Approach To Cerebral Imaging. Anonymous. Georg Thieme Verlag, Stuttgart.

Wells, K.B., Stewart, A., Hays, R.D., Burnam, M.A., Rogers, W., Daniels, M., Berry, S., Greenfield, S., Ware, J., 1989. The functioning and well-being of depressed patients. Results from the medical outcomes study. JAMA 262, 914–919.

Wilson, R.S., Mendes de Leon, C.F., Benett, D.A., Bienias, J.L., Evans, D.A., 2004. Depressive symptoms and cognitive decline in a community population of older persons. J. Neurol. Neurosurg. Psychiatry 75, 126–129.

Yaffe, K., Blackwell, T., Gore, R., Sands, L., Reus, V., Browner, W.S., 1999. Depressive symptoms and cognitive decline in nondemented elderly women: a prospective study. Arch. Gen. Psychiatry 56, 425–430.

Yesavage, J.A., Brink, T.L., Rose, T.L., Lum, O., Huang, V., Adey, M., Leirer, V.O., 1982. Development and validation of a geriatric depression screening scale: a preliminary report. J. Psychiatr. Res. 17, 37–49.

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原 著

都市部住宅地域における在宅高齢者の口腔状態：鶴ヶ谷プロジェクト

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Oral health status in an elderly urban population: the Tsurugaya project

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Abstract : To clarify the interrelations among oral health status, masticatory function, dietary behavior and the influence of these factors on geriatric syndromes, such as compromised physical functions, dementia, and depression, we performed a dental checkup program as a part of the Comprehensive Geriatric Assessment (CGA) for 1,172 residents, 70 years or older, in Tsurugaya district, Sendai (the Tsurugaya Project). The oral health status of residents of Tsurugaya who lived at home was evaluated and compared with the results of a nationwide examination in Japan, Report on the Survey of Dental Disease (1999). The mean number of natural teeth in our elderly subjects was significantly greater than that in the subjects of the nationwide examination (14.1 vs 10.4). The proportion of subjects who had 20 or more teeth in Tsurugaya was higher than that in the nationwide examination. There was no difference in the frequency of prosthodontic replacement of missing teeth between our subjects and the nationwide examination. As for periodontal condition, the proportion of subjects with no periodontal problem was greater in Tsurugaya than in the nationwide examination. In addition, proportion of subjects with severe periodontitis was lower in Tsurugaya than that in the nationwide examination. These features were considered to be related to factors such as living environment, attitude to dental health, and economic situation in an elderly urban population.

Key words : oral health status, dental checkup program, elderly population, natural teeth, Tsurugaya Project

緒　言

人口の高齢化が進み，ADLの低下，認知機能の低下などによって「生活機能障害」を起こした，いわゆる要介護高齢者が急増している[1]。そのような高齢者の中には，口腔衛生の悪化に伴う歯周疾患や歯の欠損による咀嚼障害を有するものが多く，薬剤，全身疾患などが原因で唾液分泌量低下や味覚障害を生じることもある。これらの障害は食欲を減退させ，食を楽しむ機会を奪うことから，高齢者の心理やQOLに及ぼす影響は大きい。また，咀嚼運動の低下が栄養摂取への影響を仲立ちに，身体機能低下，うつや認知機能障害などの老年症候群に関与する可能性[2-5]が指摘されている。さらに，要介護の原因となる糖尿病や脳心血管障害などの全身疾患の発症，進展と口腔状態との関連[6-9]も報告されていることからも，介護予防への歯科の果たす役割は増大している。しかしながら，それらの実態を裏付けるエビデンスは十分であるとは言えず，高齢者自身や介護者の口腔衛生に関する認識は未だに低い。

そこで，口腔状態，咀嚼機能および食に関するQOLの相互の関係や，これらが要介護状態に関わる全身の諸因子に及ぼす影響を明らかにすることを目的に，仙台市宮城野区保健福祉センター，東北大学大学院医学系研究科および同歯学研究科の共同事業で行われた高齢者に対する総合機能評価（Comprehensive Geriatric Assessment, CGA）において，歯科健診を実施した。

ここでは本研究の端緒として，健診結果の一部から当該地区在住高齢者の口腔状態の特徴を記述し，平成11年度歯科疾患実態調査報告[10]を用いた全国調査との比較検討を行った。

研究方法

1. 調査対象

仙台市宮城野区鶴ヶ谷地区に居住する70歳以上の全高齢者2,730名に対し，「鶴ヶ谷寝たきり予防健診」の実施案内を配布した。2002年7月から8月に健診を実施し，研究に関する同意を得た受診者を対象に調査を実施した。

2. 倫理面への配慮

本研究は東北大学大学院歯学研究科倫理委員会の承認を既に得ている。対象者には，結果の研究活用について説明し，文書による同意を得た。

3. 診査方法

口腔内診査は，事前に各項目の診査基準について十分なキャリブレーションを行った歯科医師が，診査者と記録者各1名ずつの組を5組つくり実施した。

4. 口腔内診査

① 歯の診査

口腔内に保有している現在歯については，健全歯，処置歯，未処置う蝕歯，う蝕を除く未処置歯のいずれかに分類した。未処置う蝕歯は，歯冠部咬合面が残存している歯と歯冠崩壊歯を区別した。う蝕を除く未処置歯とは，高度の咬耗，磨耗，着色，斑状歯，外傷，酸蝕症，形態異常などである。欠損補綴状況は，義歯やブリッジなどによる欠損補綴処置がなされていない要補綴歯，既に欠損補綴処置が施されている欠損補綴歯に分類した。

② 歯周組織の診査

歯周組織の診査には，Community Periodontal Index（CPI）を用いた。すなわち，口腔内を上下顎の左右側臼歯部および上下顎全歯部の6分画に分け，各分画の代表歯をCPIプローブを用いて上顎は頬側面，下顎は舌側面について診査した。代表歯は，臼歯部では第一，第二大臼歯とし2歯中の最大コードをその分画のコードとした。代表歯の一方が欠損している場合は，残存している代表歯のコードを記録し，2歯とも欠損している場合，その分画は記録なしとした。前歯部は上顎右側中切歯と下顎左側中切歯を代表歯とし，欠損している場合は対側同名歯を代替歯として診査した。代表歯，代替歯ともに欠損している場合は記録なしとした。さらに，6分画中の最大コードを受診者のCPIスコアとして健診結果の判定および分析に用いた。CPIコードと評価基準は以下の通りである。

コード0.　健全
コード1.　プロービング後の出血
コード2.　プロービングによる歯石の検出
コード3.　ポケットの深さが4 mm以上6 mm未満
コード4.　ポケットの深さが6 mm以上

5. 分析

現在歯，欠損補綴状況および歯周組織の状況について性別，年齢階層別に分析した。現在歯の構成は健全歯，処置歯，未処置歯とし，その際歯科疾患実態調査の診査基準に従い，う蝕を除く未処置歯は健全歯に含み，未処置う蝕歯および歯冠崩壊歯を未処置歯とした。年齢は70-74歳，75-79歳，80-85歳および85歳以上に層別化した。さらに，これらの結果を平成11年度歯科疾患実態調査報告による全国調査と比較検討した。

統計解析には統計ソフトSPSS ver 12.0を用い，適宜t-検定，χ^2検定，一元配置分散分析を行った。いずれも統計学的有意水準を5%とした。

結　果

1. 受診者

表1に歯科健診の受診状況を示す。健診対象者2,730名中，受診者は1,172名（42.9%）であった。受診者数は女性が多く，

表1. 歯科健診の受診者数と受診率

		合計	70-74	75-79	80-84	85-
全体	対象者	2,730	1,212	799	443	276
	受診者	1,172	605	343	161	63
	受診率	42.9%	49.9%	42.9%	36.3%	22.8%
男性	対象者	1,130	544	325	158	103
	受診者	486	270	134	59	23
	受診率	43.0%	49.6%	41.2%	37.3%	22.3%
女性	対象者	1,600	668	474	285	173
	受診者	686	335	209	102	40
	受診率	42.9%	50.1%	44.1%	35.8%	23.1%

表2. 現在歯とその構成

	現在歯	健全歯	処置歯	未処置歯
全体	14.1 (10.3)	5.7 (6.5)	7.7 (6.3)	0.7 (1.6)
性別				
男性	15.5 (10.3)	7.0 (7.2)	7.7 (6.0)	0.8 (1.8)
女性	13.1 (10.1)*	4.7 (5.7)*	7.8 (6.6)	0.6 (1.5)
年齢階層別				
70-74	17.0 (9.8)	7.1 (6.8)	9.2 (6.3)	0.7 (1.8)
75-79	12.5 (9.9)[a]	5.0 (6.1)[a]	7.0 (6.1)[a]	0.6 (1.4)
80-84	9.2 (9.6)[a,b]	3.1 (5.0)[a,b]	5.4 (6.0)[a,b]	0.7 (1.6)
85-	7.3 (8.4)[a,b]	2.5 (5.0)[a,b]	4.1 (4.5)[a,b]	0.7 (1.5)

*$p<0.05$ (vs 男性), [a]$p<0.05$ (vs 70-74), [b]$p<0.05$ (vs 75-79)
平均値 (標準偏差)

全体の 58.6% を占めたが，受診率に性差はみられなかった。年齢階層別では，階層が低いほど受診率が良好で，全体における割合は 70-74 歳で 51.6%，75-79 歳で 29.3%，80-84 歳で 13.7%，85 歳以上で 5.4% であった。

2. 現在歯

現在歯および現在歯を構成する健全歯，処置歯，未処置歯の一人平均歯数を表2に示す。現在歯数は 14.1 本であった。性別では男性 15.5 本，女性 13.1 本で，男性の方が女性よりも有意に多かった。年齢階層別では，高齢層ほど現在歯数は少なく，80-84 歳と 85 歳以上間を除く全ての階層間に有意差が認められた。健全歯数は 5.7 本であった。健全歯も現在歯同様，男性で有意に多く (男性 7.0 本，女性 4.7 本)，高齢層ほど少なかった。処置歯数に性差はなかったが，高齢層ほど有意に少なかった。未処置歯数に性差，年齢階層差は認められなかった。

3. 欠損補綴状況 (表3)

一人平均の喪失歯数は 14.2 本であった。性別では，男性 12.9 本，女性 15.1 本で女性で有意に多かった。年齢階層別では，高齢層ほど喪失歯数は多かった。欠損補綴歯数に性差はなかったが，高齢層ほど多い傾向にあり，70-74 歳と他の全ての階層間および 75-79 歳と 80-84 歳間に有意差が認められた。要補綴歯数に性差，年齢階層差は認められなかった。

表3. 喪失歯と欠損補綴状況

	喪失歯	欠損補綴歯	要補綴歯
全体	14.2 (10.0)	12.3 (10.6)	1.6 (4.6)
性別			
男性	12.9 (9.9)	11.3 (10.3)	1.2 (4.0)
女性	15.1 (9.9)*	12.9 (10.8)	1.9 (5.0)
年齢階層			
70-74	11.4 (9.5)	9.6 (9.8)	1.4 (4.1)
75-79	15.8 (9.6)[a]	14.0 (10.5)[a]	1.5 (4.4)
80-84	19.0 (9.3)[a,b]	16.6 (10.9)[a,b]	2.2 (5.9)
85-	20.9 (8.2)[a,b]	17.6 (10.6)[a]	2.9 (6.3)

*$p<0.05$ (vs 男性), [a]$p<0.05$ (vs 70-74), [b]$p<0.05$ (vs 75-79)
平均値 (標準偏差)

4. 歯周組織状態

歯周組織の状態はデータ欠損者を除く 1,141 名を対象に分析した。分析対象者のうち，6分画全てに代表歯がない者は 23.4% (男性 20.8%，女性 25.3%) であった。年齢階層別では 70-74 歳で 15.1%，75-79 歳で 25.4%，80-84 歳で 42.0%，85 歳以上で 46.6% と，階層が高いほど代表歯を持たない者が多かった。図1には，最低でも1分画に代表歯があった 874 名の CPI スコアの内訳を示す。全体では，半数に 4 mm 以上のポケット (スコア 3, 4) が存在し，スコア1および2を含めると 88.0% に何らかの歯周疾患の所見がみられた。性別では，各スコアの割合に有意な差はなかった。年齢階層別では，高齢層ほどスコア 3, 4 の割合が多い傾向にあった。85 歳以上では，いずれの年齢層に対しても有意にスコア 0 の割合が小さく，スコア 2 の割合が大きかった。スコア1の者はいなかった。

5. 全国調査との比較

1) 調査対象者

本健診と全国調査 (平成 11 年度歯科疾患実態調査報告) の対象者における男女比，年齢階層比はほぼ一致していた (図2)。

2) 現在歯

一人平均現在歯数は，全国値の 10.4 本に対し有意に多かった (14.1 本)。性別，年齢階層別でも高い値を示し，80-84 歳を除く全ての階層間に有意差がみられた (図3)。

図4には現在歯数を有する者の割合を歯数別に算出し，分布を示した。無歯顎者が極めて多く，その他の現在歯数には様々な割合で分布するという特徴が，鶴ヶ谷地区と全国に共通してみられた。しかしながら，鶴ヶ谷地区における無歯顎者率は，全国値の 28.4% に対し，17.4% と低値だった。対照的に，多数の現在歯を保有する者の割合は高く，20 歯以上保有者率は，全国値の 23.5% を大幅に上回る 40.9% であった (図5)。この傾向は，性別，年齢階層別の比較でも同様にみられた。さらに，観察対象を 80 歳以上に絞った 8020 達成者率は，全国値

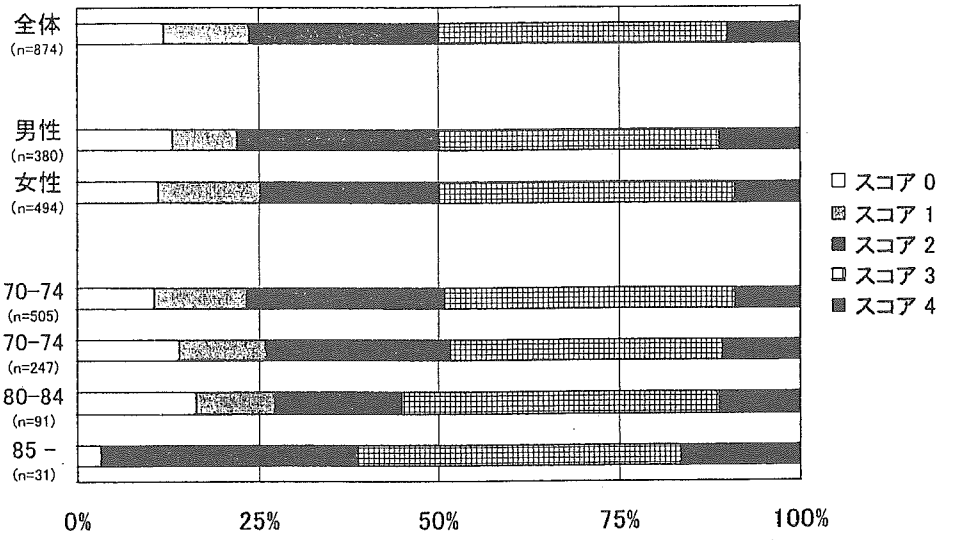

図1.　歯周組織状態

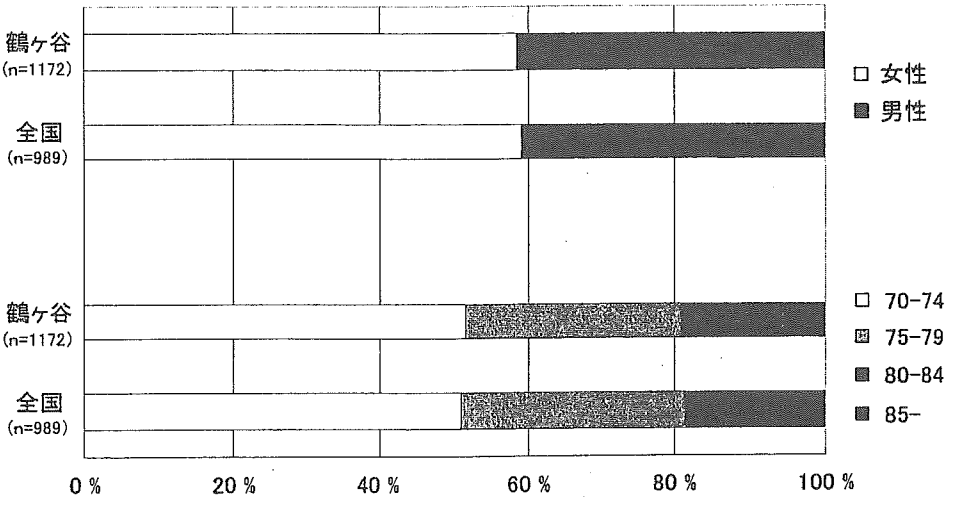

図2.　鶴ヶ谷健診と全国調査における対象者の比較

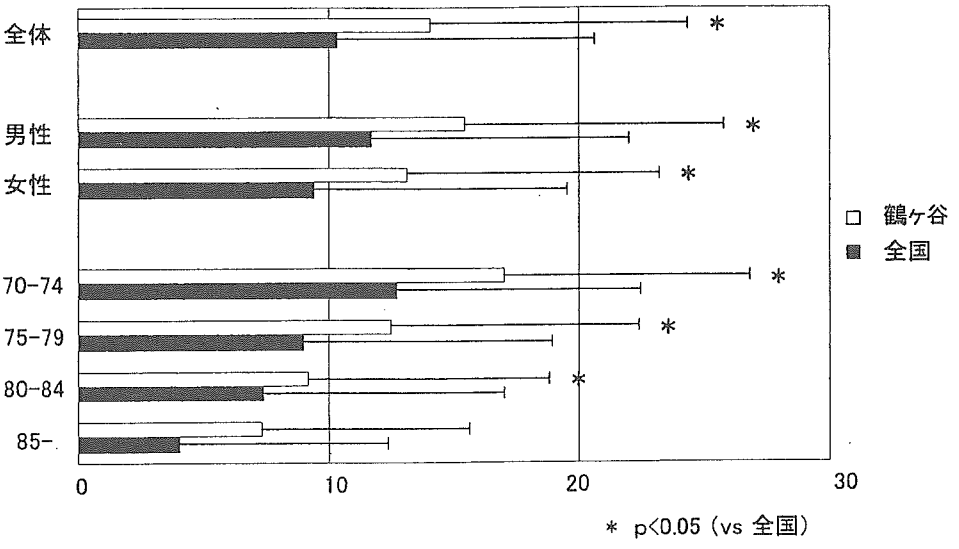

図3.　一人平均現在歯数の比較

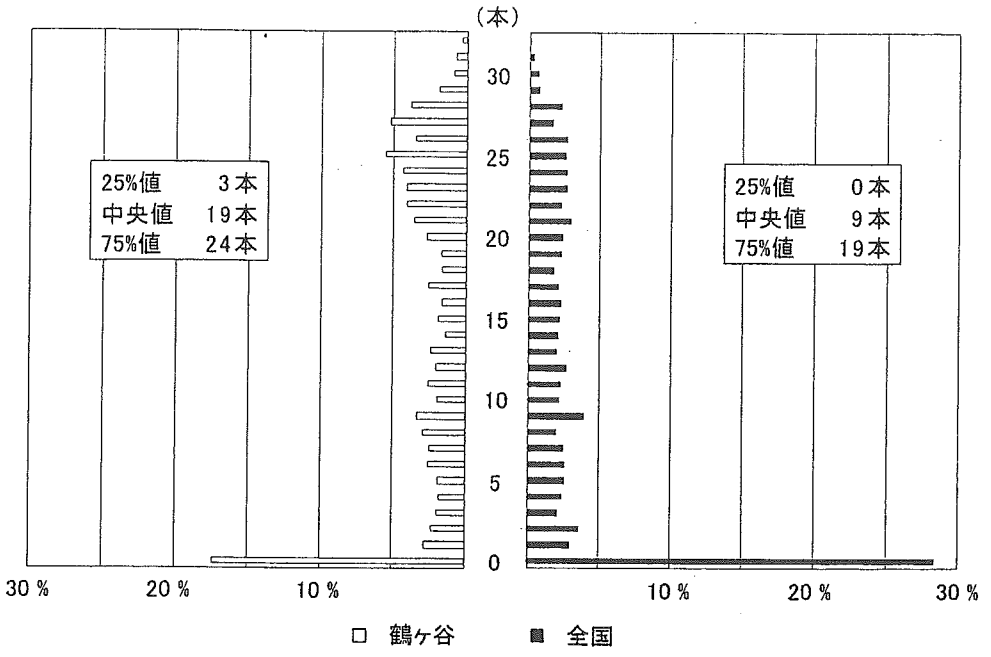

図 4.　調査対象者の現在歯数別分布

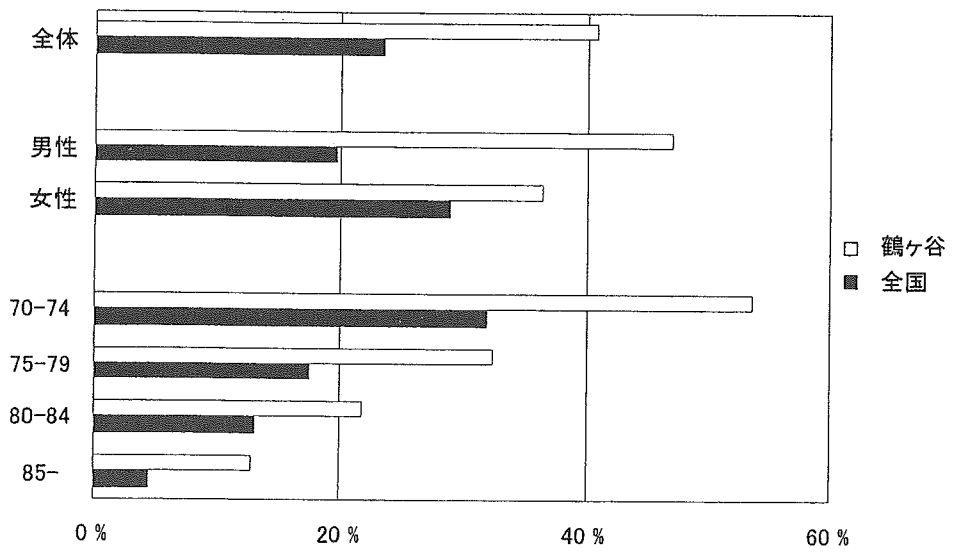

図 5.　20 歯以上保有者率の比較

の 9.9% に対し，19.2% であった。

現在歯の構成は，全国調査に比べ，健全歯の占める割合が高く，未処置歯の割合が低い傾向を示した (図 6)。

3)　欠損補綴状況 (図 7)

一人平均欠損補綴歯数は 12.3 本で，全国調査の 16.0 本に比べ少なかった。喪失歯全体に占める欠損補綴歯の割合は，全体，性別，年齢階層別のいずれにおいても 80〜90% であり，有意な差は認められなかった。

4)　歯周組織状態 (図 8)

受診者全体における CPI スコアの分布は，スコア 0〜4 までそれぞれ 12.0%, 12.0%, 26.1%, 40.0%, 9.8% であったのに対し，全国値では 8.2%, 9.4%, 24.8%, 44.0%, 13.6% であり，スコア 0 の健常者が多く，スコア 3, 4 の歯周疾患の進行した者の割合が低い傾向がみられた。この傾向は，性別では男性に，年齢階層別では 70-74 歳，75-79 歳の低い階層に顕著に認められた。85 歳以上にその傾向はみられなかった。

考　　察

1.　調査対象

健診の対象となった鶴ヶ谷地区は，65 歳以上の高齢者の割合を示す高齢化率が 24.4% に達しており，全国平均の 19.0%[11] を大きく上回る超高齢化地域である。健診対象の 70

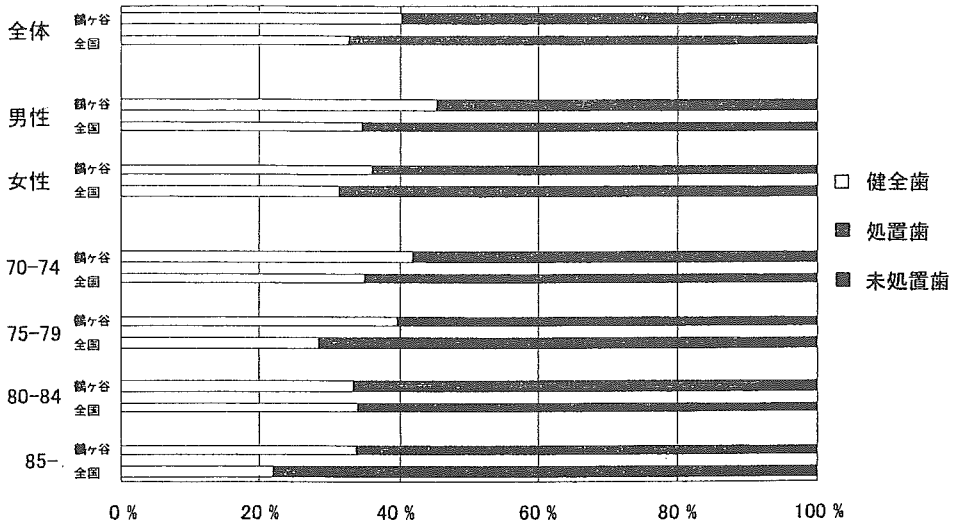

図6.　現在歯構成の比較

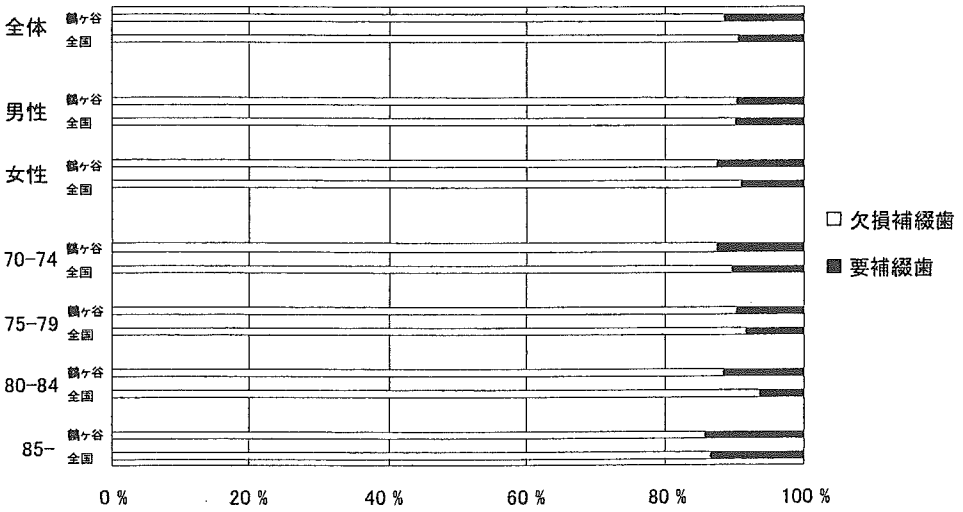

図7.　欠損補綴状況の比較

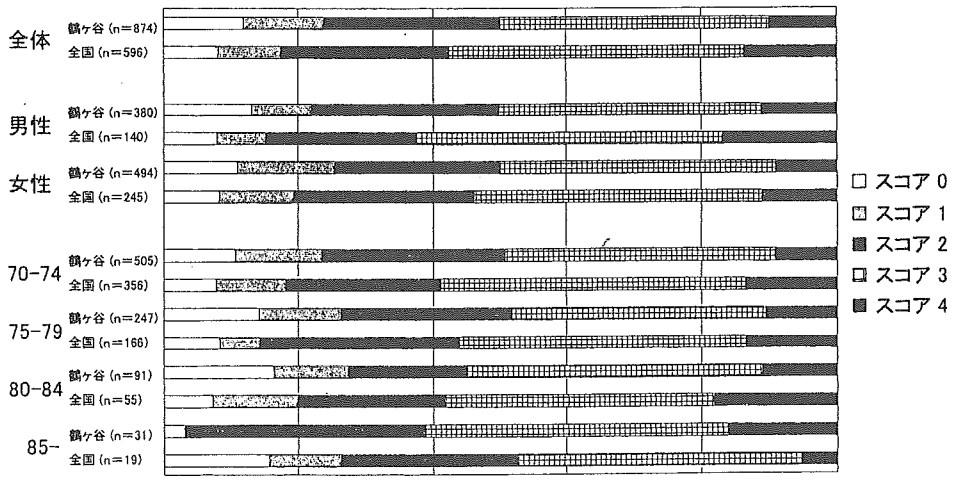

図8.　歯周組織状態の比較

歳以上高齢者に関しても，全国値の 13.3%[11] に対し 16.1% と高い。したがって，更なる高齢人口の増加が予測される将来のモデルとして，鶴ヶ谷地区が健診対象となった。健診受診率は 42.9% であった。性別，年齢階層別の受診率に偏りはなく，同地区の人口構成における性比，年齢階層比とほぼ一致した集団であった。この集団は健診に来ることのできる心身共に比較的健康な高齢者であり，悉皆的とは言えないものの，同地区の同年齢層における他の基本健康診査受診率が 20% 程度であるのに対し，その 2 倍以上の高い受診率であった。

2. 口腔状態

健診の結果，現在歯は女性より男性に多く，加齢に伴い減少していた。この傾向は全国調査も同様である。しかしながら一人平均の現在歯数は全体，性別，各年齢階層を通して全国値よりも多かった。さらに歯数別の分布から，無歯顎者の占める割合が低く多数歯保有者率が高いことが，全体として平均歯数を引き上げていることが明らかとなった。8020 達成者の比較からも，多数歯保有者率の高さがうかがわれた。現在歯の構成では，全国調査と比較して健全歯が多く未処置歯が少なかった。欠損補綴状況に全国調査との差は認められなかった。歯周組織の状態は全国調査と比べ，全体では軽症傾向であった。このことから，本健診受診者の現在歯が全国平均と比べ歯周病学的に良好な状態で存在していることが示唆された。

本健診でみられた鶴ヶ谷地区と全国調査における口腔状態の違いの要因として，鶴ヶ谷地区の地域性が考えられ，その一つとして住民の居住環境があげられる。同地区は 1960 年代に作られたニュータウンであり，立地も良いため，歯科医療に関する情報やサービスを比較的得られやすい。調査対象者の多くは，そうした環境下で壮年期を送っており，その生活史が現在の口腔状態に影響していると推察される。さらに，受診率が高かったことや低層アパートから一戸建て分譲住宅まで，ブロックごとに異なる居住形態が集まることなどから，住民の健康意識や社会経済的な背景因子にも特徴があると考えられ，健診結果に反映された可能性もある。一方で，本調査が集団検診方式であるのに対し，歯科疾患実態調査は訪問調査を含めた悉皆調査であることから，両者を一概に比較することへの問題点も残る。しかしながら，本研究での比較により少なくとも ADL の比較的高い高齢者の口腔状態は無作為抽出による全国平均よりも良好であることが明らかとなった。換言するならば，良好な口腔環境の保全が高い ADL 維持の要件の一つである可能性が浮き彫りとなったといえる。

いずれにせよ鶴ヶ谷地区のような都市部住宅地域は全国に数多く，今後同様の特徴を有する地域が増加することが予想される。

3. 今後の研究活動

健診の結果，口腔状態の中でも，とりわけ現在歯の状況に全国調査と異なる特徴を有することが明らかとなった。これまで，現在歯数が咀嚼能力を規定する最大要因であることが報告されており，高齢者の咀嚼機能を予測する一定の指標とされている[12-14]。また，多数の歯を失っている高齢者においては現在歯と欠損補綴歯を合わせた機能歯数を指標にする考え方もある[15,16]。

本研究では，口腔状態の診査のみならず眞木らの咀嚼能力指数スケール[17] による咀嚼能力の主観的評価やデンタルプレスケールを用いた咬合力測定などの機能評価，ならびに栄養調査や食行動に関するアンケート調査なども実施している。そこで，今後は本調査で得られた口腔状態と咀嚼機能との関連のみならず，栄養摂取状態や食の QOL など，多面的な影響について検索してゆく予定である。また同時に，他科との連携により口腔の諸評価項目と，骨粗鬆症，運動機能障害，抑うつ，認知機能障害などの老年症候群に関する評価指標との関連を明らかにすることも今後の課題である。

内容要旨：介護予防における効果的な歯科的介入を実現するにあたり，口腔状態,咀嚼機能および食に関する QOL の相互関係や，これらが高齢者の心身機能低下 (老年症候群) に及ぼす影響を明らかにすることは不可欠である。そこで都市部住宅地域 (仙台市宮城野区鶴ヶ谷地区) に在住する 70 歳以上高齢者を対象とした運動，うつ，認知機能等の総合機能評価事業において歯科健診を実施した。本研究では，この健診結果の一部から現在歯とその構成，欠損補綴状況および歯周組織の状態を分析し，その特徴を明らかにした。さらに，全国調査である平成 11 年度歯科疾患実態調査報告との比較検討を行った。その結果，当該地区在住高齢者では，全国調査に比べ一人平均現在歯数が有意に多かった (14.1 本対 10.4 本)。また，現在歯保有者の歯数別分布において，無歯顎者率が低く，多数の現在歯保有者の割合が高かった。20 歯以上保有者率および 8020 達成者率は全国を大きく上回った。一方，欠損補綴状況に全国調査との違いはみられなかった。歯周組織の状態は，比較的健全な者が多く，歯周疾患の進んだ者の割合が低かった。本研究の対象となった鶴ヶ谷地区はかつての新興住宅地で，現在は高齢化の進んだ都市部住宅地域である。そのような地域にける歯科医療環境，健康意識，経済状態などの要素が，在宅高齢者の口腔状態に影響している可能性が推察された。

文　献

1) 平成 15 年度　介護保険事業状況報告 (年報)，厚生労働省老健局介護保健課

2) Osterberg, T., Mellstrom, D. and Sundh, V.: Dental health and functional ageing. A study of 70-year-old people.

Community Dent Oral Epidemiol. 18(6): 313-8, 1990.
3) 寺岡加代，柴田　博，渡辺修一郎，熊谷　修：高齢者の咀嚼機能と身体状況との関連性について．老年誌 11: 169-173, 1997.
4) Shimazaki, Y., Soh, I., Saito, T., Yamashita, Y., Koga, T., Miyazaki, H. and Takehara, T.: Influence of dentition status on physical disability, mental impairment, and mortality in institutionalized elderly people. J Dent Res. 80: 340-5, 2001.
5) Nordenram, G., Ryd-Kjellen, E., Johansson, G., Nordstrom, G. and Winblad, B.: Alzheimer's disease, oral function and nutritional status. Gerodontology. 13: 9-16, 1996.
6) Taylor, G.W., Burt, B.A., Becker, M.P., Genco, R.J., Shlossman, M., Knowler, W.C. and Pettitt, D.J.: Severe periodontitis and risk for poor glycemic control in patients with non-insulin-dependent diabetes mellitus. J Periodontol. 67: 1085-1093, 1996.
7) Saito, T., Shimazaki, Y., Kiyohara, Y., Kato, I., Kubo, M., Iida, M. and Koga, T.: The severity of periodontal disease is associated with the development of glucose intolerance in non-diabetics: the Hisayama study. J Dent Res. 83: 485-90, 2004.
8) Joshipura, K.J., Hung, H.C., Rimm, E.B., Willett, W.C. and Ascherio, A.: Periodontal disease, tooth loss, and incidence of ischemic stroke. Stroke. 34: 47-52, 2003.
9) Desvarieux, M., Demmer, R.T., Rundek, T., Boden-Albala B., Jacobs, D.R., Jr., Sacco, R.L. and Papapanou, P.N.: Periodontal microbiota and carotid intima-media thickness: the Oral Infections and Vascular Disease Epidemiology Study (INVEST). Circulation. 111: 576-82, 2005.
10) 厚生労働省医政局歯科保健課編：平成11年度歯科疾患実態調査報告．口腔保健協会，東京，2001.
11) 総務省統計局：人口推計年報―平成15年10月1日現在推計人口―．日本統計協会，東京，2004.
12) 後藤真人，石井拓男，榊原悠紀田郎：成人歯科保健の指標としての「噛めかた」の検討　第2報　年齢別喪失歯数別検討．口衛誌 37: 444-445, 1987.
13) Leak, J.L.: An index of chewing ability. J Public Health Dent. 50: 262-267, 1988.
14) 石上和男，佐々木健，永瀬吉彦，矢野正敏，渡辺雄三，小林秀雄，安藤雄一，小林清吾，堀井欣一：喪失歯数と咀嚼能力の関連について．口衛誌 39: 424-425, 1989.
15) 渡辺郁馬：老年者の摂食・咀嚼状態．歯界展望 91: 299-308, 1998.
16) 平野浩彦，渡辺　裕，石山直欣，渡辺郁馬，鈴木隆雄，那須郁夫：老年者咀嚼能力に影響する因子の解析．老年歯学 9: 184-189, 1995.
17) 眞木吉信，杉原直樹，高江洲義矩．面接調査に基づく老年者の咀嚼能力指数スケールの開発と評価．老年歯学 9: 3, 1995.

Green tea consumption and cognitive function: a cross-sectional study from the Tsurugaya Project[1–3]

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ABSTRACT

Background: Although considerable experimental and animal evidence shows that green tea may possess potent activities of neuroprotection, neurorescue, and amyloid precursor protein processing that may lead to cognitive enhancement, no human data are available.

Objective: The objective was to examine the association between green tea consumption and cognitive function in humans.

Design: We analyzed cross-sectional data from a community-based Comprehensive Geriatric Assessment (CGA) conducted in 2002. The subjects were 1003 Japanese subjects aged ≥70 y. They completed a self-administered questionnaire that included questions about the frequency of green tea consumption. We evaluated cognitive function by using the Mini-Mental State Examination with cutoffs of <28, <26, and <24 and calculated multivariate-adjusted odds ratios (ORs) of cognitive impairment.

Results: Higher consumption of green tea was associated with a lower prevalence of cognitive impairment. At the <26 cutoff, after adjustment for potential confounders, the ORs for the cognitive impairment associated with different frequencies of green tea consumption were 1.00 (reference) for ≤3 cups/wk, 0.62 (95% CI: 0.33, 1.19) for 4–6 cups/wk or 1 cup/d, and 0.46 (95% CI: 0.30, 0.72) for ≥2 cups/d (*P* for trend = 0.0006). Corresponding ORs were 1.00 (reference), 0.60 (95% CI: 0.35, 1.02), and 0.87 (95% CI: 0.55, 1.38) (*P* for trend = 0.33) for black or oolong tea and 1.00 (reference), 1.16 (95% CI: 0.78, 1.73), and 1.03 (95% CI: 0.59, 1.80) (*P* for trend = 0.70) for coffee. The results were essentially the same at cutoffs of <28 and <24.

Conclusion: A higher consumption of green tea is associated with a lower prevalence of cognitive impairment in humans. *Am J Clin Nutr* 2006;83:355–61.

KEY WORDS Cognitive function, elderly, green tea, Japanese, Mini-Mental State Examination

INTRODUCTION

Dementia is a rapidly growing public health concern as a result of aging of the population (1, 2). In developed countries, dementia has a reported prevalence of ≈1.5% at age 65 y, doubling every 4 y to reach ≈30% at age 80 y (1). Environmental factors associated with the risk of Alzheimer disease (AD), a common cause of dementia, remain largely undefined, although several risk factors for vascular dementia have been identified (1, 3–6).

Experimental and animal studies have shown that tea and tea polyphenols (which include catechins and their derivatives), particularly those from green tea, may possess potent neuroprotective activity that can help to ameliorate neurodegenerative diseases such as AD and Parkinson disease (PD) (7). Green tea catechins, especially (−)-epigallocatechin-3-gallate (EGCG), formerly thought to be simple radical scavengers, are now considered to invoke a spectrum of cellular mechanisms related to neuroprotective as well as neurorescue activities (8–10). One of these mechanisms includes protective effects against β-amyloid (Aβ)–induced neurotoxicity by enhancing the release of the nonamyloidogenic soluble form of amyloid precursor protein (APP) (8). Aβ protein is formed by proteolytic cleavage of APP (11) and is the main constituent of the neuritic plaques that are the physiologic hallmark of AD (12). In addition, EGCG was shown to have neuroprotective activity in a mice model of PD (13), and an epidemiologic study indicated that the risk of PD was reduced if tea consumption was ≥2 cups/d (14). Despite this considerable evidence that tea, especially green tea, can protect against neurodegenerative diseases, to our knowledge, no data are available on any association between green tea intake and dementia or cognitive impairment in humans.

We therefore designed this cross-sectional analysis to investigate the association between consumption of green tea and cognitive function in elderly Japanese subjects, among whom green tea was widely consumed. We considered it important to search for modifiable factors underlying cognitive impairment

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because early detection and management of cognitive decline contribute to the prevention of dementia rather than to treatment (15, 16).

SUBJECTS AND METHODS

Study population

The Tsurugaya Project was a community-based Comprehensive Geriatric Assessment (CGA) conducted among elderly Japanese subjects living in Tsurugaya district, a suburban area of Sendai City in northern Japan, between July and October 2002 (17, 18). CGA is a structured approach to measuring the physical, mental, and social functioning of elderly people to assess early deterioration that may result in the need for long-term care and to promote healthy aging (19, 20).

At the time of the study, 2730 people aged ≥70 y were living in the Tsurugaya district. We sent letters to all of these people and invited them to participate in the health survey. Of those invited, 1198 participated in the survey and 1178 (43.2%) gave written informed consent to be included in the analysis. The study protocol was approved by the institutional review board of Tohoku University Graduate School of Medicine.

Data about consumption of green tea, black or oolong tea, and coffee and cognitive function were obtained from 1151 of the subjects who gave written informed consent. We excluded 148 subjects with missing data on body weight, height, blood glucose concentrations, blood pressure values, or depressive symptoms (described in Measurements). Thus, data from 1003 subjects contributed to the final analyses.

Measurements

The questionnaire in the CGA included items about the frequency of recent consumption of 5 beverages (green tea, black or oolong tea, coffee, cola or juice, 100% fresh vegetable juice) and 55 items about food intake during the previous month. The frequency of consumption of green tea was divided into 8 categories: never, <1 cup (0.1 L)/wk, 1 cup/wk, 2–3 cups/wk, 4–6 cups/wk, 1 cup/d, 2–3 cups/d, and ≥4 cups/d. In the study region, the volume of a typical cup of green tea is 100 mL. We grouped the subjects into 3 categories according to their beverage consumption: ≤3cups/wk, 4–6 cups/wk or 1 cup/d, and ≥2 cups/d.

The questionnaire in the CGA also included *1*) demographic characteristics (age, sex, and duration of education); *2*) social factors (visiting friends); *3*) lifestyle habits (smoking, alcohol use, and physical activity); and *4*) physical health [history of chronic medical conditions such as stroke or myocardial infarction, regular intake of supplements and medication, and self-rated health (excellent, good, normal, poor, or very poor)].

Cognitive function was tested by using the Japanese language version of the 30-point Mini-Mental State Examination (MMSE) (21). The test was administered by specially trained research assistants. The MMSE includes questions on orientation to time and place, registration, attention and calculation, recall, language, and visual construction. This screening test was originally created for a clinical setting (21) and is used extensively in epidemiologic studies (22). Higher MMSE scores indicate higher cognitive function, and the maximum score is 30 points. The analyses were conducted by using 3 cutoff points to define different levels of cognitive impairment. The initial cutoff point was <26, because a score of <26 points on the MMSE generally indicates cognitive impairment (23). The second was <28, which we regarded as slight cognitive impairment, and the third was <24, which we regarded as relatively severe cognitive impairment. In the initial analyses, the group with cutoff points of <26 included subjects with cutoff points of <24, and the group with cutoff points of <28 included subjects with cutoff points of <26 and <24. In further analyses, we reanalyzed the data by using cutoff points of <26 or <28 after excluding subjects with a MMSE score of <24.

Data were obtained about *1*) body mass index (BMI; in kg/m^2; as calculated from participants' measured weight and height); *2*) the presence or absence of diabetes mellitus, defined as a nonfasting blood glucose concentration ≥ 140 mg/dL or a history of diabetes mellitus; *3*) the presence or absence of hypertension, defined as a self-measured systolic blood pressure ≥ 135 mm Hg (measured at home) or a history of hypertension; *4*) the presence or absence of depressive symptoms, as assessed by using the Japanese version of the 30-item Geriatric Depression Scale (24); and *5*) physical functioning status, assessed by using the 6-item physical functioning status measure of the Medical Outcomes Study (MOS) Short-form General Health Survey (lower MOS scores indicate lower physical functioning status) (25).

Statistical analysis

The subjects' characteristics according to categories of green tea consumption were compared by using analysis of variance or chi-squared test, as appropriate. We used multivariate logistic regression analysis to calculate odds ratios (ORs) for cognitive impairment relative to the consumption frequencies of green tea or other beverages, with the lowest frequency category (≤3 cups/wk) treated as the reference group. Trend tests were performed by including the ordinal variable in a linear regression analysis. In these analyses, we regarded the following data as covariates: age (continuous variable); sex; consumption of green tea (≤3 cups/wk, 4–6 cups/wk or 1 cup/d, ≥2 cups/d; when calculating the ORs for consumption of black or oolong tea or coffee); consumption of black or oolong tea (≤3 cups/wk, 4–6 cups/wk or 1 cup/d, ≥2 cups/d; when calculating the ORs for consumption of green tea or for coffee); consumption of coffee (≤3 cups/wk, 4–6 cups/wk or 1 cup/d, ≥2 cups/d; when calculating the ORs for the consumption of green tea or black or oolong tea); BMI (<18.5, 18.5–24.9, 25.0–29.9, ≥30.0); diabetes mellitus (presence or absence); hypertension (presence or absence); history of stroke (presence or absence); history of myocardial infarction (presence or absence); depressive symptoms (Geriatric Depression Scale scores of <11 or ≥11); duration of education (≤12 y or >12 y); living with a spouse (yes or no); self-rated health (excellent or good or other); visiting friends (yes or no); physical functioning status (MOS scores of 0–1, 2–4, or 5–6); energy intake (continuous variable); intake of nondietary vitamin C or E including supplement vitamin C, supplement vitamin E, prescribed vitamin C, and prescribed vitamin E (yes or no); consumption of fish (<1 time/wk, 1–6 times/wk, or ≥1 time/d); consumption of green or yellow vegetables (<1 time/wk, 1–6 times/wk, or ≥1 time/d); mild leisure-time physical activity such as walking (yes or no); vigorous leisure-time physical activity such as tennis or jogging (yes or no); smoking (never, former, currently smoking <20 cigarettes/d, and currently smoking ≥20 cigarettes/d); and use of alcohol (never, former, and currently drinking).

Interactions between consumption of green tea and all confounders were tested through the addition of cross-product terms

TABLE 1
Characteristics of the study subjects according to categories of green tea consumption[1]

Characteristics	Green tea consumption			P^2
	≤3 cups/wk (n = 170)	4–6 cups/wk or 1 cup/d (n = 108)	≥2 cups/d (n = 725)	
Women (%)	51.2	47.2	60.0	0.01
Age (y)[3]	74.2 ± 4.4	74.6 ± 4.3	74.8 ± 4.7	0.23
Mini-Mental State Examination score				
$\bar{x}$ ± SD	26.7 ± 3.3	27.3 ± 2.6	27.6 ± 2.5	0.0006
<28 (%)	48.8	44.4	39.2	0.06
<26 (%)	25.3	17.6	14.3	0.002
<24 (%)	11.2	8.3	6.3	0.09
Black or oolong tea consumption (%)				
≥2 cups/d	32.4	14.8	19.3	
4–6 cups/wk or 1 cup/d	11.8	31.5	17.4	<0.0001
Coffee consumption (%)				
≥2 cups/d	21.2	18.5	10.5	
4–6 cups/wk or 1 cup/d	27.1	37.0	31.3	0.0004
BMI (%)[4]				
<18.5 kg/m^2	6.5	3.7	4.7	
25.0–29.9 kg/m^2	29.4	32.4	30.5	
≥30.0 kg/m^2	4.1	3.7	4.1	0.96
Diabetes mellitus (%)[5]	22.4	26.9	22.1	0.54
Hypertension (%)[6]	69.4	67.6	68.1	0.94
History of stroke (%)	8.8	9.3	4.0	0.007
History of myocardial infarction (%)	12.4	17.6	10.1	0.06
Depressive symptoms (%)[7]	41.8	34.3	30.8	0.02
Duration of education ≤12 y (%)	30.0	31.5	30.5	0.97
Living with a spouse (%)	63.5	71.3	61.9	0.17
Self-rated health excellent or good (%)	57.6	63.8	67.3	0.06
Visiting friends (%)[8]	66.1	73.3	77.5	0.008
Physical functioning status (%)[9]				
Capable of moderate but not vigorous activity	27.1	20.4	25.7	
Only capable of low physical activity	15.3	12.0	8.7	0.06
Energy intake (kcal/d)[3]	1528.4 ± 417.8	1626.8 ± 389.4	1619.5 ± 391.8	0.02
Intake of nondietary antioxidants (%)[10]	11.8	11.1	16.0	0.20
Fish consumption (%)				
≥1 time/d	3.0	2.8	2.2	
1–6 times/wk	75.2	75.7	75.8	0.98
Green or yellow vegetable consumption (%)				
≥1 time/d	29.2	26.9	41.4	
1–6 times/wk	63.7	71.3	57.5	<0.0001
Mild leisure-time physical activity ≥1 time/wk (%)[11]	51.7	52.9	57.7	0.38
Vigorous leisure-time physical activity ≥1 time/wk (%)[12]	4.8	7.8	8.5	0.32
Smoking (%)				
Never	42.9	49.1	60.6	
1–19 cigarettes/d	11.9	11.3	8.6	
≥20 cigarettes/d	6.0	2.8	2.8	0.001
Alcohol use (%)				
Never	45.1	34.7	47.1	
Current	38.9	50.5	41.5	0.10

[1] 1 cup = 0.1 L.
[2] Determined by ANOVA or chi-square test.
[3] All values are $\bar{x}$ ± SD.
[4] Calculated from participants' measured weight and height.
[5] Defined as a nonfasting blood glucose concentration of ≥140 mg/dL or a history of diabetes mellitus.
[6] Defined as a self-measured systolic blood pressure of ≥135 mm Hg (measured at home) or a history of hypertension.
[7] Measured based on the Japanese version of the 30-item Geriatric Depression Scale, with a cutoff point of ≥11.
[8] Answer to the question, "Do you visit your friends?"
[9] Assessed by using the 6-item physical functioning status measure of the Medical Outcomes Study Short-form General Health Survey.
[10] Nondietary antioxidants included supplemental vitamin C, supplemental vitamin E, prescribed vitamin C, and prescribed vitamin E.
[11] For example, walking.
[12] For example, tennis and jogging.

TABLE 2
Odds ratios (ORs) and 95% CIs from logistic regression models for the association between consumption of green tea and cognitive impairment[1]

Logistic regression models	Green tea consumption			*P* for trend[2]
	≤3 cups/wk	4–6 cups/wk or 1 cup/d	≥2 cups/d	
Cognitive impairment, defined as MMSE score <28				
Model 1[3]	1.00 (reference)	0.84 (0.52, 1.36)	0.68 (0.48, 0.94)	0.02
Model 2[4]	1.00 (reference)	0.82 (0.50, 1.34)	0.61 (0.44, 0.87)	0.004
Model 3[5]	1.00 (reference)	0.83 (0.50, 1.38)	0.62 (0.43, 0.88)	0.005
Model 4[6]	1.00 (reference)	0.86 (0.52, 1.43)	0.69 (0.48, 0.98)	0.03
Model 5[7]	1.00 (reference)	0.85 (0.51, 1.40)	0.62 (0.43, 0.89)	0.005
Cognitive impairment, defined as MMSE score <26				
Model 1[3]	1.00 (reference)	0.63 (0.35, 1.15)	0.50 (0.33, 0.74)	0.0007
Model 2[4]	1.00 (reference)	0.61 (0.33, 1.13)	0.43 (0.29, 0.66)	< 0.0001
Model 3[5]	1.00 (reference)	0.64 (0.34, 1.21)	0.43 (0.28, 0.67)	0.0001
Model 4[6]	1.00 (reference)	0.63 (0.33, 1.19)	0.51 (0.33, 0.78)	0.003
Model 5[7]	1.00 (reference)	0.66 (0.35, 1.27)	0.47 (0.30, 0.74)	0.0008
Cognitive impairment, defined as MMSE score <24				
Model 1[3]	1.00 (reference)	0.72 (0.31, 1.66)	0.54 (0.31, 0.95)	0.03
Model 2[4]	1.00 (reference)	0.69 (0.30, 1.62)	0.47 (0.26, 0.83)	0.008
Model 3[5]	1.00 (reference)	0.82 (0.35, 1.96)	0.48 (0.27, 0.88)	0.01
Model 4[6]	1.00 (reference)	0.69 (0.29, 1.64)	0.55 (0.30, 1.00)	0.05
Model 5[7]	1.00 (reference)	0.77 (0.32, 1.89)	0.48 (0.25, 0.89)	0.02

[1] Multivariate logistic regression analysis was used to calculate ORs and 95% CIs for cognitive impairment relative to the consumption frequencies of green tea, with the lowest frequency category (≤3 cups/wk) treated as the reference group. Cognitive function was tested by using the Japanese language version of the 30-point Mini-Mental State Examination. 1 cup = 0.1 L.

[2] Trend tests were performed by including the ordinal variable in a linear regression analysis.

[3] Crude model.

[4] Adjusted for age and sex.

[5] Adjusted for model 2 + black or oolong tea consumption, coffee consumption, BMI, diabetes mellitus, hypertension, history of stroke, and history of myocardial infarction.

[6] Adjusted for model 2 + depressive symptoms, duration of education, living with a spouse, self-rated health, visiting friends, and physical functioning status.

[7] Adjusted for model 2 + energy intake, intake of nondietary vitamin C or E, fish consumption, green or yellow vegetable consumption, mild leisure-time physical activity, vigorous leisure-time physical activity, smoking, and alcohol use.

to the regression model. All statistical analyses were performed with the use of SAS software, version 9.1 (26). All the statistical tests that we report were two-sided. A P value of < 0.05 was accepted as statistically significant.

RESULTS

The subjects' characteristics according to categories of green tea consumption are shown in **Table 1**. Of the subjects, 16.9% consumed ≤3 cups green tea/wk, 10.8% consumed 4–6 cups/wk or 1 cup/d, and 72.3% consumed ≥2cups/d. The mean ± SD overall MMSE score was 27.4 ± 2.7. The prevalence of cognitive impairment decreased with increasing consumption of green tea for every cutoff point (P for the cutoff points of <28, <26, <24 = 0.06, 0.002, 0.09, respectively). Subjects who consumed ≥2 cups green tea/d were more likely to be women, have better self-rated health ($P = 0.06$), visit friends, have more total energy intake, consume green or yellow vegetables, never have smoked, and never have used alcohol ($P = 0.10$). They were less likely to consume black or oolong tea or coffee, have a history of stroke or myocardial infarction ($P = 0.06$), have depressive symptoms, and have limited physical functioning status ($P = 0.06$). No apparent associations were observed among mean age, BMI, presence or absence of diabetes mellitus or hypertension, duration of education, living with a spouse, intake of nondietary antioxidants, consumption of fish, or mild and vigorous leisure-time activities and frequency of green tea consumption.

Statistically significant inverse associations were observed between green tea consumption and cognitive impairment (**Table 2**). With the use of the <26 MMSE score cutoff point, the crude ORs of cognitive impairment associated with the different frequencies of green tea consumption were 1.00 (reference) for ≤3 cups/wk, 0.63 (95% CI: 0.35, 1.15) for 4–6 cups/wk or 1 cup/d, and 0.50 (95% CI: 0.33, 0.74) for ≥2 cups/d. We included a variety of potential confounders in our multivariate logistic models; however, the results did not change substantially even after adjustment for these variables. The results for MMSE score cutoff points of <28 and <24 were essentially the same as those for the <26 cutoff point.

In the final model used to investigate the association between different frequencies of green tea consumption and cognitive impairment, we chose the following data as covariates according to their relative contribution to the model outlined in Table 2 and their clinical importance: age, sex, consumption of green tea (when calculating ORs for consumption of black or oolong tea or coffee), consumption of black or oolong tea (when calculating ORs for consumption of green tea or coffee), consumption of coffee (when calculating ORs for consumption of green tea or black or oolong tea), presence or absence of diabetes mellitus,

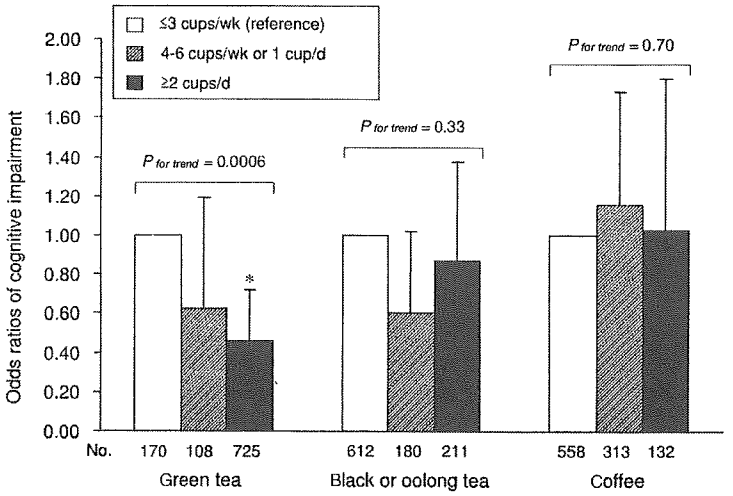

FIGURE 1. Odds ratios (ORs) for the association between different frequencies of beverage consumption and cognitive impairment. The bars indicate adjusted ORs for the association between different beverage consumption frequencies and cognitive impairment, respectively; error bars represent the corresponding 95% CIs. Multivariate logistic regression analysis was used to calculate ORs for cognitive impairment relative to the consumption frequencies of green tea or other beverages, with the lowest frequency category (≤3 cups/wk) treated as the reference group. Trend tests were performed by including the ordinal variable in a linear regression analysis. The ORs and 95% CIs for the ORs were adjusted for age, sex, green tea consumption (when calculating ORs for black or oolong tea or coffee consumption), black or oolong tea consumption (when calculating ORs for green tea or coffee consumption), coffee consumption (when calculating ORs for green tea or black or oolong tea consumption), presence or absence of diabetes mellitus, presence or absence of hypertension, history of stroke, depressive symptoms, duration of education, visiting friends, energy intake, intake of nondietary vitamin C or E, and fish consumption. Cognitive impairment was defined as a Mini-Mental State Examination score <26. $^{*}P < 0.001$. 1 cup = 0.1 L.

presence or absence of hypertension, history of stroke, depressive symptoms, duration of education, visiting friends, energy intake, intake of nondietary vitamin C or E, and consumption of fish. The ORs (95% CIs) in the final model (using a cutoff point of <26) and corresponding ORs (95% CIs) for consumption of black or oolong tea or coffee are shown in **Figure 1**. The multivariate ORs according to frequencies of green tea consumption were 1.00 (reference) for ≤3 cups/wk, 0.62 (95% CI: 0.33, 1.19) for 4–6 cups/wk or 1 cup/d, and 0.46 (95% CI: 0.30, 0.72) for ≥2 cups/d. In contrast, a weak or null association was observed between intake of black or oolong tea or coffee and the prevalence of cognitive impairment. The ORs for black or oolong tea were 1.00 (reference), 0.60 (95% CI: 0.35, 1.02), and 0.87 (95% CI: 0.55, 1.38), whereas those for coffee were 1.00 (reference), 1.16 (95% CI: 0.78, 1.73), and 1.03 (95% CI: 0.59, 1.80). When cutoff points of <28 or <24 were used, the results for the final model were similar to those for the <26 cutoff point (data not shown). We were unable to examine the associations between cola or juice and 100% fresh vegetable juice and cognitive impairment because an insufficient number of subjects consumed these beverages. Tests for interaction between consumption of green tea and all confounders in the final models were not statistically significant.

We repeated the analysis after expanding the highest category of green tea consumption in the final model. With a cutoff point of <26, the ORs for the different frequencies of green tea consumption were 1.00 (reference) for ≤3 cups/wk, 0.62 (95% CI: 0.33, 1.19) for 4–6 cups/wk or 1 cup/d, 0.42 (95% CI: 0.25, 0.71) for 2–3 cups/d (n = 258), and 0.49 (95% CI: 0.30, 0.79) for ≥4 cups/d (n = 467) (P for trend = 0.004). With a cutoff point of <28, the corresponding ORs were 1.00 (reference), 0.80 (95% CI: 0.48, 1.34), 0.59 (95% CI: 0.39, 0.90), and 0.67 (95% CI: 0.45, 0.98) (P for trend = 0.04). With a cutoff point of <24, the corresponding ORs were 1.00 (reference), 0.77 (95% CI: 0.32, 1.86), 0.54 (95% CI: 0.26, 1.10), and 0.50 (95% CI: 0.26, 0.98) (P for trend = 0.04).

We also repeated the analysis for the final model after excluding subjects with relatively severe cognitive impairment (MMSE score < 24; n = 74). The results did not change substantially. With a cutoff point of <26, the ORs for the different frequencies of green tea consumption were 1.00 (reference) for ≤ 3cups/wk, 0.55 (95% CI: 0.24, 1.27) for 4–6 cups/wk or 1 cup/d, and 0.44 (95% CI: 0.25, 0.78) for ≥2 cups/d (P for trend = 0.006). With a cutoff point of <28, the corresponding ORs were 1.00 (reference), 0.82 (95% CI: 0.47, 1.41), and 0.68 (95% CI: 0.46, 1.00) (P for trend = 0.05).

DISCUSSION

Our study showed inverse dose-response relations between consumption of green tea and the prevalence of cognitive impairment. In contrast, a weak or null relation between consumption of black or oolong tea or coffee and cognitive impairment was observed. To our knowledge, this is the first study to examine the association between consumption of green tea and cognitive function in humans.

Our study had several methodologic strengths. We recruited subjects from the general population, and a substantial variation was observed in the consumption of green tea among our subjects. We conducted a CGA that allowed us to carefully consider cardiovascular risk factors, which were causes of vascular dementia. Our study had a reasonably large sample size, which gave us the opportunity to test the association between consumption of green tea and various grades of cognitive impairment (from slight to relatively severe).

Several methodologic limitations should be considered in the interpretation of our results. First, our study had a cross-sectional

design; therefore, no temporal relation between consumption of green tea and cognitive function can be inferred.

Second, our observational study design does not allow us to fully exclude the possibility of residual confounding by unmeasured factors. For example, healthier and more active individuals might have more opportunities to consume green tea. Among the Japanese, green tea is often consumed as a social activity, and this in itself may contribute to maintaining higher cognitive function (27). However, we controlled for many potential confounders, and the findings were robust to adjustments for these confounders.

Finally, because functional impairments of daily living were not fully assessed here, we cannot diagnose the presence or absence of dementia or the subtype of dementia syndromes, but we did evaluate cognitive impairment by using MMSE scores. However, cognitive decline is generally regarded as a core symptom of dementia. Furthermore, reduced cognition may be a key predictor of the development of dementia and may be considered a preclinical marker of the early stages of dementia (15, 16). Therefore, we believe that our data provide a useful clue to effective preventive interventions for dementia.

Green tea polyphenols, especially EGCG, might explain the observed association with improved cognitive function (7–10). Green tea is much richer in catechins than other beverages; Khokhar et al (28) reported that green tea contains 67.5 mg catechins/100 mL, whereas black tea contains only 15.5 mg/100 mL. The weak or null relations observed between consumption of black or oolong tea or coffee and cognitive impairment might reflect the important neuroprotective effects of catechins described in numerous experimental and animal studies (7–10). EGCG is brain permeable (29–31), and its neuroprotective and neurorescue effects were explained in terms of various mechanisms in addition to its well-established antioxidant and iron-chelating properties (7). These properties include modulation of cell survival and cell cycle genes (9) and promotion of neurite outgrowth activity (10). Furthermore, Levites et al (8) have shown that EGCG exerts neuroprotective and neurorescue effects against Aβ toxicity by regulating the secretory processing of nonamyloidogenic APP through the protein kinase C pathway. In addition to the above-mentioned experimental and animal evidence, recent epidemiologic studies have suggested that red wine, which is also rich in polyphenols, may be associated with reduced risk of dementia (32, 33).

In addition to polyphenols, green tea contains vitamin C, caffeine, and other nutrients (34). Intake of vitamin C accompanied by high consumption of green tea might contribute to the observed association (3–6). Green tea contains 6 mg vitamin C/100 mL (10 g tea leaf/430 mL water, 90 °C, 1 min) (34) and is, in fact, the most common source of vitamin C (13.6%) among the population in our study region (35). Therefore, we cannot exclude a possible effect of vitamin C in the green tea on cognitive function. However, our results were not substantially changed even after adjustment for intake of nondietary vitamin C or E, indicating that the effects of vitamin C may be small. The contribution of caffeine to higher cognitive function also appears to be small because of the null relation observed between consumption of coffee and cognitive impairment. Green tea contains 0.02 g caffeine/100 mL (10 g tea leaf/430 mL water, 90 °C, 1 min), whereas coffee contains 0.06 g caffeine/100 mL (10 g coffee powder/150 mL water, 100 °C) (34). Nutrients in green tea other than polyphenols, vitamin C, and caffeine remain to be studied.

In conclusion, the present results suggest that higher consumption of green tea is associated with lower prevalence of cognitive impairment in humans. The results might partly explain the relatively lower prevalence of dementia, especially AD, in Japan than in Europe and North America (1). Given the high prevalence, worldwide rapid increase, and clinical significance of dementia (1, 2), any association between the intake of green tea, a drink with little toxicity and no calorific value, and cognitive function could have considerable clinical and public health relevance. The results of this cross-sectional study generate a new hypothesis and warrant further investigation.

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SK, AH, KO, and TS participated in the study design, data acquisition, data analysis, data interpretation, preparation of the written report, and final review of the report. TM, SE, SA, RN, HA, and IT participated in the study design, data acquisition, data interpretation, and final review of the report. None of the authors had any conflict of interest.

REFERENCES

1. Ritchie K, Lovestone S. The dementias. Lancet 2002;360:1759–66.
2. Essink-Bot ML, Pereira J, Packer C, Schwarzinger M, Burstrom K. Cross-national comparability of burden of disease estimates: the Eur Disability Weights Project. Bull World Health Organ 2002;80:644–52.
3. Nourhashemi F, Gillette-Guyonnet S, Andrieu S, et al. Alzheimer disease: protective factors. Am J Clin Nutr 2000;71(suppl):S643–9.
4. Luchsinger JA, Mayeux R. Dietary factors and Alzheimer's disease. Lancet Neurol 2004;3:579–87.
5. Cummings JL. Alzheimer's disease. N Engl J Med 2004;351:56–67.
6. Haan MN, Wallace R. Can dementia be prevented? Brain aging in a population-based context. Annu Rev Public Health 2004;25:1–24.
7. Mandel S, Youdim MB. Catechin polyphenols: neurodegeneration and neuroprotection in neurodegenerative diseases. Free Radic Biol Med 2004;37:304–17.
8. Levites Y, Amit T, Mandel S, Youdim MB. Neuroprotection and neurorescue against Abeta toxicity and PKC-dependent release of nonamyloidogenic soluble precursor protein by green tea polyphenol (−)-epigallocatechin-3-gallate. FASEB J 2003;17:952–4.
9. Levites Y, Amit T, Youdim MB, Mandel S. Involvement of protein kinase C activation and cell survival/cell cycle genes in green tea polyphenol (−)-epigallocatechin 3-gallate neuroprotective action. J Biol Chem 2002;277:30574–80.
10. Reznichenko L, Amit T, Youdim MB, Mandel S. Green tea polyphenol (−)-epigallocatechin-3-gallate induces neurorescue of long-term serum-deprived PC12 cells and promotes neurite outgrowth. J Neurochem 2005;93:1157–67.
11. Kang J, Lemaire HG, Unterbeck A, et al. The precursor of Alzheimer's disease amyloid A4 protein resembles a cell-surface receptor. Nature 1987;325:733–6.
12. Selkoe DJ. Cell biology of the amyloid beta-protein precursor and the mechanism of Alzheimer's disease. Annu Rev Cell Biol 1994;10:373–403.
13. Levites Y, Weinreb O, Maor G, Youdim MB, Mandel S. Green tea polyphenol (−)-epigallocatechin-3-gallate prevents *N*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced dopaminergic neurodegeneration. J Neurochem 2001;78:1073–82.
14. Checkoway H, Powers K, Smith-Weller T, Franklin GM, Longstreth WT Jr, Swanson PD. Parkinson's disease risks associated with cigarette smoking, alcohol consumption, and caffeine intake. Am J Epidemiol 2002;155:732–8.
15. Linn RT, Wolf PA, Bachman DL, et al. The 'preclinical phase' of probable Alzheimer's disease. A 13-year prospective study of the Framingham cohort. Arch Neurol 1995;52:485–90.
16. Small BJ, Fratiglioni L, Viitanen M, Winblad B, Backman L. The course of cognitive impairment in preclinical Alzheimer disease: three- and 6-year follow-up of a population-based sample. Arch Neurol 2000;57:839–44.
17. Hozawa A, Ebihara S, Ohmori K, et al. Increased plasma 8-isoprostane levels in hypertensive subjects: the Tsurugaya Project. Hypertens Res 2004;27:557–61.

18. Ohmori K, Ebihara S, Kuriyama S, et al. The relationship between body mass index and a plasma lipid peroxidation biomarker in an older, healthy Asian community. Ann Epidemiol 2005;15:80–4.
19. Rubenstein LZ, Josephson KR, Wieland GD, English PA, Sayre JA, Kane RL. Effectiveness of a geriatric evaluation unit. A randomized clinical trial. N Engl J Med 1984;311:1664–70.
20. Stuck AE, Aronow HU, Steiner A, et al. A trial of annual in-home comprehensive geriatric assessments for elderly people living in the community. N Engl J Med 1995;333:1184–9.
21. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–98.
22. Launer LJ. Overview of incidence studies of dementia conducted in Europe. Neuroepidemiology 1992;11(suppl 1):S2–13.
23. Siu AL. Screening for dementia and investigating its causes. Ann Intern Med 1991;115:122–32.
24. Brink TL, Yesavage JA, Lum O, Heersema PH, Adey M, Rose TL. Screening tests for geriatric depression. Clin Gerontol 1982;1:37–44.
25. Stewart AL, Hays RD, Ware JE. The MOS Short-form General Health Survey. Reliability and validity in a patient population. Med Care 1988; 26:724–35.
26. SAS Institute Inc. SAS/STAT User's Guide, release 9.1 edition. Cary, NC: SAS Institute Inc, 2004.
27. Fratiglioni L, Paillard-Borg S, Winblad B. An active and socially integrated lifestyle in late life might protect against dementia. Lancet Neurol 2004;3:343–53.
28. Khokhar S, Magnusdottir SG. Total phenol, catechin, and caffeine contents of teas commonly consumed in the United Kingdom. J Agric Food Chem 2002;50:565–70.
29. Nakagawa K, Miyazawa T. Absorption and distribution of tea catechin, (−)-epigallocatechin-3-gallate, in the rat. J Nutr Sci Vitaminol (Tokyo) 1997;43:679–84.
30. Suganuma M, Okabe S, Oniyama M, Tada Y, Ito H, Fujiki H. Wide distribution of [^{3}H](−)-epigallocatechin gallate, a cancer preventive tea polyphenol, in mouse tissue. Carcinogenesis 1998;19:1771–6.
31. Abd El Mohsen MM, Kuhnle G, Rechner AR, et al. Uptake and metabolism of epicatechin and its access to the brain after oral ingestion. Free Radic Biol Med 2002;33:1693–702.
32. Letenneur L. Risk of dementia and alcohol and wine consumption: a review of recent results. Biol Res 2004;37:189–93.
33. Luchsinger JA, Tang MX, Siddiqui M, Shea S, Mayeux R. Alcohol intake and risk of dementia. J Am Geriatr Soc 2004;52:540–6.
34. Science and Technology Agency of Japan: Standard Tables of Food Composition in Japan. 5th revised ed. Tokyo, Japan: Printing Bureau, Ministry of Finance, 2001 (in Japanese).
35. Ogawa K, Tsubono Y, Nishino Y, et al. Dietary sources of nutrient consumption in a rural Japanese population. J Epidemiol 2002;12:1–8.

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Short communication

Blood type B might imply longevity

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Abstract

The aim of the present study was to investigate the association between blood groups and life expectancy. We compared frequencies of ABO blood group in 269 centenarians (persons over 100 years) living in Tokyo and those in regionally matched controls ($n=7153$). Frequencies of blood types A, O, B, and AB in centenarians were 34.2, 28.3, 29.4, and 8.2%, respectively, while those in controls were 38.6, 30.1, 21.9, and 9.4%, respectively. Blood type B was observed more frequently in centenarians than in controls ($\chi^2=8.41$, $P=0.04$). This tendency also was true in comparison between centenarians and 118 elderly old individuals of the 7153. Approximate one-third of the centenarians were free from serious diseases such as malignancy. However, blood types were not associated with such medical records. Our findings suggest that blood type B might be associated with exceptional longevity. Responsible mechanisms need to be investigated.

Keywords: Centenarian; Blood group; Longevity

1. Introduction

A variety of medical literature has been concerned with blood groups. However, only a small number of issues have been proven to be of clinical importance: the ABO blood type in transfusion, the Rh antigen in incompatible pregnancy, and the Duffy antigen in malarial infection. Recently, blood type O individuals have been reported to have lower plasma concentrations of von Willebrand factor (VWF), a marker of blood coagulability, than persons with other blood types (O'Donnell and Laffan, 2001). Since elevated VWF carries increased risk for ischemic heart disease, cardiovascular events might be less frequent in individuals with blood type O. In other words, associations are possible between blood groups and life expectancy. We therefore investigated frequencies of ABO blood groups in the very old, specifically centenarians.

2. Methods

Of 1206 centenarians living in Tokyo at the time of our study, 269 individuals, 202 women and 67 men, in ages from 100 to 109 years (Mean 101.2 [Std Dev 1.8]) gave informed consent and agreed to a visit for our medical examinations. We identified the ABO blood group using their blood samples and examined their medical records with respect to hypertension, cardiovascular disease, apoplexy, diabetes, femoral fracture, malignancy, and chronic lung disorder. As a regionally matched control group, we selected 7153 individuals (1673 women and 5480 men) aged 17–93 years (mean 54.8 [Std Dev 11.0]) who came to the Keio Health Consulting Center for annual medical check-ups in 2003. Of the 7153, the following

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Table 1
Comparison of blood group frequencies

	Blood type			
	A	O	B	AB
Observation				
Centenarians ($n=269$)	92 (34.2)	76 (28.3)	79 (29.4)	22 (8.2)
Controls ($n=7153$)	2759 (38.6)	2153 (30.1)	1570 (21.9)	671 (9.4)
Old controls ($n=740$)	288 (38.9)	219 (29.6)	159 (21.5)	74 (10.0)
Elderly old controls ($n=118$)	48 (40.7)	34 (28.8)	27 (22.9)	9 (7.6)
Expectation				
General population[a]	109 (38.7)	83 (29.3)	63 (22.2)	28 (10.0)
Tokyo area[b]	108 (38.3)	83 (29.1)	63 (22.4)	29 (10.2)

Data are numbers followed by percentages in parentheses. Differences between centenarians and controls and between observed and expected frequencies were investigated by χ^2-tests. Observation in centenarians was significantly different from that in controls (χ^2 [d.f.=3]=8.41, $P=0.04$) and from expectations (χ^2 [d.f.=3]=12.68, $P=0.005$ for Japan; χ^2 [d.f.=3]=11.91, $P=0.007$ for metropolitan Tokyo). Notably, blood type B was observed more frequently in centenarians. This predominance of blood type B, although not being statistically significant, was observed in comparison between centenarians and old controls (χ^2 [d.f.=3]=7.17, $P=0.06$) and between centenarians and elderly old controls (χ^2 [d.f.=3]=2.25, $P=0.52$).

[a] Calculated from data for 4464349 individuals in a 1978 survey throughout Japan.

[b] Calculated from data for 293688 Tokyo-area individuals among the above 4464349.

two subgroups were constituted: Old control group consisting of 740 individuals over 70 years (mean 74.8 [Std Dev 4.4]) and elderly old control group of 118 over 80 years (mean 82.8 [Std Dev 2.8]). Differences in frequencies were investigated by χ^2-tests. A $P<0.05$ was considered to be statistically significant.

3. Results

Frequencies of blood types A, O, B, and AB in the centenarian group were 34.2, 28.3, 29.4, and 8.2%, respectively; those in the control group were 38.6, 30.1, 21.9, and 9.4%, respectively (Table 1). Observed frequencies differed significantly between these two groups (χ^2 [d.f.=3]=8.41, $P=0.04$). Notably, blood type B was observed more frequently in centenarians than in controls. This predominance of blood type B, although not being statistically significant, was observed in comparison between centenarian group and old control subgroup (χ^2 [d.f.=3]=7.17, $P=0.06$) and between centenarian group and elderly old control subgroup (χ^2 [d.f.=3]=2.25, $P=0.52$). We next compared the frequencies of ABO blood groups in the centenarians with those in a general Japanese population as calculated from a 1978 survey conducted in 4464349 individuals throughout Japan (Fujita et al., 1978). A similar result showing an increased frequency of blood type B in centenarians was obtained (χ^2 [d.f.=3]=12.68, $P=0.005$). This also was true when the centenarians were compared with 293688 Tokyo-area individuals among the 4464349 (χ^2 [d.f.=3]=12.02, $P=0.007$). The frequency distribution of blood types in the 1978 survey was almost the same as that in a 1933 survey of 121200 individuals (Furuhata, 1933) and that for 5819007 blood donors profiled in an annual report of the Japanese Red Cross (year 2000) (The Japanese Red Cross Society, 2002). Our findings suggest that to some degree blood type B might be associated with exceptional longevity.

The following important diagnoses were recorded in centenarians: hypertension ($n=78$), cardiovascular disease ($n=51$), apoplexy ($n=37$), diabetes ($n=9$), femoral fracture ($n=66$), malignancy ($n=24$), and chronic lung disorder ($n=29$). Approximate one-third of the centenarians were free from these important diseases. However, blood types were not associated with such medical records (Table 2) (χ^2 [d.f.=3]=4.16, $P=0.25$). This finding implies that blood type B might be related to surviving serious diseases rather than escaping them.

4. Discussion

One would expect an abundance of centenarians with blood type O, since plasma concentrations of VWF, a cardiac risk factor, are lower in blood type O individuals. However, the frequency of blood type O in centenarians tended to be lower than expected. Instead, we found

Table 2
Relationship between blood groups and medical history

Blood groups	Medical history of important diseases	
	Absence	Presence
A ($n=92$)	32 (34.8)	60 (65.2)
O ($n=76$)	19 (25.0)	57 (75.2)
B ($n=79$)	18 (22.8)	61 (77.2)
AB ($n=22$)	8 (36.4)	14 (63.6)
Total ($n=269$)	77 (28.6)	192 (71.4)

Data are numbers followed by percentages in parentheses. Relationship between blood groups and medical history was investigated by χ^2-tests (χ^2 [d.f.=3]=4.16, $P=0.25$).

a possible association of blood type B with exceptional longevity. Differences in ABO blood groups are determined by antigens in the glycocalyx on the surface of the erythrocyte. These antigens are present in most tissues as well as on erythrocytes. Therefore, differences in the glycocalyx expressed by cells might elicit differing responses in biomedical phenomena apart from hemagglutination. Henry et al. summarized patterns in which blood types may be associated with various diseases, stating that bacterial infections tend to attack individuals with blood type A, while viral infections tend to be associated with blood type O. Also, cancers and clotting disorders tend to be associated with blood type A, while autoimmune diseases and bleeding disorders are associated with blood type O (Henry and Samuelsson, 2000). According to these tendencies, blood type B individuals might be more likely to escape serious illnesses, and therefore show longevity. On the other hand, our findings imply that blood type B might contribute to longevity via biomedical mechanisms favorable for surviving serious diseases rather than escaping them. In future, blood groups will need to be investigated from an aspect of glyconomics, or the study of sugar-modifications to proteins that affect structure and function.

References

Furuhata, T., 1933. On the serological position of the Japanese. Proc. Jpn. Acsd. Soc. 8, 564–573.

Fujita, Y., Tanimura, M., Tanaka, K., 1978. The distribution of the ABO blood groups in Japan. Jpn. J. Human Genet. 23, 63–109.

Henry, S., Samuelsson, B., 2000. ABO polymorphisms and their putative biological relationships with disease, in: King, M.-J. (Ed.), Human Blood Cells: Consequences of Genetic Polymorphisms and Variations. Imperial College Press, London, pp. 15–103.

O'Donnell, J., Laffan, M.A., 2001. The relationship between ABO histo-blood group, factor VIII and von Willebrand factor. Transfus. Med. 11, 343–351.

The Japanese Red Cross Society, 2002. Annual report. The Japanese Red Cross Society, Tokyo.

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Association analysis between longevity in the Japanese population and polymorphic variants of genes involved in insulin and insulin-like growth factor 1 signaling pathways

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Abstract

Recent studies have demonstrated a significant association between mutations in genes involved in the insulin/IGF1 signaling pathway and extension of the life span of model organisms. In this study which compared 122 Japanese semisupercentenarians (older than 105) with 122 healthy younger controls, we examined polymorphic variations of six genes which are involved in insulin/IGF1 signaling. These genes were *FOXO1A*, *INSR*, *IRS1*, *PIK3CB*, *PIK3CG*, and *PPARGC1A*. We investigated the possible association of each gene locus and longevity by haplotype-based association analyses using 18 SNPs from public databases and the published literature. One *INSR* haplotype, which was comprised of 2 SNPs in linkage disequilibrium, was more frequent in semisupercentenarians than in younger controls.

Keywords: Aging; Centenarian; Gene polymorphism; Insulin/IGF1 signaling; Longevity

1. Introduction

Recent studies using model organisms have demonstrated a significant association between mutations in genes involved in the insulin/insulin-like growth factor 1 (IGF1) signaling pathway and extension of the life span. The first examples of such genes were found in *Caenorhabditis elegans* (Kenyon et al., 1993). They include *daf-2*, an ortholog of the insulin/IGF1 receptor gene family, and *daf-16*, an ortholog of the forkhead transcription factors which regulate insulin/IGF1-induced gene transcription.

Another example is *age-1* which is the *C. elegans* ortholog of the gene encoding the catalytic subunit of phosphoinositide-3-kinase, a protein involved in insulin/IGF1 signal transduction (Morris et al., 1996). A long-lived mutant of the *insulin-like receptor* gene (*InR*) was also reported in *Drosophila melanogaster* (Tatar et al., 2001). At almost the same time, the ablation of the *D. melanogaster* gene *chico*, which encodes an insulin receptor substrate, was reported to extend the life span of the fly (Clancy et al., 2001). Regulations of life span by insulin receptor and IGF1 receptor were also reported in mice (Bluher et al., 2003; Holzenberger et al., 2003). Based on these studies, genes involved in the insulin/IGF1 signaling pathway are believed to play a role in longevity throughout evolution. In fact, polymorphic variations of the genes for insulin-like growth factor 1 receptor (*IGF1R*) and phosphoinositide-3-kinase have been reported to affect human longevity (Bonafe et al., 2003).

In this study, we compared 122 Japanese semisupercentenarians (SSCs) (older than 105) with 122 healthy younger controls. We examined polymorphic variations of the genes for six proteins, forkhead box O1A (*FOXO1A*), insulin

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