Table 4. Relative risks for total death according to quintiles of each lipid parameters after excluding subjects with hepatic abnormality or died within 3 years

## Total Death

| | | Quintiles | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| | | Quintile 1 | Quintile 2 | Quintile 3 | Quintile 4 | Quintile 5 | Trend P |
| TC | No | 1293 | 1282 | 1324 | 1305 | 1311 | |
| | Median (range) | 158 (94–171) | 181(172–189) | 199 (190–208) | 219 (209–232) | 250 (233–425) | |
| | No. of events | 96 | 95 | 82 | 68 | 92 | |
| | RR (95%CI) | 1.22 (0.90–1.64) | 1.27 (0.94–1.70) | 1.00 reference | 0.76 (0.55–1.05) | 0.99 (0.74–1.34) | 0.011 |
| | P | 0.194 | 0.119 | reference | 0.102 | 0.967 | |
| HDLC | No | 1297 | 1305 | 1321 | 1293 | 1299 | |
| | Median (range) | 37 (15–42) | 46 (42–49) | 53 (49–57) | 62 (57–67) | 75 (67–141) | |
| | No. of events | 109 | 90 | 96 | 82 | 56 | |
| | RR (95%CI) | 0.92 (0.70–1.21) | 0.85 (0.64–1.14) | 1.00 reference | 0.91 (0.68–1.22) | 0.77 (0.55–1.078) | 0.543 |
| | P | 0.792 | 0.280 | reference | 0.532 | 0.123 | |
| NonHDLC | No | 1300 | 1303 | 1308 | 1301 | 1303 | |
| | Median (range) | 103 (51–115) | 125 (115–135) | 144 (135–153) | 165 (154–179) | 198 (179–344) | |
| | No. of events | 86 | 81 | 92 | 79 | 95 | |
| | RR (95%CI) | 1.27 (0.94–1.71) | 1.06 (0.78–1.43) | 1.00 reference | 0.82 (0.60–1.10) | 0.97 (0.72–1.29) | 0.028 |
| | P | 0.122 | 0.715 | reference | 0.188 | 0.816 | |
| TC/HDLC | No | 1303 | 1303 | 1303 | 1303 | 1303 | |
| | Median (range) | 2.6 (1.5–2.9) | 3.1 (2.9–3.4) | 3.7 (3.4–4.0) | 4.4 (4.0–5.0) | 5.7 (5.0–13.7) | |
| | No. of events | 72 | 74 | 90 | 92 | 105 | |
| | RR (95%CI) | 1.12 (0.85–1.59) | 0.93 (0.68–1.26) | 1.00 reference | 0.92 (0.69–1.23) | 0.98 (0.74–1.30) | 0.381 |
| | P | 0.333 | 0.635 | reference | 0.580 | 0.897 | |

TC, total cholesterol; HDLC, high–density lipoprotein cholesterol; NonHDLC, non high–density lipoprotein cholesterol; TC/HDLC, TC to HDLC ratio

Table 5. Relative risks for CVD death according to quintiles of each lipid parameters after excluding subjects with hepatic abnormality or died within 3 years

| CVD Death | | Quintiles | | | | | |
|---|---|---|---|---|---|---|---|
| | | Quintile 1 | Quintile 2 | Quintile 3 | Quintile 4 | Quintile 5 | Trend P |
| TC | No | 1293 | 1282 | 1324 | 1305 | 1311 | |
| | Median (range) | 158 (94–171) | 181(172–189) | 199 (190–208) | 219 (209–232) | 250 (233–425) | |
| | No. of events | 26 | 30 | 21 | 20 | 25 | |
| | RR (95%CI) | 1.29 (0.72–2.32) | 1.55 (0.89–2.72) | 1.00 | 0.89 (0.48–1.64) | 1.06 (0.59–1.90) | 0.148 |
| | P | 0.387 | 0.123 | reference | 0.710 | 0.609 | |
| HDLC | No | 1297 | 1305 | 1321 | 1293 | 1299 | |
| | Median (range) | 37 (15–42) | 46 (42–49) | 53 (49–57) | 62 (57–67) | 75 (67–141) | |
| | No. of events | 33 | 21 | 32 | 24 | 12 | |
| | RR (95%CI) | 0.83 (0.51–1.36) | 0.60 (0.35–1.04) | 1.00 | 0.78 (0.46–1.33) | 0.51 (0.26–0.98) | 0.444 |
| | P | 0.792 | 0.071 | reference | 0.367 | 0.044 | |
| NonHDLC | No | 1300 | 1303 | 1308 | 1301 | 1303 | |
| | Median (range) | 103 (51–115) | 125 (115–135) | 144 (135–153) | 165 (154–179) | 198 (179–344) | |
| | No. of events | 21 | 29 | 23 | 22 | 27 | |
| | RR (95%CI) | 1.26 (0.69–2.30) | 1.54 (0.88–2.67) | 1.00 | 0.93 (0.52–1.67) | 1.12 (0.64–1.96) | 0.259 |
| | P | 0.450 | 0.127 | reference | 0.810 | 0.701 | |
| TC/HDLC | No | 1303 | 1303 | 1303 | 1303 | 1303 | |
| | Median (range) | 2.6 (1.5–2.9) | 3.1 (2.9–3.4) | 3.7 (3.4–4.0) | 4.4 (4.0–5.0) | 5.7 (5.0–13.7) | |
| | No. of events | 17 | 23 | 26 | 26 | 30 | |
| | RR (95%CI) | 0.98 (0.53–1.81) | 1.0.1 (0.58–1.78) | 1.00 | 0.92 (0.54–1.59) | 0.99 (0.58–1.67) | 0.912 |
| | P | 0.916 | 0.916 | reference | 0.776 | 0.813 | |

CVD, cardiovascular disease; TC, total cholesterol; HDLC, high–density lipoprotein cholesterol; NonHDLC, non high–density lipoprotein cholesterol; TC/HDLC, TC to HDLC ratio

肥満(BMI)と脳卒中の関連

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## I 肥満　と BMI (Body Mass Index)

　日本肥満学会では、「肥満は脂肪組織の過剰な蓄積状態」と定義されているが、体内の脂肪組織の量を正確に測定することは難しい。

　体格の指標には様々なものがあるが、体重と身長を測定するだけで簡単に計算できる指標として BMI（Body Mass Index ＝ 体重(kg) / 身長(m) $^2$）がある。これは体脂肪量とよく相関すると考えられている。

## II 欧米の肥満とわが国の肥満

　大規模な疫学研究は、欧米で行われていることが多いが、欧米の肥満の基準とアジア地域の肥満の基準は異なっている。WHO（世界保健機関）では BMI≧30kg/m² を肥満としているが、日本肥満学会の定義では、BMI≧25kg/m² を肥満と判定している。さらに、長期の追跡研究においてアジアの集団を対象に実施されているものは少ない。アジア地域の成人男女において、BMI の平均値は欧米の BMI と比較して低いが、アジアの民族は欧米の同じ値の BMI の人より、脂肪の割合が高いことが知られている。

　わが国において BMI の平均値は年々上昇しており、特に男性にその傾向が著しい[2]。このように、肥満の及ぼす影響は欧米諸国のみの問題ではなく、わが国を含むアジアの諸国においても同様に深刻である。

## III 脳卒中

　脳血管障害について WHO（1970）は、脳の病理学的変化に基づいて、くも膜下出血、脳内出血、脳虚血性壊死（脳梗塞）の3型に分類している。わが国の死亡者数は 2005 年で 132,847 人（死亡率 105.3 人口 10 万対）と、全死亡の 12.3％を占める。また、患者調査によると 2005 年の総患者数は 136 万 5 千人にのぼる。

## IV 脳卒中における BMI の位置づけ

　高い Body Mass Index (BMI)は虚血性心疾患の危険因子として知られているが、脳卒中死亡との関連については議論の残るところである。Stroke Council of the American Heart Association のガイドラインの中では、肥満は"less well documented or potentially modifiable risk factors"に分類されている [1]。いくつかの先行研究では特に脳梗塞において、肥満と脳卒中の関連は正であると認めているが、U字型を示すとの報告もある。

脳血管疾患はわが国の死因の第3位であり、介護が必要となった原因の第1位を占める。患者の生活の質や社会的負担も含めて、予防は重要であり、変化可能な因子である肥満と脳卒中の関係を明らかにすることは公衆衛生学的にも意義深い。

V NIPPON DATA80(19年追跡)におけるBMIと脳卒中

BMIが年齢およびその他の因子を調整した全脳卒中、脳梗塞、脳出血死亡に及ぼす影響について、Coxの比例ハザードモデル を用いてハザード比を求めた。BMIの区分は、WHOの基準に従ったが、ほとんどの対象者が含まれてしまう普通体重のカテゴリーは2分し、<18.5, 18.5-22.9, 23.0-24.9, 25.0-29.9, ≧30kg/m²の5グループに分けて、23.0-24.9kg/m²を基準とした。

BMIグループ別にみた脳梗塞死亡のハザード比と95%信頼区間を図1に示した。U字型の関連がBMIと脳梗塞死亡で観察された。男女合わせた解析ではハザード比の上昇に統計学的有意差が認められた。男女別の解析の結果を表1に示す[3]。それぞれ最も高いBMIグループ（≧30kg/m²）で、統計学的に有意差は認められなかったが最も高いハザード比を示した。低いBMIでハザード比が上昇する傾向は男性にのみ限って見られた。

全脳卒中死亡のハザード比は、脳梗塞と同じような傾向を示したが、年齢、喫煙、飲酒習慣といった交絡因子のみを調整したモデルでは有意差は認められなかった。

悪性腫瘍や慢性炎症性疾患の影響や因果の逆転を考慮して、追跡開始最初の2年間を除いた解析を行ったが、同じような結果が観察された。

VI 解釈上の注意

いくつかの追跡研究は脳卒中、特に脳梗塞ではBMIが高くなるとリスクが高くなると報告している。また、研究としては腹部の肥満が全身の肥満よりリスクの上昇と関連するとしているものもある。肥満は高血圧、糖尿病、高コレステロール血症と強く関連していることが知られており、メタボリックシンドロームが脳梗塞のリスクになっているということも確立している。しかし、HDLコレステロール値や中性脂肪、HOMA indexなどメタボリックシンドロームの鍵となる因子を測定していないためこれ以上の評価が困難で今後の課題と考える。

男性の低いBMIグループで高いハザード比が観察された理由の一つとして致死率が考えられる。本研究ではエンドポイントが死亡のみを扱っているため、死亡以外の転帰をとったものの影響が含まれない。

観察研究で体重と死亡率の関係を観察する際、いくつかの方法論的な問題がある。一つはもともと疾患があるために体重が減少しているということ（因果の逆転）と、喫煙による交絡、それから高血圧、高コレステロール血症、高血糖などによって本来の肥満の影響が薄められてしまうということである。実際、血圧、総コレステロール

値などは男女ともに高い BMI グループで高い傾向を示すが、その反対に喫煙者の割合は、低い BMI で高い傾向を示す。そのため、低 BMI のリスクを解釈する際は十分な注意が必要である。

　脳梗塞死亡のハザード比に関して男性でU字が観察されたが、女性では観察されなかった。BMI の平均は女性では年齢が高くなるにつれて高くなる傾向があったのに対し、男性では、BMI の平均は 40 代、50 代で高くなり、その後年齢が高くなるに従って低くなるので、年齢の影響がモデルで調整しても完全に取り除けないのではないかと推測される。このように因果の逆転と、交絡の影響をコホート研究から完全に調整することは難しい。したがって、低 BMI と死亡のリスクを評価、考察する際は十分に注意しなければならない。

Ⅶまとめ

　日本の代表集団である NIPPON DATA からは、BMI と脳梗塞死亡においてU字の関係が見られ、BMI≧30kg/m² ではハザード比が有意に高かった。また、低い BMI のハザード比の上昇は男性に限って観察された。

【文献】

1) Goldstein LB, Adams R, Becker K, Furberg CD, Gorelick PB, Hademenos G, Hill M, Howard G, Howard VJ, Jacobs B, Levine SR, Mosca L, Sacco RL, Sherman DG, Wolf PA, del Zoppo GJ: Primary prevention of ischemic stroke: a statement for healthcare professionals from the stroke council of the American Heart Association. Stroke 2001;32:280-299.

2) Yoshiike N, Seino F, Tajima S, Arai Y, Kawano M, Furuhata T, Inoue S: Twenty-year changes in the prevalence of overweight in Japanese adults: the national nutrition survey 1976-95. Obes Rev 2002;3:183-190.

3) Oki I, Nakamura Y, Okamura T, Okayama A, Hayakawa T, Kita Y, Ueshima H. NIPPON DATA80 Research Group. Body mass index and risk of stroke mortality among a random sample of Japanese adults: 19-year follow-up of NIPPON DATA80. Cerebrovasc Dis 2006; 22: 409-415.

# 図1．BMI(Body Mass Index)と脳梗塞死亡の関連（男女計）
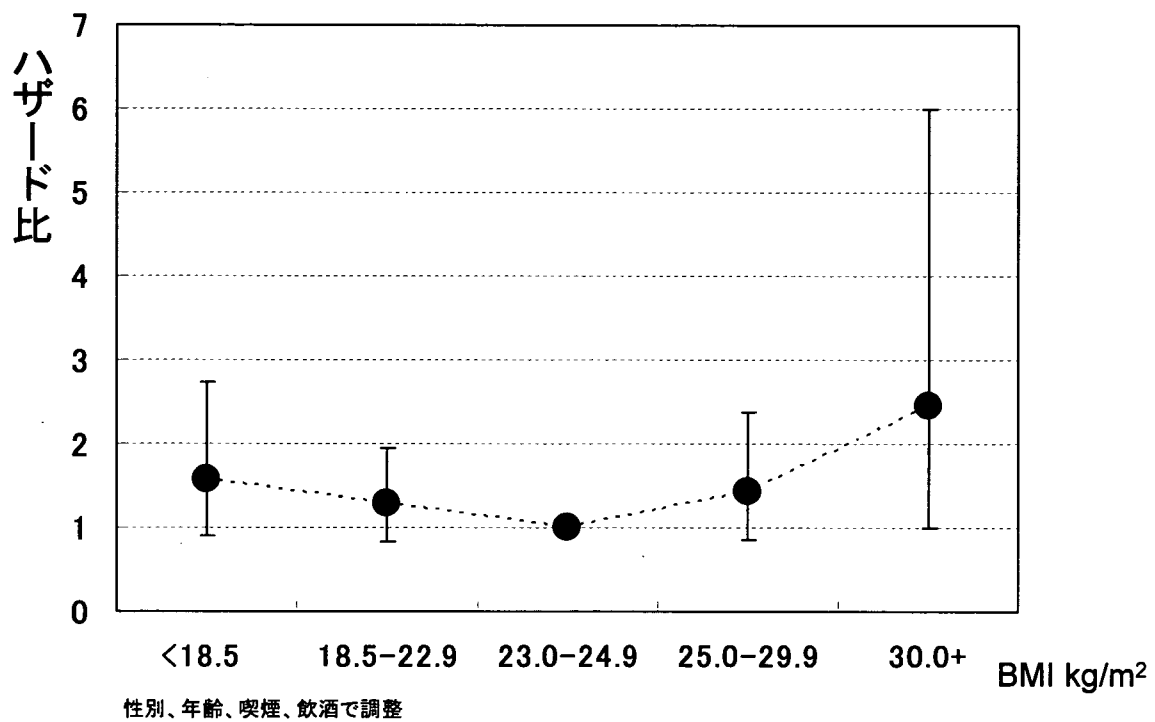## NIPPON DATA80(19年追跡)



性別、年齢、喫煙、飲酒で調整

**表1. BMI(Body Mass Index)別全脳卒中、脳梗塞、脳出血のハザード比と95% 信頼区間**
**NIPPON DATA80(19年追跡)**

| Body Mass Index (kg/m²) | 全脳卒中 | | 脳梗塞 | | 脳出血 | |
|---|---|---|---|---|---|---|
| | ハザード比 (95% 信頼区間) | | ハザード比 (95% 信頼区間) | | ハザード比 (95% 信頼区間) | |
| 男 | | | | | | |
| <18.5 | 1.64 ( 0.89 , 3.03 ) | | 2.64 ( 1.22 , 5.70 ) | | 0.92 ( 0.23 , 3.74 ) | |
| 18.5-22.9 | 1.58 ( 0.99 , 2.51 ) | | 1.85 ( 0.97 , 3.53 ) | | 1.40 ( 0.57 , 3.44 ) | |
| 23.0-24.9 | 1.00 ( reference ) | | 1.00 ( reference ) | | 1.00 ( reference ) | |
| 25.0-29.9 | 1.62 ( 0.91 , 2.9 ) | | 2.02 ( 0.91 , 4.45 ) | | 1.39 ( 0.45 , 4.34 ) | |
| ≥30.0 | 3.60 ( 0.84 , 15.36 ) | | 4.59 ( 0.59 , 35.75 ) | | 5.75 ( 0.69 , 48.1 ) | |
| 女 | | | | | | |
| <18.5 | 0.79 ( 0.40 , 1.55 ) | | 0.92 ( 0.37 , 2.26 ) | | 1.06 ( 0.27 , 4.18 ) | |
| 18.5-22.9 | 0.95 ( 0.63 , 1.44 ) | | 0.91 ( 0.51 , 1.63 ) | | 0.99 ( 0.40 , 2.42 ) | |
| 23.0-24.9 | 1.00 ( reference ) | | 1.00 ( reference ) | | 1.00 ( reference ) | |
| 25.0-29.9 | 0.97 ( 0.59 , 1.58 ) | | 1.04 ( 0.53 , 2.05 ) | | 0.58 ( 0.17 , 1.99 ) | |
| ≥30.0 | 1.47 ( 0.68 , 3.17 ) | | 1.72 ( 0.63 , 4.68 ) | | 1.79 ( 0.37 , 8.63 ) | |

年齢・喫煙・飲酒で調整

# 喫煙と高血圧は日本人の循環器疾患死亡の何％を説明するのか？

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*背景：*高血圧と喫煙は循環器疾患死亡の主要な危険因子であることが知られている。この２つの危険要因が循環器疾患死亡に寄与する割合は、肥満が少なく糖尿病や高脂血症の頻度の小さいわが国において大きいことが予測される。しかしながらこれら２つの危険因子によってどの程度の循環器疾患死亡や総死亡が説明されるかについての検討はまだ無かった。

*方法：*国民の代表性集団とみなすことができる NIPPON DATA80 の対象者のうち、循環器疾患の既往のない 8912 名の男女を追跡した。対象者をそれぞれ非喫煙非高血圧群、喫煙非高血圧群、非喫煙高血圧群、喫煙高血圧群の４群に分類した。この集団の循環器疾患死亡、総死亡のリスク比をコックス比例ハザードモデルを用いて推定し、喫煙・高血圧の循環器疾患死亡ならびに総死亡に対する人口寄与危険度割合を算出した。

*結果：*19 年間の観察期間中に男性で 313 例、女性で 291 例の循環器疾患死亡を観察した。また同様に男性で 948 例、女性で 766 例の総死亡を観察した。集団全体における喫煙・高血圧が循環器疾患死亡に占める人口寄与危険度割合は男性で 35.1％、女性で 22.1％であった。この寄与は若年者で大きく、60 歳未満の男性においては、喫煙と高血圧で循環器疾患死亡の 57.4％、女性では循環器疾患死亡の 40.7％がそれぞれ説明された。一方、60 歳以上集団においてはその寄与は比較的小さかった（男性　26.3％、女性 18.1％）。

*結論：*防煙教育・禁煙等の喫煙対策、高血圧の予防が日本及び肥満の頻度が少ないアジア地域において、循環器疾患死亡減少に大きな利益をもたらす可能性が示された。この効果は若年者でより大きいことが示唆されており、幼少期、青年期からの防煙教育、高血圧予防が重要であることが明らかとなった。この時期に健康的な生活習慣が獲得されれば、中・壮年期以降における循環器死亡の予防にも大きく寄与すると考えられる。

*Original Article*

# Joint Impact of Smoking and Hypertension on Cardiovascular Disease and All-Cause Mortality in Japan: NIPPON DATA80, a 19-Year Follow-Up

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Hypertension and smoking are major risk factors for death due to cardiovascular disease (CVD). These attributions for CVD mortality should be higher in the countries where obesity-related conditions are uncommon. However, the joint effect of these risk factors on CVD and all-cause mortality have not been described. We followed a representative 8,912 Japanese men and women without a history of stroke and heart disease. Participants were categorized into 4 groups as follows: a group of individuals who neither smoked nor had hypertension (HT), a group of current smokers, a group with HT, and a group of current smokers with HT. We further calculated population-attributable fractions (PAF) of CVD and all-cause mortality based on relative hazards assessed by proportional hazard regression models. After 19 years of follow-up, we observed 313 and 291 CVD and 948 and 766 all-cause deaths for men and women, respectively. The PAF of CVD mortality due to smoking or HT were 35.1% for men and 22.1% for women. The PAF of CVD mortality was higher in participants <60 years of age (57.4% for men and 40.7% for women) *vs.* those who were older (26.3% for men and 18.1% for women). Aggressive attempts to discourage smoking and to curb HT could yield large health benefits in Japan and throughout Asia, particularly for those aged <60 years. Efforts to warn about the adverse consequence of HT and smoking during adolescence and youth could yield the greatest health benefits, since positive behaviors adopted early are more easily continued into middle adulthood and later life. (*Hypertens Res* 2007; 30: 1169–1175)

*Key Words*: hypertension, smoking, population attributable fraction, epidemiology, prospective studies

# Introduction

Hypertension (HT) is one of the strongest risk factors for cardiovascular disease (CVD) (*1*). Smoking is also an important risk factor for CVD mortality (*2*). The prevalence of smoking and HT in Japan (*3, 4*) and in other Asian countries is excessive (*5–9*). Thus, the impact of HT and smoking on CVD mortality should be high in Japanese and throughout Asia.

Although several studies have described the higher population-attributable risk fraction (PAF) of CVD due to HT alone or smoking alone in Japan (*10, 11*) and in other Asian populations (*8, 9*), the numbers of CVD and all-cause deaths that could jointly be explained by HT and smoking in Japan have not been examined. Understanding the joint contribution of HT and smoking to CVD could help guide Japan and other Asian countries in formulating programs that warn of the adverse consequences of these risk factors, particularly in areas where obesity-related conditions are relatively uncommon (*12*).

In addition, since previous studies have suggested that the relative risk of smoking alone or HT alone on CVD mortality is stronger in younger than in older individuals (*10, 11*), the combined impact of HT and smoking on CVD and all-cause mortality might also differ by age group.

Therefore, to describe the amount of CVD and all-cause mortality that could be explained by current smoking and HT in Japan, we calculated the age-specific joint impact of smoking and HT on CVD and all-cause mortality using a representative national survey with a high follow-up rate.

# Methods

## Study Participants

The subjects of this cohort study participated in the National Cardiovascular Survey of 1980. The standardized procedures used in that survey have been described elsewhere (*13*). All household members ≥30 years of age were surveyed in 300 census tracts that were randomly selected throughout Japan.

The number of individuals selected was 13,771. Among these, 10,546 individuals had completed baseline information regarding age, gender, and blood pressure (BP). The sample comprised the National Integrated Project for Prospective Observation of Noncommunicable Disease and Its Trends in the Aged (NIPPON DATA80) (*4, 13–15*). Thus, 76.6% of the overall population was available for analysis. From this sample, we excluded participants with a history of stroke (*N*=117), coronary heart disease (*N*=163) or other heart diseases (*N*=475). An additional 32 were excluded who lacked data on BP, glucose, cholesterol, and smoking and drinking habits. There were 847 participants who were excluded because they had missing residential information and mortality follow-up. The final sample thus included 8,912 participants (3,963 men and 4,949 women). Compared to those not excluded (*N*=8,912), the excluded group due to loss to follow-up was younger (self-reported age: 46.3 years *vs.* 49.6 years) and less likely to smoke cigarettes (33% *vs.* 39%). These differences, however, appeared to be modest. There were no differences with respect to gender (women comprised 56% of both groups) or age-adjusted BP.

## Data Collection

The baseline survey included medical examinations, BP measurements, blood tests, and a self-administered questionnaire about lifestyle. Trained staff at local health centers in the respective districts performed the examinations in community centers. A history of heart disease, stroke and diabetes, as well as smoking and drinking habits was obtained from the questionnaire. Height and weight were measured with the subjects wearing light clothing and no shoes. The subjects were asked to note whether they were current smokers, had quit smoking, or had never smoked, and smokers were asked to note the number of cigarettes smoked each day. We treated ex-smokers and those who had never smoked as nonsmokers in this study. Single measurements of systolic and diastolic BP (SBP and DBP) were obtained after a 5 min rest by trained public health nurses at each public health center using a standard mercury sphygmomanometer. HT was defined as an SBP ≥140 mmHg, a DBP ≥90 mmHg, or the current use of antihypertensive medication (*1*). Non-fasting blood samples were collected. The precision and accuracy of the assay for measuring serum total cholesterol (TC) were certified by the Lipid Standardization Program administered by the Centers for Disease Control and Prevention, Atlanta, USA (*16*). Diabetes was defined as a serum glucose value ≥200 mg/dL or a self-reported history of diabetes. For alcohol consumption, subjects were asked whether they were never drinkers, past drinkers, occasional drinkers, or regularly drinkers on a daily basis.

## Follow-Up Survey

NIPPON DATA80 has completed follow-up surveys until 1999. The underlying causes of death were coded for the Japanese National Vital Statistics according to the 9th International Classification of Disease (ICD-9) until the end of 1994 and according to the 10th International Classification of Disease (ICD-10) from the beginning of 1995. Details of the classification used in the present study have been described elsewhere (*13*). Permission to use the National Vital Statistics was obtained from the Management and Coordination Agency of the Government of Japan. Approval for this study was obtained from the Institutional Review Board of Shiga University of Medical Science (No. 12-18, 2000).

## Statistical Analysis

To examine the association of the combined effects of smok-

**Table 1. Baseline Characteristics According to the Combination of Blood Pressure and Smoking Status: NIPPON DATA80, 1980, Japan**

| Characteristics | Younger (age <60 years) | | | | | Older (age ≥60 years) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Normotensive | | Hypertensive | | | Normotensive | | Hypertensive | | |
| | Non-smoker | Current smoker | Non-smoker | Current smoker | p-value* | Non-smoker | Current smoker | Non-smoker | Current smoker | p-value* |
| **Men** | | | | | | | | | | |
| N | 580 | 1,178 | 450 | 829 | | 90 | 161 | 320 | 355 | |
| Age | 42.6 | 42.2 | 46.7 | 47.2 | <0.01 | 68.9 | 67.5 | 69.9 | 68.1 | <0.01 |
| BMI (kg/m²) | 22.6 | 22.1 | 23.7 | 23.2 | <0.01 | 21.4 | 20.9 | 22.5 | 21.6 | <0.01 |
| Diabetes (%) | 4 | 4 | 6 | 8 | <0.01 | 8 | 11 | 9 | 15 | 0.054 |
| Total cholesterol (mg/dL) | 186.8 | 183.3 | 196.7 | 188.5 | <0.01 | 184.3 | 176.5 | 187.0 | 180.6 | <0.01 |
| Drinking status | | | | | | | | | | |
|   Never (%) | 24 | 19 | 19 | 12 | <0.01 | 33 | 34 | 26 | 22 | <0.01 |
|   Past (%) | 5 | 4 | 3 | 3 | | 16 | 7 | 11 | 8 | |
|   Occasional (%) | 36 | 29 | 30 | 22 | | 27 | 19 | 20 | 17 | |
|   Daily (%) | 35 | 48 | 48 | 63 | | 24 | 40 | 43 | 52 | |
| **Women** | | | | | | | | | | |
| N | 2,403 | 216 | 1,060 | 92 | | 312 | 41 | 741 | 84 | |
| Age | 42.3 | 42.1 | 49.4 | 48.8 | <0.01 | 67.4 | 67.1 | 69.1 | 69.1 | <0.01 |
| BMI (kg/m²) | 22.3 | 21.9 | 24.1 | 24.0 | <0.01 | 21.8 | 21.7 | 23.4 | 22.1 | <0.01 |
| Diabetes (%) | 1 | 1 | 6 | 4 | <0.01 | 10 | 10 | 8 | 8 | 0.92 |
| Total cholesterol (mg/dL) | 182.5 | 185.6 | 195.8 | 199.7 | <0.01 | 199.6 | 190.6 | 202.4 | 197.6 | <0.01 |
| Drinking status | | | | | | | | | | |
|   Never (%) | 79 | 46 | 84 | 48 | <0.01 | 81 | 71 | 84 | 67 | <0.01 |
|   Past (%) | 1 | 5 | 1 | 3 | | 1 | 5 | 2 | 5 | |
|   Occasional (%) | 19 | 36 | 13 | 35 | | 15 | 15 | 10 | 19 | |
|   Daily (%) | 2 | 13 | 2 | 14 | | 2 | 10 | 4 | 10 | |

$N$, number of participants; BMI, body mass index; non-smoker, never smoked and ex-smoker. *Test by analysis of variance for continuous variable and $\chi^2$ test for categorical variables.

ing and HT on mortality, participants were categorized as: 1) neither smokers nor HT, 2) smokers only, 3) HT only, and 4) smoker with HT. We compared basic characteristics among the four groups using means for continuous variables and percentages for dichotomous variables. We separately analyzed men and women and those <60 years and ≥60 years of age. We estimated the multivariate adjusted relative hazards (RH) and the 95% confidence intervals (95% CI) for the effect of the combination of smoking and HT on CVD and on all-cause mortality using Cox proportional hazard models. We treated those who were neither smokers nor HT as a reference group. The multivariate adjusted model included the following possible confounding factors: age, body mass index, diabetes, TC, and alcohol consumption category (never, past, occasional, and daily). We also calculated the PAF of CVD and all-cause mortality due to the combination of smoking and HT using methods described elsewhere (17). The PAF was also recalculated for comparison with other Japanese studies (4, 10).

# Results

## Baseline Characteristics

The mean age±SD was 50.0±13.0 years for men and 50.2±13.1 years for women. The prevalence of HT was 49.3% for men and 40.0% for women. The prevalence of current smoking was 63.7% for men and 8.8% for women. Table 1 shows the baseline characteristics according for each of the four smoking and HT groups. For both men and women, the hypertensive groups were older, more obese, more likely to have diabetes, more likely to have higher TC levels, and more likely to consume alcohol on a daily basis than the normotensive groups. The differences were statistically significant. Male current smokers were leaner, had lower TC levels, and were more likely to consume alcohol on a daily basis than male nonsmokers. Female current smokers were more likely to consume alcohol and to have a lower body mass index than female nonsmokers. No other differences in risk factors were found to be significant.

**Table 2.** Relative Hazard (RH) and 95% Confidence Interval (CI) for Cardiovascular Disease (CVD) or All Cause Mortality According to the Combination of Blood Pressure (BP) and Smoking Status by Age Group: NIPPON DATA80, 1980–1999

| | Younger (age <60 years) | | | | | Older (age ≥60 years) | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | Normotensive | | Hypertensive | | | Normotensive | | Hypertensive | | |
| | Non-smoker | Current | Non-smoker | Current | Total | Non-smoker | Current | Non-smoker | Current | Total |
| **Men** | | | | | | | | | | |
| Person-year | 10,623 | 21,437 | 8,232 | 14,692 | 54,984 | 1,295 | 2,260 | 4,165 | 4,708 | 12,428 |
| CVD death | 6 | 19 | 13 | 51 | 89 | 17 | 29 | 78 | 100 | 224 |
| CVD mortality rate (per 1,000 person-years) | 0.6 | 0.9 | 1.6 | 3.5 | 1.6 | 13.1 | 12.8 | 18.7 | 21.2 | 18.0 |
| RH (95% CI) for CVD mortality* | 1 | 1.58 (0.63–3.97) | 1.96 (0.73–5.22) | 3.86 (1.62–9.19) | | 1 | 1.02 (0.56–1.87) | 1.27 (0.74–2.17) | 1.72 (1.02–2.89) | |
| Excess CVD death | | 7.0 | 6.4 | 37.8 | 51.1 | | 0.7 | 16.4 | 41.8 | 58.9 |
| PAF for CVD death (%) | | 7.8 | 7.1 | 42.4 | 57.4 | | 0.3 | 7.3 | 18.6 | 26.3 |
| All cause death | 40 | 115 | 50 | 143 | 348 | 47 | 99 | 209 | 245 | 600 |
| All cause mortality rate (per 1,000 person-years) | 3.8 | 5.4 | 6.1 | 9.7 | 6.3 | 36.3 | 43.8 | 50.2 | 52.0 | 48.3 |
| RH (95% CI) for all cause mortality* | 1 | 1.40 (0.98–2.01) | 1.21 (0.79–1.84) | 1.69 (1.17–2.42) | | 1 | 1.24 (0.87–1.76) | 1.32 (0.95–1.82) | 1.47 (1.07–2.02) | |
| Excess all cause death | | 33.0 | 8.5 | 58.1 | 99.6 | | 18.9 | 50.2 | 78.3 | 147.4 |
| PAF for all cause death (%) | | 9.5 | 2.4 | 16.7 | 28.6 | | 3.2 | 8.4 | 13.1 | 24.6 |
| **Women** | | | | | | | | | | |
| Person-year | 44,630 | 3,990 | 19,427 | 1,656 | 69,703 | 4,947 | 601 | 10,971 | 1,133 | 17,652 |
| CVD death | 16 | 3 | 28 | 5 | 52 | 49 | 3 | 160 | 27 | 239 |
| CVD mortality rate (per 1,000 person-years) | 0.4 | 0.8 | 1.4 | 3.0 | 0.7 | 9.9 | 5.0 | 14.6 | 23.8 | 13.5 |
| RH (95% CI) for CVD mortality* | 1 | 2.58 (0.75–8.93) | 2.19 (1.13–4.22) | 5.88 (2.07–16.72) | | 1 | 0.46 (0.14–1.48) | 1.23 (0.88–1.71) | 2.01 (1.25–3.23) | |
| Excess CVD death | | 1.8 | 15.2 | 4.1 | 21.2 | | 0.0 | 29.6 | 13.6 | 43.2 |
| PAF for CVD death (%) | | 3.5 | 29.2 | 8.0 | 40.7 | | 0.0 | 12.4 | 5.7 | 18.1 |
| All cause death | 100 | 13 | 85 | 10 | 208 | 117 | 19 | 373 | 49 | 558 |
| All cause mortality rate (per 1,000 person-years) | 2.2 | 3.3 | 4.4 | 6.0 | 3.0 | 23.7 | 31.6 | 34.0 | 43.2 | 31.6 |
| RH (95% CI) for all cause mortality* | 1 | 1.63 (0.90–2.94) | 1.07 (0.79–1.47) | 1.77 (0.91–3.46) | | 1 | 1.23 (0.75–2.01) | 1.28 (1.03–1.59) | 1.61 (1.15–2.26) | |
| Excess all cause death | | 5.0 | 5.8 | 4.4 | 15.2 | | 3.5 | 80.7 | 18.6 | 102.9 |
| PAF for all cause death (%) | | 2.4 | 2.8 | 2.1 | 7.3 | | 0.6 | 14.5 | 3.3 | 18.4 |

PAF, population attributable fraction; non-smoker, never smoked and ex-smoker. *Adjusted for age, body mass index, diabetes, total cholesterol, and drinking status.

## Follow-Up Data

There were 67,412 and 87,355 person-years of follow-up in men and women, respectively (up to 19 years per person). During this time, a total of 948 men and 766 women died, and 313 and 291 of these deaths were due to CVD, respectively.

In this study, we combined never smokers and ex-smokers into one category because of the small number of ex-smokers. In addition, the risk factor–adjusted RH for deaths due to CVD for ex-smokers *vs.* never smokers was nearly one (RH=1.09 for men and RH=1.18 for women). This was also true for all-cause deaths (RH=1.14 for men and RH=1.18 for women).

Since CVD mortality in smokers with HT was higher in those <60 years of age than in those ≥60 years (*p* for interaction: <0.01 for men and 0.03 for women), we analyzed these groups separately. Table 2 further shows that the age-stratified joint impact of smoking and HT on CVD mortality was stronger in participants <60 years old *vs.* participants who were older.

For younger men, the risk factor–adjusted RH for CVD mortality was significantly higher in smokers with HT *vs.* the reference value (RH=3.86; 95% CI: 1.62–9.19). This value tended to be higher, but not significantly so, in the smoking only (RH=1.58; 95% CI: 0.63–3.97) and HT only (RH=1.96; 95% CI: 0.73–5.22) groups. Compared to the reference group, the risk factor–adjusted RH for CVD mortality among younger women was significantly higher in smokers with HT (RH=5.88; 95% CI: 2.07–16.72) and participants with HT only (RH=2.19; 95% CI: 1.13–4.22). The PAFs of CVD mortality in the smoking only, HT only, and smoking with HT groups were 7.8%, 7.1%, and 42.4%, respectively. Smoking and HT accounted for 57.4% of CVD deaths among younger men. Smoking and HT also accounted for 40.7% of CVD deaths among younger women. These proportions were higher than those observed in older participants (26.3% in men and 16.6% in women). However, the number of excess CVD deaths due to smoking and HT among men were similar between the younger and older subgroups (51.1 for younger and 58.9 for older male participants). In contrast, the excess deaths due to CVD among young women was half that in those who were older (21.2 for younger and 43.2 for older female participants). The overall sum of excess CVD deaths (PAF) due to smoking and HT was 110.0 (35.1%) for men and 64.4 (22.1%) for women.

Similar to the CVD findings, the risk factor–adjusted RH for all-cause mortality was higher in the smoking only, HT only, and smoking plus HT groups than in the group with neither factor. The PAFs of all-cause mortality due to smoking combined with HT were 28.6% for younger men, 24.6% for older men, 7.3% for younger women, and 18.4% for older women. The sum of the excess of all-cause deaths (PAF) due to smoking and HT were 247.0 (26.1%) for men and 118.1 (15.4%) for women.

## Discussion

Evidence suggests that smoking and HT account for a large proportion of CVD and all-cause mortality in Japan. In the present report, although the number of excess CVD deaths due to smoking and HT were similar between younger and older men, the PAF was more than double in those who were younger. The number of excess deaths due to CVD among young women was half the number among older women. Because of the exceptionally high RHs, the PAF was also more than doubled in those who were younger. These findings confirm the importance of discouraging smoking and eliminating HT. They further suggest that aggressive attempts to warn about the adverse consequences of smoking and HT at an early age could yield significant health benefits in Japan, particular for those <60 years. Similar findings may also apply to other Asian countries where smoking and HT are highly prevalent.

It is well known that smoking has an important effect on CVD and all cause mortality in Japan (*4, 10*). The NIPPON DATA80 (*4*) showed that the PAF of CVD mortality due to smoking was 27.5% for men and 5.0% for women, while the PAF for all-cause mortality was 15.0% for men and 4.0% for women. These values were similar to those of Iso *et al.* (*10*), who found that 23.5% and 6.0% of CVD mortality could be explained by smoking status. Other Japanese studies have also reported similar values for the PAF for all-cause mortality (*18–20*) due to smoking (range of PAF: 22–34% for men and 0–5% for women), and other Asian studies have yielded PAFs that are comparable to those in Japan (*8*).

Similarly, HT is also a potent CVD risk factor (*9, 11, 13, 21*). However, few studies have described the PAF of CVD deaths due to HT defined as an SBP ≥140 mmHg, a DBP ≥90 mmHg, or the current use of antihypertensive medication in Japan (*9*). A few studies have described the PAF for CVD death due to non-optimal BP (SBP ≥120 mmHg or DBP ≥80 mmHg or current use of antihypertensive medication) (*11, 14*). These studies found that the PAF of non-optimal BP was very high. Thus, both HT and smoking definitely contribute to a large proportion of CVD or all-cause deaths. These findings should be applied to other Asian populations, most of which have a high prevalence of smoking and HT and few obesity-related CVD risk factors, such as diabetes or hypercholesterolemia (*4–6*). In fact, a recent study has reported that a large fraction of CVD was attributable to HT (*9*).

However, the joint impact of smoking and HT on CVD and all-cause mortality is relatively unknown. Since Rothman described that the sum of disease attributable to various causes in reality has no upper limit (*22*), simple addition of these PAFs might not express the true contributions of the risk factors. Thus, it makes sense that the PAF should be calculated using a combination of smoking and HT when trying to determine their joint impact.

We found that the PAF for CVD mortality was higher in

younger than in older populations. This is consistent with previous findings. Iso *et al.* reported that excess CVD mortality associated with cigarette smoking is more evident in middle-age (40–64 years of age) than in the elderly (65–79 years) (*10*). Sairenchi *et al.* also reported that the PAF for CVD mortality due to non-optimal BP is higher in younger than in elderly persons (*11*). Although we could not conclude why the PAF for CVD mortality was higher in the younger than in the older population in the present work, this difference might be partly explained by an age-related increase in the risk for CVD in nonsmoking elderly individuals without HT; the crude CVD mortality rate in nonsmoking elderly participants without HT was more than 20 times as large as that in non-smoking younger persons without HT. The PAF is defined by both RH and the prevalence. Since the prevalence of HT was greater in older than in younger participants, the difference in the PAF for CVD mortality between younger and older participants observed in our study could be explained by the higher RH in the younger participants. Thus, earlier intervention to discourage smoking and warn against the hazard of HT should have a greater benefit in those who are young, with continued carry-over into later life. Similar interventions in the elderly are also important, because the number of excess CVD deaths due to smoking and HT were higher among those aged 60 or older *vs.* those who were younger.

The strength of our study was the use of a representative population with a high response rate and long follow-up period. Thus, our results could be applicable to the entire Japanese population. The study also has several limitations that should be considered. First, these data were based on participants who lived 25 years ago. Since Japanese lifestyles have recently undergone dramatic changes, it may be that these data are less applicable today. However, the 2003 National Health and Nutrition Survey in Japan showed that the prevalence of current smoking among younger men (30–59 years) has remained high (54.4–56.8%) and that the prevalence is increasing among younger women (10.7–18.1%). These values were also rather high when compared with the sample in the present study (*23*). The prevalence of HT remained similarly high in the 2003 survey (10.1% for the age group of 30–39 years, 30.8% for 40–49 years, 36.4% for 50–59 years, 52.4% for 60–69 years and 57.5% for those aged ≥70 years, with men and women combined) (*23*). Thus, the prevalence of both smoking and HT continues to be a major public health problem, and developing intervention strategies to warn of the adverse health consequence of smoking and HT should be a top priority. Secondly, we defined HT as an SBP ≥140 mmHg, a DBP ≥90 mmHg, or the current use of antihypertensive medications. Therefore, our results might underestimate the true PAF due to HT compared with other studies that used optimal BP levels (SBP <120 mmHg and DBP <80 mmHg) as a reference. Furthermore, since we obtained only single BP values for each participant, some measurement error may have occurred. Such error could have resulted in conservative findings. Finally, we combined never and ex-smokers into one category because of the small number of deaths that were observed in the ex-smoker group, particularly among those who were young. Although combining never and ex-smokers into a single group could have resulted in an underestimation of the impact of smoking on our PAFs, this may not have been the case in this instance because, after adjusting for risk factors, the rate of all-cause and CVD mortality were nearly identical in never and ex-smokers.

In conclusion, our results suggest that eliminating two major CVD risk factors, namely, smoking and HT, would prevent 35% of CVD deaths in men and 22% of CVD deaths in women. Moreover, eliminating these factors would prevent 26% of all-cause deaths in men and 15% of all cause deaths in women. Intervention programs that discourage smoking and warn of the adverse consequences of HT in adolescence might eventually yield the greatest health benefits for men and women <60 years of age, since the increased capacity for healthy behaviors would be carried over into later life. It seems likely that the benefits from initial intervention programs as early in life as possible will increase longevity, not just in Japan, but throughout Asia.

## References

1.  Chobanian AV, Bakris GL, Black HR, *et al*, National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, National High Blood Pressure Education Program Coordinating Committee: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003; **289**: 2560–2572.
2.  U.S. Department of Health and Human Services: The Health Consequences of Smoking: A Report of the Surgeon General. Atlanta, U.S. Department of Health and Human Services, CDC, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2004.
3.  The Fifth National Survey of Cardiovascular Diseases. Tokyo, Chuo-Hoki Publisher, 2003 (in Japanese).
4.  Ueshima H, Choudhury SR, Okayama A, *et al*: Cigarette smoking as a risk factor for stroke death in Japan: NIPPON DATA80. *Stroke* 2004; **35**: 1836–1841.
5.  Ko M, Kim MT, Nam JJ: Assessing risk factors of coronary heart disease and its risk prediction among Korean adults: the 2001 Korea National Health and Nutrition Examination Survey. *Int J Cardiol* 2006; **110**: 184–190.
6.  Wang L, Kong L, Wu F, Bai Y, Burton R: Preventing chronic diseases in China. *Lancet* 2005; **366**: 1821–1824.
7.  Ueshima H, Zhang XH, Choudhury SR: Epidemiology of hypertension in China and Japan. *J Hum Hypertens* 2000; **14**: 765–769.

8. Martiniuk AL, Lee CM, Lam TH, *et al*, Asia Pacific Cohort Studies Collaboration: The fraction of ischaemic heart disease and stroke attributable to smoking in the WHO Western Pacific and South-East Asian regions. *Tob Control* 2006; **15**: 181–188.

9. Martiniuk AL, Lee CM, Lawes CM, *et al*, for the Asia-Pacific Cohort Studies Collaboration: Hypertension: its prevalence and population-attributable fraction for mortality from cardiovascular disease in the Asia-Pacific region. *J Hypertens* 2007; **25**: 73–79.

10. Iso H, Date C, Yamamoto A, *et al*, JACC Study Group: Smoking cessation and mortality from cardiovascular disease among Japanese men and women: the JACC Study. *Am J Epidemiol* 2005; **161**: 170–179.

11. Sairenchi T, Iso H, Irie F, *et al*: Age-specific relationship between blood pressure and the risk of total and cardiovascular mortality in Japanese men and women. *Hypertens Res* 2005; **28**: 901–919.

12. WHO Technical Report Series 894, Obesity: Preventing and Managing the Global Epidemic. Part I. The Problem of Overweight and Obesity. Geneva, World Health Organization, 2000, pp 6–37.

13. Okamura T, Kadowaki T, Hayakawa T, Kita Y, Okayama A, Ueshima H, Nippon Data80 Research Group: What cause of mortality can we predict by cholesterol screening in the Japanese general population? *J Intern Med* 2003; **253**: 169–180.

14. Iida M, Ueda K, Okayama A, *et al*, Nippon Data 80 Research Group: Impact of elevated blood pressure on mortality from all causes, cardiovascular diseases, heart disease and stroke among Japanese: 14 year follow-up of randomly selected population from Japanese—Nippon data 80. *J Hum Hypertens* 2003; **17**: 851–857.

15. Okayama A, Kadowaki T, Okamura T, Hayakawa T, Ueshima H, The NIPPON DATA80 Research Group: Age-specific effects of systolic and diastolic blood pressures on mortality due to cardiovascular diseases among Japanese men (NIPPON DATA80). *J Hypertens* 2006; **24**: 459–462.

16. Nakamura M, Sato S, Shimamoto T: Improvement in Japanese clinical laboratory measurements of total cholesterol and HDL-cholesterol by the US Cholesterol Reference Method Laboratory Network. *J Athroscler Thromb* 2003; **10**: 145–153.

17. Rockhill B, Newman B, Weinberg C: Use and misuse of population attributable fractions. *Am J Public Health* 1998; **88**: 15–19.

18. Hozawa A, Ohkubo T, Yamaguchi J, *et al*: Cigarette smoking and mortality in Japan: the Miyagi Cohort Study. *J Epidemiol* 2004; **14**: S12–S17.

19. Hara M, Sobue T, Sasaki S, Tsugane S: Smoking and risk of premature death among middle-aged Japanese: ten-year follow-up of the Japan Public Health Center–based prospective study on cancer and cardiovascular diseases (JPHC Study) cohort I. *Jpn J Cancer Res* 2002; **93**: 6–14.

20. Uno F, Ishikawa S, Nakamura Y, *et al*: Smoking and risk of all-cause mortality: the Jichi Medical School (JMS) Cohort Study. *J Epidemiol* 2005; **15**: 173–179.

21. Arima H, Tanizaki Y, Kiyohara Y, *et al*: Validity of the JNC VI recommendations for the management of hypertension in a general population of Japanese elderly: the Hisayama study. *Arch Intern Med* 2003; **163**: 361–366.

22. Rothman KJ: Epidemiology—An Introduction—. New York, Oxford University Press, 2002.

23. The National Health and Nutrition Survey in Japan. Tokyo, Daiichi Syuppan Publisher, 2003, Japan (in Japanese).

# 喫煙とコレステロールの循環器疾患死亡に対する相互作用

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*背景:* 国際比較研究により喫煙と循環器疾患死亡の関連が集団のコレステロールレベルによって異なる可能性が示されていた。しかしながら、喫煙とコレステロールの相互作用について報告を行っている論文は少ない。

*方法:* 循環器疾患の既往のない8912名の日本人集団を対象として研究を行い、コレステロールレベル4分位 ($\geq 5.40$, 4.81-5.39, 4.26-4.80 and $< 4.25$ mmol/L) ごとの喫煙の循環器疾患に対する相対ハザードをコックス比例ハザードモデルを用いて推定した。相乗的な相互作用のP値は喫煙レベル（非喫煙 vs 喫煙）とコレステロールの連続量の掛け合わせ項を用いて算出した。

*結果:* 19年間の追跡の結果、男性で313例、女性で291例の循環器疾患死亡が観察された。現在喫煙者の生涯非喫煙者に対する循環器疾患死亡の相対ハザード (RH) はコレステロール最高4分位で最も高く(RH = 2.36)、最低4分位で最も小さかった (RH = 0.85)（相互作用のP値 $< 0.01$). 男性で冠動脈疾患死亡と虚血性循環器疾患死亡（脳梗塞と冠動脈疾患死亡の複合エンドポイント）をエンドポイントにした場合、女性で虚血性循環器疾患死亡をエンドポイントにした場合も同様の相互作用が観察された。 この相互作用は生物学的なメカニズム及びわが国における非喫煙者の特殊性が影響している可能性が考えられる。

*結論:* わが国において高コレステロール者が増えてきている、高コレステロール者で喫煙の循環器疾患に対するリスクが高まることから、積極的に防煙活動・禁煙支援をしていく必要がある。

# CARDIOVASCULAR DISEASE

# Is weak association between cigarette smoking and cardiovascular disease mortality observed in Japan explained by low total cholesterol?—NIPPON DATA80

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| **Background** | An international comparison has indicated that the association between smoking and cardiovascular disease (CVD) differs according to total cholesterol (TC) levels. However, little has been published about the relationship between smoking and CVD mortality among populations with various cholesterol levels. |
| **Methods** | We calculated the adjusted relative hazard (RH) of smoking for CVD mortality among 8912 Japanese individuals without a history of stroke or heart disease, who were separated according to TC levels of $\geqslant 5.40$, 4.81–5.39, 4.26–4.80 and $<4.25$ mmol/l into groups Q4, Q3, Q2 and Q1, respectively. The P-values for multiple interactions between TC and smoking status for CVD mortality were calculated using TC as a continuous variable, dichotomized smoking status (never vs current), and by including cross-product terms in the regression models. |
| **Results** | After 19 years of follow-up, 313 men and 291 women died of CVD. The RH of CVD mortality among men who currently smoked compared with those who never smoked was increased with higher TC (RH = 2.36 in Q4) and decreased in those with lower TC (RH = 0.85 in Q1) (interaction, $P < 0.01$). The profiles for coronary heart disease (CHD) mortality and ischaemic CVD (composite endpoint of CHD and ischaemic stroke) in men and for ischaemic CVD mortality in women were identical. The interaction might be explained by a biological mechanism and by frailty of those who have never smoked with lower TC. |
| **Conclusions** | Counteractive measures should be implemented against smoking targeted towards Japanese with elevated TC levels. |
| **Keywords** | Cigarette smoking, total cholesterol, cardiovascular diseases, interaction, prospective studies, Japan |

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Cigarette smoking is a known risk factor for both coronary heart disease (CHD) and stroke.[1] However, although the rate of cigarette smoking is high among Japanese men, mortality from ischaemic heart disease is strikingly lower than that in the USA.[2,3] Smoking is thus considered a weaker CHD risk factor in Japan than in Western countries.[4,5] However, cigarette smoking is closely related to CHD among Japanese immigrants living in Hawaii.[4] Thus, the between-population difference in CHD might be explained not by ethnicity but by environmental factors. Similar to Japan, the Seven Countries Study showed

a weaker relationship between smoking and the incidence of CHD in southern Europe than in Northern Europe and Yugoslavia.[6] People living in Asia and in southern Europe at the time of the early follow up by the Seven Countries Study had low average total cholesterol (TC) levels.[4-6] Furthermore, some recent studies investigating the aetiology of subclinical atherosclerosis found that low-density lipoprotein cholesterol is more important for early atheroma formation, whereas smoking plays a more important role at the later stages of atherosclerosis.[7,8]

Japanese studies reported before 2000 indicated that cigarette smoking is not a consistent risk factor for stroke.[9-11] However, recent analyses have revealed a close relationship between cigarette smoking and stroke in Japan.[12-15] Some investigators have postulated that this change is due to a recent increase in dietary fat intake and a relative increase of the blood TC level in the general population.[3,13] Thus, the association between smoking and cardiovascular diseases (CVD) might differ according to TC level. The aim of the present study was to determine whether TC level affects the association between smoking and CVD using a representative Japanese sample.

## Methods

The subjects of this cohort study participated in the Japanese 1980 National Cardiovascular Survey, which was conducted together with a National Nutrition Survey. Nutrition is surveyed annually in Japan using standardized procedures and a questionnaire.[13,16] All household members aged 30 years or older in 300 randomly selected census tracts throughout Japan are included. The 1980 survey included medical examinations, blood pressure (BP) measurements, blood tests and a self-administered questionnaire about lifestyle. Trained staff at local health centres in the respective districts performed the medical examinations at local health and community centres. A history of illness, including heart disease, stroke and diabetes, as well as smoking and drinking habits was obtained from the questionnaire. Height and body weight were measured, while the subjects wore light clothing and no shoes. The participants were questioned about whether they were current smokers, ex-smokers or had never smoked. Smokers were asked to describe the number of cigarettes smoked per day. Similarly, alcohol consumption was determined as never, past, current occasionally or current daily. A standard sphygmomanometer was used to measure systolic and diastolic BP. The precision and accuracy of serum TC in non-fasting blood samples were verified by the Lipid Standardization Program administered by the Center for Disease Control and Prevention, Atlanta, GA, USA.[17] Diabetes was defined as non-fasting serum glucose of 11.1 mmol/l (200 mg/dl) or a self-reported history of diabetes.

A total of 10 546 individuals, aged 30 years or older, for whom baseline information regarding age, gender and blood pressure was complete in the 1980 data set constituted the study cohort (NIPPON DATA80).[13,16] We excluded those with a history of stroke ($n = 117$), CHD ($n = 163$), other heart disease ($n = 475$), no information about confounding factors ($n = 4$), those without complete information about smoking or TC ($n = 28$)

and 847 participants who were lost to follow-up. Consequently, we analysed data from 8912 participants.

As described elsewhere,[12,15] the underlying causes of death in the Japanese National Vital Statistics were coded according to the 9th (ICD-9) and 10th (ICD-10) International Classifications of Disease for deaths through 1994 and thereafter, respectively. Details about the classification and permission to use the National Vital Statistics were obtained from the Management and Coordination Agency of the Government of Japan. The Institutional Review Board of the Shiga University of Medical Science approved the study protocol (No. 12–18, 2000).

### Statistical analysis

To examine the association between cigarette smoking and CVD mortality according to TC level, participants were divided into quartiles Q4, Q3, Q2 and Q1 according to TC levels of $\geqslant 5.40$ mmol/l ($\geqslant 209$ mg/dl), 4.81–5.39 mmol/l (186–208 mg/dl), 4.26–4.80 mmol/l (165–185 mg/dl) and Q1 (TC, $<4.25$ mmol/l ($<164$ mg/dl). We compared the basic characteristics among the groups according to a combination of smoking and TC levels using the mean for continuous variables and ratios (%) for dichotomous variables.

Age-adjusted CVD mortality rate, relative hazards (RH) and the 95% confidence intervals (95%CI) for cigarette smoking was estimated according to TC level using the Cox proportional hazard model. Individuals who had never smoked were categorized as the reference group. We estimated the RH using age-adjusted and multivariate-adjusted models, and included the following possible confounding factors in the latter model: age, body mass index (BMI), systolic BP, use of anti-hypertensive medication, diabetes and alcohol consumption (never, past, occasional and daily). The significance of multiplicative interactions between TC (continuous) and smoking status were examined using cross-product terms in the regression model. The interaction was assessed for CVD mortality, CHD mortality, ischaemic stroke mortality and ischaemic CVD (composite endpoint of CHD and ischaemic stroke) mortality. We also separately analysed the relationship between smoking and CVD or ischaemic CVD mortality according to cholesterol level by age group ($\leqslant 69$ and $>69$ years, as the median age of the deceased was 69 years). SAS software (version 9.1) was used for all statistical analyses.

## Results

The mean $\pm$ SD baseline age of the participants was $50.1 \pm 13.1$ years and 55.5% were women. The mean TC level was $4.81 \pm 0.85$ mmol/l ($186.2 \pm 32.8$ mg/dl) for men and $4.91 \pm 0.88$ mmol/l ($190.2 \pm 33.9$ mg/dl) for women. Proportions of current smokers, ex-smokers and never smokers were 63.7, 18.1 and 18.2% for men and 8.8, 2.1 and 89.2% for women, respectively.

Table 1 shows the baseline characteristics of the study participants according to smoking status and TC level. Proportions of current smokers across ascending TC groups were 68.8, 65.6, 62.0 and 57.6% for men and 7.7, 8.6, 9.3 and 9.3% for women in Q1, Q2, Q3, and Q4, respectively. The mean BMI and systolic BP were higher in groups of both men and women with higher TC. Similarly, the proportion of participants

**Table 1** Baseline characteristics of participants according to smoking status and total cholesterol level. NIPPON DATA80, 1980, Japan

| Total cholesterol level | Q1( <4.25 mmol/l)[a] | | | Q2+Q3 (4.26–5.39 mmol/l)[a] | | | Q4( ≥ 5.40 mmol/l)[a] | | |
| Smoking status | Never | Ex-smoker | Current | Never | Ex-smoker | Current | Never | Ex-smoker | Current |
|---|---|---|---|---|---|---|---|---|---|
| **Men** | | | | | | | | | |
| Number of participants | 173 | 149 | 709 | 366 | 361 | 1283 | 184 | 207 | 531 |
| Age (years) | 51.1 | 54.3 | 50.1 | 51.0 | 52.0 | 49.1 | 48.7 | 53.1 | 47.8 |
| Total cholesterol (mmol/l) | 3.84 | 3.80 | 3.83 | 4.81 | 4.80 | 4.77 | 5.93 | 6.01 | 5.97 |
| Body mass index (kg/m²) | 22.4 | 21.7 | 21.4 | 22.9 | 22.7 | 22.3 | 24.0 | 23.3 | 23.5 |
| Systolic blood pressure (mmHg) | 136.3 | 138.9 | 136.2 | 137.5 | 139.1 | 138.2 | 141.1 | 141.7 . | 137.7 |
| Antihypertensive medication (%) | 9 | 11 | 7 | 12 | 9 | 8 | 11 | 14 | 9 |
| Diabetes (%) | 1 | 5 | 6 | 7 | 4 | 7 | 8 | 10 | 10 |
| Drinking status | | | | | | | | | |
| Never (%) | 28 | 25 | 17 | 29 | 16 | 18 | 25 | 21 | 18 |
| Past (%) | 3 | 8 | 5 | 5 | 7 | 4 | 4 | 11 | 5 |
| Occasional (%) | 39 | 21 | 25 | 34 | 26 | 24 | 33 | 24 | 25 |
| Daily (%) | 29 | 46 | 53 | 33 | 49 | 54 | 38 | 44 | 52 |
| **Women** | | | | | | | | | |
| Number of participants | 1074 | 22 | 91 | 2152 | 50 | 217 | 1187 | 31 | 125 |
| Age (years) | 44.6 | 48.8 | 47.3 | 50.0 | 53.3 | 50.7 | 55.1 | 58.7 | 54.5 |
| Total cholesterol (mmol/l) | 3.87 | 3.89 | 3.81 | 4.81 | 4.91 | 4.83 | 6.03 | 6.16 | 5.98 |
| Body mass index (kg/m²) | 22.2 | 21.2 | 21.5 | 22.8 | 22.9 | 22.0 | 23.7 | 24.2 | 23.7 |
| Systolic blood pressure (mmHg) | 128.1 | 134.7 | 127.4 | 132.3 | 136.8 | 131.1 | 139.6 | 146.6 | 141.1 |
| Antihypertensive medication (%) | 6 | 9 | 7 | 9 | 10 | 7 | 17 | 29 | 14 |
| Diabetes (%) | 2 | 5 | 2 | 4 | 12 | 3 | 6 | 3 | 7 |
| Drinking status | | | | | | | | | |
| Never (%) | 81 | 50 | 45 | 82 | 52 | 53 | 82 | 52 | 58 |
| Past (%) | 1 | 9 | 2 | 1 | 6 | 6 . | 1 | 16 | 4 |
| Occasional (%) | 16 | 32 | 37 | 15 | 34 | 29 | 15 | 19 | 29 |
| Daily (%) | 2 | 9 | 15 | 2 | 8 | 12 | 2 | 13 | 9 |

[a] <4.25 mmol/l, <164 mg/dl; 4.26–5.39 mmol/l, 165–208 mg/dl; ≥5.40mmol/l, ≥ 209 mg/dl.

taking anti-hypertensive medication was higher in the groups with higher TC. The mean age of the women was higher in the higher TC group, but this did not apparently differ among the men. Compared with current smokers and those who had never smoked, ex-smokers tended to be older and more of them were taking anti-hypertensive medication and had diabetes. The proportions of those who had never consumed alcohol were higher among those who had never smoked.

After 19 years of follow-up, 313 men and 291 women died of CVD. Table 2 shows the risk of CVD mortality associated with cigarette smoking according to TC levels. The adjusted RH of current cigarette smoking for CVD mortality among men was the highest in Q4 (RH = 2.36; 95%CI: 1.14–4.87) and the lowest in Q1 (RH = 0.85; 95%CI: 0.49–1.49). The P-value for interactions between smoking status (ever vs never) and TC level (continuous) for CVD mortality were 0.01. This interaction was also unchanged, when we excluded ex-smokers (P for interaction <0.01). Table 2 indicates that the findings for women were inconsistent.

Because the higher CVD mortality rate in those who had never smoked with lower TC was due to frailty, we further excluded early death that occurred within 5 years. However, the observed significant interactions were unchanged (P for interaction, 0.02).

Disease-specific analyses revealed that the P-values for interactions between smoking status and total cholesterol were 0.03 for CHD deaths and 0.01 for ischaemic CVD (CHD + ischaemic stroke) in men (Table 3). Although an interaction between smoking status and TC for total CVD mortality was not apparent in women, the relationship between cholesterol and ischaemic CVD was closer in smokers than in non-smokers among women (P for interaction, 0.02 for ischaemic CVD).

Because the age distribution differed by TC categories in women, we analysed interactions between smoking and cholesterol for CVD or ischaemic CVD separately by age group (≤69 and >69 years). For most of the age-specific analyses except the relationship between smoking and CVD mortality according to TC level in women aged >69 years, the relationship of TC with diseases was also closer in current smokers than in those who had never smoked (data not shown).

## Discussion

The present study found that the relationship between cigarette smoking and CVD mortality is affected by TC level in men. This pattern was also observed for CHD mortality and ischaemic CVD in men and for ischaemic CVD mortality in women.

**Table 2** Relative hazards (RH) and 95% confidence intervals (95%CI) of cardiovascular disease (CVD) mortality in relation to cigarette smoking status according to total cholesterol level. NIPPON DATA80, 1980–1999, Japan

| Total Cholesterol | Men | | | Women | | |
|---|---|---|---|---|---|---|
| | Never smoked | Ex-smoker | Current smoker | Never smoked | Ex-smoker | Current smoker |
| **Q1 (<4.25 mmol/l)** | | | | | | |
| Person-year | 2839.5 | 2281.1 | 11807.8 | 19283.8 | 364.7 | 1512.2 |
| n of CVD mortality | 20 | 12 | 51 | 36 | 2 | 9 |
| Age-adjusted CVD mortality rate | 4.1 | 2.5 | 2.9 | 3.5 | 5.9 | 7.3 |
| Age-adjusted RH | 1 | 0.56 (0.27–1.15) | 0.70 (0.42–1.17) | 1 | 1.60 (0.39–6.67) | 2.65 (1.27–5.53) |
| Multivariate-adjusted RH | 1 | 0.64 (0.31–1.34) | 0.85 (0.49–1.49) | 1 | 1.42 (0.33–6.02) | 3.11 (1.37–7.04) |
| **Q2 (4.26–4.80 mmol/l[a])** | | | | | | |
| Person-year | 2973.2 | 3084.5 | 11623.3 | 18863.6 | 316.2 | 1777.1 |
| n of CVD mortality | 11 | 11 | 54 | 53 | 1 | 4 |
| Age-adjusted CVD mortality rate | 1.2 | 2.6 | 4.2 | 3.2 | 5.0 | 2.5 |
| Age-adjusted RH | 1 | 1.42 (0.61–3.31) | 1.94 (1.00–3.74) | 1 | 0.94 (0.13–6.78) | 0.75 (0.27–2.09) |
| Multivariate-adjusted RH | 1 | 1.32 (0.56–3.11) | 1.72 (0.88–3.37) | 1 | 0.44 (0.06–3.47) | 0.52 (0.17–1.60) |
| **Q3 (4.81–5.39 mmol/l[a])** | | | | | | |
| Person-year | 3263.6 | 3106.0 | 10416.8 | 19286.7 | 499.4 | 1991.9 |
| n of CVD mortality | 14 | 17 | 51 | 62 | 4 | 8 |
| Age-adjusted CVD mortality rate | 3.0 | 3.4 | 3.9 | 3.0 | 6.6 | 2.8 |
| Age-adjusted RH | 1 | 1.03 (0.51–2.10) | 1.58 (0.87–2.88) | 1 | 1.40 (0.51–3.89) | 0.90 (0.43–1.89) |
| Multivariate-adjusted RH | 1 | 1.53 (0.72–3.23) | 1.81 (0.98–3.33) | 1 | 1.52 (0.51–4.56) | 1.03 (0.48–2.22) |
| **Q4 (≥5.40 mmol/l[a])** | | | | | | |
| Person-year | 3279.6 | 3488.2 | 9248.6 | 20833.7 | 527.2 | 2098.7 |
| n of CVD mortality | 10 | 19 | 43 | 91 | 4 | 17 |
| Age-adjusted CVD mortality rate | 2.0 | 3.2 | 4.7 | 3.2 | 3.7 | 5.9 |
| Age-adjusted RH | 1 | 1.35 (0.63–2.90) | 2.07 (1.04–4.16) | 1 | 1.28 (0.47–3.49) | 2.11 (1.26–3.55) |
| Multivariate-adjusted RH | 1 | 1.52 (0.69–3.35) | 2.36 (1.14–4.87) | 1 | 1.16 (0.38–3.50) | 2.67 (1.55–4.58) |

In multivariate-adjusted model, we adjusted for age, body mass index, systolic BP, use of anti-hypertensive medication, diabetes, and drinking category (never, past, occasional and daily).

[a] <4.25 mmol/l, < 164 mg/dl; 4.26–4.80 mmol/l, 165–185 mg/dl, 4.81–5.39 mmol/l: 186–208 mg/dl, ≥5.40mmol/l: ≥ 209 mg/dl.

TC, total cholesterol; n, numbers; CVD, cardiovascular disease; Crude CVD mortality rate, Crude CVD mortality rate per 1000 person-years.