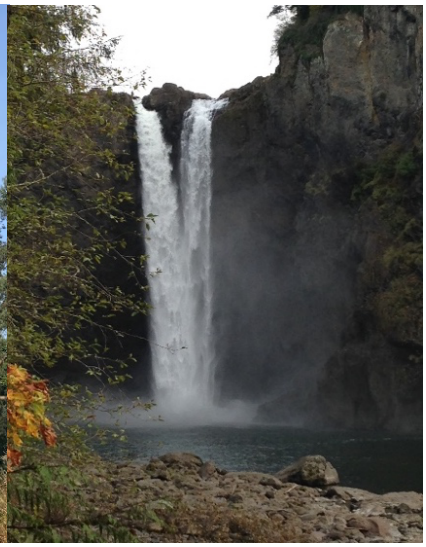
Logo of Pacific Rim Disease Prevention Center
(パシフィックリム・リム疾病予防センターのロゴマーク)

Seattle Center Space Needle
（シアトルセンターのスペースニードル）



Snoqualmie Falls（スノクオルミーの滝）

Mt. Vernon's Tulip Garden （マウントバーノンのチューリップ園）

30 年にわたる
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