めていた（26ヵ月 VS 32ヵ月）ことが示されている。日本社会で聴覚スクリーニングが，人工内耳の手術時期にどのような影響を与えたかは，平均値だけの比較では明らかではないが，日本でも同様の影響が出ていることは推測できる。報告書で述べられている全症例の補聴器装用開始時期は，平成17年度15.76ヵ月，平成18年度14.32ヵ月であり，また手術時期の平均値は，平成17年度41.73ヵ月，平成18年度38.58ヵ月であった。

難聴の原因となっている病名が判明している例のなかでは，先天性サイトメガロウイルス感染症が16例と比較的頻度が高く，症候群性の難聴のなかでは前庭水管拡張症 / Pendred 症候群が 8 例，Waardenburg 症候群が 7 例の報告があった。髄膜炎による失聴（9 例）や先天性風疹症候群（2 例）は相変わらず報告が続いており，「予防できる難聴」への継続的な取り組みは今後も必要であると考える。いわゆる Auditory neuropathy（AN）と診断された上で人工内耳を施行した児は，7 名，約 2 %程度を占めている。AN とは，無理に日本語に訳出すれば，「聴神経症」となる疾患概念であり，耳音響放射などの蝸牛機能検査では良好な反応を示すにもかかわらず，聴覚障害を呈する病態である。最近の報告[5,6]では，低年齢の難聴児にはまれならず AN（13～40%）が存在しているとされているが，こうした報告と比較すると，低い存在頻度になっている。Gibson らによる総説[7]によれば，臨床的に診断されたいわゆる AN の75%は実際には内有毛細胞の障害であり，その名称から推定されうるような後迷路性難聴が存在するのはごく一部で，AN の多くは人工内耳が有効と結論づけている。今後，難聴の遺伝子診断が国内の広い範囲で可能になれば，原因不明と診断される率は低下していくことが予測されるが，この時点での遺伝子診断による正診数は，GJB2 変異が13件（3.7%）に検出されていることにとどまっている。*GJB2* 遺伝子変異は，常染色体劣性遺伝性難聴のうちで最も頻度が高いとされ，また高度難聴になることが多いため人種を問わずしばしば高頻度に人工内耳の適応となる[8]ことが知られている。*GJB2* 変異に伴う難聴に対して人工内耳埋込術を施行した場合の術後経過については最近まで様々な議論があったが，少なくとも最近の報告[9~11]ではいずれも，*GJB2* 変異例は，短期間で速やかな言語発達が得られるが，長期的にはそれ以外の児もキャッチアップして来て差が無くなることが観察されている。

児の術前平均聴力は，この報告のなかには「記載なし」が散見されるが，平成17年107.53dB，平成18年110.38dB であった。術前補聴器装用閾値の平均値は，70dB 前後であったが，術後の人工内耳装用下での閾値は40 dB 未満となっている。この調査は，直近の人工内耳症例についての報告であるため，その長期的な言語発達についての検討ができるほどのフォローアップ期間をおいていない。このため，こうした児の聴覚医学的な，あるいは言語学的な発達の状態については，今後さらに調査を行なう必要があるが，少なくとも278例（78.3%）は，調査時点で既に聞き取りの反応が改善していると答えている。

この報告の 2 年間において，手術合併症は，全部で26件（7.3%）に認められている。うち重篤なものは，顔面神経麻痺 2 件（0.6%）術創感染 5 件（1.5%）機器の不具合 5 件（1.5%）（いずれも機器の再埋込を要した症例）が認められたことが報告されている。最近の米国からの報告[12]では，生後12ヵ月未満での人工内耳手術が一般的になっており，そ

の後の術後合併症について，50例7年間の長期臨床経過が報告されている。このなかでは全体で8件（16%）7例，うち重篤なもの3例，軽度なもの5例の合併症が報告されている。現在の日本の状態よりもより低年齢の児での人工内耳手術においても，長期にわたって比較的安定に装用が行なえていることがうかがい知ることができる。

3．これからの人工内耳

現状の人工内耳を概観し，さらにごく近い将来日本で一般的になると考えられる人工内耳の状況について予測するために，いくつかのキーワードを元に解説を加えてみたい。これのテクノロジーのうち一部は未だ日本ないしは日本語での評価が定まっているとは言えず，今後の有用性についてはあらためてこれからの状況を注意深く見つめる必要が有ることを付記しておく。

1）EASとハイブリッド

EASとは，electroacoustic stimulationの略で，高音域は人工内耳による電気刺激で，低音域は補聴器による音の増幅によって補聴を図るシステムである。EASはメドエル社が用いている用語[13]であり，コクレア社では同様のシステムをハイブリッド[14]と呼称している。いずれのシステムでも，1）高音域には補聴困難な程の高度な難聴があり，2）低音に比較的良好な（50dB～）の聴力を有しており，3）非進行性の経過をたどる場合に適応になる。この手術を施行するためには，低音の良好な聴力を術後も保ったまま人工内耳の挿入を行なうことが必要とされるので，より低侵襲での手術法が工夫されるようになっている。メドエル社およびコクレア社によるEAS専用インプラントでは，いずれも短く，侵襲性の低い電極で，蝸牛への損傷が少なくて済む形になっている。ただし，日本語使用者における難聴の場合，低音の残聴を効果的に用いて良好なコミュニケーションが可能な患者をしばしば経験するため，英語圏での臨床データがそのまま日本語利用者にも適応可能であるかどうかなど，まだ疑問も多い。

2）人工内耳の低年齢化

人工内耳を用いた音声言語をベースに言語発達を促そうと考える場合，そして，実際に対象となる児が人工内耳を要するほどの高度難聴が有ると考えられる場合，理論的にはなるべく低年齢から人工内耳を使い始めた方がよりよい音声言語の認知と，それに引き続く良好な音声言語の発達が望めると考えられる。しかし，実際のアウトカムとして，長期に渡る経過を十分にフォローアップした報告はほとんど見られなかった。最近の報告[15]では，人工内耳時期によって3群に分けたグループにおいて，人工内耳手術4から9年後の聴取能としてCAP（Category of Auditory Performance），語彙としてPPVTR（Peabody Picture Vocabulary Test（Revised））受容文法（Test of Reception of Grammar, TROG）発話明瞭度（Speech Intellegibility Rating, SIR）について検討している。この報告では，生後11ヵ月の時点で人工内耳を使用し始めたグループでは，それ以降のグループと比較して，聴取能や発話の明瞭度では差が見られなかったが，語彙および受容文法では早期手術群でより優れていたことを報告している。しかし，実際には，新生児聴覚スクリーニングが導入されることによって，より低年齢での人工内耳手術が可能になっていることが報告されている。最近のベルギーからの報告でも同様に，より高度な言語能力の発達が得られる[16]ことが報告されている。現状での本邦での人工内耳適応基準における年齢

の目安は，「原則1歳6ヵ月以上」とされ，「髄膜炎後蝸牛閉塞など，1歳6ヵ月未満での手術を要する場合がある」との付記がされている。欧米からのこうした評価が確立すれば，当然手術年齢に関する適応基準も今後議論の対象になることが考えられる。

3）両側人工内耳

両側人工内耳に関しても，マイケルムーア監督作品「シッコ（SiCKO）」で取り上げられていたことに物語られる様に，欧米を中心に急速に普及しつつある。補聴器での経験からしても，医学的には両側人工内耳の有用性は明らかであるといえる。むしろ論点となっているのは，その医療経済の視点からの効率性や，両側同時装用が有利か，それとも逐次装用で十分か，という問題である。さらに言えば，逐次装用をするにしても，どの程度タイミングがずれても許容範囲なのかということについてはまだ多くの議論がある。様々なタイムポイントで逐次的両側人工内耳埋込術を行なった児での報告[17]では，騒音下の聞き取りでは両耳での聴取がより優れていたが，第二手術が4歳以前であれば，手術時期には関係なく聞き取りには差が無かったとの報告もある一方で，二回目の手術までの期間が短い方がよりよい聞き取りが得られているという報告もある[18]。この論文では，語音聴取の問題だけが取り上げられており，同時手術か，逐次手術かの問題は今後さらに言語発達や学習の状況もふまえて長期の検討が必要となると考える。両耳手術をした際の前庭機能障害の推移など，両側ならではの副損傷についても検討する必要がある[12,16,19]。さらに，どの程度までbimodal（片耳に人工内耳，片耳に補聴器）で十分であり，どの程度の聴力からbilateral（両耳に人工内耳）が有利なのか，という議論[20]も継続的に取り上げられている。

4）骨固定型骨導補聴器（Bone anchored hearing aid: BAHA）

人工内耳とは異なるが，骨固定型骨導補聴器の日本への導入も，特に両側先天性外耳道閉鎖症患者には新しい福音となりうる。この技術は1970年代にスェーデンで開発された。耳後部の乳突部に，チタン製の固定器具（fixture）を埋め込み，そのフリンジ部にサウンドプロセッサーという振動子を結合する。適応になるのは先天性外耳道閉鎖症などの高度な伝音難聴であり，これを用いることによってヘッドバンドや眼鏡無しで，骨導補聴器を使用することができる点である。現在成人での臨床治験が進行しており，この検討で有用性が認められた場合には，近い将来に保険診療として認められる可能性がある。欧米では既に広い範囲で行なわれており，4歳以上の先天性外耳道閉鎖症児での適応が認められている。

5）人工内耳の国内における位置づけ

人工内耳における極めて国内的な問題として，人工内耳が医療制度や福祉制度の上でどのように位置づけられるか，という観点がある。人工内耳機器の法制上での位置づけは，「医療用消耗材料」であり，補聴器の位置づけ（補装具）とは異なる扱いとなっている。このため，交換や修理が容易であった補聴器とは法制上の取り扱いが異なるため，修理費用やプロセッサの交換が自費となり，装用者と，その家族の金銭的な負担が大きかった。平成18年の通達（保医発第0306005号）[19]によって，「人工内耳材料の交換に係る費用は，破損した場合などにおいて算定できるが，単なる機種の交換には算定できない」と明確に規定された。このルールが明確になったことによって自己負担額の軽減が可能となった。すなわち新機種への交換などに用いることはで

きないが，故障部品の交換は，病院窓口での3割自己負担（乳幼児医療が使える年齢の場合には負担額なし）で入手することができる。ただし，この制度には，当初から修理についての費用負担を考慮に入れられていないという問題点がある。保険で認められた部品交換は3割の自己負担で入手できるが，内部の部品交換などの修理対応となった場合には動産保険以外には費用負担をカバーする方法はない。また，医療保険での部品交換に応じられる病院が全国でも限られていることも多く，実際の運用における妨げになっていることも多い。一部の地域では人工内耳の交換[20]や電池購入[21]にも補助がある自治体も有る。人工内耳体外部が故障した場合，部品交換への対応にしても居住地域，故障時期や部品の内容によって，メーカー補償（部品によっては1年から3年などのメーカー補償期間が設定されている場合があり，期間中の不具合であれば無償交換の対象となる），保険適応，動産保険のいずれが有利な条件であるかは異なるので，人工内耳の担当者や病院のソーシャルワーカーなどと相談してみることが必要である。

6）新世代の人工内耳

最近相次いで新しいタイプの人工内耳インプラントが本邦で使用可能となった。まずコクレア社では，フリーダムプロセッサが一足早く使用できるようになっていたが，本年6月からはその専用インプラントである，フリーダムインプラントが使用できるようになっている。このインプラントでは，より高速で動作するチップを備えており，将来のプロセッサアップグレードに対応できるようになっている。メドエルは，ヨーロッパで広く用いられているパルサー（PULSAR）を日本市場に導入した。パルサーと同時に新型のスピーチプロセッサ（OPUS）も導入されているが，特筆すべきは，この新しいタイプのプロセッサへのアップグレードを無償（専用バッテリーは有償）で行なうことをアナウンスしている点である。上述したように人工内耳の欠点の一つは高額なランニングコストに有るが，より高性能なプロセッサを全ての使用者に，継続的かつ安価に提供しようとする態度は評価されるべきである。日本バイオニクスによるバイオニックイヤーシステムも，一度日本から撤退した後，最新機種90Kによって再度日本市場への浸透を図っている。各社ともに使用しているインプラントの小型化と高速化を進めており，また人工内耳電極挿入による蝸牛への損傷を最小限にとどめつつ手術が行なえるように工夫されてきている。

4．最後に

冒頭で取り上げた日本耳鼻咽喉科学会の予備調査の結果[3]では，人工内耳手術に際して，その意志決定に関連した専門職についての質問を行なったところ，197件がそのなかに「教育関係者」の存在があったことを回答している。適応基準[1]のなかにも「小児の人工内耳では，手術前から術後の療育に至るまで，家族および医療施設内外の専門職種との一貫した協力体制がとれていることを前提条件とする。」という記載がなされている。これは適応決定を自分の意志で行なうことができない小児人工内耳の特殊性をふまえた上で，「家族，保護者はもちろん，手術施設内外の聴覚・音声言語指導の療育にかかわる人達との意見の一致が欠かせないと考え，特にその項目を設定した。」ことが「概要と解説」[2]のなかで述べられている。人工内耳は病院のなかだけで完結しうる医療では無い。人工内耳についての最新の知見を多くの専門職が共有

することは有用であると考えるので，本稿がその一助となれば幸いである。

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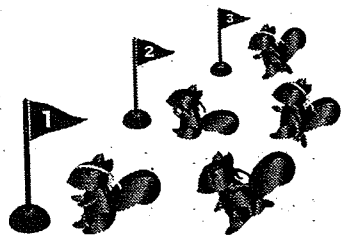

研究成果の刊行に関する一覧表

視覚障害の発生と重症化を予防する手法に関する介入研究

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
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Nine-Year Incidence and Risk Factors for Age-Related Macular Degeneration in a Defined Japanese Population

The Hisayama Study

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Purpose: To estimate the 9-year incidence and risk factors for age-related macular degeneration (AMD) in a general Japanese population.

Design: Population-based, cohort study.

Participants: In 1998, a total of 1775 Hisayama residents aged ≥40 years underwent a baseline eye examination. Of those, 1401 subjects (78.9%) took part in the follow-up eye examination in 2007 and were enrolled in the present study.

Methods: At both time points, the characteristics of AMD were determined by grading color fundus photographs using the Wisconsin Age-Related Maculopathy Grading System.

Main Outcome Measures: Incident early and late AMD.

Results: The age-standardized, 9-year cumulative incidence of early AMD was 10.0%, and that of late AMD was 1.4%. Men were found to have a significantly higher incidence of late AMD than women (age-adjusted odds ratio [OR], 2.97; 95% confidence interval [CI], 1.25–7.09). The incidence of both early and late AMD increased significantly with age. Multiple logistic regression analysis showed that older age (per 1 year; OR, 1.10; 95% CI, 1.05–1.16), smoking habits (OR, 3.98; 95% CI, 1.07–14.7), and higher circulating white blood cell (WBC) count (per 1000 cells/mm^3) (OR, 1.38; 95% CI, 1.07–1.79) were significantly associated with the development of late AMD.

Conclusions: Our findings suggest that the 9-year incidences of late AMD are lower among the Japanese than among white people in Western countries, and it is higher than among black people. Smoking habits and higher circulating WBC count are significant risk factors for the development of late AMD in the Japanese.

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Age-related macular degeneration (AMD) is the leading cause of irreversible visual impairment and blindness in elderly populations in developed countries.[1] Despite the magnitude of this problem, the pathogenesis of AMD remains poorly understood. It is thus very important to determine the precise incidence of AMD and to identify its risk factors to develop preventive measures of the disease. To date, several population-based studies[2–7] including ours[8] have provided valuable information on incidence and risk factors for AMD. The risk factors examined include iris color,[2] hypertension,[3] atherosclerosis,[4] smoking habits,[5,8] higher total/high-density lipoprotein ratio,[6] and higher white blood cell (WBC) count.[7] However, information on the long-term risk of AMD is scarce[9–11] and nonexistent in Asians including Japanese.

The aim of this article was to examine the 9-year incidence of early and late AMD and its risk factors in a prospective study of a general Japanese population.

Materials and Methods

Study Population

The Hisayama Study is an ongoing, long-term, cohort study on cardiovascular disease and its risk factors in the town of Hisayama adjoining Fukuoka City, a metropolitan area in southern Japan.[12] As a part of the study, a follow-up survey of eye diseases among residents of the town has been underway.[8,13] In 1998, a total of 1775 individuals (688 men and 1775 women) aged ≥40 years underwent a baseline eye examination. Of those, 1404 subjects (79.1%) took part in the follow-up eye examination in 2007. After excluding 3 subjects who had ungradable photographs of either eye, 1401 (78.9% of the original cohort) were enrolled in the present study.

Ophthalmic Examination and Definition of Age-related Maculopathy

The methods used for the baseline eye examination have been described in detail previously.[13] Briefly, each participant under-

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went ophthalmic examination after pupil dilatation with 1.0% tropicamide and 10% phenylephrine. Fundus photographs (45°) were taken using a Topcon TRC NW-5 fundus camera (Topcon Corporation, Tokyo, Japan), and the 35-mm color transparencies were made using Fujichrome slide film (Sensia II; Fujifilm, Tokyo, Japan). At the 9-year follow-up eye examination, fundus photographs (45°) were taken using a Topcon digital TRC NW-6SF fundus camera (Topcon Corporation). Photographs were taken of 1 field per eye.

Both examinations used a similar, masked photographic grading technique based on the International Age-related Maculopathy Epidemiological Study Group grading protocol and the grids of the Wisconsin Age-related Maculopathy Grading System.[14,15] The Wisconsin Age-related Maculopathy Grading System grid was adapted to the magnification of the camera. This protocol divides AMD into early and late stages. Early-stage AMD was defined by the presence of large drusen (soft distinct and soft indistinct) or retinal pigment epithelium pigmentary abnormalities (hyperpigmentation or hypopigmentation),[15] within the grid in the absence of late AMD in either eye. Late-stage AMD was defined as the presence of neovascular AMD or geographic atrophy. Neovascular AMD included serous or hemorrhagic detachment of the retinal pigment epithelium or sensory retina, and the presence of subretinal or subretinal pigment epithelium hemorrhages or subretinal fibrous scar tissue.[15] Geographic atrophy was characterized by sharply edged, roughly round, or oval areas of retinal pigment epithelium hypopigmentation, with clearly visible choroidal vessels.[15] The minimum area of geographic atrophy was a circle $\geq$175 μm in diameter. In our study, 2 experienced graders (MY, TI), masked to the subject information, assessed the AMD. Interobserver and intraobserver variability were analyzed. The level of agreement between the graders was 0.80 and 0.86 for most features. Finally, we determined the final diagnosis for disagreement cases after discussion.

Data Collection

Blood pressure was measured 3 times after the subject had rested for $\geq$5 minutes in the sitting position. The average of the 3 measurements was used for the analysis. Hypertension was defined as systolic blood pressure $\geq$140 mmHg, diastolic blood pressure $\geq$90 mmHg, or current use of antihypertensive medication. Blood samples were collected from an antecubital vein after an overnight fast of $\geq$12 hours. After taking the fasting blood specimen, a 75-g oral glucose tolerance test was performed with a 75-g glucose equivalent carbohydrate load (Trelan G; Shimizu Pharmaceutical Inc., Shimizu, Japan). Diabetes was defined as a fasting plasma glucose level $\geq$7.0 mmol/L, a 2-hour postloading glucose level $\geq$11.1 mmol/L, or a medical history of diabetes. Serum total cholesterol, high-density lipoprotein cholesterol, and triglyceride levels were determined enzymatically using an autoanalyzer (TBA-80S; Toshiba Inc., Tokyo, Japan), and dyslipidemia was defined as a total cholesterol level $\geq$5.7 mmol/L, high-density lipoprotein cholesterol $<$1.0 mmol/L, serum triglyceride level $\geq$1.7 mmol/L, or the current use of antihyperlipidemic medication. The WBC counts were determined using a Coulter counter (STKS; Beckman Coulter Inc., Fullerton, CA). Information on smoking habits and alcohol intake was obtained using a standard questionnaire by trained interviewers at the initial examination. Subjects were classified as either current or past habitual use or as nonuser. Body height and weight were measured in light clothing without shoes, and the body mass index (kg/m^2) was calculated.

Statistical Methods

We calculated the 9-year incidences of AMD. Age-adjusted cumulative incidences of AMD were calculated by means of the direct method using the World Health Organization standard population in 1998. Incident early AMD was defined by the appearance at follow-up of either soft drusen or retinal pigmentary abnormalities in either eye of persons in whom no early or late AMD was present at baseline. Incident late AMD was defined by the development at follow-up of neovascular AMD or geographic atrophy in either eye of persons in whom no late AMD was present at baseline. We examined the relationships between risk factors at baseline and the incidence of early and late AMD. We considered the following 9 possible risk factors for AMD: age, gender, hypertension, diabetes, dyslipidemia, smoking habits, alcohol intake, body mass index, and WBC count. Age, body mass index, and WBC count were treated as continuous variables and the others as categorical variables. Each categorical variable was coded as either 1 or 0 depending on the presence or absence of the factor, respectively. Mean values were compared by the Student t test, and frequencies by the chi-square test. We estimated the age-adjusted and multivariate odds ratio (OR) and 95% confidence interval (CI) of each potential risk factor by using a logistic regression analysis. The SAS software package (SAS Inc, Cary, NC) was used to perform the statistical analyses. A 2-sided P value of less than 0.05 was considered statistically significant.

Ethical Considerations

This study was approved by the Human Ethics Review Committee of Kyushu University Graduate School of Medical Sciences, and was carried out in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants.

Results

Table 1 shows the mean values or frequencies of potential risk factors for AMD at baseline by gender. Men were older than women. The frequencies of early AMD, hypertension, diabetes, smoking habits, and alcohol intake, and mean WBC count were higher for men than for women, whereas women had the higher frequency of dyslipidemia. There was no difference in mean body mass index between the genders.

The age-adjusted, 9-year, cumulative incidences of early and late AMD lesions are shown by gender in Table 2. After excluding

Table 1. Mean Values or Frequencies of Potential Risk Factors for Age-related Macular Degeneration (AMD) by Gender at Baseline: The Hisayama Study, 1998 Early AMD and late AMD are Prevalence

Variables	Men	Women
n	524	877
Age (y), means ± SD	61±10	59±10
Early AMD (%)	18.7	11.6
Late AMD (%)	1.3	0.3
Hypertension (%)	49.4	37.6
Diabetes (%)	16.6	6.6
Dyslipidemia (%)	46.4	54.1
Body mass index (kg/m^2)	23.4±2.9	23.1±3.4
Smoking habits (%)	74.8	7.1
Alcohol intake (%)	69.1	19.6
White blood cells (×10^3/mm^3)	6.2±1.6	5.4±1.3

Table 2. Age-Standardized 9-Year Cumulative Incidences of Early and Late Age-related Macular Degeneration (AMD) by Gender: The Hisayama Study, 1998–2007

	Men		Women		All Subjects	
	Population at Risk	*Age- standardized† Incidence, n (%)*	*Population at Risk*	*Age- standardized† Incidence, n (%)*	*Population at Risk*	*Age- standardized† Incidence, n (%)*
Early AMD	426	50 (9.0)	775	93 (10.4)	1201	143 (10.0)
Pigmentary abnormalities	426	17 (3.3)	775	9 (1.3)*	1201	26 (2.0)
Soft distinct and indistinct drusen	426	33 (5.7)	775	84 (8.8)*	1201	117 (8.0)
Late AMD	517	15 (2.6)	874	8 (0.8)*	1391	23 (1.4)
Geographic atrophy	517	1 (0.1)	874	0 (0.0)	1391	1 (0.04)
Neovascular AMD	517	14 (2.5)	874	8 (0.8)*	1391	22 (1.4)

*P<0.05, men vs women.
†The incidence was standardized for age with the World Health Organization standard population.

190 participants with early AMD and 10 participants with late AMD at the baseline eye examination, a total of 143 participants (10.0%) developed incident early AMD during the follow-up. The incidence of early AMD was slightly but not significantly higher in women than in men. In regard to subtype of early AMD, the incidence of retinal pigmentary abnormalities was significantly higher in men than in women, whereas the incidence of drusen was significantly higher among women. After excluding 10 participants with late AMD at the baseline eye examination, a total of 23 participants (1.4%) developed late AMD during the follow-up. The incidence of late AMD was significantly higher in men than in women (age-adjusted OR, 2.97; 95% CI, 1.25–7.09) owing mainly to the significantly higher incidence of neovascular AMD in men.

Figure 1 demonstrates the age-specific incidences of early and late AMD by gender. The incidences of early and late AMD significantly increased with advancing age in both genders. In each age group, the incidence of early AMD was consistently higher in women than in men, whereas the incidence of late AMD was higher in men in age groups of ≥50 years.

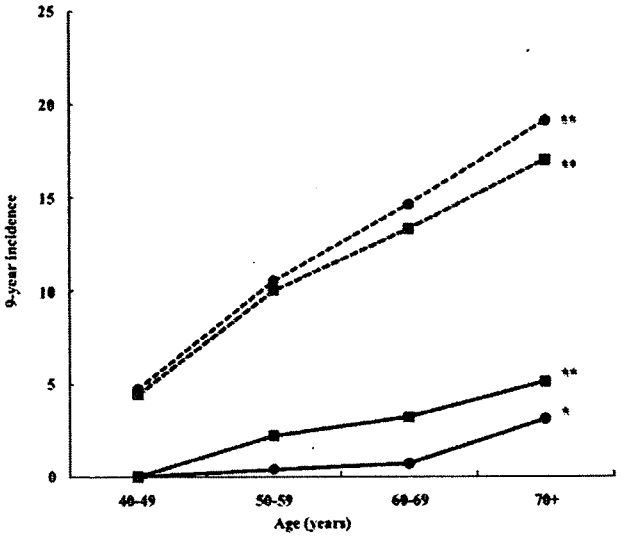

Figure 1. Age-specific 9-year incidences of early and late age-related macular degeneration by gender, the Hisayama Study. Broken line, early age-related macular degeneration; solid line, late age-related macular degeneration; black squares, men; black circles, women **P<0.01; *P<0.05 for trend.

Table 3 presents the age-adjusted, 9-year incidence of late AMD by presence or absence of early AMD at baseline. Progression to late AMD was approximately 4.4% among persons with early AMD and 0.7% among persons without early AMD. Progression to neovascular AMD was 1.8% among persons with pigmentary abnormalities and was 5.2% among persons with soft distinct and indistinct drusen. Overall, eyes with drusen at baseline were more likely to develop neovascular AMD.

The results of age- and multivariate-adjusted logistic regression analyses of risk factors for the development of early and late AMD are shown in Table 4. After adjusting for age, no associations were found between these risk factors and incident early AMD; however, male gender, smoking habits, and higher WBC count were significant risk factors for the development of late AMD. In multivariate analysis, older age, smoking habits, and higher WBC count were significantly associated with late AMD.

Discussion

To our knowledge, this is the first population-based cohort study to investigate the long-term incidence and risk factors for AMD in Japan. The findings showed that the overall, 9-year, cumulative incidence of early AMD was 10.0%, and that of late AMD was 1.4%. Both incidences increased with advancing age. Progression to late AMD was approximately 4.4% among persons with early AMD. On multivariate analysis, smoking and higher circulating WBC count were independently associated with the development of late AMD.

Previously, several long-term, population-based studies estimated the incidence of AMD. It is reported that the 10-year cumulative incidence of early AMD was 12.1% in the Beaver Dam Eye Study in the United States[9] and 14.1% in the Blue Mountains Eye Study in Australia,[11] both of which focused on a white population. The Barbados Eye Study of the predominantly black population of African descent reported a 9-year incidence of early AMD of 12.6%.[16] Even when accounting for the 1-year shorter follow-up period, our 9-year incidence of early AMD seemed to be somewhat lower than that reported in the Beaver Dam Eye Study or the Blue Mountains Eye Study. The 9-year incidence of early AMD we found (10.0%) was also lower than that reported in the Barbados Eye Study performed in a black population. Early AMD is less com-

Table 3. Age-standardized 9-Year Incidences of Late Age-related Macular Degeneration (AMD) by Presence or Absence of Early AMD at Baseline: The Hisayama Study, 1998–2007

	Geographic Atrophy		Neovascular AMD		Any Late AMD	
	Population at Risk	*Age-standardize* Incidence, n (%)*	*Population at Risk*	*Age-standardized* Incidence, n (%)*	*Population at Risk*	*Age-standardized* Incidence, n (%)*
Early AMD (−)	1,191	0 (0.0)	1,191	12 (0.7)	1,191	12 (0.7)
Early AMD (+)	190	1 (0.3)	190	10 (3.9)	190	11 (4.4)
Pigmentary abnormalities	69	1 (1.7)	69	2 (1.8)	69	3 (2.2)
Soft distinct and indistinct drusen	121	0 (0.0)	121	8 (5.2)	121	8 (5.2)

*The incidence was standardized for age with the World Health Organization standard population.

mon among the Japanese population than among white people and black people in Western countries. This difference in the incidence of early AMD among these studies could be due to the differences in study participants' characteristics (e.g., age and proportion of gender among studies), to dietary factors, to genetic factors, or perhaps to the differences in methodology among these studies.

The incidence of late AMD we found (1.4%) was lower than that reported in studies performed in white populations (Beaver Dam Eye Study, 2.1%[9]; Blue Mountains Eye Study, 3.7 %[11]) but was higher than that found in the Barbados Eye Study (0.7%), which focused on a black population.[16] This suggests that late AMD is less common among the Japanese compared with white people, and it is more common among the Japanese compared with black people. Some studies have reported racial differences in the prevalence and incidence of AMD.[17,18] The reason for different incidences among different races is not clear. However, the lower risk of occurrence of late AMD in black population was previously postulated to reflect a protective effect of melanin.[19] Weiter et al[20] have also reported that increased ocular pigmentation (iris color and fundus pigmentation) tends to decrease the risk of developing AMD, whereas Friedman et al[17] speculated that white people are genetically predisposed to have more severe maculopathy. Racial difference in late AMD incidence among the cohort studies including ours could be due to the differences in ocular pigmentation, or perhaps to genetic factors.

In the current study, the 9-year incidence of neovascular AMD was 1.4%, and that of geographic atrophy was 0.04%; nearly all incident late AMD cases were neovascular AMD (n = 22), and there was only 1 case of incident geographic atrophy. In contrast, the Blue Mountains Eye Study has reported that the 10-year incidence of neovascular AMD was 2.2%, and that of geographic atrophy was 1.7%. The incidence of geographic atrophy we found was much lower than that reported in the Blue Mountains Eye Study. The lower prevalence rates of geographic atrophy were also observed in our previous study[8] and in another Japanese population survey.[21] The reason for this different incidence, especially of geographic atrophy between Japanese and white population, is not clear. It could be due to the differences in environmental exposure or genetic factors among races.

The current study found that the incidence of early and late AMD significantly increased with advancing age in both genders. The etiology and pathogenesis of AMD are largely unknown. The consistent association with increasing age found in this study corroborated findings from many

Table 4. Age- and Multivariate-Adjusted Odds Ratios of Risk Factors for the Development of Early and Late Age-related Macular Degeneration (AMD): The Hisayama Study, 1998–2007

	Early AMD		Late AMD			
	Age Adjusted		*Age Adjusted*		*Multivariate Adjusted*	
Risk factor	*OR*	*95% CI*	*OR*	*95% CI*	*OR*	*95% CI*
Age (per 1 year)					1.10**	1.05–1.16
Gender (male)	0.92	0.63–1.33	2.97*	1.25–7.09	0.86	0.24–3.05
Hypertension	0.85	0.59–1.24	0.79	0.34–1.86		
Diabetes	0.70	0.37–1.31	0.68	0.16–2.95		
Dyslipidemia	0.92	0.65–1.31	1.32	0.56–3.08		
Body mass index (per 1 kg/m^2)	1.01	0.95–1.07	1.01	0.88–1.15		
Smoking habits	1.07	0.73–1.55	4.59**	1.86–11.3	3.98*	1.07–14.7
Alcohol intake	1.04	0.72–1.50	1.88	0.81–4.36		
White blood cells (per $10^3/mm^3$)	1.03	0.91–1.16	1.52**	1.19–1.95	1.38*	1.07–1.79

CI, confidence interval; OR, odds ratio.
Multivariate adjustment was made for age, gender, smoking habit, and white blood cells.
*P<0.05; **P<0.01.

other studies,[9,11,16] confirming the age-related nature of the disease.

We found a significantly higher incidence of late AMD in men than in women. We have already reported that early and late AMD were more prevalent among men than women in a cross-sectional study of Hisayama residents.[13] A similar finding was also observed in another cross-sectional study in Japan.[21] In contrast, most studies conducted in Western, white populations have shown a higher prevalence of late AMD in women.[11,22] The reason for this difference is precisely unknown, but smoking habits, which are known to be a major risk factor for AMD,[7,22,23] are likely to contribute to a higher incidence of late AMD in Japanese men, because the proportion of habitual smoking is much higher for men than women in Japan.

The results of this study provide prospective evidence that cigarette smoking increases the risk of developing late AMD. Compared with those who never smoked, those who had smoked in the past or were currently smoking had approximately a 4.0 times higher risk of late AMD, after adjusting for other potential risk factors. These findings are consistent with other cross-sectional and cohort data, which showed that cigarette smoking was related to the development of late AMD.[7,22,23] Smoking habits remain highly prevalent among Japanese men (74.8% in our men), which translates to a 73.8% of population-attributable fraction for late AMD in our men that are attributable to their smoking behavior. Because smoking is a well-recognized, modifiable risk factor for AMD, smoking cessation is an important public health measure to reduce the burden of AMD, particularly among Japanese men.

We found that a higher WBC count was associated with incident late AMD, independent of age, gender, and smoking status. A similar association was also observed in the Blue Mountains Eye Study.[7] Several recent experimental evidences suggest that the association between higher WBC count and late AMD is plausible, including the role of inflammatory mechanisms in subretinal neovascularization[24] and drusen development.[25] Chronic inflammatory cells, including macrophage leukocytes, have been observed in excised neovascular membranes from patients with late AMD.[26] Ultrastructural study on subretinal neovascularization associated with late AMD suggested that activated WBC are involved in the promotion of neovascular proliferation and exudation from new vessels.[24] These findings provide important evidence of an essential link between inflammation and late AMD development and suggest that local inflammatory processes that have long been known to be associated with subretinal neovascularization and drusen development may be reflected in the systemic inflammatory marker of higher WBC count.

This study has several limitations. First, losses to follow-up, an issue inherent to all long-term cohort studies, could have introduced selection bias, resulting in either an underestimation or overestimation of AMD incidence. Second, the early AMD definition used in this study is less strict and includes more early AMD cases than the definitions used by the Beaver Dam[11] and the Blue Mountains[13] Eye Studies: Drusen were defined as either indistinct or distinct drusen in our study, whereas they were defined as indistinct soft drusen in the abovementioned studies. If this study used the same early AMD definition used in other 2 studies, the early AMD incidence could have been lower than the currently reported 10%.

In conclusion, the results of this study suggest that early and late AMD is less common among the Japanese compared with white people in Western countries, although late AMD is more common among the Japanese compared with black people, and that older age, smoking habits and higher WBC count are relevant risk factors for late AMD in the Japanese. This finding provides important epidemiologic evidence of an essential link between inflammation and late AMD development, and also support the use of anti-inflammatory agents in the treatment of late AMD.

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Retina

Prevalence and Systemic Risk Factors for Retinal Vein Occlusion in a General Japanese Population: The Hisayama Study

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Purpose. To examine the prevalence of retinal vein occlusion (RVO) and its systemic relevant factors in a general Japanese population aged 40 years or older.

Methods. In 1998, 1775 Hisayama residents consented to participate in the study. Each participant underwent a comprehensive examination that included ophthalmic testing. RVO was determined by grading color fundus photographs. Logistic regression analysis was performed to determine risk factors for RVO.

Results. Of the 1775 subjects examined, 38 had RVO. The prevalence of RVO was 2.1% (2.0% for branch RVO and 0.2% for central RVO). After adjustment for age and sex, it was found that systolic and diastolic blood pressures, hypertension, and hematocrit were significantly associated with RVO. In multivariate analysis, age (per 10 years; odds ratio [OR], 1.47; 95% confidence interval [CI], 1.04–2.08), hypertension (OR, 4.25; 95% CI, 1.82–9.94), and hematocrit (per 10%; OR, 3.09; 95% CI, 1.10–1.22) remained independently significant risk factors for RVO. Both high-normal blood pressure and hypertension were significantly associated with RVO. Furthermore, compared with normotensive subjects without high hematocrit, the likelihood of RVO was markedly high in subjects having both high blood pressure and high hematocrit (age- and sex-adjusted OR, 36.0; 95% CI, 4.43–292).

Conclusions. The findings suggest that the prevalence of RVO is higher in the Japanese than in other Asians or Caucasians and that older age, higher hematocrit, and both hypertension and high-normal blood pressure are significant risk factors for RVO in the Japanese. (*Invest Ophthalmol Vis Sci.* 2010;51:000–000) DOI:10.1167/iovs.09-4453

Retinal vein occlusion (RVO) is a cause of significant loss of vision in elderly populations in developed countries.[1] Despite the magnitude of this problem, the available treatment options remain limited.[2,3] Furthermore, RVO has also been associated with increased risk of cardiovascular disease.[4–6] In developing measures to prevent this disease, it is thus very important to determine the prevalence of RVO and to identify its systemic risk factors. To date, several population-based studies,[6–11] mostly in Caucasian populations, have provided valuable information on the prevalence and systemic risk factors for RVO. These include hypertension,[6–11] diabetes,[10] smoking habits,[10] dyslipidemia,[7,9] and a history of angina.[9] However, there have been only a limited number of population-based epidemiologic studies on RVO in Japanese and other Asians.[9,11,12]

The purpose of this article was to examine the prevalence of RVO and its systemic relevant factors in a cross-sectional study of a general Japanese population.

Methods

Study Population

The Hisayama Study is an ongoing long-term prospective cohort study on cardiovascular disease and its risk factors in Hisayama, a town adjoining Fukuoka City, a metropolitan area in southern Japan.[13,14] As a part of the follow-up survey, we performed a cross-sectional examination, including an eye examination, of Hisayama residents aged 40 years or older in 1998.[15] Among 4187 residents in that age group, 1775 (42.4%; 688 men and 1087 women) were enrolled in the present study.

Ophthalmic Examination and Definition of RVO

The methods used for the ophthalmic examination have been published in detail.[15] Briefly, each participant underwent a comprehensive ophthalmic examination, including a stereoscopic fundus examination with indirect ophthalmoscopy and examination with a slit-lamp biomicroscope with a superfield lens (Volk, Mentor, OH), after pupil dilation with 1.0% tropicamide and 5% phenylephrine. Fundus photographs (45°) were taken of both eyes of each participant with a nonmydriatic fundus camera (TRC NW-5; Topcon, Tokyo, Japan) and slide film (Fujichrome Sensia II; Fujifilm, Tokyo, Japan). We photographed one field, centered at a point midway between the temporal edge of the optic disc and the fovea in both eyes. The presence of RVO was determined based on the grading of fundus examinations by indirect ophthalmoscopy and slit lamp and the color fundus photographs. All photographs were evaluated by retinal specialists (MY and TI) who were masked to the participants' data. The presence or absence of central or branch RVO was defined according to a standardized protocol.[6,10,16] Recent central RVO was characterized by retinal edema, optic disc hyperemia or edema, scattered superficial and deep retinal hemorrhages, and venous dilation. Old central RVOs were characterized by occluded and sheathed retinal veins or vascular anastomosis at the optic disc. Branch RVOs involved a more localized area of the retina in the sector of the obstructed venule and were characterized by scattered superficial and deep retinal hemorrhages, venous dilation, intraretinal microvascular abnormalities, and occluded and sheathed

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TABLE 1. Mean Values or Frequencies of Risk Factors by Status of Retinal Vein Occlusion

Variable	Non-RVO (n = 1736)	RVO (n = 38)	P
Age, y	62 ± 11	67 ± 7	0.002
Sex (men), %	38.5	50.0	0.15
Systolic blood pressure, mm Hg	133 ± 21	147 ± 18	<0.0001
Diastolic blood pressure, mm Hg	77 ± 11	81 ± 10	0.02
Hypertension, %	43.7	81.6	<0.0001
Total cholesterol, mmol/L	5.3 ± 0.9	5.4 ± 1.1	0.73
High-density lipoprotein cholesterol, mmol/L	1.5 ± 0.4	1.6 ± 0.4	0.16
Triglycerides, mmol/L	1.20 (0.59-2.98)	1.02 (0.51-2.19)	0.14
Body mass index, kg/m^2	23.1 ± 3.1	23.2 ± 3.5	0.77
Diabetes, %	12.6	10.5	0.70
White blood cells, $\times 10^3$/mm^3	5.8 ± 1.5	6.1 ± 1.6	0.15
Platelets, $\times 10^4$/mm^3	21.9 ± 5.2	19.8 ± 6.0	0.02
Hematocrit, %	40.1 ± 4.1	41.6 ± 3.6	0.03
ECG abnormalities, %	17.1	29.0	0.06
History of cardiovascular disease, %	2.7	5.3	0.42
Smoking habit (yes), %	17.5	18.4	0.88
Alcohol intake (yes), %	36.5	44.7	0.30
Regular exercise (yes), %	16.7	23.7	0.51

Data are expressed as the mean ± SD or percentages. Geometric mean value and 95% prediction interval of triglycerides are shown because of the skewed distribution.

RVO, retinal vein occlusion

retinal venules. The presence of any RVO was defined as the presence of branch or central RVO in either eye.

Data Collection

Information on smoking habits, alcohol intake, and regular exercise during leisure time was obtained by trained interviewers using a standard questionnaire. Smoking habits and alcohol intake were classified as either current use or not. Those subjects who engaged in sports or other forms of exertion three or more times per week during their leisure time were designated as the regular exercise group. The questionnaire also investigated history of cardiovascular disease, including stroke and coronary heart disease.

Blood pressure was measured three times in the sitting position after the subject had rested for at least 5 minutes. The average of the three measurements was used for the analysis. According to the 2007 European Society of Hypertension (ESH) and European Society of Cardiology (ESC) Practice Guidelines,[17] blood pressure levels were categorized as follows: optimal (systolic <120 mm Hg and diastolic <80 mm Hg), normal (120–129/80 to 84 mm Hg), high-normal (130–139/85 to 89 mm Hg), and hypertension (≥140/≥90 mm Hg or current use of antihypertensive medication).

Plasma glucose levels were determined by the glucose-oxidase method, and diabetes mellitus was defined by a 75-g oral glucose tolerance test or by fasting (≥7.0 mM) or postprandial (≥11.1 mM) blood glucose level, or by the use of hypoglycemic agents. Serum total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride levels were determined enzymatically by using an autoanalyzer (TBA-80S; Toshiba Inc., Tokyo, Japan). White blood cell (WBC) and platelet counts and hematocrit levels were determined with a cell counter (STKS; Coulter Inc., Hialeah, FL). ECG abnormalities were defined as left ventricular hypertrophy (Minnesota code,[18] 3-1) or ST depression (4-1, 2, 3). Body height and weight were measured in light clothing without shoes, and the body mass index (in kilograms per square meter) was calculated.

Statistical Methods

We considered the following 18 possible risk factors for RVO: age, sex, systolic and diastolic blood pressures, hypertension, total cholesterol, HDL cholesterol, triglycerides, body mass index, diabetes mellitus, WBC count, platelet count, hematocrit, ECG abnormalities, history of cardiovascular disease, smoking habits, alcohol intake, and regular exercise. Mean values were compared by Student's t-test, and frequencies by the χ^2 test. We estimated the age- and sex-adjusted and multivariate-adjusted odds ratio (OR) and 95% confidence interval (CI) for each potential risk factor by using logistic regression analysis (SAS software; SAS Institute, Cary, NC[19]). A two-sided $P < 0.05$ was considered statistically significant.

Ethical Considerations

This study was approved by the Human Ethics Review Committee of Kyushu University Graduate School of Medical Sciences and was performed in accordance with the Declaration of Helsinki. The study subjects provided written informed consent to participate in the study.

TABLE 2. Age-Specific Prevalence of RVO by Sex

Age Range, y	Men			Women			All Subjects			
	Subjects, n	Branch RVO, n (%)	Central RVO, n (%)	Subjects, n	Branch RVO, n (%)	Central RVO, n (%)	Subjects, n	Branch RVO, n (%)	Central RVO, n (%)	All RVO, n (%)
40-49	92	0 (0.0)	0 (0.0)	201	0 (0.0)	0 (0.0)	293	0 (0.0)	0 (0.0)	0 (0.0)
50-59	154	2 (1.3)	0 (0.0)	284	5 (1.8)	0 (0.0)	438	7 (1.6)	0 (0.0)	7 (1.6)
60-69	231	5 (2.2)	3 (1.3)	335	10 (3.0)	0 (0.0)	566	15 (2.7)	3 (0.5)	18 (3.2)
70-79	178	7 (3.9)	0 (0.0)	212	2 (0.9)	0 (0.0)	390	9 (2.3)	0 (0.0)	9 (2.3)
80+	33	2 (6.1)	0 (0.0)	55	2 (3.6)	0 (0.0)	88	4 (4.6)	0 (0.0)	4 (4.6)
Total	688	16 (2.3)	3 (0.4)	1087	19 (1.8)	0 (0.0)	1775	35 (2.0)	3 (0.2)	38 (2.1)
P_{trend}		0.01	0.87		0.15			0.005	0.66	0.005

RVO, retinal vein occlusion

TABLE 3. Age- and Sex-Adjusted and Multivariate-Adjusted OR of Relevant Factors of RVO

Association	Age- and Sex-Adjusted OR	Age- and Sex-Adjusted 95% CI	Multivariate-Adjusted OR	Multivariate-Adjusted 95% CI
Age, per 10 years			1.47*	1.04–2.08
Sex (men), %			0.93	0.42–2.07
Systolic blood pressure, per 10 mm Hg	1.23†	1.07–1.41		
Diastolic blood pressure, per 10 mm Hg	1.46*	1.09–1.97		
Hypertension	4.53†	1.94–10.6	4.25†	1.82–9.94
Total cholesterol, per 1 mmol/L	1.20	0.83–1.74		
High-density lipoprotein cholesterol, per 1 mmol/L	2.22	0.94–5.25		
Triglycerides, per 1 mmol/L	0.63	0.36–1.10		
Body mass index, per 1 kg/m^2	1.04	0.94–1.15		
Diabetes	0.65	0.23–1.87		
White blood cells, per 10^3/mm^3	1.15	0.94–1.40		
Platelets, per 10^4/mm^3	0.94	0.88–1.01		
Hematocrit, per 10 %	3.09*	1.13–8.46	1.10*	1.00–1.22
ECG abnormalities	1.57	0.76–3.26		
History of cardiovascular disease	0.91	0.21–3.91		
Smoking habit	0.95	0.39–2.34		
Alcohol intake	1.42	0.67–3.01		
Regular exercise	1.24	0.58–2.68		

* $P < 0.05$.
† $P < 0.01$.

RVO, retinal vein occlusion
OR, odds ratio ; CI, confidence interval

RESULTS

T1 Table 1 shows the mean values or frequencies of potential risk factors according to the presence or absence of RVO. The geometric mean values and 95% prediction intervals of triglycerides are shown because of the skewed distribution. Subjects with RVO were older than those without RVO. Subjects with RVO had higher mean systolic and diastolic blood pressures and hematocrits, as well as a higher frequency of hypertension, whereas those without RVO had a lower mean platelet count.

T2 The age-specific prevalences of RVO are shown by sex in Table 2. Of the 1775 subjects examined, 38 (2.1%) had RVO. Of the subjects with RVO, 35 (92.1%) had branch RVO. The prevalence of branch RVO was slightly but not significantly higher in the men than in the women (2.3% vs. 1.8%). Central RVO was observed only in the men (0.4%). The prevalence of all RVO significantly increased with advancing age in all the subjects ($P_{trend} = 0.005$), whereas the prevalence of branch RVO significantly increased with advancing age only in the men ($P_{trend} = 0.01$).

The results of age- and sex-adjusted and multivariate-adjusted logistic regression analyses of relevant factors for RVO are presented in Table 3. After adjusting for age and sex, we found that systolic and diastolic blood pressures, hypertension, and hematocrit were significantly associated with RVO. In multivariate analysis, age (per 10 years; OR, 1.47; 95% CI, 1.04–2.08), hypertension (OR, 4.25; 95% CI, 1.82– 9.94), and hematocrit (per 10%) (OR, 3.09; 95% CI, 1.10–1.22) remained independently significant relevant factors for RVO. T3

T4 Table 4 demonstrates the age- and sex-adjusted OR of RVO according to blood pressure levels and quartiles of hematocrit. The age- and sex-adjusted OR of RVO significantly increased with elevated blood pressure levels ($P_{trend} < 0.001$). Compared with those with optimal or normal blood pressure, the OR of RVO was significantly higher, not only in the subjects with hypertension (age- and sex-adjusted OR, 11.9; 95% CI, 2.78–50.9), but also in the subjects with high-normal blood pressure (age- and sex-adjusted OR, 6.81; 95% CI, 1.30–35.6). The age- and sex-adjusted OR of RVO also significantly increased with rising hematocrit levels ($P_{trend} = 0.003$): the likelihood of RVO was significantly higher in the fourth quartile than in the first (age- and sex-adjusted OR, 6.03; 95% CI, 1.85–19.7).

TABLE 4. Age- and Sex-Adjusted OR of RVO According to Blood Pressure Levels and Quartiles of Hematocrit

Risk Factor Level	Subjects, *n*	Cases, *n*	Age- and Sex-Adjusted OR (95% CI)	P_{trend}
Blood pressure level				
Optimal	469	1	1.00 (reference)	<0.001
Normal	276	1		
High-normal	240	5	6.81 (1.30–35.6)*	
Hypertension	790	31	11.9 (2.78–50.9)†	
Hematocrit				
First quartile, <37.7	436	5	1.00 (reference)	0.004
Second quartile, 37.7–39.9	447	7	1.40 (0.44–4.46)	
Third quartile, 40.0–42.6	445	8	1.81 (0.58–5.70)	
Fourth quartile, ≥42.7	446	18	6.03 (1.85–19.7)*	

* $P < 0.05$.
† $P < 0.01$.

RVO, retinal vein occlusion
OR, odds ratio ; CI, confidence interval

TABLE 5. Age- and Sex-Adjusted OR of RVO According to the Presence or Absence of High Blood Pressure and High Hematocrit

	Subjects, *n*	Cases, *n*	Age- and Sex-Adjusted OR (95% CI)	*P*
Normal blood pressure + low hematocrit	595	1	1.00 (reference)	
Normal blood pressure + high hematocrit	150	1	4.81 (0.28–82.2)	0.28
High blood pressure + low hematocrit	742	20	11.9 (1.57–90.9)	0.02
High blood pressure + high hematocrit	288	16	36.0 (4.43–292)	<0.01

~~Normal blood pressure, optimal or normal blood pressure; high blood pressure, high normal blood pressure or hypertension; low hematocrit, first to third quartiles (<42.7%); high hematocrit, fourth quartile (≥42.7%).~~ Normal blood pressure : Optimal + Normal, High blood pressure : High normal + Hypertension
Low nematocrit : first-third quartiles(<42.7%), Higt hematocrit : fourth quartiles(≥42.7%)
OR, odds ratio ; CI, confidence interval

Further, we examined both the combined and separate effects of high blood pressure and elevated hematocrit levels on RVO in the groups according to the presence or absence of high blood pressure (high normal blood pressure or hypertension) and high hematocrit level (fourth quartile, ≥42.7%). As T5 shown in Table 5, compared with normotensive subjects without high hematocrit, the OR of RVO was significantly increased in subjects with high blood pressure alone (age- and sex-adjusted OR, 11.9; 95% CI, 1.57–90.9), whereas the OR of RVO was slightly but not significantly increased in subjects with high hematocrit alone (age- and sex-adjusted OR, 4.81; 95% CI, 0.28–82.2). Furthermore, the OR of RVO was markedly high in subjects having both high blood pressure and high hematocrit (age- and sex-adjusted OR, 36.0; 95% CI, 4.43–292). However, the interaction between high blood pressure and high hematocrit level was not significant ($P = 0.35$).

DISCUSSION

In a cross-sectional examination of a general Japanese population, we demonstrated that the prevalence of RVO was 2.1% and that age, high blood pressure, and elevation of hematocrit levels were independent relevant risk factors for RVO. In addition, the likelihood of RVO increased significantly in subjects having both high blood pressure and high hematocrit.

The prevalence of RVO has also been estimated in several T6 other population-based studies (Table 6). The disease prevalence was reported to be 1.6% in the Blue Mountains Eye Study in Australia[16] and 1.1% in the Multiethnic Study of Atherosclerosis in the United States.[7] A study on a Chinese population, the Beijing Eye Study, reported an RVO prevalence of 1.2%,[12] and a study of a Malay population, the Singapore Malay Eye Study, reported a prevalence of 0.7%.[9] The prevalence of RVO in the present study (2.1%) seemed to be somewhat higher than those in the previous studies. Although the variation in disease prevalence among these studies could be due to differences in the characteristics of subjects and in the methodologies, our findings of a higher prevalence suggest that RVO is more common among the Japanese population than among other Asian or Western populations, since the same grading protocols and RVO definitions were used in most of those studies.[7,9,12,16] Indeed, some studies have shown racial differences in the prevalence of RVO.[9,10] The reason for such differences remains uncertain, although genetic or environmental factors could contribute to the discrepancy.

In the present study, we found that the prevalence of RVO increased significantly with advancing age. The etiology and pathogenesis of RVO are largely unknown. The consistent association with increasing age found in this study is in accordance with the findings in many others,[6,7,9] confirming the age-related nature of the disease.

Our data indicated a clear association between hypertension and RVO, which is consistent with clinical knowledge and the findings of other population-based studies.[6–8,10–12] Our results also showed that not only hypertension but also high-normal blood pressure was significantly associated with RVO. The Framingham Heart Study indicated that the risk of cardiovascular disease is significantly increased in patients with high-normal blood pressure and higher blood pressure levels.[20] Based on these findings, it may be reasonable to suppose that high-normal blood pressure promotes systemic arteriosclerosis, including retinal vascular changes, and thereby causes RVO. Therefore, subjects with high-normal blood pressure should be considered at high risk for RVO. Strict control of elevated blood pressure may be important in preventing the disease.

We found that a higher hematocrit level was associated with RVO, independent of age, sex, and hypertension. A previous case-control study also indicated that hematocrit was significantly higher in a branch RVO group than in the control subjects.[21] Moreover, another study reported a significantly higher prevalence of elevated hematocrit in subjects with central RVO than in control subjects.[22] RVO is caused by thrombosis of the vein, but the role played by various hematologic abnormalities in its etiology and pathogenesis remains unclear and controversial. It is known that elevated hematocrit increases blood viscosity.[22] Therefore, increased hematocrit may augment the risk of RVO through the increase in blood viscosity.

The present study showed an extremely increased likelihood of RVO in subjects who had both hypertension and a higher hematocrit level. Although the mechanism underlying this phenomenon is not clearly understood, a possible explanation is that hypertension is a strong risk factor for systemic arteriosclerosis, including retinal arteriosclerosis,[5,8] and sclerotic arteriolar walls in the retina may com-

TABLE 6. Prevalence of RVO in the Hisyama Study and Other Population-Based Studies

Study	Country	Subjects, *n*	Age ~~Range~~	*n* (Prevalence %)
Blue Mountains Eye Study[16]	Australia	3654	49–	59 (1.6)
Multiethnic Study of Atherosclerosis[7]	United States	6147	45–	65 (1.1)
Beijing Eye Study[12]	China	4439	40–	58 (1.3)
Singapore Malay Eye Study[9]	Singapore	3280	40–	22 (0.7)
Hisayama Study[15]	Japan	1775	40–	38 (2.1)

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press the underlying veins at arteriovenous crossings, leading to reduced blood flow, which in turn could facilitate the development of a thrombus and downstream venous occlusion. It is therefore speculated that increased hematocrit levels markedly enhance the likelihood of RVO by hyperviscosity in people whose retinal vessel walls have already been damaged by hypertension.

This study has several limitations. First, we ascertained RVO cases by using one photographic field per eye, whereas in most previous population-based studies, two to six photographic fields were taken per eye. This difference could have resulted in underestimation of the prevalence of RVO if peripheral lesions were overlooked. Second, the number of our RVO cases is relatively small, and therefore the CIs around the prevalence and ORs are very wide. It might be misleading to compare the prevalence in this study with that in other population-based studies, and there is a possibility that the ORs are inflated due to the small samples. The estimates of our study should be interpreted with caution. Third, because of the cross-sectional design of this study, it is still unclear how risk factors are related to the onset of RVO. Further prospective investigation would help to clarify this issue.

In conclusion, the results of this study suggest that RVO is more common among the Japanese than among other Asians or Caucasians and that older age, higher hematocrit, and not only hypertension but also high-normal blood pressure are risk factors for RVO in the Japanese. In addition, among subjects who have both high blood pressure and higher hematocrit, the likelihood of RVO was substantially increased. Therefore, patients having both high blood pressure and higher hematocrit should be considered a population at high risk for RVO and continued preventive efforts should be made in these patients to reduce the burden of the disease.

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The Prevalence of Age-Related Macular Degeneration in Asians

A Systematic Review and Meta-Analysis

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Objective: To determine the prevalence of age-related macular degeneration (AMD) in Asian populations and to compare this with prevalence in white populations.

Design: A clear understanding of AMD prevalence in Asians is essential to meet future demands for eye health care.

Methods: We searched published literature reporting AMD prevalence in Asian populations. We limited studies examined to those using standardized grading systems (either the Wisconsin Age-Related Maculopathy Grading System or the International classification proposed by the International ARM Epidemiological Study Group). We used metaanalytical methods to calculate age-specific pooled prevalence of AMD using inverse-variance weighting in a random effect model. We also calculated pooled estimates of age-standardized prevalence. A metaregression model was used to examine gender differences and differences between Asian and white populations.

Results: We identified 9 studies reporting AMD prevalence from 4 Asian populations. Pooled prevalence estimates of early and late AMD in Asian populations aged 40 to 79 years were 6.8% (95% confidence interval [CI], 4.6%–8.9%) and 0.56% (95% CI, 0.30%–0.81%), respectively; corresponding prevalence estimates in white populations were 8.8% (95% CI, 3.8%–13.8%) and 0.59% (95% CI, 0.35%–0.84%), respectively. Reliable prevalence estimates of AMD in Asian persons aged ≥80 years were not available owing to small subject numbers in this age category.

Conclusions: Among persons aged 40 to 79 years, the age-specific prevalence of late AMD in Asians was comparable with that reported from white populations, but early AMD signs were less common among Asians. Further studies in Asian populations are warranted to investigate whether certain specific AMD phenotypes or subtypes, such as polypoidal choroidal vasculopathy, are more common.

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Age-related macular degeneration (AMD) has been recognized as one of the leading causes of vision loss in elderly people in Western populations.[1] It has been also suggested that racial/ethnic differences in prevalence of AMD exist, but to date, racial/ethnic differences have only been documented between black and white populations.[2–5]

Asia is expected to see a substantial increase in the number of older persons in the next few decades,[6] and it has been estimated that 25% of Asians will be aged ≥60 years by 2050. A clear knowledge of the epidemiology of AMD in Asia is therefore essential to meet future demands for eye health care and social support for persons with AMD, as well as to prioritize expensive new treatments (e.g., use of anti–vascular endothelial growth factor agents).

A traditional view has been that AMD is less frequent in Asians than in whites,[7] based on earlier observations from hospital-based samples of Asian countries. In Japan, for example, the estimated prevalence of AMD, according to a report of a multicenter, hospital-based study, was only 0.035% in persons aged ≥50 years in 1993.[8] However, estimates from hospital-based study samples do not provide the best information on the prevalence or impact of AMD in the general community. The lack of reliable, population-based data from Asian prevents meaningful interracial/ethnic comparisons between Asian and white populations.[9] In the last 10 years, however, an increasing number of studies have reported the epidemiology of AMD in Asian populations.[10–17] Most important, these recent studies have adopted standardized methods to classify AMD lesions.

It is also suggested that frequency of subtypes of late AMD might be different between Asians and whites. For example, it is now recognized that polypoidal choroidal vasculopathy (PCV) lesions are frequently observed in Asian patients with exudative AMD.[18,19] Polypoidal choroidal vasculopathy has been shown to have similarities and differences compared with typical neovascular AMD in genetic predisposition,[20–23] clinical[18,19,24] and pathologic[25] characteristics, and response to photodynamic therapy[26–28] or anti–vascular endothelial growth factor agents;[29] whether

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