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分担研究報告書

緑茶摂取と肺炎死亡リスクに関する研究

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研究要旨

緑茶の成分であるカテキンは、細胞・動物レベルの実験により、様々な感染源に対する抗微生物作用が示されてきた。しかし、ヒトにおける緑茶摂取習慣と肺炎の関連は明らかでない。本研究の目的は、地域住民を対象とした前向きコホート研究により、緑茶摂取習慣と肺炎死亡リスクとの関連を明らかにすることである。対象は、宮城県大崎保健所管内に居住する40歳から79歳の国民健康保険加入者約50,000人であり、緑茶摂取頻度の質問に無回答の者、がん・心筋梗塞・脳卒中の既往があると回答した者などを除外した40,572人（男性：19,079人、女性：21,493人）を追跡した。12年間の追跡の結果、406例の肺炎死亡が観察された。女性では、緑茶摂取頻度の増加に伴い肺炎死亡リスクの減少がみられ、肺炎死亡リスクのハザード比（95%信頼区間）は、緑茶摂取頻度が1杯未満/日に対し、1-2杯/日では0.59（0.36-0.98）、3-4杯/日では0.55（0.33-0.91）、5杯以上/日では0.53（0.33-0.83）であった（*P* for trend: 0.008）。しかし、男性では同様の関連はみられなかった。本研究の結果、日本人女性では、緑茶摂取頻度と肺炎死亡リスクとの間に負の関連が認められた。

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A．研究目的

日本において、肺炎による死亡は全死亡数の約10%を占め、死亡原因の第4位となっている。これまでに、魚摂取、脂肪酸摂取、喫煙、アルコール摂取、運動などの生活習慣と肺炎との関連について前向きコホート研究の結果が報告されているが、喫煙が肺炎のリスクを高めること以外には結論が得られていない。

緑茶の成分であるカテキンは、抗微生物作用が注目されており、細胞・動物レベルの実験により様々な感染源に対する効果が示されてきた。しかし、ヒトにおける緑茶摂取習慣と肺炎の関連は明らかでない。

本研究の目的は、地域住民を対象とした大崎国保コホート研究の12年間の追跡データより、緑茶摂取習慣と肺炎死亡リスクとの関連を明らかにすることである。

B．研究方法

1）研究デザイン

大崎国保コホート研究は、宮城県の大崎保健所管内に居住する40歳から79歳の国民健康保険加入者全員約5万人を対象としている。1994年9月から12月に生活習慣などに関するベースライン調査を行い、1995年1月以降の死亡を追跡している。ベースライン調査は、

性、年齢などの基本的情報、病歴、身体活動能力、嗜好、食品摂取頻度調査票を含む食習慣などの健康に関する自記式質問票による調査であった。調査は訓練を受けた調査員が対象者宅を訪問して協力を依頼し、同意が得られた者について数日後に調査員が再度訪問して質問票を回収した。対象者54,996人に対し、有効回答者数は52,029人（95%）であった。

追跡調査においては、1995年1月から国民健康保険の「喪失異動データ」とのレコードリンケージにより対象者の死亡または転出による異動を追跡している。また死亡原因については死亡動態調査小票の閲覧により追跡を行っている。死亡動態調査小票閲覧については、総務省告示第706号（平成19年12月27日、官報第4738号記載）にて承認された。

2）倫理面への配慮

本研究は東北大学医学部倫理委員会の承認のもとに行われている。

3）本研究における解析対象者

ベースライン調査の有効回答者 52,029 人のうち、1995年1月の追跡開始時までに死亡または転出により異動した者（776人）、緑茶摂取頻度の質問に無回答の者（6,791人）、栄養摂取量が極度に多いまたは少ない者（440人）、がん・心筋梗塞・脳卒中の既往があった者（3,450人）を除外した40,572人（男性：19,079人、女性：21,493人）を追跡した。

4）分析項目およびエンドポイント

食品摂取頻度調査票の緑茶摂取頻度を分析項目として使用した。緑茶摂取頻度は、「飲む回数をお答えください。」という質問に対し、「飲まない、ときどき飲む、1－2杯/日、3－4杯/日、5杯以上/日」から一つを選択してもらった。この食品摂取頻度調査票については、事前に食事記録による妥当性の検証を行っており、緑茶摂取頻度における相関係数は男性0.71、女性0.53であった。

肺炎死亡については、国際疾病分類（ICD-10）により分類された「インフルエンザと肺炎」(J10-18)による死亡を対象とした。

5）分析方法

1995年1月1日から2006年12月31日までの12年間の追跡により、緑茶摂取頻度と肺炎死亡リスクとの関連について、男女別に分析を行った。食品摂取頻度調査票における緑茶摂取頻度で回答された「飲まない」群、「ときどき飲む」群を1杯未満/日群としてまとめ、1－2杯/日、3－4杯/日、5杯以上/日の4群に分け、1杯未満/日群に対するその他の群の肺炎死亡リスクを算出した。また、「飲まない」群、「ときどき飲む」群をまとめずに5群とし、「飲まない」群に対するその他の群の肺炎死亡リスクも算出した。死亡リスクの算出は、Cox 比例ハザードモデルを用いて、年齢、教育期間、BMI、1日の歩行時間、身体活動能力、高血圧・糖尿病・胃潰瘍・結核の各既往歴、喫煙歴、飲酒歴、1日の総摂取エネルギー量、みそ汁・大豆製品・魚・緑黄色野菜・コーヒーの1日の摂取量または摂取頻度を潜在的交絡因子と考え、モデルに組み込み補正した。なお、教育期間以下の項目はいずれもベースライン調査時の自己回答によっている。解析は、統計解析ソフト SAS Version 9.1 (SAS Inc、Cary NC)を用いた。

次に、年齢とともに肺炎死亡が増加すること、身体活動能力が低下している者では誤嚥性肺炎を引き起こす可能性があると考えられること、喫煙は肺炎のリスクファクターであることから、以下の層別化解析を行った。年齢(70歳未満、70歳以上)、身体活動能力(強・中等度の活動が可能、軽度の活動が可能、セルフケアのみ可能または活動できない)、喫煙歴（非喫煙者、過去喫煙者または現在喫煙者）による層別化解析である。

さらに、これまでに本コホートの結果より、緑茶摂取頻度の多い者で脳卒中死亡リスクが低下したことを報告していることから、脳卒中死亡に対する緑茶の効果と、肺炎死亡に対する緑茶の効果を鑑別する必要性があった。

そこで、高血圧の既往歴がなく、かつ喫煙歴がない者を脳卒中リスクが低いと考え、これらの対象者のみで解析を行った。

このほか、ベースライン時に診断されていなかった疾患などの影響により食事状況に変化があることも考えられるため、追跡開始後3年以内の死亡者を除いた解析も行った。

C．研究結果

12年間の追跡の結果、406例の肺炎死亡が観察された。追跡期間中に、6,033人が国民健康保険からの異動により追跡不能となり、追跡率は85.1%であった。

緑茶摂取頻度と肺炎死亡リスクとの関連を表1に示す。女性では、緑茶摂取頻度の増加に伴い肺炎死亡リスクの減少がみられたが、男性ではそのような関連はみられなかった。女性での肺炎死亡リスクのハザード比（95%信頼区間）は、緑茶摂取頻度が1杯未満/日に対し、1-2杯/日では0.59（0.36-0.98）、3-4杯/日では0.55（0.33-0.91）、5杯以上/日では0.53（0.33-0.83）であった（*P* for trend: 0.008）。この結果は、年齢のみで補正した結果と大きく変わらず、また追跡開始後3年以内の死亡者を除いた解析結果とも大きく変わらなかった。飲まない、ときどき飲む、1-2杯/日、3-4杯/日、5杯以上/日の5群での解析では、飲まない群に対し、ときどき飲む群ではハザード比0.56（0.30-1.02）、1-2杯/日では0.41（0.22-0.76）、3-4杯/日では0.38（0.21-0.70）、5杯以上/日では0.36（0.21-0.65）であった（*P* for trend: 0.002）。なお、緑茶摂取頻度と性別には交互作用が認められ（*P*= 0.01）、他の補正項目には認められなかった。

女性における年齢、身体活動能力、喫煙歴による層別化解析の結果を表2に示す。年齢による層別化解析では、70歳未満、70歳以上の両群において、緑茶摂取頻度が1杯未満/日に対する肺炎死亡リスクのハザード比の点推定値が低下していた。この結果は、65歳、75歳を境界として層別化解析を行っても同様であった。一方、表中には示していないが、男性ではこのような関連は認められなかった。次に、身体活動能力による層別化解析でも、すべてのグループ（強・中等度の活動が可能、

表1　緑茶摂取頻度による肺炎死亡リスク[1]（大崎国保コホート研究：95.1-06.12）

	緑茶摂取頻度（杯/日）				
	<1	1-2	3-4	≥5	*P* for trend
	男性（n=19,079）				
観察人年	57,481	42,963	38,830	51,309	
死亡数	75	52	55	93	
年齢補正ハザード比（95%信頼区間）	1.00（referent）	0.90（0.63-1.28）	0.81（0.57-1.15）	0.91（0.67-1.23）	0.49
多変量補正ハザード比[2]（95%信頼区間）	1.00（referent）	0.98（0.69-1.41）	1.02（0.71-1.45）	1.15（0.83-1.59）	0.38
多変量補正ハザード比[3]（95%信頼区間）	1.00（referent）	0.97（0.65-1.45）	1.07（0.73-1.56）	1.21（0.86-1.71）	0.24
	女性（n=21,493）				
観察人年	47,426	44,411	50,528	73,879	
死亡数	43	24	26	38	
年齢補正ハザード比（95%信頼区間）	1.00（referent）	0.54（0.33-0.89）	0.48（0.30-0.78）	0.44（0.29-0.68）	0.0004
多変量補正ハザード比[2]（95%信頼区間）	1.00（referent）	0.59（0.36-0.98）	0.55（0.33-0.91）	0.53（0.33-0.83）	0.008
多変量補正ハザード比[3]（95%信頼区間）	1.00（referent）	0.65（0.39-1.09）	0.56（0.33-0.94）	0.50（0.31-0.81）	0.005

[1]Cox比例ハザードモデルを用いてハザード比を算出。

[2]年齢（連続変数）、教育期間（10年未満、10年以上）、BMI（18.5未満、18.5-24.9、25.0以上）、歩行時間（1時間未満/日、1時間以上/日）、身体活動能力（強・中等度の活動が可能、軽度の活動が可能、セルフケアのみ可能または活動できない）、高血圧既往歴（あり、なし）、糖尿病既往歴（あり、なし）、胃潰瘍既往歴（あり、なし）、結核既往歴（あり、なし）、喫煙歴（非喫煙者、過去喫煙者、現在喫煙者20本未満/日、現在喫煙者20本以上/日）、飲酒歴（非飲酒者、過去飲酒者、現在飲酒者）、1日の総摂取エネルギー量（連続変数）、1日のみそ汁の摂取（あり、なし）、1日の大豆製品・魚・緑黄色野菜の各摂取量（いずれも連続変数）、1日のコーヒー摂取頻度（1杯未満、1杯以上）で補正したハザード比。

[3]追跡開始後3年以内の死亡者を除外して解析したハザード比。

表２　女性における緑茶摂取頻度と肺炎死亡リスクの関連についての層別化解析[1]
（大崎国保コホート研究：95.1-06.12）

	緑茶摂取頻度（杯/日）				P for trend	P for interaction
	<1	1-2	3-4	≥5		
【年齢】						0.15
70歳未満（n=17,235）						
観察人年	39,752	36,582	40,865	58,538		
死亡数	11	7	5	8		
多変量補正ハザード比[2]（95%信頼区間）	1.00 (referent)	0.69 (0.26-1.82)	0.38 (0.13-1.13)	0.42 (0.16-1.10)	0.05	
70歳以上（n=4,258）						
観察人年	7,673	7,829	9,662	15,341		
死亡数	32	17	21	30		
多変量補正ハザード比[2]（95%信頼区間）	1.00 (referent)	0.56 (0.31-1.02)	0.61 (0.35-1.08)	0.57 (0.34-0.96)	0.06	
【身体活動能力】						0.32
強・中等度の活動が可能（n=14,372）						
観察人年	31,638	30,038	34,326	51,240		
死亡数	11	4	9	12		
多変量補正ハザード比[3]（95%信頼区間）	1.00 (referent)	0.33 (0.10-1.05)	0.52 (0.20-1.31)	0.46 (0.20-1.11)	0.18	
軽度の活動が可能（n=4,316）						
観察人年	8,976	8,499	10,603	15,049		
死亡数	11	12	3	12		
多変量補正ハザード比[3]（95%信頼区間）	1.00 (referent)	1.00 (0.43-2.35)	0.23 (0.06-0.84)	0.58 (0.24-1.36)	0.07	
セルフケアのみ可能または活動できない（n=2,235）						
観察人年	5,350	4,564	4,634	5,844		
死亡数	21	7	13	12		
多変量補正ハザード比[3]（95%信頼区間）	1.00 (referent)	0.38 (0.16-0.92)	0.62 (0.30-1.30)	0.45 (0.22-0.95)	0.07	
【喫煙歴】						0.31
非喫煙者（n=15,317）						
観察人年	32,973	32,321	37,575	52,132		
死亡数	26	21	21	25		
多変量補正ハザード比[4]（95%信頼区間）	1.00 (referent)	0.81 (0.45-1.46)	0.67 (0.37-1.21)	0.56 (0.32-0.99)	0.04	
過去喫煙者（n=439）または現在喫煙者（n=1,229）						
観察人年	4,682	2,880	2,751	6,124		
死亡数	7	1	0	3		
多変量補正ハザード比[4]（95%信頼区間）	1.00 (referent)	0.11 (0.01-1.09)	-	0.13 (0.02-0.67)	0.01	

[1]Cox比例ハザードモデルを用いてハザード比を算出。

[2]年齢（連続変数）、教育期間（10年未満、10年以上）、BMI（18.5未満、18.5-24.9、25.0以上）、歩行時間（1時間未満/日、1時間以上/日）、身体活動能力（強・中等度の活動が可能、軽度の活動が可能、セルフケアのみ可能または活動できない）、高血圧既往歴（あり、なし）、糖尿病既往歴（あり、なし）、胃潰瘍既往歴（あり、なし）、結核既往歴（あり、なし）、喫煙歴（非喫煙者、過去喫煙者、現在喫煙者20本未満/日、現在喫煙者20本以上/日）、飲酒歴（非飲酒者、過去飲酒者、現在飲酒者）、1日の総摂取エネルギー量（連続変数）、1日のみそ汁の摂取（あり、なし）、1日の大豆製品・魚・緑黄色野菜の各摂取量（いずれも連続変数）、1日のコーヒー摂取頻度（1杯未満、1杯以上）で補正したハザード比。

[3]年齢（連続変数）、教育期間（10年未満、10年以上）、BMI（18.5未満、18.5-24.9、25.0以上）、歩行時間（1時間未満/日、1時間以上/日）、高血圧既往歴（あり、なし）、糖尿病既往歴（あり、なし）、胃潰瘍既往歴（あり、なし）、結核既往歴（あり、なし）、喫煙歴（非喫煙者、過去喫煙者、現在喫煙者20本未満/日、現在喫煙者20本以上/日）、飲酒歴（非飲酒者、過去飲酒者、現在飲酒者）、1日の総摂取エネルギー量（連続変数）、1日のみそ汁の摂取（あり、なし）、1日の大豆製品・魚・緑黄色野菜の各摂取量（いずれも連続変数）、1日のコーヒー摂取頻度（1杯未満、1杯以上）で補正したハザード比。

[4]年齢（連続変数）、教育期間（10年未満、10年以上）、BMI（18.5未満、18.5-24.9、25.0以上）、歩行時間（1時間未満/日、1時間以上/日）、身体活動能力（強・中等度の活動が可能、軽度の活動が可能、セルフケアのみ可能または活動できない）、高血圧既往歴（あり、なし）、糖尿病既往歴（あり、なし）、胃潰瘍既往歴（あり、なし）、結核既往歴（あり、なし）、飲酒歴（非飲酒者、過去飲酒者、現在飲酒者）、1日の総摂取エネルギー量（連続変数）、1日のみそ汁の摂取（あり、なし）、1日の大豆製品・魚・緑黄色野菜の各摂取量（いずれも連続変数）、1日のコーヒー摂取頻度（1杯未満、1杯以上）で補正したハザード比。

軽度の活動が可能、セルフケアのみ可能または活動できない）において、緑茶摂取頻度１杯未満/日に対する肺炎死亡リスクのハザード比の点推定値が低下していた。これについても、男性では明らかな関連は認められなかった。喫煙歴による層別化解析では、非喫煙者では緑茶摂取頻度の増加に伴い肺炎死亡リスクの有意な低下がみられたが、男性ではいずれのグループでも明らかな関連は認められなかった。

次に、脳卒中リスクが低いと考えられる対象者（高血圧の既往歴なし、かつ喫煙歴なし）13,735人について解析した結果は、以下の通りであった。緑茶摂取頻度が１杯未満/日に対する肺炎死亡リスクのハザード比は、１-２杯/日では 0.65（0.30-1.40）、３-４杯/日では 0.80（0.41-1.57）、５杯以上/日では 0.77（0.41-1.43）であり、点推定値が低下していた（*P* for trend: 0.52）。

D．考　察

本研究は、緑茶摂取と肺炎死亡リスクとの関連を明らかにした初めての前向きコホート研究であり、女性において緑茶摂取と肺炎死亡リスクとの間に負の関連が認められた。この結果は、カテキンの抗微生物作用に関するこれまでの細胞・動物レベルの実験の結果に一致する。

今回、緑茶摂取と肺炎死亡リスクには、女性では負の関連が認められたが、男性では明らかな関連が認められず、性別により異なる結果となった。男性では、女性に比べ喫煙者が多いことから、この違いは喫煙の影響によるものと推測された。しかし、喫煙歴による層別化解析の結果より、女性では非喫煙者において肺炎死亡リスクの低下が認められたものの、男性では喫煙歴による関連の違いが認められなかった。また、緑茶摂取頻度と喫煙歴には交互作用が認められなかった。そのため、本研究では緑茶摂取と肺炎死亡リスクとの関連における男女差の原因は明らかにすることはできなかった。

これまでに本コホートでは、緑茶摂取頻度の多い者で脳卒中死亡リスクが低下したことを報告している。そのため、今回得られた緑茶摂取頻度の増加に伴う肺炎死亡リスク低下の関連は、脳卒中のように肺炎を引き起こすような疾患に対する緑茶の効果を反映した結果である可能性も考えられた。しかし、脳卒中リスクが低いと考えられる対象者（高血圧の既往歴なし、かつ喫煙歴なし）のみでの解析においても、同様の結果が得られた。また日本では、死亡原因は ICD-10 の原死因選択ルールに基づき選択されている。そのため、例えば、脳卒中に関連して発症したと考えられる肺炎は脳卒中として分類され、脳卒中に関連せずに発症したと考えられる肺炎は肺炎と診断される。以上の点より、今回得られた結果は、肺炎に対する緑茶の効果を示した結果であると考えられる。

また緑茶摂取が多いほど肺炎死亡リスクが低いという結果は、誤嚥性肺炎を引き起こすような衰弱した身体状況により仲介された関連である可能性が考えられた。しかし、今回の解析対象は、「インフルエンザと肺炎」（ICD-10、J10-18）であり、誤嚥性肺炎を含む「固形物及び液状物による肺臓炎」（同、J69）は対象としなかった。また、統計学的に交絡因子を制御した上で解析を行い、追跡開始後３年以内の死亡者を除いた解析でも同様の結果であった。さらに、年齢上昇とともに肺炎死亡が増加することから、年齢による層別化解析を行ったが、女性においては、70 歳未満でも 70 歳以上でも、緑茶摂取頻度の増加とともに肺炎死亡リスクが低下していた。次に、身体活動能力が低下している者では誤嚥性肺炎を引き起こす可能性があると考えられるため、身体活動能力による層別化解析を行ったが、すべてのグループ（強・中等度の活動が可能、軽度の活動が可能、セルフケアのみ可能または活動できない）において、緑茶摂取頻度の増加とともに肺炎死亡リスクが低下していた。以上より、緑茶摂取が多いほど肺炎死亡リスクが低いという本研究の結果は、誤嚥性肺炎を引き起こすような衰弱した身体状況により仲介された関連である可能性は少ないと考える。

今回得られた女性での肺炎死亡リスクのハザード比は、緑茶摂取頻度が１杯未満/日に対し、1－2杯/日では 0.59、3－4杯/日では 0.55、５杯以上/日では 0.53 であり、1－2杯/日の摂取から急激にリスクが低下する閾値反応が認められた。飲まない、ときどき飲む、1－2杯/日、3－4杯/日、５杯以上/日の５群での解析においても、同様に閾値反応が認められた。この結果については、摂取頻度が最も少ない群の対象者は、それ以外の群の対象者とは食事内容や健康状態が異なるためではないかという懸念がある。しかし、解析の際には、食事内容、健康状態も含め交絡因子と考えられる要因をモデルに組み込み補正しており、年齢補正モデルからの大きなハザード比の変化もみられなかった。また、果物・野菜の摂取が全死因死亡・がん死亡・循環器疾患死亡リスクを低下させる

という先行研究では、本研究と同様に閾値反応が報告されていることから、緑茶、果物、野菜などに含まれるポリフェノールでは、このような閾値反応的な効果を示す可能性が考えられる。

最後に、本研究では、緑茶摂取に関する情報はベースライン時の一時点で得られている、肺炎の原因について不明である、残差交絡の可能性がある、脳卒中を原因とする肺炎を除外できていない可能性がある、という点で限界がある。ベースライン調査後の緑茶摂取頻度の変化は不明であるが、その変化は双方向（摂取頻度が増加あるいは減少）であると考えられるため、本結果は過小評価の可能性がある。次に、肺炎の原因については、死亡診断書には原因菌の記載はないため、死亡した406例の96%は「肺炎、病原体不詳」(ICD-10、J18)に分類されていた。しかし、肺炎の原因を調査した先行研究でも、多くの原因は不明となっており、原因菌を明らかにすることは困難であると考えられる。交絡因子については、潜在的交絡因子と予測される項目については、統計学的に制御を試みている。また、脳卒中など他の疾患を原因とする肺炎の除外については、死因分類が ICD-10 の原死因選択ルールに基づいている点、誤嚥性肺炎を含む「固形物及び液状物による肺臓炎」による死亡は対象としていない点から、除外できていない可能性は小さいと考えられる。

E．結　論

日本人の一般住民を対象とした前向きコホート研究において、女性では、緑茶摂取頻度の増加に伴い肺炎死亡リスクの減少がみられたが、男性では同様の関連はみられなかった。

F．健康危険情報

なし

G．研究発表

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H．知的財産権の出願・登録状況

なし

Ⅳ．研究成果の刊行に関する一覧

研究成果の刊行に関する一覧

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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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[2] Supported by a Health Sciences Research Grant for Health Services (H18-Choju-Ippan-014, H20-Choju-Ippan-001, H20-Junkankitou [Seisyu]-Ippan-013), Ministry of Health, Labour, and Welfare, Japan.

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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

≥1 cup/d). To correct the estimate for socioeconomic status, the models were adjusted for years of education. Time spent walking was used as an indicator of physical activity because it is the most common type of physical activity among middle-aged and older individuals in Japan. The validity and reproducibility of the question on time spent walking has been reported previously (18). Before including the above variables into the multivariate models, interactions between green tea consumption and confounders were tested through the addition of cross-product terms to the multivariate model.

We conducted stratified analyses by age, physical function status, and smoking status. We stratified by age (<70 y or ≥70 y), because death from pneumonia increases with age (19, 20). We also stratified by physical function status, because we considered that the participants with limited physical function (MOS score of 0–1) would be at high risk of aspiration pneumonia. In addition, stratified analysis by smoking status was conducted, because smoking is a risk factor for pneumonia (4, 5). For stroke, our previous study found an inverse association between green tea consumption and death from stroke (15). Therefore, to

TABLE 1
Baseline characteristics of men according to green tea consumption (n = 19,079)

	Green tea consumption				
Characteristics	<1 cup/d (n = 5775)	1–2 cups/d (n = 4313)	3–4 cups/d (n = 3897)	≥5 cups/d (n = 5094)	P value[1]
Age (y)	57.2 ± 10.7[2]	57.3 ± 10.8	59.8 ± 10.3	61.4 ± 9.9	<0.0001
Years of education [n (%)]					<0.0001
<10 y	3460 (62.6)	2356 (56.6)	2206 (58.5)	3041 (61.6)	
≥10 y	2067 (37.4)	1808 (43.4)	1564 (41.5)	1894 (38.4)	
BMI [n (%)]					<0.006
<18.5 kg/m^2	179 (3.3)	138 (3.4)	103 (2.7)	193 (3.9)	
18.5–24.9 kg/m^2	3824 (69.6)	2929 (71.0)	2713 (72.2)	3489 (71.3)	
≥25.0 kg/m^2	1489 (27.1)	1056 (25.6)	942 (25.1)	1215 (24.8)	
Time spent walking [n (%)]					<0.006
<1 h/d	2676 (49.9)	2062 (51.0)	1960 (53.7)	2443 (51.4)	
≥1 h/d	2685 (50.1)	1979 (49.0)	1693 (46.3)	2308 (48.6)	
Physical function status [n (%)]					<0.0001
Able to perform vigorous or moderate activity	4663 (83.0)	3579 (85.2)	3258 (85.6)	4251 (85.3)	
Capable of light activity	627 (11.1)	411 (9.8)	388 (10.2)	527 (10.6)	
Capable of self-care or unable to do anything	329 (5.9)	210 (5.0)	160 (4.2)	203 (4.1)	
History of hypertension [n (%)]					<0.0001
Yes	1238 (21.4)	1003 (23.3)	986 (25.3)	1248 (24.5)	
No	4537 (78.6)	3310 (76.7)	2911 (74.7)	3846 (75.5)	
History of diabetes mellitus [n (%)]					0.09
Yes	386 (6.7)	284 (6.6)	304 (7.8)	371 (7.3)	
No	5389 (93.3)	4029 (93.4)	3593 (92.2)	4723 (92.7)	
History of gastric ulcer [n (%)]					0.002
Yes	1102 (19.1)	848 (19.7)	794 (20.4)	1116 (21.9)	
No	4673 (80.9)	3465 (80.3)	3103 (79.6)	3978 (78.1)	
History of tuberculosis [n (%)]					<0.0001
Yes	205 (3.5)	151 (3.5)	206 (5.3)	307 (6.0)	
No	5570 (96.5)	4162 (96.5)	3691 (94.7)	4787 (94.0)	
Smoking status [n (%)]					<0.0001
Never	1151 (21.7)	804 (20.4)	722 (19.9)	824 (17.5)	
Former	1289 (24.3)	964 (24.4)	1022 (28.2)	1349 (28.6)	
Current, <20 cigarettes/d	930 (17.6)	713 (18.0)	650 (17.9)	898 (19.1)	
Current, ≥20 cigarettes/d	1926 (36.4)	1471 (37.2)	1230 (34.0)	1640 (34.8)	
Alcohol consumption [n (%)]					<0.0001
Never	931 (16.5)	615 (14.6)	563 (14.8)	918 (18.5)	
Former	540 (9.6)	379 (9.0)	372 (9.8)	547 (11.1)	
Current	4161 (73.9)	3214 (76.4)	2865 (75.4)	3490 (70.4)	
Total energy intake (kcal/d)	1783 ± 612.5	1812 ± 603.3	1852 ± 587.7	1901 ± 591.3	<0.0001
Daily dietary consumption					
Miso (soybean paste) soup [n (%)]	4914 (85.1)	3807 (88.3)	3504 (89.9)	4633 (91.0)	<0.0001
Soybean products (g/d)	47 ± 28.7	50 ± 28.3	53 ± 27.7	57 ± 26.9	<0.0001
Total fish (g/d)	55 ± 35.5	58 ± 34.8	61 ± 34.3	67 ± 34.6	<0.0001
Green or yellow vegetables (g/d)	62 ± 42.9	67 ± 43.2	72 ± 43.3	78 ± 45.9	<0.0001
Coffee, ≥1 cup/d [n (%)]	2357 (44.3)	1892 (50.9)	1415 (42.5)	1513 (35.7)	<0.0001

[1] ANOVA or chi-square test.
[2] Mean ± SD (all such values).

distinguish the relation between green tea consumption and pneumonia risk and that between green tea consumption and stroke risk, we conducted a sensitivity analysis with the use of a subset of data that was restricted to participants with a very low risk of stroke, who had no history of hypertension, and had never smoked.

To minimize the possibility that diet or lifestyle factors had changed in response to subclinical disease, we repeated all analyses after excluding participants who had died in the first 3 y of follow-up. To ensure that the estimates were not biased by multicollinearity, the age-adjusted HRs for the green tea consumption categories were also calculated and compared with the multivariate-adjusted HRs.

RESULTS

Baseline characteristics of the participants according to green tea consumption category are shown in **Table 1** and **Table 2**.

TABLE 2
Baseline characteristics of women according to green tea consumption (n = 21,493)

	Green tea consumption				
Characteristics	<1 cup/d (n = 4877)	1–2 cups/d (n = 4458)	3–4 cups/d (n = 4950)	≥5 cups/d (n = 7208)	P value[1]
Age (y)	58.5 ± 10.8[2]	59.6 ± 10.5	61.2 ± 9.7	62.2 ± 9.2	<0.0001
Years of education [n (%)]					<0.0001
<10 y	2683 (58.9)	2288 (54.3)	2545 (54.0)	3980 (58.0)	
≥10 y	1689 (41.1)	1926 (45.7)	2167 (46.0)	2877 (42.0)	
BMI [n (%)]					0.003
<18.5 kg/m^2	209 (4.6)	158 (3.7)	192 (4.1)	252 (3.7)	
18.5–24.9 kg/m^2	2942 (64.3)	2770 (65.3)	3096 (65.5)	4,335 (62.9)	
≥25.0 kg/m^2	1422 (31.1)	1317 (31.0)	1438 (30.4)	2301 (33.4)	
Time spent walking [n (%)]					0.0006
<1 h/d	2444 (55.7)	2295 (56.1)	2670 (59.2)	3836 (58.7)	
≥1 h/d	1941 (44.3)	1794 (43.9)	1843 (40.8)	2703 (41.3)	
Physical function status [n (%)]					<0.0001
Able to perform vigorous or moderate activity	3171 (67.1)	2963 (68.6)	3313 (68.4)	4925 (70.0)	
Capable of light activity	936 (19.8)	859 (19.9)	1039 (21.4)	1482 (21.1)	
Capable of self-care or unable to do anything	621 (13.1)	496 (11.5)	494 (10.2)	624 (8.9)	
History of hypertension [n (%)]					<0.0001
Yes	1203 (24.7)	1212 (27.2)	1413 (28.5)	2157 (29.9)	
No	3674 (75.3)	3246 (72.8)	3537 (71.5)	5051 (70.1)	
History of diabetes mellitus [n (%)]					0.06
Yes	252 (5.2)	204 (4.6)	264 (5.3)	413 (5.7)	
No	4625 (94.8)	4254 (95.4)	4686 (94.7)	6795 (94.3)	
History of gastric ulcer [n (%)]					0.70
Yes	531 (10.9)	510 (11.4)	545 (11.0)	774 (10.7)	
No	4346 (89.1)	3948 (88.6)	4405 (89.0)	6434 (89.3)	
History of tuberculosis [n (%)]					0.0002
Yes	123 (2.5)	102 (2.3)	161 (3.2)	253 (3.5)	
No	4754 (97.5)	4356 (97.7)	4789 (96.8)	6955 (96.5)	
Smoking status [n (%)]					<0.0001
Never	3370 (87.5)	3231 (91.6)	3654 (92.9)	5062 (89.3)	
Former	112 (2.9)	84 (2.4)	91 (2.3)	152 (2.7)	
Current, <20 cigarettes/d	236 (6.1)	138 (3.9)	146 (3.7)	316 (5.6)	
Current, ≥20 cigarettes/d	136 (3.5)	73 (2.1)	44 (1.1)	140 (2.4)	
Alcohol consumption [n (%)]					<0.0001
Never	2883 (70.7)	2697 (73.0)	3092 (74.9)	4341 (72.4)	
Former	220 (5.4)	146 (3.9)	159 (3.9)	248 (4.1)	
Current	977 (23.9)	853 (23.1)	876 (21.2)	1407 (23.5)	
Total energy intake (kcal/d)	1188 ± 365.9	1231 ± 347.9	1268 ± 329.8	1310 ± 330.4	<0.0001
Daily dietary consumption					
Miso (soybean paste) soup [n (%)]	4004 (82.1)	3886 (87.2)	4409 (89.1)	6395 (88.7)	<0.0001
Soybean products (g/d)	43 ± 24.2	47 ± 23.1	50 ± 22.0	51 ± 21.5	<0.0001
Total fish (g/d)	47 ± 30.6	50 ± 30.3	54 ± 29.0	57 ± 29.7	<0.0001
Green or yellow vegetables (g/d)	72 ± 47.0	81 ± 47.4	85 ± 46.6	89 ± 48.4	<0.0001
Coffee, ≥1 cup/d [n (%)]	1829 (42.2)	1783 (47.0)	1599 (39.1)	1715 (29.4)	<0.0001

[1] ANOVA or chi-square test.
[2] Mean ± SD (all such values).

Men and women with higher green tea consumption were significantly older and had a history of hypertension and tuberculosis, but they were less likely to have time spent walking. They were also more likely to have a higher energy intake and to consume individual foods such as miso soup, soybean products, total fish, and total green or yellow vegetables. No apparent associations were observed between green tea consumption categories and years of education and alcohol consumption. Men were more likely to have a history of gastric ulcer, but they were less likely to be obese and to have never smoked. Women were more likely to be obese and to have a history of diabetes mellitus.

Over 12 y of follow-up (406,824 person-years), we documented 406 deaths from pneumonia. A total of 6033 participants were lost to follow-up during the study period because of withdrawal from the NHI system, and the follow-up rate was 85.1%. The association between green tea consumption and the HRs and associated 95% CIs of death from pneumonia are shown in **Table 3**. We found inverse associations between green tea consumption and death from pneumonia in women but not in men. In women, the multivariate HRs of death from pneumonia 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 (*P* for trend: 0.008). Comparison between the age-adjusted model and the multivariate model suggested that the estimates were not biased by multicollinearity. The multivariate HRs of death from pneumonia according to the 5 categories of green tea consumption, without combining the lower 2 categories, were 1.00 (reference) for never, 0.56 (95% CI: 0.30, 1.02) for occasional, 0.41 (95% CI: 0.22, 0.76) for 1–2 cups/d, 0.38 (95% CI: 0.21, 0.70) for 3–4 cups/d, and 0.36 (95% CI: 0.21, 0.65) for ≥5 cups/d (*P* for trend: 0.002). When we excluded the 47 participants who died within the first 3 y of follow-up, the results did not change substantially.

We also tested the interaction between green tea consumption and confounders through the addition of cross-product terms to the multivariate model. Interaction between green tea consumption and sex was statistically significant ($P = 0.01$), but no interaction between green tea consumption and the other variables was observed.

The multivariate HRs of death from pneumonia according to green tea consumption stratified by age, physical function status, and smoking status in women are shown in **Table 4**. Among participants aged <70 y and participants aged ≥70 y, the point estimates of the HRs for death from pneumonia were below unity. In contrast, in men, no apparent association was observed between green tea consumption and HRs of death from pneumonia among participants aged <70 y and those aged ≥70 y. Although we additionally conducted stratified analyses by age at 65 y and 75 y, the results also did not change substantially. For physical function status, in men, no apparent association was observed between green tea consumption and the HRs of death from pneumonia in all subgroups. In women, in all subgroups, the point estimates of the HRs for death from pneumonia were below unity, although the trend test showed no statistically significant relations. Among never smokers in women, green tea consumption was substantially associated with a low risk of death from pneumonia. Because the number of deaths from pneumonia in former smokers and current smokers was insufficient for separate analysis, we combined the data of the former smokers and current smokers. In contrast, for men, no apparent association was observed between green tea consumption and the HRs of death from pneumonia among the participants in all subgroups.

When analysis was restricted to the 13,735 participants with a low risk of stroke, who had no history of hypertension and had never smoked, the point estimates of the HRs for death from pneumonia were below unity. The multivariate HRs were 1.00

TABLE 3
Hazard ratios (HRs) of death from pneumonia according to green tea consumption in Japan[1]

	Green tea consumption				
	<1 cup/d	1–2 cups/d	3–4 cups/d	≥5 cups/d	*P* for trend
Men (*n* = 19,079)					
Person-years	57,481	42,963	38,830	51,309	
No. of deaths	75	52	55	93	
Age-adjusted HR[2]	1.00 (referent)	0.90 (0.63, 1.28)	0.81 (0.57, 1.15)	0.91 (0.67, 1.23)	0.49
Multivariate HR[2,3]	1.00 (referent)	0.98 (0.69, 1.41)	1.02 (0.71, 1.45)	1.15 (0.83, 1.59)	0.38
Multivariate HR[2–4]	1.00 (referent)	0.97 (0.65, 1.45)	1.07 (0.73, 1.56)	1.21 (0.86, 1.71)	0.24
Women (*n* = 21,493)					
Person-years	47,426	44,411	50,528	73,879	
No. of deaths	43	24	26	38	
Age-adjusted HR[2]	1.00 (referent)	0.54 (0.33, 0.89)	0.48 (0.30, 0.78)	0.44 (0.29, 0.68)	0.0004
Multivariate HR[2,3]	1.00 (referent)	0.59 (0.36, 0.98)	0.55 (0.33, 0.91)	0.53 (0.33, 0.83)	0.008
Multivariate HR[2–4]	1.00 (referent)	0.65 (0.39, 1.09)	0.56 (0.33, 0.94)	0.50 (0.31, 0.81)	0.005

[1] HRs were calculated by Cox proportional hazard regression analysis.
[2] 95% CIs in parentheses.
[3] Adjusted for age (continuous variable); years of education (<10 or ≥10 y); BMI (in kg/m^2; <18.5, 18.5–24.9, or ≥25.0); time spent walking (<1 or ≥1 h/d); physical function status (those able to perform vigorous or moderate activity, those capable of light activity, or those capable of self-care or unable to do anything); 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, or currently drinking); daily total energy intake (continuous variables); 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 daily consumption of coffee (<1 or ≥1 cup).
[4] Participants who died in the first 3 y of follow-up were excluded from this analysis.

TABLE 4
Stratified analysis of the association between green tea and death from pneumonia in women[1]

	Green tea consumption					
	<1 cup/d	1–2 cups/d	3–4 cups/d	≥5 cups/d	*P* for trend	*P* for interaction
Age						0.15
<70 y (*n* = 17,235)						
Person-years	39,752	36,582	40,865	58,538		
No. of deaths	11	7	5	8		
Multivariate HR[2,3]	1.00 (referent)	0.69 (0.26, 1.82)	0.38 (0.13, 1.13)	0.42 (0.16, 1.10)	0.05	
≥70 y (*n* = 4258)						
Person-years	7673	7829	9662	15,341		
No. of deaths	32	17	21	30		
Multivariate HR[2]	1.00 (referent)	0.56 (0.31, 1.02)	0.61 (0.35, 1.08)	0.57 (0.34, 0.96)	0.06	
Physical function status						0.32
Able to perform vigorous or moderate activity (*n* = 14,372)						
Person-years	31,638	30,038	34,326	51,240		
No. of deaths	11	4	9	12		
Multivariate HR[3,4]	1.00 (referent)	0.33 (0.10, 1.05)	0.52 (0.20, 1.31)	0.46 (0.20, 1.11)	0.18	
Capable of light activity (*n* = 4316)						
Person-years	8976	8499	10,603	15,049		
No. of deaths	11	12	3	12		
Multivariate HR[3,4]	1.00 (referent)	1.00 (0.43, 2.35)	0.23 (0.06, 0.84)	0.58 (0.24, 1.36)	0.07	
Capable of self-care or unable to do anything (*n* = 2235)						
Person-years	5350	4564	4634	5844		
No. of deaths	21	7	13	12		
Multivariate HR[3,4]	1.00 (referent)	0.38 (0.16, 0.92)	0.62 (0.30, 1.30)	0.45 (0.22, 0.95)	0.07	
Smoking status						0.31
Never (*n* = 15,317)						
Person-years	32,973	32,321	37,575	52,132		
No. of deaths	26	21	21	25		
Multivariate HR[3,5]	1.00 (referent)	0.81 (0.45, 1.46)	0.67 (0.37, 1.21)	0.56 (0.32, 0.99)	0.04	
Former (*n* = 439) or current (*n* = 1229)						
Person-years	4682	2880	2751	6124		
No. of deaths	7	1	0	3		
Multivariate HR[3,5]	1.00 (referent)	0.11 (0.01, 1.09)	—	0.13 (0.02, 0.67)	0.01	

[1] Hazard ratios (HRs) were calculated by Cox proportional hazard regression analysis and were adjusted for age (continuous variable); years of education (<10 or ≥10 y); BMI (in kg/m^2; <18.5, 18.5–24.9, or ≥25.0); time spent walking (<1 or ≥1 h/d); 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); alcohol consumption (never, former, or currently drinking); daily total energy intake (continuous variables); 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 daily consumption of coffee (<1 or ≥1 cup).

[2] Additionally adjusted for physical function status (those able to perform vigorous or moderate activity, those capable of light activity, or those capable of self-care or unable to do anything) and smoking status (never, former, currently smoking <20 cigarettes/d, or currently smoking ≥20 cigarettes/d).

[3] 95% CIs in parentheses.

[4] Additionally adjusted for smoking status (never, former, currently smoking <20 cigarettes/d, or currently smoking ≥20 cigarettes/d).

[5] Additonally adjusted for physical function status (those able to perform vigorous or moderate activity, those capable of light activity, or those capable of self-care or unable to do anything).

(reference) for <1 cup/d, 0.65 (95% CI: 0.30, 1.40) for 1–2 cups/d, 0.80 (95% CI: 0.41, 1.57) for 3–4 cups/d, and 0.77 (95% CI: 0.41, 1.43) for ≥5 cups/d (*P* for trend: 0.52).

DISCUSSION

This is the first prospective cohort study to have investigated the association between green tea consumption and death from pneumonia. Our study showed an inverse association between green tea consumption and death from pneumonia in women. This finding was consistent with in vitro and animal studies that have shown activities of catechins against a variety of infectious agents (9–13).

Our study showed a discrepancy between men and women for the association between green tea consumption and risk of death from pneumonia. We first considered that this discrepancy might be attributable to the effect of cigarette smoking, because the smoking rate was higher in men than in women. However, inverse associations were observed among never smokers in women (Table 4), and no apparent associations were observed for any smoking status among men. In addition, no interaction between green tea consumption and smoking status was observed. We therefore secondly considered that catechin activities might differ between men and women. It has been reported that tea catechins may have estrogenic activity, which might partly account for the discrepancy between men and women

(21). However, the reasons for the discrepancy remain largely uncertain.

Our previous study also indicated an inverse association between green tea consumption and death as a result of cardiovascular disease, and this inverse association was stronger in women (15). Therefore, the present results could be interpreted as not only an effect of green tea in preventing pneumonia, but also as an effect of green tea in preventing other diseases that are associated with pneumonia risk, such as stroke. We did not follow the incidence of stroke that had occurred after the baseline survey. However, the results of sensitivity analysis of participants with a low risk of stroke, who had no history of hypertension and had never smoked, showed an inverse association between green tea consumption and risk of death from pneumonia. In Japan, primary cause of death has been determined according to the rules for selecting the underlying cause of death in the ICD-10. Therefore, death from pneumonia associated with previous stroke was classified as stroke, and pneumonia unrelated to previous stroke was classified as pneumonia. The present results might therefore be interpreted as an effect of green tea against infection.

The observed inverse associations between green tea consumption and death from pneumonia might be mediated by health and comorbidities that lead to aspiration pneumonia. However, we limited deaths from influenza and pneumonia (J10–J18), and we did not include aspiration pneumonia (J69). We also statistically controlled for a variety of potential confounding factors in the multivariate-adjusted model and conducted analyses after excluding participants who had died in the first 3 y of follow-up. In addition, we conducted a stratified analysis by age, because death from pneumonia increases with age (19, 20). The inverse association between green tea consumption and risk of death from pneumonia was consistently observed in women, irrespective of whether they were aged <70 y or aged ≥ 70 y. We also conducted a stratified analysis by physical function status, because we considered that participants with limited physical function would be at higher risk of aspiration pneumonia. The inverse association between green tea consumption and risk of death from pneumonia was consistently observed, irrespective of whether participants were able to perform vigorous or moderate activity, light activity, or merely self-care or unable to do anything unaided. The finding that their 95% CIs were not significant might have been due to lack of statistical power. Therefore, the observed inverse associations between green tea consumption and death from pneumonia might not be mediated by health and comorbidities that lead to aspiration pneumonia.

Our finding of an inverse association between green tea consumption and death from pneumonia appeared to be a threshold effect. In women, the multivariate HRs of death from pneumonia compared with <1 cup/d were 0.59 for 1–2 cups/d, 0.55 for 3–4 cups/d, and 0.53 for ≥ 5 cups/d. The results of analysis according to the 5 categories, without combining the lower 2 categories of green tea consumption, also showed a threshold effect. In other words, persons consuming ≥ 1 cup/d might receive the benefit from the beverage. There may be differences in dietary intake and health characteristics besides green tea consumption between the lowest fourth and the highest three-fourths of the distribution. However, in our models we adjusted for various potential confounders, and the estimates did not change substantially from the age-adjusted estimates. Furthermore, a previous study showed that higher intakes of fruit and vegetables were associated with lower risk of death from all causes, cancer, and cardiovascular disease, and that the association appeared to be a threshold effect (22). Taken together, the results might indicate that polyphenols, contained in fruit and vegetables as well as green tea, might operate through a threshold effect.

Our study had several limitations. First, we collected the information on green tea consumption only once before the follow-up period. Therefore, measurement error caused by changes in green tea consumption over time among the subjects could have distorted our results. However, this misclassification may be nondifferential and would tend to result in underestimation of the effect of green tea consumption. Second, we had no information about the cause of pneumonia. Of 406 deaths from pneumonia, 96% were classified as organism unspecified (J18) because such information was not provided on the death certificates. However, the causative agent responsible for pneumonia is rarely identified, even in rigorous epidemiologic studies of pneumonia (23, 24). Third, although we statistically controlled for a variety of potential confounding factors in the multivariate-adjusted model, conducted analyses after excluding participants who had died in the first 3 y of follow-up, and conducted a stratified analysis by age and physical function status, we were unable to eliminate residual confounding. In addition, we were unable to fully exclude the possibility that the death from pneumonia might have included pneumonia associated with previous stroke, although the primary cause of death was determined according to the rules for selecting the underlying cause of death in the ICD-10. Aspiration pneumonia also might have been coded as death from pneumonia, although we limited deaths from pneumonia (J10–J18), and we did not include aspiration pneumonia (J69). Therefore, clinical trials are ultimately necessary to confirm the protective effect of green tea on death from pneumonia.

In conclusion, this prospective cohort study has shown an inverse association between green tea consumption and death from pneumonia among Japanese women. Our data showed the effect of green tea consumption against pneumonia and support the possibility that green tea components exert antiviral and antimicrobial activities against a variety of infectious agents.

The authors' responsibilities were as follows—IW: designed the study, analyzed and interpreted the data, and prepared the manuscript; SK: designed the study, acquired the data, analyzed and interpreted the data, prepared the manuscript, and supervised the study; MK, TS, KOM, NK, and AH: acquired data and analyzed and interpreted the data; and IT: designed the study, acquired and interpreted the data, obtained funding, and supervised the study. None of the authors had a conflict of interest.

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Original Article

Factors Associated With Psychological Distress in a Community-Dwelling Japanese Population: The Ohsaki Cohort 2006 Study

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ABSTRACT

Background: In Asia, there has been no population-based epidemiological study using the K6, a 6-item instrument that assesses nonspecific psychological distress.

Methods: Using cross-sectional data from 2006, we studied 43 716 (20 168 men and 23 548 women) community-dwelling people aged 40 years or older living in Japan. We examined the association between psychological distress and demographic, medical, lifestyle, and social factors by using the K6, with psychological distress defined as 13 or more points out of a total of 24 points.

Results: The following variables were significantly associated with psychological distress among the population: female sex, young and old age, a history of serious disease (hypertension, diabetes mellitus, stroke, myocardial infarction, or cancer), current smoking, former alcohol drinking, low body mass index, shorter daily walking time, lack of social support (4 of 5 components), and lack of participation in community activities (4 of 5 components). Among men aged 40 to 64 years, only "lack of social support for consultation when in trouble" and a history of diabetes mellitus remained significant on multivariate analysis. Among men aged 65 years or older, age was not significantly associated with psychological distress, and the significant association with current smoking disappeared on multivariate analysis. Among women aged 40 to 64 years, a history of stroke was not associated with psychological distress. Among women aged 65 years or older, the significant association with current smoking disappeared on multivariate analysis.

Conclusions: A number of factors were significantly associated with psychological distress, as assessed by the K6. These factors differed between men and women, and also between middle-aged and elderly people.

Key words: cross-sectional; K6; population-based; psychological distress

INTRODUCTION

Mental health is an important component of overall well-being. About 14% of the global disease burden has been attributed to mental illness, mostly due to the chronically disabling nature of depression and other common mental disorders.[1,2] Although numerous studies have produced systematic evidence regarding the risk factors for physical health, the understanding of factors related to mental health, particularly in Asian countries, is still limited.[2]

In 2002, in an attempt to devise a method to easily assess mental health in general population surveys, Kessler and colleagues developed a scale of nonspecific psychological distress—the K6—that comprises only 6 questions.[3] The K6 was originally developed to identify persons with a high likelihood of developing mental conditions, such as depression and mood or anxiety disorders.[4] However, the K6 and the K10 (the K6 plus 4 additional questions related to symptoms of distress) have also been used to estimate the prevalence of nonspecific psychological distress in general population surveys,[5] and as part of the World Health Organization's World Mental Health Surveys.[6] Although it is brief enough to be added to lengthy general health questionnaires, a major limitation of the K6 is that it does not

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provide information on the particular psychiatric diagnosis or diagnoses a respondent may have. Nevertheless, researchers have begun to use the K6 for studies in clinical settings,[7] as well as in epidemiological studies[8,9] and large, nationally representative surveys. Despite the frequent use of the K6, no population-based epidemiological study has used this scale to clarify the factors associated with mental health in Asian countries.

The objective of the present study was to use the K6 to identify factors associated with psychological distress in a community-dwelling Japanese population. We also briefly describe the overall design of the study, as this is the first report from a new prospective cohort study, the Ohsaki Cohort 2006 Study.

METHODS

Study design, setting, and participants

The Ohsaki Cohort 2006 Study is a prospective cohort study, from which we analyzed cross-sectional data from a baseline survey. The source population for the baseline survey comprised community-dwelling individuals aged 40 years or older who were included in the Residential Registry for Ohsaki City, Miyagi Prefecture, northeastern Japan, as of December 1, 2006. The Residential Registry identified 78 101 persons (36 397 men; 41 704 women) living in the area.

The baseline survey was conducted from December 1 to December 15, 2006. A questionnaire was distributed by the heads of individual administrative districts to individual households, and returned by mail. Of the 78 101 persons, 866 were ineligible due to death, move-out, or hospitalization, yielding an eligible population of 77 235. The baseline questionnaires (described below) were collected from 50 210 persons, and valid responses were received from 49 855 (22 547 men and 27 308 women), who ultimately formed the study population of cohort participants. Among the study population, 26 512 persons (53.2%) were aged 40 to 64 years, and 23 343 (46.8%) were aged 65 years or older. The response rate was calculated by dividing the study population by the total eligible population, yielding 64.5%. The corresponding response rates, with respect to sex and age categories, were 54.9% and 60.4% among men and women aged 40 to 64 years, respectively, and 77.1% and 73.2% among men and women aged 65 years or older, respectively.

When analyzing the prevalence of psychological distress and its associations with demographic, medical, lifestyle, and social factors, we excluded participants for whom K6 data were missing ($n = 6139$). Consequently, the analyzed population comprised 43 716 participants (20 168 men and 23 548 women; 56.6% of the eligible population).

Baseline survey

The baseline questionnaires for persons aged 40 to 64 years consisted of the following details in sequence: (1) history of diseases, (2) family history of diseases, (3) health status during the preceding year, (4) smoking status, (5) alcohol drinking status, (6) dietary habits,[10] (7) job status and educational status, (8) present and past body weight and height, (9) health status in general, (10) sports and exercise,[11,12] (11) psychological distress (K6),[3,4] (12) social support,[13] (13) participation in community activities, (14) dental status, and (15) reproductive factors (among women).

The baseline questionnaires for persons aged 65 years or older consisted of the following details in sequence: (1) a frailty checklist (the Kihon checklist),[14] (2) history of diseases, (3) health status during the preceding year, (4) smoking status, (5) alcohol drinking status, (6) dietary habits,[10] (7) past body weight and height, (8) health status in general, (9) pain, (10) daily activities, (11) sports and exercise,[11,12] (12) psychological distress (K6),[3,4] (13) social support,[13] (14) participation in community activities, and (15) dental status.

Questionnaire items for persons aged 65 years or older were identical to those for persons aged 40 to 64 years, except that the former excluded family history of diseases, job status and educational status, present and past body weight and height, and reproductive factors in women, and included the frailty checklist, past body weight and height, pain, and daily activities.

Measurement of psychological distress

The K6 was used as an indicator of psychological distress.[3,4] The 6 questions were as follows: "Over the last month, how often did you feel: (1) nervous, (2) hopeless, (3) restless or fidgety, (4) so sad that nothing could cheer you up, (5) that everything was an effort, (6) worthless?" Participants were asked to respond by choosing "all of the time" (4 points), "most of the time" (3 points), "some of the time" (2 points), "a little of the time" (1 point), and "none of the time" (0 points). Total point score therefore ranged from 0 to 24. The K6 has been developed using modern psychometric theory and has been shown to be superior to some existing scales in brevity and psychometric properties.[3,4,15] The Japanese version of the K6 has been recently developed, using the standard back-translation method, and has been validated.[16] As suggested by Kessler and colleagues,[15] we classified participants with scores of 13 points or more as having psychological distress.

Measurement of other variables

The degree of social support available to each person was assessed by asking the following questions[13]: (1) Do you have someone with whom you can consult when you are in trouble?, (2) Do you have someone with whom you can consult when your physical condition is bad?, (3) Do you have someone who can help you with your daily housework?, (4) Do you have someone who can take you to a hospital when you do not feel well?, and (5) Do you have someone

who can take care of you when you are ill in bed? This social support questionnaire consisted of 5 questions, each requiring an answer of yes or no. This questionnaire was only available in Japanese, and its validity and reliability were not evaluated.

The frailty checklist is a tool developed by the Japanese Ministry of Health, Labour, and Welfare to screen for frail persons and is designed to measure actual task performance.[14] Researchers have also begun to use this tool in epidemiological surveys.[14]

Ethical issues

The return of questionnaires completed by the participants was regarded as consent to participate in the study, which involved cross-sectional analysis of the baseline survey data and the longitudinal study of subsequent mortality and immigration. The study protocol was reviewed and approved by the Ethics Committee of Tohoku University Graduate School of Medicine.

Statistical analysis

We used univariate and multivariate logistic regression analysis to calculate the odds ratios (ORs) for psychological distress (a K6 total score of ≥13 points) relative to demographic, medical, lifestyle, and social factors. In these analyses, we investigated the following factors: sex, age (40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84, ≥85 years), history of hypertension (yes, no), history of diabetes mellitus (yes, no), history of stroke (yes, no), history of myocardial infarction (yes, no), history of cancer (yes, no), smoking status (never, former, current), alcohol drinking (never, former, current), body mass index (kg/m^2) calculated with self-reported weight and height; <18.5, 18.5–24.9, ≥25.0), daily walking time (<30 min/day, 30 min–1 hour/day, ≥1 hour/day), social support (yes, none), participation in community activities (yes, none). In the multivariate models, the above variables were all adjusted for each other. Analyses were repeated by stratifying the population by sex and age categories (40–64 years, 65 years or older). When analyzing the data for men and women aged 40 to 64 years, we further added current employment status (yes, no) and duration of education (≤12 years, >12 years) as covariates. All statistical analyses were performed with SAS version 9.1 (SAS Inc., Cary, NC, USA), and all statistical tests were 2-sided. A P value less than 0.05 was considered to indicate statistical significance.

RESULTS

Prevalence proportion, and univariate and multivariate analysis of psychological distress among the total population

The crude prevalence proportion of psychological distress in the analyzed population was 6.7% (2921/43 716; 95% confidence interval [CI], 6.5 to 6.9). Univariate analysis showed that the following were significantly associated with a higher prevalence of psychological distress: female sex, young and old age, a history of serious disease, a current smoking habit, a former alcohol drinking habit, low BMI, shorter daily walking time, lack of social support, and lack of participation in community activities.

After mutual adjustment for the variables shown in Table 1, women had approximately 1.6 times the odds of psychological distress, relative to men. There was a U-shaped association between age category (5-year categories from 40–44 to ≥85 years) and the prevalence of psychological distress, with a nadir for those aged 65 to 69 years.

History of hypertension, diabetes mellitus, stroke, myocardial infarction, or cancer were all associated with a significantly higher prevalence of psychological distress in the multivariate models (Table 1). Among these diseases, a history of stroke was most strongly associated with psychological distress, and had more than 2 times the odds of psychological distress, relative to those who had no history of stroke.

A current smoking habit (vs never smoker), former smoking habit (vs never smoker), former alcohol drinking habit (vs never drinker), low BMI (vs normal BMI), and less daily walking time (vs time spent walking ≥1 hr) were associated with a higher odds for psychological distress, even in multivariate analysis (Table 1). In contrast, a moderate daily walking time (vs time spent walking ≥1 hr) was associated with a significantly lower odds.

Among the variables studied, lack of social support for consultation when in trouble was most strongly associated with a high prevalence of psychological distress in the multivariate models, although the association between other components of lack of social support and psychological distress was substantially attenuated in multivariate analysis (Table 1). The multivariate-adjusted OR (95% CI) for psychological distress associated with lack of social support for consultation when in trouble was 2.24 (1.97 to 2.56). The association of lack of participation in community activities with psychological distress was also attenuated, but lack of participation in neighborhood association activities, sports or exercise, volunteering, and community social gatherings were all associated with a higher prevalence of psychological distress, even in multivariate analysis.

Stratified analysis by sex and age categories (40 to 64 years, 65 years or older)

Stratified analysis by sex and age categories (40 to 64 years, 65 years or older) yielded results similar to those for the participants as a whole (Table 1), but the statistically significant associations that had been observed between several factors and psychological distress disappeared in each stratum.