while cardiac work falls dramatically, and is increasingly being perceived as a potential key lesion in the failing heart.

On the other hand, there is the possibility that UA itself may induce LVH. Previous reports have shown that UA impairs NO generation and induces endothelial dysfunction and smooth muscle cell proliferation[9] Moreover, UA is able to induce inflammatory mediators, such as tumor necrosis factor, in vitro and potentially stimulates mitogen-activated protein kinases, which are known to induce cardiac hypertrophy![10] Indeed, accumulating data support the idea that UA possesses specific toxic or other properties that could contribute to cardiac hypertrophy and heart failure pathophysiology. These findings reveal that UA may be the cause of cardiac hypertrophy in part, attributable to an increase in its serum level, via stimulation of endothelial dysfunction, smooth muscle cell proliferation, and inflammation.

So far there is strong evidence that increased UA is associated with atherosclerosis and an increased risk of cardiovascular events. The findings of Mitsuhashi et al. also suggest that the serum level of UA affects cardiac hypertrophy in men! However, whether UA per se is a cause of cardiovascular disease, especially cardiac hypertrophy, remains to be settled. Prospective randomized studies targeting UA reduction are necessary to finish this discussion.

This finding by Mitsuhashi et al[1] is not only potentially of value in preventing cardiac hypertrophy but also raises interesting questions regarding the pathophysiological action of UA on the cardiovascular system.

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各論

高齢者 D
—ガイドラインと今後の 定健診

●高血圧 ●メタボリックシンドロー
●TONE

7．高齢者のメタボリックシンドロームにおける血圧管理

斎藤 重幸

SUMMARY

■メタボリックシンドローム(MetS)は内臓脂肪を基盤とした高血圧を含む危険因子の集積で，動脈硬化性疾患の易発症状態である．わが国でのMetSの頻度は高齢者男性で50%，女性で30%程度に及ぶ．高齢者でのMetSのCVD発症リスクは非高齢者より低いものであるが，リスク集積は認知症，CKD，糖尿病発症などとも関連し，特に高血圧の治療が重要になる．MetSを合併した高齢者では肥満の是正が重要であり，減量により高齢者でも一定程度の降圧効果が期待されるが，生活習慣の改善に当たってはQOL低下，認知症進行，低血圧による転倒事故などに注意を払う必要がある．降圧薬療法でMetSの背景にある肥満，インスリン抵抗性を踏まえた治療が必須でACE阻害薬，ARBが中心となる．

はじめに

メタボリックシンドローム(MetS)は内臓脂肪蓄積型肥満を背景として，血圧高値，耐糖能異常，脂質異常が合併した易動脈硬化性発症状態として定義される．わが国では，2005年に関連8学会より合同で診断基準が発表され，これを基に2008年からは40～74歳までの特定健診・特定保健指導制度が開始されている．わが国のMetSの特徴は肥満を腹囲径でスクリーニングし，腹囲径で男性85 cm以上，女性90 cm以上を腹部肥満としてこれを必須項目とすることで，正常高値血圧以上の血圧高値，空腹時血糖値110 mg/dL以上(特定健診では100 mg/dL以上)の高血糖，中性脂肪150 mg/dL以上あるいはHDLコレステロール40 mg/dL未満の脂質異常の2項目以上が集積するとMetSと診断される．

年齢にかかわらずMetSの診断基準は同一であるが，特定保健指導では，前期高齢者では動機付け支援までであり，年齢により特定健診後の対処方法は異なる．本稿では，高齢者のMetSの臨床意義と高血圧治療に関して概説する．

高齢者のメタボリックシンドロームの意義

わが国は世界で有数の長寿国であるが，全年齢層での死因の第2位，3位が脳血管障害，心疾患であり，現在この多くを，脳梗塞，虚血性心疾患などの動脈硬化性疾患が占める．そして，高齢者になるに従い心疾患・脳血管疾患の死亡割合が増加する．特に女性ではこの傾向が顕著で，80歳以上の死因の37%が心疾患と脳血管疾患である(図1)[1]．さらに，心疾患・脳血管疾患(CVD)は，認知症や転倒，骨折の背景要因でもあり，CVD予防は予後の延長，ADLの確保から要介護者の増加防止に至る社会負担の軽減のために重要となる．MetSは，内臓脂肪蓄積型肥満に着目しこれに合併するCVD多危険因子を肥満の是正により，一元的に管理しようとする概念である．進行した高血圧，糖尿病，動脈硬化には，それぞれについての厳格な管理が必要なことは明白であるが，それによって予防できない動脈硬化性疾患への対策にはMetSの予防と管理が重要であると考えられる．動脈硬化の進展と動脈硬化性疾患の発症は，複合的な危険因子の長期間にわたる曝露の後に起こる

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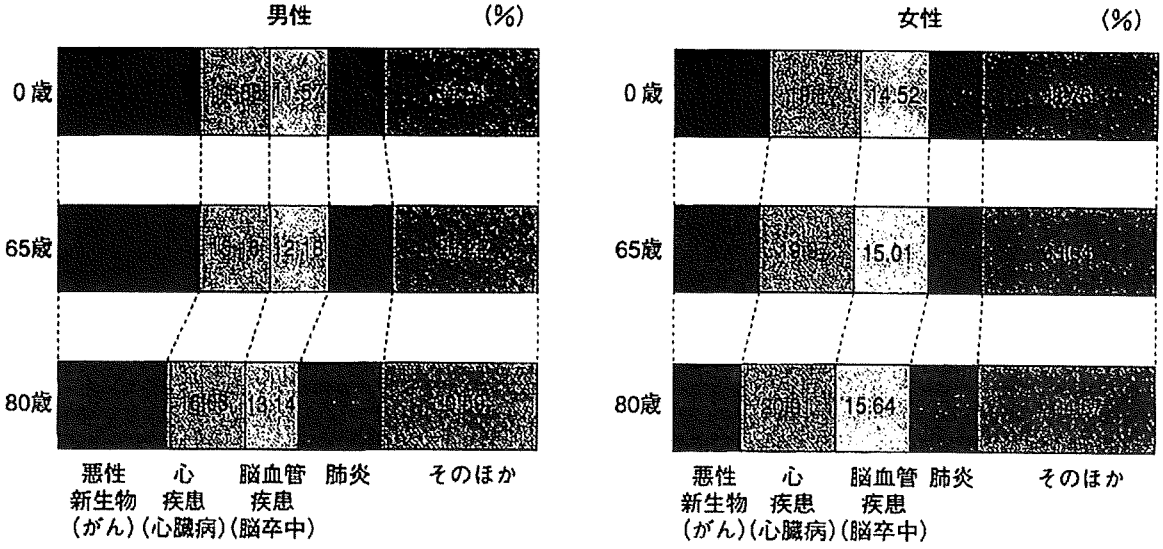

図1　0歳，65歳，80歳の死亡原因(平成17年)

ことは明らかである．高齢者での心血管疾患の予防のために，若年時よりのMetSへの介入が必要である．

高齢者のメタボリックシンドローム(MetS)の病態

生理的加齢，病的加齢いずれにおいても，加齢に従い血圧値，血糖値は上昇し，体脂肪分布も変化する．したがって高齢者でのMetSの頻度は上昇する．図2[2]は，国民栄養調査時に評価された日本人のMetSの頻度である．20歳以上全体では男性の45.6%，女性の16.7%，70歳以上では男性の55.3%，女性の30.4%が腹部肥満診断基準を満たし，かつMetS診断基準を1つ以上合併しており，これがわが国の動脈硬化性疾患の高リスク者であると考えられる．しかしながら，この中には既に高血圧，糖尿病，脂質異常症などの治療者が含まれ，管理の状況や罹病期間もまちまちであり，MetSとして一定のリスクを持つものではない．

高齢者のメタボリックシンドローム(MetS)の予後

教室で継続している前向き疫学研究(端野・壮瞥町研究)では，NCEP-ATPⅢ基準でのMetSは非MetSに比して心疾患発症リスクが1.8倍に上昇することを報告している[3]．65歳以上の高齢者で同様な解析を行うと，心血管疾患発症には非MetS群と比べてMetS群で有意の差違がなかった．このとき，予後規定因子として高血圧リスクが最大である．

Mozaffarianらは高齢者を対象に，NCEP-ATPⅢ基準のMetSと死亡リスクをCardiovascular Health Studyの対象より評価した(図3)[4]．Cardiovascular Health Studyは米国の65歳以上を対象としたコホート研究であるが，CVD既往のない4,258人を追跡した．平均年齢は73歳．男性の31%，女性の38%がMetSであり，15年間の追跡で2,116人が死亡している．多変量解析でMetSの死亡率は，非MetSに比し相対リスク1.22(95%信頼区間：1.11～1.34)であった．しかしながら死亡リスク上昇は，空腹時高血糖があるMetSで相対リスク1.41(1.27～1.57)，高血圧があるMetSで相対リスク1.26(1.15～1.39)だが，空腹時高血糖がないMetSでは相対リスク0.97(0.85～1.11)，高血圧がないMetSでは0.92(0.71～1.19)で，リスク上昇はみられなかった．高血圧や空腹時高血糖のないMetSの死亡における集団寄与リスクは認められなかった．CVD既往者を加えた検討でも同様であ

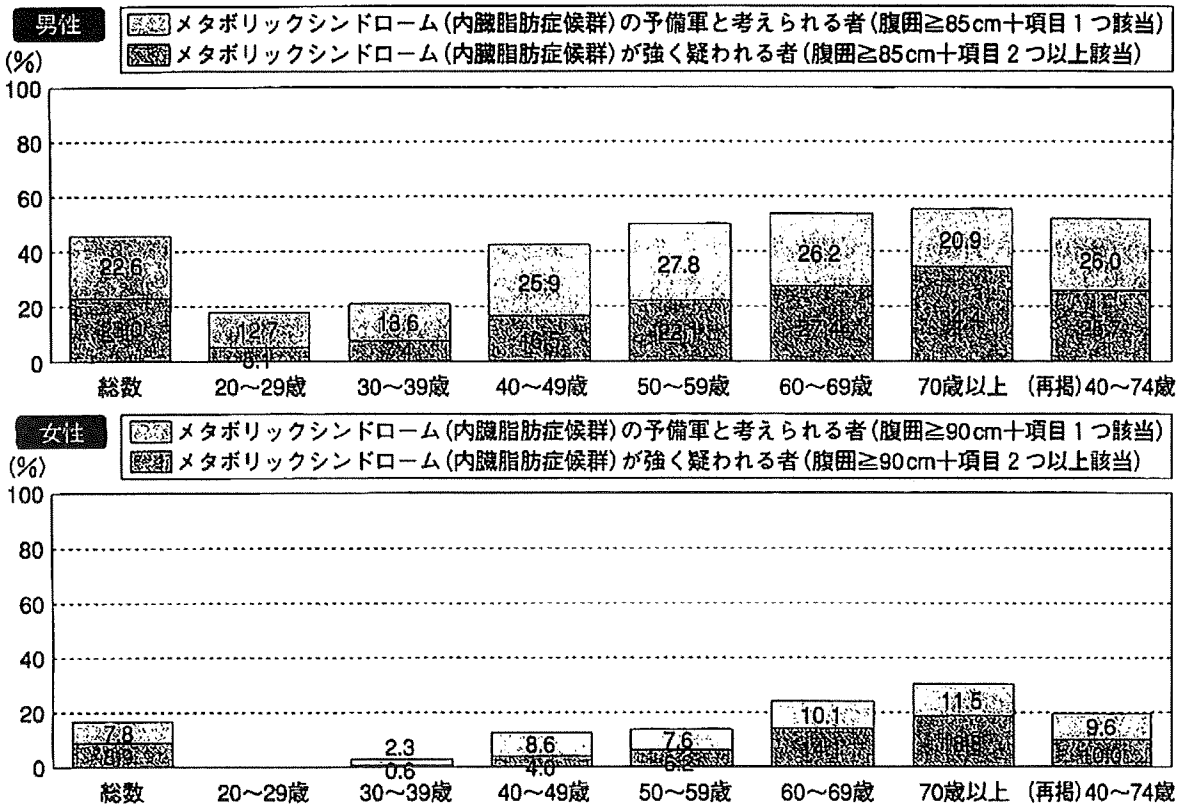

図2　メタボリックシンドローム(内臓脂肪症候群)の状況(20歳以上)
—平成16年　国民健康・栄養調査結果—

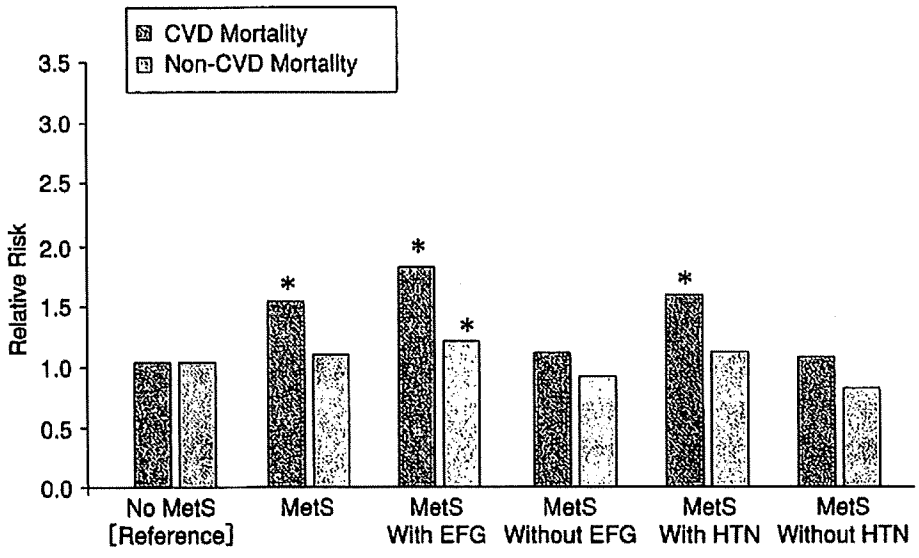

図3　65歳以上高齢者でのメタボリックシンドローム(MetS)の有無による心血管疾患死亡(CVD)と非CVD死亡の相対危険
EFG：空腹時高血糖，HTN：高血圧，文献4より改変引用．

り，高齢者においてMetSには，高血圧，空腹時高血糖以上の予後予測能はないことを示している．

またSattarらは，70歳以上高齢者を対象としたProspective Study of Pravastatin in the Elderly at Risk(PROSPER)とBritish Regional Heart Study(BRHS)からMetSのCVD死亡リスクを検討した[5]．MetSのCVD死亡の相対危険は1.07(0.86～1.32)であり有意なリスク上昇をもたらしておらず，高齢になるほどMetSのリスクは低下することを示した．以上，内外の成績より，高齢者で診断されたMetSの予後予測能は既存の危険因子よりは劣るものと考えられる．

高齢者のMetSのCVDリスクは明確ではないが，MetSに高血圧，糖尿病が合併すると明らかに高齢者の生命予後を劣化し，CVDリスクを上昇させることも事実である．また，高齢者におけるMetSは，認知症[6]や尿中微量アルブミン増加[7]，慢性腎臓病(CKD)[8]にも関係し，生命予後やCVD発症に関連していると考えられ，こうした合併症の管理にも降圧療法が極めて重要である．

高齢者メタボリックシンドローム(MetS)の降圧療法

日本高血圧学会の高血圧治療ガイドライン2009[9]では，MetS合併時の高血圧治療指針は高齢者と非高齢者は同様である．高血圧に糖尿病が合併するとそれだけで高リスクであり，ただちに降圧薬療法の開始となり，降圧目標も130/80 mmHg未満となる．糖尿病のない場合は，140/90 mmHg以上で降圧薬療法を開始する．130～139/85～89 mmHgでは生活習慣改善を行うが，MetSでは特に食事・運動療法による内臓脂肪蓄積型肥満の是正が重要である．

食事療法は降圧薬の種類と用量を減らすことにつながり，治療のコンプラシアンスを改善もする．

生活習慣改善で注意しなければならないのは，高齢者における極端かつ性急な生活習慣の変更は高齢者のQOLを著しく損なう可能性があり，身体的な影響にも及ぶ場合もあることである．高齢者での生活習慣改善には，暦年齢よりも実年齢に則した無理のない実施を心掛けるべきであり，認知症の進行，経過中の身体状況，心理状況変化などの把握には，家族などからの情報も含めて留意すべきである．また高齢者では，起立性低血圧や食後血圧低下の頻度が高いことに加え，摂食量減少などによって血圧が低下することも多いので，生活習慣改善も緩徐に行い，経過中の血圧の動揺に十分注意を払い，家庭血圧も参考にして慎重に管理する必要がある．

一般に減量の降圧効果は確立されており，4.5 kgの減量で有意の降圧を来すことがTONE[10]で報告されている．減量により降圧薬の投与量を減じることができ，代謝指標も併せて改善されるが，高齢者では背景に隠れている心疾患や筋力低下などに注意して，無理のない長期的な減量を指導すべきである．運動療法開始前に心血管病の有無を確認すべきであり，虚血性心疾患，心不全，腎不全，骨関節疾患などの合併がある場合は積極的な運動は不可能であり，適切な運動処方が必要である．

メタボリックシンドローム(MetS)の降圧薬療法

内臓脂肪蓄積型肥満を伴うMetSには，インスリン抵抗性が存在する．高齢者におけるMetS合併高血圧の降圧薬療法にもインスリン抵抗性を改善する薬剤の使用が好ましいと考えられ，アンジテンシン変換酵素(ACE)阻害薬やアンジテンシン受容体ブロッカー(ARB)の使用が推奨される．

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4．端野・壮瞥町研究
—日本人地域住民における無症候性閉塞性動脈硬化症(ASO)の頻度と脂質異常症との関連

Fujiwara T, et al：
Prevalence of asymptomatic arteriosclerosis obliterans and its relationship with risk factors in inhabitants of rural communities in Japan：Tanno-Sobetsu study.

Ankle brachial index (ABI) の評価から，地域一般住民の無症候性の慢性閉塞性動脈硬化症(ASO)の頻度と関連因子を検討すると，ABI 0.9 未満の ASO は 2.7 %存在し，総コレステロール，non-HDL コレステロールとの関連が見いだされた．

方　法

背　景

日本人は生活様式の変化，特に食生活の欧米化，日常活動度の低下によりコレステロールレベルの上昇や糖尿病の増加など動脈硬化危険因子の構造が大きく変化し，虚血性心疾患や脳梗塞などの動脈硬化性疾患の増加が予想される[1)-4)]．これは同時に末梢動脈硬化，特に慢性閉塞性動脈硬化症(arteriosclerosis obliterans：ASO)の頻度にも影響していると考えられるが，本邦における ASO の疫学に関する報告は少なく，特に地域住民におけるものは極めて少ない．これは ASO 初期病変が無症候性であり診断が困難であること，症状からの診断では脊椎疾患などとの鑑別が困難であることなどによる．ASO は高齢者において ADL，QOL を低下させるのみばかりでなく，生命予後にも影響を与えることから，早期発見，治療が重要である．

四肢血圧の同時測定が容易である機器(Form PWV/ABI)が開発され，比較的簡便に大人数における上肢/下肢血圧比の評価が可能となり，無症候性 ASO の診断が可能となった[5)]．そこで，本研究では北海道二地域で地域住民検診を受診した集団に対し，Form PWV/ABI を用いて ankle brachial index (ABI)の測定を行い無症候性 ASO の頻度を調査するとともに動脈硬化危険因子との関係を検討し，早期 ASO の管理方法を採った．

対象と方法

対象は 2001 年，2002 年北海道端野町，壮瞥町の地域住民検診を受診し ABI を測定した 40 歳から 92 歳の男性 544 人(平均年齢 65.7 ± 9.8 歳)，女性 854 人(平均年齢 63.2 ± 10.0 歳)の計 1,398 人．対象地域農村で農業従事者が多く，65 歳以上の年齢は 54.2 %である．すべての対象は早朝空腹時に採血を行い，安静座位にて随時血圧を測定した．採血検体は空腹時血糖(FPG)，ヘモグロビン A_{1c} (HbA_{1c})，総コレステロール (TC)，中性脂肪(TG)，HDL コレステロール(HDL-C)を測定した．計算法により LDL コレステロール (LDL-C)，non-HDL コレステロー

ル(non-HDL-C)を評価した．また地域保健師の問診から既往，現在の喫煙の有無について調査し，医師の診察により脊柱管狭窄症を評価した．ABIは日本コーリン社のForm PWV/ABIを用いて測定標準法により測定した．左右いずれかのABIが0.9未満をASOと定義した．

ABIと対象者の収縮期血圧(SBP)，拡張期血圧(DBP)，FRG，TC，TG，HDL-Cについての関連を，また，ASOと高血圧，糖尿病，脂質異常症，喫煙，肥満などの危険因子との関連について検討した．

結　果

対象となった男性544人，女性854人の平均年齢は男性65.7 ± 9.8歳，女性63.2 ± 10.0歳，全体で64.2 ± 10.0歳，左右平均のABIは男性1.093 ± 0.081歳，女性1.090 ± 0.071歳と男女差を認めず，正規分布を示した．ASOの頻度は対象者全体では2.7 %，男性3.1 %，女性2.5 %であった．60歳未満で男性は1.6 %，女性は0.7 %，全体では1.0 %，60歳以上の高齢者では男性3.6 %，女性3.3 %，全体で3.4 %であり，全体($p = 0.011$)，女性($p = 0.019$)では有意に60歳以上の群でASOの頻度が多かったが，男性では有意差を認めなかった．男女による危険因子の比較ではTG(男性124.1 ± 87.0 mg/dL，女性96.3 ± 46.9 mg/dL：$p < 0.005$)，FPG(男性102.9 ± 24.7 mg/dL，女性95.4 ± 18.6 mg/dL：$p < 0.005$)，喫煙率(男性75.0 %，女性10.5 %：$p < 0.005$)は男性が高く，TC(男性188.8 ± 28.4 mg/dL，女性208.8 ± 31.2 mg/dL：$p = 0.028$)，HDL-C(男性49.4 ± 15.2 mg/dL，女性52.5 ± 11.9 mg/dL：$p < 0.005$)，SBP(男性134.9 ± 18.4 mmHg，女性137.7 ± 23.3 mmHg：$p < 0.005$)は女性で高かった．BMI(男性23.9 ± 3.0 kg/m^2，女性23.8 ± 3.3 kg/m^2：$p = 0.168$)，DBP(男性78.4 ± 18.4 mmHg，女性76.1 ± 11.8 mmHg：$p = 0.083$)に男女差は認められなかった．男性，女性ともにTCとABIの単相関は有意な負の相関を示したが，他の危険因子では有意な相関は認められなかった．ABIを従属変数とした重回帰分析を行うと，TC値と喫煙が有意な説明因子として採択された(表1)．

表1　平均ABI値と関連因子との重回帰分析の結果

Age	-0.042	-1.449	0.150
SBP	-0.014	-0.460	0.646
TC	-0.104	-3.688	0.000
TG	0.053	1.833	0.067
FPG	-0.002	-0.080	0.936
BMI	-0.002	-0.079	0.94
Smoking	-0.088	-3.105	0.002

SBP：systolic blood pressure；収縮期血圧，TC：total cholesterol；総コレステロール，TG：triglyceride；中性脂肪，FPG：fasting plasma glucose；空腹時血糖，BMI：body mass index

次に，ASO群と非ASO群で年齢，TC，FPG，SBP，BMIの平均値を比較したところ，年齢はASO群で68.6 ± 10.1歳，非ASO群で64.1 ± 9.9歳($p = 0.006$)，FPGはASO群104 ± 26.9 mg/dL，非ASO群98.1 ± 21.3 mg/dLとASO群で高値であった．TCはASO群で208.7 ± 30.9 mg/dL，非ASO群で200.8 ± 31.6 mg/dL($p = 0.129$)，SBPはASO群で(142.2 ± 211 mmHg非ASO群で136.5 ± 21.6 mmHg($p = 0.104$)，BMIはASO群24.3 ± 4.0，非ASO群23.8 ± 3.2($p = 0.340$)と差違を認めなかった．また，ASO群と非ASO群それぞれの，喫煙，高血圧，糖尿病，脂質異常症，肥満を有する頻度を比較すると，喫煙者はASO群36.8 %，非ASO群で19.8 %($p = 0.010$)，糖尿病はASO群18.4 %，非ASO群9.0 %($p = 0.048$)とASO群で有意に高率であった．また，脂質異常症を有する群はASO群，非ASO群各々，65.8 %，51.7 %とASO群で高い傾向($p = 0.087$)を認めた．高血圧，糖尿病，脂質異常症，喫煙，肥満の動脈硬化危険因子の集積数とその頻度を，男女別に検討したところ，男性では危険因子が集積するにつれASOの頻度が増加していく傾向がみられ，女性ではリスクが3個以上でASOの頻度が増加した．

考　察

今回われわれはASOの定義としてABI 0.9未満を採用した．通常上肢の血圧より下肢の血圧が高いことから，ABIは1.0～1.5が正常とされている[6]．ABI 0.9未満を血管造影にて実際に動脈硬化が陽性となるsensitivityは90 %，specificityは95 %であったと報告されており[7]また，多くの欧米の報告ではABI 0.9

未満をASOと定義している[7)-10)]．今回ABIの測定にForm PWV/ABIを用いた．Form ABI/PWVは短時間でABIを測定することができ，測定者間の誤差も生じにくいので検診など多人数の測定に有用である．過去の報告において下肢痛，間歇性跛行などの症状を有するASOの頻度はASO全体の22％と報告されておりその多くは無症候性である[11)]．潜在的なASOのスクリーニングとしてForm ABI/PWVは簡便であり今回のような地域住民検診に有用であると思われる．

これまでのASOの頻度に関する報告の中で，ABIが0.9未満をASOと定義している報告では，55歳以上の男女7,715人を対象としたRotterdam Studyでは男性16.9％．女性20.5％，45歳～64歳の男女15,792人を対象としたARIC studyでは男性3％，女性3％であり[7)10)-12)]，国内報告では，男性894人を対象とした，NI-HON-SAN studyでは，ASOの頻度は7.9％，青森の糖尿病患者190人を対象とした研究では頻度が8.4％であった[13)-16)]などの報告があり，年齢，基礎疾患等の違いでばらつきが認められる．

本調査ではASOの頻度は男女全体では2.7％，男性3.1％，女性2.5％であった．欧米の報告よりも頻度は少ない結果となった．また60歳で分けると，60歳未満で男性は1.6％，女性は0.7％，全体では1.0％．60歳以上の高齢者では男性3.6％，女性3.3％，全体で3.4％であり，男女とも有意に60歳以上の群でASOの頻度が多く，高年齢層ほどASOの頻度が高くなるものと思われる．

ABIの異常の危険因子についてはいくつかの報告があり，高血圧，糖尿病，血清総コレステロール，喫煙との正の相関，HDL-Cとは負の相関があるといわれている．今回われわれの調査においても，ASO群における喫煙者の割合は36.8％，非ASO群で19.8％と有意にASO群の方が，喫煙者が多く，同様に糖尿病を有する頻度はASO群18.4％，非ASO群9.0％と有意にASO群で糖尿病の頻度が高値であった．脂質異常症を有する群はASO群，非ASO群各々，65.8％，51.7％とASO群で高い傾向を認め，従来の動脈硬化危険因子との関連が，日本人一般集団でも確認された．

本研究の結果より喫煙，糖尿病とASOとの関連が示唆され，またABIは喫煙，コレステロール値と負の相関があることが示された．本研究は断面研究であり因果関係について言及することはできないが，喫煙者においてASOの頻度が高くABIとも相関しており，重要な危険因子と考えられる．ASOの予防には脳血管疾患，冠動脈疾患等，全身の動脈硬化性疾患と同様生活習慣病の改善が必要であり，特にそのなかでも禁煙は重要であると思われた．

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Original Contribution

Green Tea Consumption and Hematologic Malignancies in Japan

The Ohsaki Study

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Several biologic studies have reported that green tea constituents have antitumor effects on hematologic malignancies. However, the effects in humans are uncertain. The authors used data from the Ohsaki National Health Insurance Cohort Study in Japan to evaluate the association between green tea consumption and the risk of hematologic malignancies. Study participants were 41,761 Japanese adults aged 40–79 years without a history of cancer at baseline who answered a food frequency questionnaire survey in 1994. During 9 years of follow-up beginning in 1995, the authors documented 157 hematologic malignancies, including 119 cases of lymphoid neoplasms and 36 cases of myeloid neoplasms. Hazard ratios were calculated by using the Cox proportional hazards regression model. Risk of hematologic malignancies was inversely associated with green tea consumption. The multivariate-adjusted hazard ratio of hematologic malignancies for 5 cups/day or more compared with less than 1 cup/day of green tea was 0.58 (95% confidence interval: 0.37, 0.89). The corresponding risk estimate was 0.52 (95% confidence interval: 0.31, 0.87) for lymphoid neoplasms and 0.76 (95% confidence interval: 0.32, 1.78) for myeloid neoplasms. This inverse association was consistent across sex and body mass index strata. In conclusion, green tea consumption was associated with a lower risk of hematologic malignancies.

catechin; cohort studies; hematologic neoplasms; Japan; risk; tea

Abbreviations: EGCG, (-)-epigallocatechin-3-gallate; FFQ, food frequency questionnaire; ICD-O-3, *International Classification of Diseases for Oncology*, Third Edition; NHI, National Health Insurance.

Hematologic malignancies are known to have a wide geographic distribution; incidence rates are relatively high in Western countries and low throughout Asia, including Japan and developing countries (1). According to "Global Cancer Statistics, 2002" by Parkin et al. (1), age-standardized incidence rates per 100,000 for non-Hodgkin lymphoma were higher than 10.0 for men and 6.5 for women in North America and in western, northern, and southern Europe, while they were lower than 6.5 for men and 4.0 for women in eastern and southern Asia, including Japan. Similarly, the rates of Hodgkin lymphoma were higher than 2.0 in North and Central America and in Europe and lower than 1.0 in southeastern Asia (1). The reasons for this discrepancy are still unclear. Many epidemiologic studies have explored the risk factors for hematologic malignancies. Cigarette smoking (2–5), high alcohol consumption (5), obesity (6–9), height (6), occupational exposures (10), infection with some viruses, and immunodeficiency (11–13) are thought to induce some types of hematologic malignancies. However, preventive factors for hematologic malignancies are not well known and are a public health concern because the incidence of hematologic malignancies has been increasing worldwide (1).

Currently, there is extensive interest in the health benefits of green tea. Thus, green tea and its major constituent, tea polyphenols, have been widely studied as preventive factors for various diseases, including cancers (14–20). Several biologic studies have reported that green tea constituents, such

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as (-)-epigallocatechin-3-gallate (EGCG), exert antitumor effects against hematologic malignancies by inducing apoptosis and/or suppressing angiogenesis (21–25). However, epidemiologic studies on this topic have been few; to our knowledge, only 3 case-control studies have been conducted (26–28). Two reported that green tea intake was associated with a lower risk of leukemia (26, 28), and another study reported that higher intake of tea flavonoids was inversely associated with the risk of non-Hodgkin lymphoma (27).

This evidence may help explain the low incidence of hematologic malignancies in Asian countries, where consumption of green tea is the highest in the world. However, further evidence from cohort studies or intervention trials is needed to obtain some consensus on this issue. We therefore designed this population-based cohort study to investigate the association between green tea consumption and the risk of hematologic malignancies in a rural area of Japan, where green tea is widely consumed.

MATERIALS AND METHODS

Study cohort

We conducted a population-based cohort study based on data from the Ohsaki National Health Insurance (NHI) Cohort, the details of which have been described previously (29–31). In brief, from October through December 1994, we delivered self-administered questionnaires, including items on dietary intake, to all NHI beneficiaries aged 40–79 years living in the catchment area of the Ohsaki Public Health Center, Miyagi Prefecture, in northeastern Japan. The Ohsaki Public Health Center, a local government agency, provides preventive health services for residents of 14 municipalities in the northern part of Miyagi Prefecture. The study area is a typical rural area of Japan, where the main industry is agriculture.

Of 54,996 eligible individuals, 52,029 returned usable questionnaires; the response rate was 94.6%. We started prospective collection of the NHI withdrawal history files on January 1, 1995, to ascertain the date of and reason for withdrawal from NHI. We excluded 776 participants who had withdrawn from NHI before the baseline questionnaire survey. Thus, 51,253 participants (24,573 men and 26,680 women) were finally entered into the study as our cohort participants. The ethics committee of Tohoku University School of Medicine reviewed and approved the study protocol. We considered the return of self-administered questionnaires signed by the participants to imply their consent to take part in the study.

For the current analysis, we excluded 7 participants (1 man and 6 women) who had incomplete data in the cancer incidence registry, as well as 3,148 participants (1,557 men and 1,591 women) who, as ascertained from self-reports and the cancer registry, had been diagnosed as having cancer before the baseline survey was conducted. We also excluded 6,337 participants (3,266 men and 3,071 women) who had provided incomplete responses regarding frequency of green tea consumption. Consequently, we entered data for 41,761 eligible participants (19,749 men and 22,012 women) into our analysis.

Dietary assessment

We assessed dietary intake of participants at the baseline survey by using the self-administered questionnaire, which included a food frequency questionnaire (FFQ). In this FFQ, we asked participants to report their frequency of recent consumption of 36 food items and 4 beverages, including green tea. The FFQ provided 5 categories of response to describe participants' frequency of green tea consumption: never, occasionally, 1–2 cups/day, 3–4 cups/day, and 5 cups/day or more. The volume of a typical cup of green tea was 100 mL in the study region (19). The questionnaire also consisted of items on personal and family history of disease, physical status, drinking and smoking habits, and occupational and educational status.

We conducted a validation study of the FFQ, as reported previously (32). Spearman's rank coefficient for the correlation between green tea consumption as assessed by the FFQ and four 3-day food records was 0.71 for men and 0.53 for women, and the correlation between consumption measured by 2 FFQs administered 1 year apart was 0.63 for men and 0.64 for women. We examined the total energy intake of each participant from the FFQ responses by converting the selected frequency category for each food to daily intake, using portion sizes based on the median values observed in the validation study (32).

Ascertainment of cases and follow-up

The endpoint of our analysis was the incidence of all hematologic malignancies defined by morphology codes 9590/3–9989/3 in accordance with the *International Classification of Diseases for Oncology*, Third Edition (ICD-O-3) (33). Hematologic malignancies included the following diseases: Hodgkin and non-Hodgkin lymphomas (ICD-O-3 codes 9590/3–9729/3), plasma cell tumors (ICD-O-3 codes 9731/3–9734/3), mast cell tumors (ICD-O-3 codes 9740/1–9742/3), neoplasms of histiocytes and accessory lymphoid cells (ICD-O-3 codes 9750/3–9758/3), immunoproliferative diseases (ICD-O-3 codes 9760/3–9769/1), leukemias (ICD-O-3 codes 9800/3–9948/3), chronic myeloproliferative disorders (ICD-O-3 codes 9950/3–9964/3), other hematologic disorders (ICD-O-3 codes 9970/1 and 9975/1), and myelodysplastic syndromes (ICD-O-3 codes 9980/3–9989/3). Cases were further categorized as follows: lymphoid neoplasms including Hodgkin and non-Hodgkin lymphomas (ICD-O-3 codes 9590/3–9729/3), plasma cell tumors (ICD-O-3 codes 9731/3–9734/3), lymphoid leukemias (ICD-O-3 codes 9820/3–9837/3), hairy cell leukemia (ICD-O-3 codes 9940/3), aggressive NK-cell leukemia (ICD-O-3 codes 9948/3), and lymphoproliferative disorder not otherwise specified (ICD-O-3 codes 9970/1); and myeloid neoplasms including myeloid leukemias (ICD-O-3 codes 9840/3–9931/3), chronic myelomonocytic leukemia not otherwise specified (ICD-O-3 codes 9945/3), juvenile myelomonocytic leukemia (ICD-O-3 codes 9946/3), chronic myeloproliferative disorders (ICD-O-3 codes 9950/3–9964/3), myeloproliferative disease not otherwise specified (ICD-O-3 codes 9975/1), and myelodysplastic syndromes (ICD-O-3 codes 9980/3–9989/3) according to

ICD-O-3 and the *World Health Organization Classification of Tumors* (34).

We ascertained the incidence of cancer through computerized record linkage to the Miyagi Prefecture Cancer Registry, one of the oldest and most accurate population-based cancer registries in Japan (35). Between 1993 and 1997, the percentages registered by death certificates only were, for lymphoma, 23% for men and 21% for women and, for leukemia, 36% for men and 37% for women (35).

We prospectively counted person-years of follow-up for each of the participants from January 1, 1995, until the date of diagnosis of hematologic malignancies, the date of withdrawal from NHI, the date of death, or the end of the follow-up period (December 31, 2003), whichever occurred first. For follow-up, we periodically reviewed the NHI withdrawal history files. When a participant in this study withdrew from the NHI system because of death, emigration, or occupational change, the date of withdrawal and the reason were coded in the files. Follow-up of participants who had withdrawn from the NHI system was discontinued because we were unable to obtain subsequent information on them. During the study period, 5,427 participants (2,147 men and 3,280 women: 13.0% of the total) were lost to follow-up.

Statistical analysis

We combined the lower 2 categories of green tea consumption (never, occasionally) into the single category "less than 1 cup/day" for the purpose of this analysis because of the small number of participants and cases in each category. We used the Cox proportional hazards regression model to estimate hazard ratios and 95% confidence intervals for the incidence of hematologic malignancies according to levels of green tea consumption and to adjust for potential confounding variables, using SAS version 9.1 statistical software (SAS Institute, Inc., Cary, North Carolina). We calculated incidence rates of hematologic malignancies by dividing the number of incident cases by the number of person-years in each stratum of green tea consumption. The hazard ratio was computed as the incidence rate among participants in each green tea consumption stratum divided by the rate among participants in the lowest intake stratum (less than 1 cup/day), which was chosen as the reference group. All hazard ratios were calculated as age and sex adjusted and as multivariate adjusted. The P values for the test of linear trends were calculated by scoring the green tea consumption category as an ordinal variable (less than 1 cup/day = 1–5 cups/day or more = 4). All reported P values were 2-sided, and the estimates with $P < 0.05$ were considered statistically significant. We also conducted additional analyses after categorizing hematologic malignancies as lymphoid neoplasms and myeloid neoplasms.

We evaluated and compared the risk across sex and body mass index strata to assess whether any impact of green tea consumption on the risk of hematologic malignancies differed across sex and/or obesity status. To avoid any possible bias resulting from the influence of undiagnosed cancers present at baseline, we repeated the analysis after excluding participants who had been given a diagnosis of cancer within the first 3 years of follow-up and started follow-up from January 1, 1998, 3 years from the baseline date.

We considered the following variables to be potential confounders prior to the analyses: age (continuous variable, years), sex, family history of leukemia (yes or no), history of blood transfusion (yes or no), job status (nonfarmers or farmers, including former farmers), educational level (less than high school, high school, some college or higher), height ($\leq$155, 155–164, $\geq$165 cm), body mass index ($<$18.5, 18.5–24.9, $\geq$25.0 kg/m^2), cigarette smoking (never smoked, former smoker, current smoker of $<$20 cigarettes/day, current smoker of $\geq$20 cigarettes/day), alcohol drinking (never drank, former drinker, current drinker of $<$45.6 g ethanol/day, current drinker of $\geq$45.6 g ethanol/day), fish consumption ($\leq$2 times/week, 3–4 times/week, every day), soybean products consumption ($\leq$2 times/week, 3–4 times/week, every day), daily miso soup consumption (yes or no), coffee consumption (never, occasionally, $\geq$1 cup/day), and total caloric intake (continuous variable, kcal/day). To avoid overfitting a model, we included these variables apart from age and sex in our final multivariate-adjusted model as confounders only if each variable met both of the following criteria: 1) it was associated with both green tea consumption and risk of hematologic malignancies (i.e., the probabilities of being exposed and diseased varied more than 5% among the strata of a potential confounder); and 2) after adding the variable into the age- and sex-adjusted model, the hazard ratio point estimate changed more than 1%. In the FFQ, alcohol consumption was classified in terms of "go," a traditional Japanese unit for measuring the amount of alcoholic beverages equal to approximately 180 mL of sake, containing 22.8 g of ethanol.

RESULTS

Participants who consumed more green tea than others tended to be older and were more likely to consume fish and soybean products, the typical sources of protein in the Japanese traditional daily diet (Table 1). Meat consumption was not associated with green tea consumption (data not shown). Men, but not women, who consumed more green tea were less likely to be heavy alcohol drinkers and obese. Furthermore, participants who consumed more green tea were more likely to smoke less, but this association was not obvious when we stratified them by sex.

During 326,012 person-years of follow-up (154,348 person-years for men and 171,664 person-years for women; mean = 7.8, maximum = 9.0 years), we documented 157 hematologic malignancies (in 88 men and 69 women); included were 119 cases of lymphoid neoplasms (66 men and 53 women) and 36 cases of myeloid neoplasms (20 men and 16 women). We found a significant inverse association between green tea consumption and the risk of hematologic malignancies in our participants (Table 2). The multivariate-adjusted hazard ratios for the incidence of hematologic malignancies were 0.88 (95% confidence interval: 0.57, 1.38) for 1–2 cups/day, 0.90 (95% confidence interval: 0.59, 1.39) for 3–4 cups/day, and 0.58 (95% confidence interval: 0.37, 0.89) for 5 cups/day or more (P for trend = 0.02) compared with less than 1 cup/day of green tea consumption. After

Table 1. Characteristics of Subjects (n = 41,761) According to Green Tea Consumption at Baseline, the Ohsaki Cohort, Japan, 1995–2003[a]

Characteristic	Green Tea Consumption, Cups/Day							
	Men (n = 19,749)				Women (n = 22,012)			
	<1 (n = 6,039)	1–2 (n = 4,479)	3–4 (n = 4,008)	≥5 (n = 5,223)	<1 (n = 5,054)	1–2 (n = 4,567)	3–4 (n = 5,046)	≥5 (n = 7,345)
Age in years, mean (SD)	57.9 (10.7)	58.1 (10.8)	60.5 (10.4)	61.9 (9.8)	59.3 (10.9)	60.4 (10.6)	61.8 (9.7)	62.8 (9.2)
Educational level								
Less than high school	62.4	56.9	58.6	61.7	59.4	54.8	54.2	58.3
High school	30.7	34.8	32.4	30.3	33.2	36.5	37.1	33.4
Some college or higher	6.9	8.4	9.0	8.0	7.4	8.7	8.7	8.3
Body mass index, kg/m^2								
<18.5	3.3	3.1	2.7	3.5	4.7	3.6	4.0	3.5
18.5–24.9	69.7	70.9	71.7	71.3	64.0	65.0	65.2	62.9
≥25.0	27.0	26.0	25.6	25.2	31.3	31.4	30.8	33.7
Cigarette smoking, cigarettes/day								
Never	20.7	19.1	19.1	16.8	86.8	90.9	92.2	88.2
Former	24.5	24.1	27.6	27.9	3.0	2.4	2.3	2.7
Current, <20	20.6	21.6	21.0	22.5	6.8	4.7	4.4	6.6
Current, ≥20	34.2	35.2	32.3	32.9	3.3	2.1	1.1	2.5
Alcohol drinking, g of ethanol/day								
Never	16.3	14.6	15.1	18.3	70.8	73.0	75.2	72.3
Former	10.6	9.8	10.3	11.6	5.5	4.0	3.8	4.3
Current, <45.6	59.9	63.2	63.0	59.5	22.7	22.3	20.6	22.9
Current, ≥45.6	13.2	12.4	11.6	10.6	1.0	0.6	0.4	0.6
Fish consumption,[b] times/week								
≤2	31.3	28.3	23.9	19.1	29.1	25.3	20.1	17.0
3–4	34.5	36.1	37.7	35.1	36.7	37.8	40.0	36.7
Every day	34.2	35.6	38.4	45.9	34.2	36.9	39.9	46.3
Soybean products consumption, times/week								
≤2	27.2	21.7	18.3	14.2	21.2	15.1	10.8	10.3
3–4	33.5	33.2	33.5	29.7	30.1	28.2	27.9	24.9
Every day	39.3	45.2	48.3	56.1	48.7	56.7	61.2	64.8

Abbreviation: SD, standard deviation.
[a] All values except those for age are expressed as percentages.
[b] Maximum intake of fresh fish, boiled fish paste, and dried fish.

dividing all hematologic malignancies into lymphoid neoplasms and myeloid neoplasms, we observed similar trends in the former, but not the latter, group.

We observed associations similar to those in our primary analysis across the strata of sex and body mass index (Table 3). Furthermore, the likelihood ratio tests between the models with and without interaction were not statistically significant for both sex and body mass index; the P values were 0.80 and 0.99, respectively. Because the numbers of participants and cases in the body mass index stratum of less than 18.5 kg/m^2 were very small, we integrated it and the stratum of 18.5–24.9 kg/m^2 into a new stratum of less than 25.0 kg/m^2 in this stratified analysis.

The risks did not change considerably after we started follow-up 3 years after the baseline date (data not shown).

DISCUSSION

We observed a significant inverse association between green tea consumption and the risk of hematologic

Table 2. Hazard Ratios and 95% Confidence Intervals for the Incidence of Hematologic Malignancies According to Green Tea Consumption, the Ohsaki Cohort, Japan, 1995–2003

	Green Tea Consumption, Cups/Day				*P* for Trend[a]
	<1 (*n* = 11,093)[b]	1–2 (*n* = 9,046)	3–4 (*n* = 9,054)	≥5 (*n* = 12,568)	
All hematologic malignancies					
No. of person-years	85,080	70,127	71,075	99,730	
No. of cases (*n* = 157)	46	34	39	38	
Age- and sex-adjusted hazard ratio	1.00	0.88	0.93	0.62	0.04
95% confidence interval		0.57, 1.38	0.61, 1.43	0.40, 0.95	
Multivariate-adjusted hazard ratio[c]	1.00	0.88	0.90	0.58	0.02
95% confidence interval		0.57, 1.38	0.59, 1.39	0.37, 0.89	
Lymphoid neoplasms					
No. of person-years	85,100	70,143	71,099	99,759	
No. of cases (*n* = 119)	34	29	30	26	
Age- and sex-adjusted hazard ratio	1.00	1.02	0.97	0.57	0.03
95% confidence interval		0.62, 1.67	0.59, 1.58	0.34, 0.96	
Multivariate-adjusted hazard ratio[c]	1.00	1.00	0.92	0.52	0.01
95% confidence interval		0.61, 1.65	0.56, 1.52	0.31, 0.87	
Myeloid neoplasms					
No. of person-years	85,151	70,205	71,180	99,773	
No. of cases (*n* = 36)	11	5	9	11	
Age- and sex-adjusted hazard ratio	1.00	0.54	0.89	0.74	0.67
95% confidence interval		0.19, 1.56	0.37, 2.15	0.32, 1.71	
Multivariate-adjusted hazard ratio[c]	1.00	0.57	0.91	0.76	0.70
95% confidence interval		0.20, 1.64	0.37, 2.23	0.32, 1.78	

[a] *P* values for trend were calculated by treating the green tea consumption categories as an ordinal variable and as 2-sided.

[b] Less than 1 cup/day was chosen as the reference group.

[c] Adjusted for age (continuous variable, years), sex, educational level (<high school, high school, ≥college), cigarette smoking (never smoked, former smoker, current smoker of <20 cigarettes/day, current smoker of ≥20 cigarettes/day), alcohol drinking (never drank, former drinker, current drinker of <45.6 g ethanol/day, current drinker of ≥45.6 g ethanol/day), fish consumption (≤2 times/week, 3–4 times/week, every day), and soybean products consumption (≤2 times/week, 3–4 times/week, every day).

malignancies during 9 years of follow-up in a large population-based cohort of Japanese that included 157 cases of hematologic malignancies. This association was more apparent for lymphoid neoplasms after we categorized hematologic malignancies as lymphoid and myeloid neoplasms. Compared with participants who consumed less than 1 cup/day of green tea, those who consumed 5 cups/day or more had a 42% lower risk of hematologic malignancies and a 48% lower risk of lymphoid neoplasms.

To our knowledge, this population-based cohort study is the first to find an association between green tea consumption and hematologic malignancies; no cohort study and only 3 case-control studies have been known to assess the relation between consumption of green tea or its constituents and hematologic malignancies. In a study from China, longer duration, higher quantity, and frequency of green tea intake were associated with a reduced risk for 107 leukemia cases and 110 controls (26). A study from the United States reported that higher intake of epicatechins, one of the flavonoids present richly in green tea, was associated with lower risk of non-Hodgkin lymphoma in 466 cases and 390 controls (27). The most recent case-control study of 252 leukemia cases and 637 controls from Taiwan reported an inverse association between green tea consumption and the risk of leukemia for individuals aged 16–29 years (28). These results were consistent with those of our study; however, case-control studies are not free from selection bias or recall bias related to retrospective measurement of exposure and other possible confounding factors after a diagnosis of disease.

Table 3. Hazard Ratios and 95% Confidence Intervals for the Incidence of Hematologic Malignancies According to Green Tea Consumption, Stratified by Sex and Body Mass Index, the Ohsaki Cohort, Japan, 1995–2003

	Green Tea Consumption, Cups/Day				*P* for Trend[a]
	<1[b]	1–2	3–4	≥5	
Sex					
Men (n = 19,749)					
No. of person-years	46,846	34,859	31,310	41,333	
No. of cases (n = 88)	30	17	20	21	
Age-adjusted hazard ratio	1.00	0.75	0.85	0.63	0.15
95% confidence interval		0.41, 1.35	0.48, 1.50	0.36, 1.10	
Multivariate-adjusted hazard ratio[c]	1.00	0.75	0.82	0.57	0.07
95% confidence interval		0.41, 1.35	0.47, 1.46	0.32, 1.00	
Women (n = 22,012)					
No. of person-years	38,235	35,267	39,764	58,398	
No. of cases (n = 69)	16	17	19	17	
Age-adjusted hazard ratio	1.00	1.11	1.05	0.62	0.14
95% confidence interval		0.56, 2.19	0.54, 2.03	0.31, 1.22	
Multivariate-adjusted hazard ratio[c]	1.00	1.09	1.01	0.58	0.10
95% confidence interval		0.55, 2.16	0.52, 1.99	0.29, 1.16	
Body mass index, kg/m^2					
<25.0 (n = 28,162)					
No. of person-years	56,667	47,482	48,601	66,647	
No. of cases (n = 101)	30	20	26	25	
Age- and sex-adjusted hazard ratio	1.00	0.78	0.91	0.60	0.10
95% confidence interval		0.45, 1.38	0.54, 1.55	0.35, 1.03	
Multivariate-adjusted hazard ratio[c]	1.00	0.78	0.89	0.56	0.06
95% confidence interval		0.44, 1.38	0.52, 1.51	0.33, 0.97	
≥25.0 (n = 11,586)					
No. of person-years	23,627	19,316	19,553	29,036	
No. of cases (n = 46)	14	10	11	11	
Age- and sex-adjusted hazard ratio	1.00	0.84	0.86	0.57	0.19
95% confidence interval		0.37, 1.89	0.39, 1.90	0.26, 1.27	
Multivariate-adjusted hazard ratio[c]	1.00	0.80	0.79	0.52	0.12
95% confidence interval		0.35, 1.80	0.36, 1.77	0.23, 1.16	

[a] *P* values for trend were calculated by treating the green tea consumption categories as an ordinal variable and as 2-sided.

[b] Less than 1 cup/day was chosen as the reference group.

[c] Adjusted for age (continuous variable, years), sex, educational level (<high school, high school, ≥college), cigarette smoking (never smoked, former smoker, current smoker of <20 cigarettes/day, current smoker of ≥20 cigarettes/day), alcohol drinking (never drank, former drinker, current drinker of <45.6 g ethanol/day, current drinker of ≥45.6 g ethanol/day), fish consumption (≤2 times/week, 3–4 times/week, every day), and soybean products consumption (≤2 times/week, 3–4 times/week, every day). The model stratified by sex did not include the variable for sex.

Recent animal and in vitro studies have reported that green tea and some of its constituents, especially EGCG, have antitumor activities against several types of hematologic malignancies. For instance, green tea inhibited angiogenesis and induced apoptosis in animal models of human non-Hodgkin lymphoma (21); EGCG suppressed vascular endothelial growth factor production and induced apoptosis in chronic lymphocytic leukemia B cells (22); EGCG induced apoptotic cell death in malignant B cells in vitro (23); EGCG induced apoptotic cell death in human

lymphoblastoid B cells through several pathways, such as production of intracellular reactive oxygen species (24); and EGCG and some of the other green tea catechins inhibited matrix metalloproteinase-9 secretion, thus affecting myeloid cell differentiation and angiogenesis (25). Furthermore, a clinical case report documented antitumor effects of oral green tea extracts in 4 patients with low-grade B-cell malignancies (36). This evidence supports our results and might explain the mechanisms of the observed association of green tea with a reduced incidence of hematologic malignancies.

Our present results indicate that the preventive effect of green tea consumption against hematologic malignancies seems to have a threshold effect rather than a dose-response effect. The lower risks of hematologic malignancies were obvious only in the group consuming 5 cups or more of green tea daily (Tables 2 and 3). This result is inconsistent with recent biologic studies indicating a dose-dependent manner of green tea constituents against hematologic tumor cells (22–25). These discrepancies between animal experiments and our epidemiologic observations might be due to differences in species, metabolism of green tea constituents, accuracy of exposure measurement, degree of confounding and/or bias, and essential differences in study design. Moreover, although we observed that green tea consumption was inversely associated with the incidence of all hematologic malignancies as a whole and lymphoid neoplasms, we were unable to find any significant association with myeloid neoplasms alone. Because the number of cases of myeloid neoplasm in this study was very small, we were unable to conclude whether this lack of association was due to insufficient statistical power or to pathogenetic differences between malignant lymphoid and myeloid cells, such as differences in sensitivity to green tea constituents or in the mechanisms of development, proliferation, and/or differentiation.

Infection with human immunodeficiency virus, human T-cell leukemia virus type-1, and Epstein-Barr virus is an established risk factor for hematologic malignancies (11–13). Although we were unable to acquire any information about such viral infections in our participants, infection with human immunodeficiency virus and human T-cell leukemia virus type-1 is very rare in this region (37, 38); Japan is known to have a relatively high rate of human T-cell leukemia virus type-1 infection, but the endemic area is southern Japan, far from our study area. Epstein-Barr virus is widespread throughout the world, and most adults in any country are seropositive against Epstein-Barr virus antigen (38). We thus considered that our inability to assess infection with such viruses would not substantially distort our result.

Our study had some limitations. First, 13% of all participants were lost to follow-up. Nevertheless, this proportion did not vary across the 4 green tea consumption categories: the proportions of participants lost to follow-up at the lowest to highest green tea consumption levels were 14%, 14%, 13%, and 12%.

Second, the number of cases of hematologic malignancies among our participants was modest in comparison with the Western population. Therefore, we were unable to evaluate the association between green tea consumption and risk of each subtype of hematologic malignancy (e.g., Hodgkin lymphomas, non-Hodgkin lymphomas, lymphoid leukemias, or myeloid leukemias), even though the risk factors probably vary according to subtype.

Third, the quality and completeness of the Miyagi Cancer Registry were not high enough regarding hematologic malignancies: the level of death-certificate-only diagnosed lymphoma and leukemia was higher than 20%. Such a fairly high proportion of death-certificate-only cases might have led to failure to ascertain some individuals who had hematologic malignancies but did not die during the study period.

Fourth, we were unable to obtain enough information related to occupational exposures, ionizing radiation, benzene, and so forth, which may affect the risk of hematologic malignancies (10). Even though we added a variety of potential confounders to our analysis, there were a considerable number of unmeasured confounders.

Finally, we excluded 6,337 participants from our analysis because they provided incomplete answers for, or did not answer the question on, green tea consumption. In this excluded group, 31 cases of hematologic malignancies were diagnosed. Because the distribution of baseline characteristics among those participants was similar to that among participants in the lowest green tea consumption stratum (data not shown), we assumed that they were likely to consume no or less green tea. Using this assumption, we conducted a sensitivity analysis after including those participants in the lowest stratum of green tea consumption. The result of this analysis did not differ from that of our primary analysis: the multivariate-adjusted hazard ratios were 0.86 (95% confidence interval: 0.57, 1.30), 0.90 (95% confidence interval: 0.61, 1.34), and 0.58 (95% confidence interval: 0.39, 0.87) for 1–2, 3–4, and 5 cups/day or more, respectively, compared with less than 1 cup/day.

We previously reported that green tea consumption was not associated with risk of gastric cancer (39, 40), breast cancer (41), colorectal cancer (42), prostate cancer (43), and lung cancer (44). Hematologic malignancies are the first and only malignant tumors for which we have derived a significant inverse association with green tea consumption. The differences in evidence between our previous studies and the present one indicate that hematologic malignancies may have specific characteristics that result in a response to certain green tea components.

We concluded that green tea consumption was inversely associated with the risk of hematologic malignancies in the general rural population of Japan. Our results have implications for not only primary prevention of hematologic malignancies but also treatment and/or recurrence prevention. Further biologic studies and clinical trials are necessary to confirm the role of green tea in prevention and treatment of hematologic malignancies.

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Green tea and death from pneumonia in Japan: the Ohsaki cohort study[1–3]

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ABSTRACT

Background: Experimental and animal studies have shown the activities of catechins, the main constituents of green tea, against infectious agents. No data are available on the association between green tea consumption and the risk of pneumonia in humans.

Objective: We examined the association between green tea consumption and death from pneumonia in humans.

Design: We conducted a population-based cohort study, with follow-up from 1995 to 2006. The participants were National Health Insurance beneficiaries in Japan (19,079 men and 21,493 women aged 40–79 y). We excluded participants for whom data on green tea consumption frequency were missing or who had reported a history of cancer, myocardial infarction, stroke, and extreme daily energy intake at baseline. We used Cox proportional hazards regression analysis to calculate hazard ratios (HRs) and their 95% CIs for death from pneumonia according to green tea consumption.

Results: Over 12 y of follow-up, we documented 406 deaths from pneumonia. In women, the multivariate HRs of death from pneumonia that were associated with different frequencies of green tea consumption were 1.00 (reference) for <1 cup/d, 0.59 (95% CI: 0.36, 0.98) for 1–2 cups/d, 0.55 (95% CI: 0.33, 0.91) for 3–4 cups/d, and 0.53 (95% CI: 0.33, 0.83) for ≥5 cups/d, respectively (*P* for trend: 0.008). In men, no significant association was observed.

Conclusion: Green tea consumption was associated with a lower risk of death from pneumonia in Japanese women. *Am J Clin Nutr* 2009;90:672–9.

INTRODUCTION

Pneumonia ranks as the fourth-leading cause of death in Japan, where it is responsible for ≈10% of total deaths, despite the development of effective antimicrobial chemotherapy (1). To prevent the disease, the association between lifestyles, such as fish consumption, fatty acid consumption, smoking, alcohol consumption, or exercise, and pneumonia has been investigated with prospective cohort study design (2–5). These studies showed that smoking was a risk factor for pneumonia, but no definite conclusion was available for other factors.

For thousands of years, plants have played a significant role in maintaining human health and improving the quality of human life (6). Tea catechins, the main constituents of green tea, have received attention because of their possible antiviral and antimicrobial activities (7, 8). Experimental and animal studies have shown the activities of catechins against a variety of infectious agents (9–13). To our knowledge, no epidemiologic data are available on the association between green tea consumption and the risk of pneumonia in humans. If green tea does protect humans against pneumonia, this beverage would be a useful additional agent to ease the threat of the disease.

We therefore designed this prospective study to examine the association between green tea consumption and death from pneumonia within a large population-based cohort in Japan.

SUBJECTS AND METHODS

Study population

The present data were derived from the Ohsaki National Health Insurance (NHI) beneficiaries cohort study. The details of the study project have been described in previous reports (14, 15). In brief, we delivered a self-administered questionnaire between October and December 1994 to all NHI beneficiaries, aged 40–79 y, living in the catchment area of Ohsaki Public Health Center, Miyagi prefecture, northeast Japan. The Ohsaki Public Health Center, a local government agency, provides preventive health services for the residents of 14 municipalities in Miyagi prefecture. Of 54,996 eligible individuals, 52,029 (95%) responded. The study protocol was approved by the Tohoku University School of Medicine Ethics Committee. We considered the return of self-administered questionnaires signed by the study participants to imply their consent to participate.

From 1 January 1995, we started prospective collection of data on the date of death and withdrawal from the NHI, by obtaining NHI withdrawal history files from the local NHI Association. We excluded 776 participants because they had withdrawn from the NHI before collection of the NHI withdrawal history files. Thus, 51,253 participants formed the study cohort.

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Of these study participants, we excluded those for whom data on green tea consumption frequency were missing (n = 6791) or who reported extreme daily energy intake (n = 440; sex-specific cutoffs for upper 0.5%, 3575.2 kcal/d for men and 2286.6 kcal/d for women; for lower 0.5%, 348.9 kcal/d for men and 200.0 kcal/d for women), because an extreme numerical value might reflect possible misreporting of self-reported data on the frequency of consumption of each food. We also excluded participants who reported a history of cancer (n = 1488), myocardial infarction (n = 1238), or stroke (n = 975) at the baseline, because these diseases could have affected their diet and lifestyle. Consequently, 40,572 participants (19,079 men and 21,493 women) were included in this analysis.

Measurements

The self-administered questionnaire used in the baseline survey included items on dietary intake [40-item food-frequency questionnaire (FFQ)], history of diseases, family history of diseases, drinking habit, smoking habit, job status, education, body weight, height, time spent walking per day, and physical function status. The 40-item FFQ asked about the average frequency of consumption of each food. The frequency of green tea consumption was divided into 5 categories: never, occasional, 1–2 cups/d, 3–4 cups/d, and ≥5 cups/d. Within the study region, the volume of a typical cup of green tea is 100 mL. We had previously conducted a validation study of the FFQ (16). In brief, 113 participants provided four 3-d food records within a period of 1 y and subsequently responded to the FFQ. Spearman's correlation coefficient between the amounts of green tea consumed according to the food records and the amounts consumed according to the FFQ was 0.71 for men and 0.53 for women. We examined the daily consumption of 40 food items, total energy, and nutrients from the FFQ by converting the selected frequency category for each food to a daily intake, using portion sizes based on the median values observed in four 3-d food records.

Body mass index (BMI; in kg/m^2) was calculated from self-reported data. Physical function status was assessed by using the 6-item physical function status measure of the Medical Outcomes Study (MOS) Short-Form General Health Survey. On the basis of their responses, the subjects were classified into 3 groups: those who were able to perform vigorous or moderate activity (MOS score of 5–6), those who were capable of light activity (MOS score of 2–4), and those who were capable only of self-care or unable to do anything unaided (MOS score of 0–1).

Follow-up

The endpoint was death from pneumonia. To follow-up the participants for death and migration, we reviewed the NHI Withdrawal History files for the period from 1 January 1995 to 31 December 2006. When a participant was withdrawn from the NHI system because of death, emigration, or employment, the date of withdrawal and its reason were coded on the files. Because we were unable to obtain subsequent information on the participants who withdrew from the NHI, we discontinued follow-up of participants who withdrew from the NHI system because of emigration or employment.

Data on causes of death were based on the death certificates filed at Ohsaki Public Health Center. Death certificates must be completed by a physician, and from 1995, in Japan, the cause of death has been recorded according to the rules for selecting the underlying cause of death in the *International Statistical Classification of Diseases and Related Health Problems, 10th revision* (ICD-10) (17). All death certificates are submitted to a local government office and forwarded to the Public Health Center in the area of residence. Death certificates are then sent to the Japan Ministry of Health, Labour, and Welfare, and the primary cause of death is reassessed and coded by trained physicians according to the ICD-10. We limited deaths from influenza and pneumonia (J10–J18), and we did not include aspiration pneumonia (J69) because the cause would be largely different from the former (J10–J18). Thus, for deaths from pneumonia identified in this study, pneumonia was the primary cause of death.

Statistical analysis

From 1 January 1995 to 31 December 2006, we prospectively counted the number of person-years of follow-up for each participant from the beginning of follow-up until the date of death, withdrawal from the NHI, or the end of the study period, whichever occurred first. We used Cox proportional hazards regression analysis to calculate the hazard ratios (HRs) and their 95% CIs of death from pneumonia according to green tea consumption categories and to adjust for potentially confounding variables with the SAS version 9.1 statistical software package (SAS Institute Inc, Cary, NC). For all models, the proportional hazards assumptions were tested and met through addition of time-dependent covariates to the models. Dummy variables were created for green tea consumption categories.

We combined the lower 2 categories of green tea consumption into the single category of <1 cup/d because of the small number of participants in each of these categories (7.3% never and 19.0% occasionally). The lowest category of green tea consumption (<1 cup/d) was used as a reference category. Furthermore, we repeated the analysis based on the 5 categories of green tea consumption, without combining the lower 2 categories, using the category of never as a reference. The P values for analysis of linear trends were calculated by scoring the categories, from 1 for the lowest category to 4 for the highest category, and entering the number as a continuous term in the regression model. All reported P values were 2-tailed, and $P <$ 0.05 was considered statistically significant.

We considered the following variables to be potential confounders a priori with clinical significance: age (as a continuous variable); years of education (<10 y of education or ≥10 y of education); BMI (<18.5, 18.5–24.9, or ≥25.0); time spent walking (<1 h/d or ≥1 h/d); physical function status (those who were able to perform vigorous or moderate activity, those who were capable of light activity, those who were capable of only self-care or unable to do anything unaided); history of hypertension (yes or no); history of diabetes mellitus (yes or no); history of gastric ulcer (yes or no); history of tuberculosis (yes or no); smoking status (never, former, currently smoking <20 cigarettes/d, or currently smoking ≥20 cigarettes/d); alcohol consumption (never, former, currently); daily total energy intake (continuous variable); daily consumption of miso (soybean paste) soup (yes or no); daily consumption of soybean products, total fish, and total green or yellow vegetables (for each food, continuous variable); and consumption of coffee (<1 cup/d or