Table III. Relative risks (RRs) and 95% CIs for major causes of death according to resting heart rate

Heart rate (per minute) quartiles (Stratum mean)	No. of person	Person-year	Cardiovascular Deaths (no.)	RR	95% CI	P
Male						
30–59 years old						
<60 (55)	715	12,335	10	1.00		
60–65 (63)	731	12,706	17	1.61	0.73, 3.53	.24
66–73 (69)	788	13,574	22	1.79	0.84, 3.82	.13
≥74 (82)	710	12,027	29	2.55	1.22, 5.31	.01
Predicted changes per 11/minute (ISD) increase				1.27	1.02, 1.58	.03
60 years old or more						
<60 (55)	245	3200	58	1.00		
60–65 (63)	228	2988	51	0.86	0.59, 1.26	.45
66–73 (69)	207	2757	48	0.93	0.63, 1.37	.72
≥74 (82)	232	2905	56	1.01	0.70, 1.48	.95
Predicted changes per 11/minute (ISD) increase				1.00	0.87, 1.15	.99
Female						
30–59 years old						
<64 (59)	816	14,315	5	1.00		
64–69 (67)	958	16,839	11	2.12	0.73, 6.11	.17
70–77 (73)	1,022	17,884	19	3.61	1.34, 9.72	.01
≥78 (86)	942	16,418	15	2.72	0.97, 7.61	.06
Predicted changes per 11/minute (ISD) increase				1.16	0.90, 1.49	.26
60 years old or more						
<64 (59)	324	4663	60	1.00		
64–69 (67)	263	3903	48	0.85	0.58, 1.25	.41
70–77 (73)	329	4658	64	0.90	0.63, 1.28	.54
≥78 (86)	290	4119	54	0.85	0.58, 1.24	.39
Predicted changes per 11/minute (ISD) increase				0.95	0.82, 1.09	.43

The relative risk (RR) was adjusted for age, serum albumin, body mass index, hypertension, hypercholesterolemia, diabetes, cigarette smoking (never, ex, ≤20 cigarettes/day, >20 cigarettes/day) and drinking (never, former, occasional, daily).

were measured. Public health nurses obtained information on smoking and drinking and medical history.

Statistical analysis

Age-adjusted mean values and prevalence of baseline characteristics were calculated in each group according to resting HR quartile, and the differences were tested by analysis of covariance or χ^2 tests. Cumulative survival rates were calculated by means of the Kaplan-Meier method with the log-rank test. The multivariate adjusted relative risk (RR) for all-cause and cause-specific death was calculated by means of the Cox proportional hazard model, adjusting for age, hypercholesterolemia, serum albumin, hypertension, diabetes, body mass index (BMI), smoking status (never, ex-, current with ≤20 cigarettes per day, and current with >20 cigarettes per day), and drinking status (never, former, occasional, and daily). Because some previous studies showed sex-[1,5–7] or age-specific[8] differences in the effects of HR on death, we stratified by sex and age at baseline (30 to 59 years and >60 years). Pulse pressure was also used as an independent variable in this model, following the report of Benetos et al[6] that the level of pulse pressure influenced the association of HR with cardiovascular death. In this model, pulse pressure was used instead of hypertension because these two variables are strongly correlated ($r = 0.55$, $P < .001$). Risks were calculated in comparison with the lowest quartile of HR as standard. Relative risks associated with a difference of 11 beats per minute (1 SD for both sexes) were also calculated. Analyses were repeated, excluding deaths within the first 5 years of follow-up to exclude the influence of preexisting diseases. The exclusion was performed by dealing deaths within the first 5 years as "censored."

The statistical Package for the Social Science (SPSS Japan Inc, Version 10.0J, Tokyo, Japan) was used for the analyses. All probability values were 2-tailed, and all confidence intervals were estimated at the 95% level.

Results

Table I shows age-adjusted means or prevalences in the baseline characteristics of all participants by quartile of resting HR. There were significant differences in

Coronary heart disease + heart failure				Noncancer, noncardiovascular				All cause			
Deaths (no.)	RR	95% CI	P	Deaths (no.)	RR	95% CI	P	Deaths (no.)	RR	95% CI	P
3	1.00			24	1.00			68	1.00		
7	2.15	0.55, 8.37	.27	11	0.47	0.23,0.96	.04	58	0.86	0.69, 1.22	.40
9	2.49	0.67, 9.24	.17	20	0.73	0.40,1.34	.31	86	1.18	0.85, 1.63	.32
16	3.99	1.14,14.0	.03	29	1.23	0.71,2.13	.46	96	1.45	1.06, 2.00	.02
	1.32	0.95, 1.84	.09		1.31	1.06,1.62	.01		1.21	1.08, 1.36	.00
19	1.00			44	1.00			144	1.00		
16	0.84	0.43, 1.65	.61	57	1.33	0.90,1.99	.16	148	1.03	0.82, 1.30	.78
18	1.05	0.55, 2.02	.88	36	0.94	0.61,1.47	.80	122	0.97	0.76, 1.24	.82
26	1.43	0.78, 2.65	.25	60	1.51	1.01,2.24	.04	153	1.14	0.90, 1.43	.28
	1.16	0.93, 1.46	.19		1.15	1.00,1.33	.05		1.05	0.97, 1.15	.25
1	1.00			8	1.00			32	1.00		
5	6.03	0.64,56.5	.12	8	0.93	0.35,2.48	.88	41	1.20	0.75, 1.91	.44
7	8.40	0.94,75.1	.06	18	2.06	0.89,4.77	.09	63	1.83	1.19, 2.80	.01
8	9.37	1.05,83.7	.04	19	2.41	1.04,5.59	.04	60	1.94	1.26, 3.01	.00
	1.43	0.99, 2.06	.06		1.29	1.01,1.64	.04		1.19	1.04, 1.35	.01
26	1.00			50	1.00			143	1.00		
24	1.02	0.58, 1.80	.94	40	0.77	0.50,1.18	.23	105	0.78	0.61, 1.01	.06
31	1.04	0.61, 1.77	.88	54	0.91	0.61,1.34	.63	152	0.92	0.73, 1.16	.49
18	0.66	0.36, 1.23	.19	58	1.10	0.74,1.62	.65	135	0.93	0.73, 1.19	.56
	0.88	0.71, 1.09	.24		1.08	0.94,1.25	.26		0.99	0.91, 1.08	.83

mean values for systolic blood pressure, diastolic blood pressure, pulse pressure, and serum glucose; they were higher in higher HR quartiles in both sexes. Mean values of BMI for men and albumin for women were also higher in higher quartiles of resting HR. Prevalence of antihypertensive agents users for women was lower in higher quartiles of HR. In addition, prevalence of hypertension, diabetes, hypercholesterolemia, and current smokers in men and hypertension in women varied significantly across HR quartiles.

Total person-years were 145,240, and mean follow-up period was 16.5 years. The number of total and cause-specific deaths is shown in Table II. During the follow-up, there were 1606 deaths (875 for men and 731 for women), of which 35% (n = 567, 33% for men and 38% for women) were due to cardiovascular diseases. There were 114 coronary heart disease deaths and 120 heart failure deaths, 20% and 21% of deaths due to cardiovascular disease, respectively, and 264 stroke deaths, 47% of deaths due to cardiovascular disease.

Among the total deaths, 31% (n = 503, 35% for men and 27% for women) were due to cancer. There were 117 stomach cancers, 94 lung cancers, and 46 liver cancers, representing 51% of deaths caused by cancer. These were the 3 major causes of cancer death. Of all deaths, 33% (n = 536, 32% for men and 35% for women) were due to noncardiovascular and noncancer diseases. There were 119 pneumonias, 82 "accidents, poisoning, and suicide," and 31 liver diseases, together representing 43% of deaths caused by noncardiovascular and noncancer diseases.

Table III shows the multivariate-adjusted RR for major noncancer causes of death according to HR quartile. For men 30 to 59 years of age, there was a trend of higher cardiovascular, noncancer, noncardiovascular, and all-cause death with higher HR, such that in the highest quartile of HR, there was a significantly raised risk of cardiovascular (RR, 2.55; 95% CI, 1.22 to 5.31) and all-cause death (RR, 1.45; 95% CI, 1.06 to 2.00). Relative risks associated with 1-SD increment of HR (11 beats/min) were 1.27 (95% CI; 1.02 to 1.58)

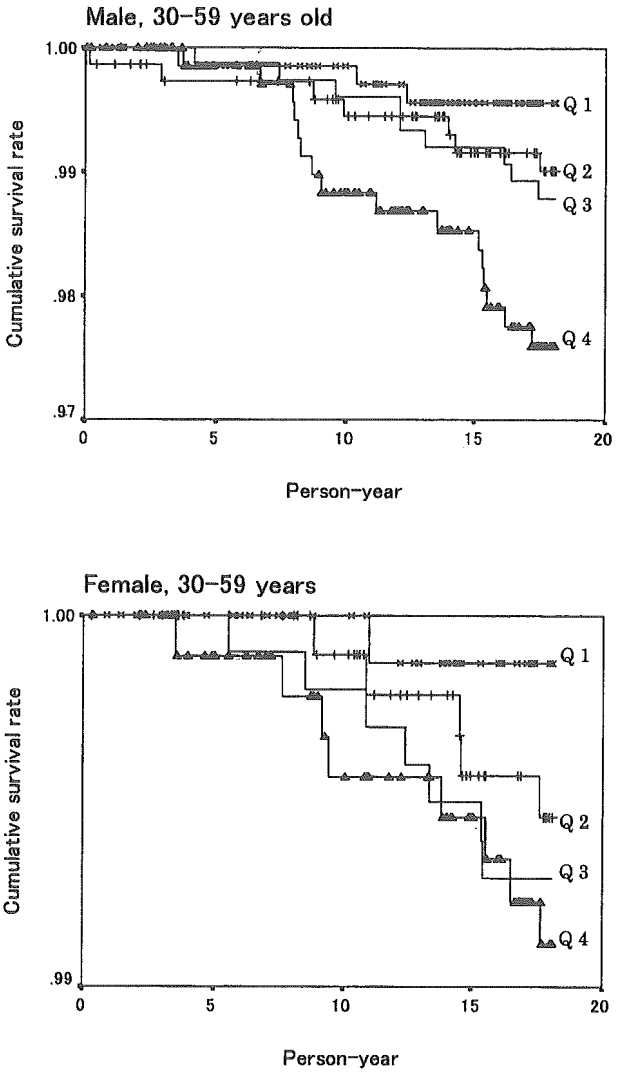
for cardiovascular disease, 1.31 (95% CI, 1.06 to 1.62) for noncancer, noncardiovascular disease, and 1.21 (95% CI, 1.08 to 1.36) for all-cause death. For women 30 to 59 years of age, there was a trend of higher noncancer, noncardiovascular, and all-cause death with higher HR, such that in the highest quartile of HR, there was a significantly raised risk of noncancer, noncardiovascular (RR, 2.41; 95% CI, 1.04 to 5.59), and all-cause death (RR, 1.94; 95% CI, 1.26 to 3.01). In addition, for cardiovascular death, there was a significantly raised risk in the second highest quartile of HR (RR, 3.61; 95% CI, 1.34 to 9.72), whereas in the highest quartile, the risk was borderline significant (P = .06). Relative risks associated with 1 SD of HR were 1.29 (95% CI, 1.01 to 1.64) for noncancer, noncardiovascular disease and 1.19 (95% CI, 1.04 to 1.35) for all-cause death. For elderly subjects (60 years old or more), only the highest quartile of HR for men showed a significant positive relation to noncancer, noncardiovascular death (RR, 1.51; 95% CI, 1.01 to 2.24). There was no association of HR to cancers in either age group and sex (data not shown).

For specific causes of cardiovascular disease death, both middle-aged men and women (30 to 59 years of age) showed raised relative risks in the highest HR quartile for coronary heart disease plus heart failure death; these were 3.99 (95 % CI, 1.14 to 14.0) and 9.37 (95% CI, 1.05 to 83.7) for men and women, based on 16 and 8 deaths, respectively. In addition, at ages ≥60 years, for men, relative risk for heart failure in the highest HR quartile was 2.61 (95% CI, 1.07 to 1.92), based on 15 deaths (data not shown). There was no relation between HR and stroke death in either age group or sex. Resting HR was not associated with cerebral infarction, cerebral hemorrhage, major site-specific cancers (stomach, lung and liver), pneumonia, "accident, poisoning, and suicide" and liver disease death (data not shown).

The results of the log-rank test for the Kaplan-Meier method were substantially consistent with the results of the Cox proportional hazard model. We showed the cumulative survival rates due to cardiac event (coronary heart disease plus heart failure death) for each HR quartiles in middle-aged participants (Figure 1).

The association between resting HR and death was investigated after excluding deaths within the first 5 years of follow-up. The pattern of results was broadly similar to that showed in Table III. For men 30 to 59 years old, the relative risks were significant for the highest quartile of HR and 1-SD increment of HR in cardiovascular disease (RR, 3.32; 95% CI, 1.41 to 7.79 for the highest quartile of HR; RR, 1.35; 95% CI, 1.07 to 1.72 for 1-SD increment), coronary heart disease and heart failure combined (RR, 6.27; 95% CI, 1.40 to 28.0; RR, 1.47; 95% CI, 1.04 to 2.08), and all-cause death (RR, 1.45; 95% CI, 1.03 to 2.05;

Figure 1



Cumulative survival rates due to cardiac event (coronary heart disease and heart failure death) for each heart rate quartile (Q1–Q4) in men and women 30 to 59 years of age. Heart rate quartiles are as follows: Q1, <60; Q2, 60–65; Q3, 66–73; Q4, ≥74 beats per minute for men; and Q1, <64, Q2, 64–69, Q3, 70–77, Q4, ≥78 beats per minute for women. Compared with Q1, Q4 in both sexes showed significantly higher mortality rates by log-rank test (P = .002 for men, P = .033 for women).

RR, 1.18; 95% CI, 1.04 to 1.34). For women 30 to 59 years old, again, patterns were similar, only results for cardiovascular disease, in the second highest HR quartile (RR, 3.97; 95% CI, 1.31 to 12.0), and for all-cause death (RR, 1.92; 95% CI, 1.19 to 3.09 for the highest quartile of HR, RR, 1.16; 95% CI, 1.01 to 1.34 for 1-SD increment) reached sta-

tistical significance. No significant relation between HR and noncancer, noncardiovascular death in men and women 30 to 59 years old was observed in this analysis.

The above-mentioned results were not substantially affected when pulse pressure was included as an independent risk factor instead of hypertension in Cox proportional hazard models.

Discussion

To our knowledge, few previous studies have examined the relation between resting HR and long-term death in Japanese living in Japan[22,23] (and Naito Y, et al, abstract in the Third International Conference of Preventive Cardiology, Oslo, 1993). However, these prior studies did not include age-specific analysis and were only limited to men. As in Western populations, higher HR was an independent predictor of all-cause death for middle-aged men and women in Japan. Resting HR also showed a significant positive correlation to coronary heart disease and heart failure death combined, but not to stroke. This coincides with results of a French study that found an association of HR with coronary death but not with stroke.[6]

In Japan, by the end of 1994, physicians used the term heart failure to not just reflect congestive heart failure, but to include sudden deaths or the mode of dying in the last stage of other diseases.[24] Therefore, it has been suggested that the death statistics for coronary heart disease have been underestimated because deaths from heart failure might include coronary events.[25] The Ministry of Health and Welfare recommended to physicians not to use "heart failure" as the mode of dying and end stage of other diseases when ICD-9 was revised to ICD-10 in 1995. Japanese vital statistics showed that coronary death rose rapidly by 25% after the ICD-10 revision in 1995, compared with the level in former periods,[26]although it still showed lower mortality rates than that of Western countries.[27,28] Because of this possible misclassification, we combined coronary heart disease with heart failure, which was associated with high HR for middle-aged men and women.

In elderly participants, high resting HR was not associated with cardiovascular death. These results are consistent with the findings of the Chicago Heart Association Detection Project in Industry.[8] The HR of elderly persons tends to be affected by various preexisting diseases, such as sinus node dysfunction or chronic obstructive pulmonary disease, which are associated with accelerated HR[29,30]; in addition, subclinical hypothyroidism is common in the elderly and is associated with decreased HR.[31] Therefore, it is difficult to interpret the relation between HR and death for older subjects even after excluding early deaths during the follow-up.

One of the mechanisms underlying excess risk for cardiovascular disease, especially for cardiac events associated with HR, is the effect of increased sympathetic nerve activity promoting atherosclerosis through a hemodynamic mechanism and producing rhythm disturbances.[32,33] A predominance of sympathetic activity over parasympathetic activity plays a critical role in the development of sudden cardiac death.[34] Sympathetic activation also increases platelet activation, which can precipitate cardiovascular events.[35] Furthermore, higher HR increases cardiac work, which increases oxygen demand and may cause myocardial ischemia.[36]

There are some limitations to the current study. First, there may be residual confounding factors affecting the relation between HR and death risk. Although we adjusted for a number of important risk factors, we could not adjust for the effect of other potential risk factors, such as forced expiratory volume as a marker of chronic obstructive pulmonary disease,[29] thyroid hormonal function,[31] physical activity,[37] and mental stress.[38] Second, the use of death data may lead to misclassification in the diagnosis of cause of deaths. However, death from stroke and cancer are known to be accurately reported on death certification in Japan.[39,40] Because of the underestimation of coronary deaths until the end of 1994 in Japan, it might be helpful in the future to examine coronary incidence as the end point. However, in the current study, we addressed this problem by combining coronary heart disease and heart failure deaths. Third, since the present study was based on HR measurement on one occasion only, the results might include regression dilution bias,[41] which might attenuate the relations of HR to long-term death. Fourth, we did not have sufficient information on the use of β-blockers at baseline, which is associated with reduced heart disease morbidity and HR,[42] although we did adjust for use of antihypertensive agents, insofar as the latter was included in the definition of hypertension. Finally, about 8% of our study population were lost to follow-up. However, we believe that this does not substantially affect the result, because the proportion of those who were lost to follow-up was not different across the HR quartiles.

In conclusion, the present study suggests that higher HR is an independent marker of cardiovascular and all-cause death for middle-aged men and women in the Japanese general population.

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研究成果の要約

鶏卵摂取量と総コレステロール値、総死亡率、疾患別死亡率の関連

Nakamura Y, Okamura T, Tamaki S et al. Egg Consumption, Serum Cholesterol, and Cause-Specific and All-Cause Mortality: NIPPON DATA80, 1980-94. American Journal of Clinical Nutrition 2004; 80:58-63.

【背景、目的】

卵黄は多量のコレステロールを含有するため先進工業国での栄養指導では鶏卵摂取は制限されている。事実米国のガイドライン ATP III では鶏卵摂取を週に 2 個までに控えるように推奨している。しかし鶏卵摂取と血清脂質、予後の関連を調べた疫学研究は極めて少ない。Framingham 研究では鶏卵摂取は血清総コレステロール値(TCH)と予後に影響を与えないと報告しているし、また 10 万人以上を対象として Hu らの研究でも鶏卵摂取量は虚血性心疾患(CHD)発症および死亡に影響を与えないとした。しかし前者の対象数は 912 例と少なく、また後者の対象は看護婦と男性医療従事者であるため研究結果が一般人全般に当てはまるかどうかに問題がある。さらにわが国では鶏卵が総摂取コレステロールに占める割合が米国に比べて大きいため(これまでの報告によると米国では鶏卵が総摂取コレステロールの 29%程度寄与するのに対し、わが国では約 48%)わが国での検討が必要である。そこでわれわれは一般住民1万例以上を対象として長期追跡した NIPPON DATA 80 研究のデータベースを用いて検討した。

【方法】

1980 年に全国保健所の中から 300 カ所を無作為抽出し、30 才以上の男女を対象に検診、頻度法による主要食品摂取に関する栄養調査と血液生化学検査を行い、その後 14 年間追跡した。鶏卵摂取量は 1 日 2 個以上、1 日 1 個、2 日に 1 個、週に 1～2 個、週に 1 個未満の 5 段階に分けて回答を得た。追跡開始時の脳梗塞、心筋梗塞既往例やデータに欠損のあった対象を除外した計 9,263 例(女 5,186 男 4,077)について検討した。

【結果】

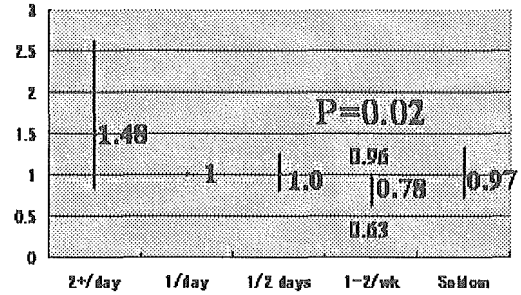
女性では鶏卵摂取量と TCH とに有意な関連があり、鶏卵摂取量が多いほど容量依存的に TCH が高かった。男性では鶏卵摂取量と TCH との間に有意な関連を認めなかった。

図には女性での背景因子の相違を調整して予後を解析する Cox 多変量解析結果を示す。鶏卵を 1 日 1 個摂取する群を基準(1 とする)としたとき総死亡率は 1 日 1 個未満摂取する 3 群で低く、特に週に 1～2 個摂取群では総死亡相対危険度が 0.78(95%信頼区間:0.63-0.96)と統計的に有意に低かった。また統計的に有意ではなかったが脳卒中-、CHD-、ガン死亡率も週に 1～2 個摂取群で低い傾向にあった。一方男性においては鶏卵摂取と総死亡率、死因別死亡率にはなんら関連は認めなかった。

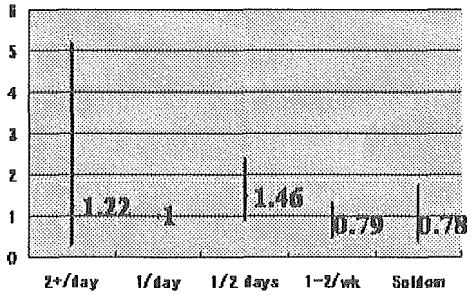
Cox解析—女性 (NIPPON DATA80)

(年齢、血圧、飲酒、喫煙他で調整)

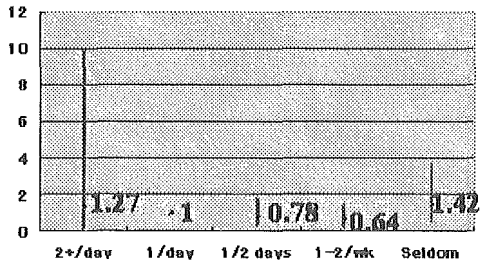
相対危険度　総死亡



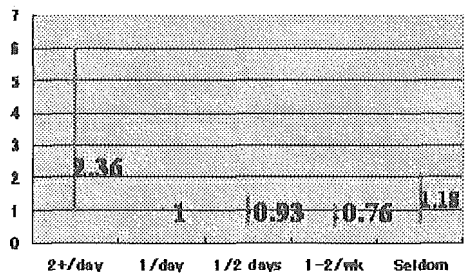
相対危険度　脳卒中



相対危険度　CHD



相対危険度　ガン



【考案】

今回の研究結果で男女に差があったのは何故であろうか。代謝・吸収の研究では鶏卵摂取と血清脂質の間に男女差は認められていない。一般住民を対象としたある研究では女性に比べ男性の方がより多種の食材からコレステロールを摂取しているとの報告もある。また、男性は女性に比べて外食も多く、自身で料理をする男性も女性より少ないと想定できる。このため頻度法調査に際して男性においては鶏卵摂取量に過誤が生じた可能性がある。従って男性において鶏卵摂取は制限しなくても安全であるとの結論は危険を伴う可能性がある。

【結論】

鶏卵摂取をある程度制限することは健康上有用であることが想定された。

Egg consumption, serum cholesterol, and cause-specific and all-cause mortality: the National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged, 1980 (NIPPON DATA80)[1–3]

Yasuyuki Nakamura, Tomonori Okamura, Shinji Tamaki, Takashi Kadowaki, Takehito Hayakawa, Yoshikuni Kita, Akira Okayama, and Hirotsugu Ueshima for the NIPPON DATA80 Research Group

ABSTRACT

Background: Because egg yolk has a high cholesterol concentration, limited egg consumption is often suggested to help prevent ischemic heart disease (IHD).

Objective: We epidemiologically examined the validity of this recommendation.

Design: We analyzed the relations of egg consumption to serum cholesterol and cause-specific and all-cause mortality by using the NIPPON DATA80 (National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged, 1980) database. At the baseline examination in 1980, a nutritional survey was performed by using the food-frequency method in Japanese subjects aged ≥30 y. We followed 5186 women and 4077 men for 14 y.

Results: The subjects were categorized into 5 egg consumption groups on the basis of their responses to a questionnaire (≥2/d, 1/d, 1/2 d, 1–2/wk, and seldom). There were 69, 1396, 1667, 1742, and 315 women in each of the 5 groups, respectively. Age-adjusted total cholesterol (5.21, 5.04, 4.95, 4.91, and 4.92 mmol/L in the 5 egg consumption categories, respectively) was related to egg consumption ($P < 0.0001$, analysis of covariance). In women, unadjusted IHD mortality and all-cause mortality differed significantly between the groups [IHD mortality: 1.1, 0.5, 0.4, 0.5, and 2.0 per 1000 person-years, respectively ($P = 0.008$, chi-square test); all-cause mortality: 14.8, 8.0, 7.5, 7.5, and 14.5 per 1000 person-years, respectively ($P < 0.0001$, chi-square test)]. In men, egg consumption was not related to age-adjusted total cholesterol. Cox analysis found that, in women, all-cause mortality in the 1–2-eggs/wk group was significantly lower than that in the 1-egg/d group, whereas no such relations were noted in men.

Conclusion: Limiting egg consumption may have some health benefits, at least in women in geographic areas where egg consumption makes a relatively large contribution to total dietary cholesterol intake. *Am J Clin Nutr* 2004;80:58–63.

KEY WORDS Eggs; total cholesterol; ischemic heart disease; National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged, 1980; NIPPON DATA80; Keys equation

INTRODUCTION

Because egg yolk has a relatively high cholesterol concentration, limited egg consumption is often recommended to reduce serum cholesterol concentrations and to help prevent ischemic heart disease (IHD) (1). Although several metabolic ward studies showed that dietary cholesterol is a major determinant of serum cholesterol concentrations (2, 3), other studies failed to show changes in serum total cholesterol concentration when eggs were added to diets that already contained moderate amounts of cholesterol (4–7). There have been few epidemiologic studies in free-living populations that explored the relation of egg consumption to serum cholesterol and IHD (8–12). A Framingham Study of 912 subjects concluded that egg consumption was not related to serum cholesterol or IHD (11). A study by Hu et al (12) of 117 933 subjects in the United States also showed no relation between consumption of ≤1 egg/d and the risk of IHD or stroke. However, in geographic areas where egg consumption makes a greater contribution to total dietary cholesterol intake than in the United States, the results may be different (13–15). Accordingly, we analyzed the relations of egg consumption to serum cholesterol concentrations and cause-specific and all-cause mortality by using the NIPPON DATA80 (National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged, 1980) database, which includes >10 000 subjects in Japan who were followed for 14 y (16–18).

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SUBJECTS AND METHODS

Subjects

The subjects in this cohort were participants in the 1980 National Survey on Circulatory Disorders (19). A total of 10 546 community-based subjects aged ≥30 y in 300 randomly selected health districts throughout Japan participated in the survey, which consisted of a medical history, physical examinations, blood tests, and a self-administered questionnaire on lifestyle, which included an essential nutritional survey performed by the food-frequency method. The cohort was followed until 1994 (NIPPON DATA80) (16–18). The overall population aged ≥30 y in the 300 participating health districts was 13 771. Therefore, the participation rate of the survey was 76.6% before exclusion for the reasons mentioned below. To clarify the cause of death, we used the National Vital Statistics. In accordance with Japan's Family Registration Law, all death certificates issued by physicians were forwarded to the Ministry of Health and Welfare via the public health centers in the district of residency. The underlying causes of death were coded according to the 9th revision of the *International Classification of Diseases* for the National Vital Statistics. We confirmed death in each health district by computer matching of data from the National Vital Statistics, with district, sex, and dates of birth and death as key codes. Of 10 546 subjects, a total of 1283 were excluded for the following reasons: past history of coronary artery disease or stroke (n = 166); some missing information on the baseline survey (n = 247); and lost to follow-up (n = 870). We analyzed the remaining 9263 subjects (5186 men and 4077 men). There was no significant difference in sex-specific mean total cholesterol concentration between the subjects who were lost to follow-up and those who were censored (194 compared with 192 mg/dL, respectively, in the women; 191 compared with 188 mg/dL, respectively, in the men). Therefore, the potential bias regarding the 870 subjects lost to follow-up was thought to be negligible. Permission to use the National Vital Statistics was obtained from the Management and Coordination Agency, Government of Japan. Ethical approval for this study was obtained from the Institutional Review Board of Shiga University of Medical Science (No. 12-18, 2000).

Biochemical and baseline examinations

The baseline surveys were conducted by public health centers. Baseline blood pressures were measured by trained observers using a standard mercury sphygmomanometer on the subjects' right arm while the subjects were seated and after they had rested for ≥5 min. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, use of antihypertensive agents, or any combination of these. Height in stocking feet and weight in light clothing were measured. Body mass index was calculated as weight (in kg) divided by the square of height (in m).

A lifestyle survey was carried out by using a self-administered questionnaire, which included questions about the average consumption of 31 food items. Egg consumption was queried on the basis of 5 categories: ≥2/d, ≈1/d, ≈1/2 d, ≈1–2/wk, and seldom. Public health nurses rechecked information with the subjects regarding consumption of eggs and other foods, smoking status, drinking habits, and present and past medical histories.

Nonfasting blood samples were drawn, centrifuged for 15 min at 1500 × g and room temperature within 60 min of collection, and then stored at −70 °C until analyses. Total cholesterol was analyzed in a sequential autoanalyzer (SMA12; Technicon, Tarrytown, NY) by using the Lieberman-Burchard direct method for total cholesterol at a single laboratory (Osaka Medical Center for Health Science and Promotion, Osaka, Japan). This laboratory is a member of the Cholesterol Reference Method Laboratory Network (20), and the precision and accuracy of measurement of serum cholesterol were certified in the Lipid Standardization Program administered by the Centers for Disease Control and Prevention, Atlanta. Serum glucose concentrations were measured by using the cupric-neocuproline method (21). Diabetes was defined as a serum glucose concentration ≥ 200 mg/dL, a past history of diabetes, or both. Serum creatinine was analyzed in a sequential autoanalyzer (SMA12/60; Technicon) by using Jaffe's method.

Statistical analysis

SAS version 8.02 for WINDOWS (SAS Institute Inc, Cary, NC) was used throughout the study. Women and men were analyzed separately. The chi-square test was used to compare dichotomous variables. To compare means between the 5 groups stratified by egg consumption, a one-way analysis of variance was used. To assess whether egg consumption affected total cholesterol concentrations, we performed an analysis of covariance by adjusting for age. Age-adjusted total cholesterol was determined.

The age-adjusted and multivariate-adjusted relative risks for all-cause or cause-specific mortality were calculated by using a Cox proportional hazard model. For multivariate analyses, age, serum creatinine, total cholesterol, blood glucose, body mass index, systolic and diastolic blood pressures, use of blood pressure–lowering drugs, cigarette smoking (never smoker; ex-smoker; current smoker, ≤20 cigarettes/d; and current smoker, >20 cigarettes/d), and alcohol intake (never drinker, ex-drinker, occasional drinker, and daily drinker) were entered as covariates. To rule out the possibility that subjects with a severe but subclinical disease might have affected the outcome, we performed the above Cox analyses after excluding subjects who died within the initial 5 y of follow-up. Tests of linear trends across groups with decreasing egg consumption were conducted by treating the median or representative values of egg consumption in the 5 categories (consumption per week: 21, 7, 3.5, 1.5, and 0.5 eggs, respectively) as continuous variables.

All P values were two-tailed, and $P < 0.05$ was considered significant. Data are presented as means ± SDs unless stated otherwise.

RESULTS

Baseline characteristics

Baseline characteristics in each egg consumption category for the women and the men are shown in **Table 1**. In both the women and the men, relatively few subjects (1.3–6.1%) were in the ≥2-eggs/d or seldom (ie, ≤1 egg/wk) group. Except for these 2 extreme categories, there were >1200 subjects in each category. In the women, those in the 2 extreme categories had significantly higher mean ages than did those in the other categories and were significantly more likely to have hypertension. Although similar tendencies were noted in the men, they were not as striking as those in the women.

Egg consumption and total cholesterol

Total cholesterol, age-adjusted total cholesterol, blood glucose, and serum creatinine concentrations and systolic and diastolic blood

TABLE 1
Baseline characteristics stratified by egg consumption among 5186 women and 4077 men with data in the NIPPON DATA80 database[1]

	Egg consumption					
Sex and characteristic	≥2/d	1/d	1/2 d	1–2/wk	Seldom	P^2
Women						
n	69	1393	1667	1742	315	
Age (y)	55.6 ± 12.9[3]	50.4 ± 12.7	49.3 ± 13.0	51.2 ± 13.3	55.4 ± 14.7	<0.0001
BMI (kg/m^2)	23.4 ± 3.8	22.7 ± 3.3	22.7 ± 3.2	23.0 ± 3.4	23.2 ± 3.7	0.0037
Hypertension (%)	49.3	38.3	37.0	43.7	51.8	<0.0001
Diabetes (%)	7.3	4.2	3.7	4.1	4.4	0.65
Daily drinker (%)	5.8	2.73	2.64	2.93	3.17	0.31
Current smoker (%)	11.6	7.5	7.8	10.6	10.5	0.0005
Men						
n	149	1364	1216	1204	144	
Age (y)	51.3 ± 12.6	51.0 ± 12.9	49.0 ± 12.7	50.6 ± 13.5	51.9 ± 13.9	0.001
BMI (kg/m^2)	22.2 ± 2.7	22.5 ± 2.9	22.5 ± 2.8	22.6 ± 2.9	22.4 ± 2.9	0.51
Hypertension (%)	49.3	38.3	37.0	43.7	51.8	<0.0001
Diabetes (%)	5.4	7.5	5.9	7.6	8.3	0.35
Daily drinker (%)	50.3	51.0	47.3	47.2	34.7	0.0001
Current smoker (%)	63.1	64.5	64.4	61.1	63.4	0.46

[1] NIPPON DATA80, National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged, 1980.
[2] Chi-square test for dichotomous variables and ANOVA for continuous variables.
[3] $\bar{x}$ ± SD (all such values).

pressures are shown in **Table 2**. In the women, a dose-response relation was noted between egg consumption and both total cholesterol and age-adjusted total cholesterol. No such relations were noted in the men, and total cholesterol and age-adjusted total cholesterol concentrations were almost the same in all categories.

Egg consumption and outcome: unadjusted outcome and multivariate Cox analyses

Unadjusted numbers of deaths due to all causes, stroke, IHD, and cancer for each category of egg consumption in the women and the men are shown in **Table 3**. Death rates are shown per 1000 person-years. In the women, all-cause, IHD, and cancer deaths differed significantly between the groups. In the men, no significant differences in outcome were noted. Because several baseline characteristics were different between the egg consumption categories, we performed multivariate analyses.

The results of age-adjusted and multivariate Cox analyses of associations between egg consumption and outcomes are shown in **Tables 4** and **5**. In the women, the multivariate-adjusted relative risk of all-cause death for those in the 1–2-eggs/wk category

TABLE 2
Baseline characteristics stratified by egg consumption among 5186 women and 4077 men with data in the NIPPON DATA80 database[1]

	Egg consumption					
Sex and characteristic	≥2/d	1/d	1/2 d	1–2/wk	Seldom	P^2
Women						
n	69	1393	1667	1742	315	
TCH (mmol/L)	5.23 ± 0.99[3]	4.97 ± 0.87	4.86 ± 0.84	4.85 ± 0.88	4.94 ± 1.01	<0.0001
aTCH (mmol/L)[4]	5.11 ± 0.10	4.98 ± 0.02	4.89 ± 0.02	4.83 ± 0.02	4.84 ± 0.05	<0.0001
Glucose (mmol/L)	7.39 ± 1.78	6.67 ± 1.83	7.11 ± 1.83	7.22 ± 1.94	7.28 ± 1.94	0.19
Creatinine (μmol/L)	78.7 ± 12.4	74.3 ± 11.5	74.3 ± 11.5	75.1 ± 21.2	76.9 ± 15.0	0.012
SBP (mm Hg)	139 ± 21	133 ± 21	132 ± 21	135 ± 22	140 ± 24	<0.0001
DBP (mm Hg)	83 ± 12	79 ± 12	79 ± 12	80 ± 12	81 ± 12	<0.0001
Men						
n	149	1364	1216	1204	144	
TCH (mmol/L)	4.73 ± 0.84	4.77 ± 0.83	4.78 ± 0.83	4.77 ± 0.86	4.77 ± 0.94	0.98
aTCH (mmol/L)[4]	4.76 ± 0.07	4.78 ± 0.02	4.78 ± 0.02	4.76 ± 0.02	4.79 ± 0.07	0.98
Glucose (mmol/L)	7.28 ± 1.89	7.28 ± 1.89	7.22 ± 2.11	7.33 ± 2.44	7.11 ± 1.72	0.0097
Creatinine (μmol/L)	90.2 ± 14.1	93.7 ± 26.5	93.7 ± 23.0	93.7 ± 15.0	95.5 ± 16.8	0.20
SBP (mm Hg)	139 ± 21	139 ± 20	137 ± 20	139 ± 22	142 ± 22	0.54
DBP (mm Hg)	84 ± 12	84 ± 12	83 ± 12	84 ± 12	84 ± 13	0.38

[1] NIPPON DATA80, National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged, 1980; TCH, total cholesterol; aTCH, age-adjusted total cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure.
[2] Chi-square test for dichotomous variables and ANOVA for continuous variables except aTCH, for which ANCOVA was used.
[3] $\bar{x}$ ± SD (all such values unless indicated otherwise).
[4] $\bar{x}$ ± SE.

TABLE 3
Unadjusted outcomes by egg consumption category during 14 y of follow-up of 5186 women and 4077 men with data in the NIPPON DATA80 database[1]

Sex and characteristic	Egg consumption					*P* (chi-square test)
	≥2/d	1/d	1/2 d	1–2/wk	Seldom	
Women						
n	69	1393	1667	1742	315	
Person-years	877	18 591	22 276	23 270	4058	
All-cause death [*n* (/TPY)]	13 (14.8)	149 (8.0)	166 (7.5)	175 (7.5)	59 (14.5)	<0.0001
Stroke death [*n* (/TPY)]	2 (2.3)	28 (1.5)	39 (1.8)	30 (1.3)	8 (2.0)	0.69
IHD death [*n* (/TPY)]	1 (1.1)	10 (0.5)	10 (0.4)	12 (0.5)	8 (2.0)	0.008
Cancer death [*n* (/TPY)]	5 (5.7)	40 (2.2)	43 (1.9)	45 (1.9)	15 (3.7)	0.043
Men						
n	149	1364	1216	1204	144	
Person-years	1934	17 652	16 008	15 610	1875	
All-cause death [*n* (/TPY)]	23 (11.9)	227 (12.9)	164 (10.2)	201 (12.9)	25 (13.3)	0.16
Stroke death [*n* (/TPY)]	1 (0.5)	37 (2.1)	32 (1.4)	37 (2.4)	5 (2.7)	0.52
IHD death [*n* (/TPY)]	0 (0)	9 (0.5)	11 (0.7)	17 (1.1)	2 (1.1)	0.23
Cancer death [*n* (/TPY)]	11 (5.7)	65 (3.7)	60 (3.7)	67 (4.3)	5 (2.7)	0.51

[1] NIPPON DATA80, National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged, 1980; TPY, 1000 person-years; IHD, ischemic heart disease.

was significantly lower than that for those in the 1-egg/d category. The relative risks of deaths from stroke, IHD, and cancer did not differ significantly between the egg consumption categories (Table 4). In the men, no significant differences in outcome between the egg consumption categories were noted (Table 5). The results of the multivariate Cox analyses after exclusion of the subjects who died within the initial 5 y of follow-up were not significantly different from those in Tables 4 and 5 (data not shown).

DISCUSSION

Egg yolk contains relatively high amounts of cholesterol, and this has led to the recommendation to limit egg intake to reduce serum cholesterol concentrations and hopefully prevent IHD. In fact, the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) recommended that at most 2 egg yolks should be consumed per week (1). Although several metabolic ward studies showed that dietary cholesterol is a major determinant of serum cholesterol concentrations (2, 3), other studies failed to detect changes in serum total cholesterol concentration when egg was added to diets that already contained moderate amounts of cholesterol (4–7). Furthermore, epidemiologic studies in the United States did not detect any associations between egg consumption and serum cholesterol concentrations or cardiovascular events (11, 12). However, in geographic areas where egg consumption makes a greater contribution to total dietary cholesterol intake than in the United States, the results may be different (13–15). The studies by Dawber et al (11) and Hu et al (12) reported that egg consumption in the United States accounts for 26–32% of total dietary cholesterol intake. In contrast, a study in

TABLE 4
Relative risks and 95% CIs of outcomes by egg consumption category in Cox analyses of women with data in the NIPPON DATA80 database[1]

	Egg consumption					*P* for trend
	≥2/d (*n* = 69)	1/d (*n* = 1393)	1/2 d (*n* = 1667)	1–2/wk (*n* = 1742)	Seldom (*n* = 315)	
Age adjusted						
All-cause death	1.57 (0.89, 2.76)	1	1.0 (0.81, 1.23)	0.82 (0.66, 1.01)	0.99 (0.74, 1.33)	0.02
P	0.12		0.97	0.06	0.93	
Stroke death	1.51 (0.36, 6.33)	1	1.42 (0.88, 2.30)	0.85 (0.51, 1.41)	0.76 (0.35, 1.66)	0.18
IHD death	1.68 (0.22, 12.9)	1	0.82 (0.36, 1.88)	0.76 (0.34, 1.66)	1.70 (0.70, 4.14)	0.90
Cancer death	2.19 (0.87, 5.53)	1	0.97 (0.64, 1.48)	0.84 (0.55, 1.27)	1.18 (0.65, 2.12)	0.10
Multivariate adjusted[2]						
All-cause death	1.48 (0.84, 2.61)	1	1.0 (0.81, 1.24)	0.78 (0.63, 0.96)	0.97 (0.72, 1.32)	0.02
P	0.17		0.98	0.02	0.86	
Stroke death	1.22 (0.29, 5.17)	1	1.46 (0.89, 2.4)	0.79 (0.47, 1.33)	0.78 (0.35, 1.73)	0.23
IHD death	1.27 (0.16, 9.80)	1	0.78 (0.35, 1.82)	0.64 (0.28, 1.44)	1.42 (0.56, 3.62)	0.71
Cancer death	2.36 (0.93, 5.98)	1	0.93 (0.61, 1.41)	0.76 (0.52, 1.20)	1.18 (0.65, 2.12)	0.06

[1] NIPPON DATA80, National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged, 1980; IHD, ischemic heart disease.

[2] Age, serum creatinine, total cholesterol, blood glucose, BMI, systolic and diastolic blood pressures, use of blood pressure–lowering drugs, cigarette smoking, and alcohol intake were entered as covariates for multivariate analyses.

TABLE 5
Relative risks and 95% CIs of outcomes by egg consumption category in Cox analyses of men with data in the NIPPON DATA80 database[1]

	Egg consumption					*P* for trend
	≥2/d (*n* = 149)	1/d (*n* = 1364)	1/2 d (*n* = 1216)	1–2/wk (*n* = 1204)	Seldom (*n* = 144)	
Age adjusted						
All-cause death	0.87 (0.57, 1.34)	1	0.88 (0.73, 1.08)	0.92 (0.77, 1.11)	0.80 (0.53, 1.21)	0.84
Stroke death	0.28 (0.03, 1.66)	1	1.04 (0.66, 1.64)	0.98 (0.63, 1.52)	0.91 (0.36, 2.40)	0.15
IHD death	—	1	1.34 (0.58, 3.10)	1.80 (0.85, 3.85)	1.51 (0.33, 6.81)	0.03
P	—		0.49	0.13	0.59	
Cancer death	1.53 (0.80, 2.88)	1	1.17 (0.83, 1.65)	1.15 (0.82, 1.61)	0.62 (0.25, 1.53)	0.51
Multivariate adjusted[2]						
All-cause death	0.89 (0.57, 1.38)	1	0.89 (0.72, 1.08)	0.94 (0.78, 1.13)	0.73 (0.48, 1.12)	0.75
Stroke death	0.25 (0.03, 1.81)	1	1.10 (0.68, 1.76)	1.09 (0.69, 1.72)	0.93 (0.36, 2.40)	0.11
IHD death	—	1	1.49 (0.63, 3.48)	1.71 (0.78, 3.76)	1.18 (0.26, 5.42)	0.08
Cancer death	1.42 (0.73, 2.76)	1	1.12 (0.79, 1.58)	1.11 (0.79, 1.57)	0.60 (0.24, 1.49)	0.57

[1] NIPPON DATA80, National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged, 1980; IHD, ischemic heart disease.

[2] Age, serum creatinine, total cholesterol, blood glucose, BMI, systolic and diastolic blood pressures, use of blood pressure–lowering drugs, cigarette smoking, and alcohol intake were entered as covariates for multivariate analyses.

Japan that used the food record method in rural and urban populations and that was conducted during a similar time as the present study reported that egg consumption in Japan accounts for ≈48% of total dietary cholesterol intake (15).

The present study found dose-response relations of egg consumption to total cholesterol and age-adjusted total cholesterol concentrations in women but not in men. On the basis of metabolic ward studies, Keys proposed an equation to predict serum cholesterol concentrations based on dietary intakes of cholesterol and saturated and polyunsaturated fatty acids (3). We surveyed essential nutritional components by the food-frequency method and therefore have no data on total calorie intake or total dietary intakes of cholesterol or saturated and polyunsaturated fatty acids. On the basis of previous studies that used the 24-h food-recall method or food record method in rural and urban populations in Japan and that had a study period similar to that of the present study (13–15), the representative daily total energy intake of female subjects can be estimated to be 1970 kcal, with 350 mg total dietary cholesterol. If egg consumption is reduced from 1/d (215 mg cholesterol/d) to 1.5/wk (46 mg cholesterol/d), total energy intake should decrease by 63 kcal (80 kcal/egg), polyunsaturated fatty acid intake should decrease from 7 to 6.4 g, and saturated fatty acid intake should decrease from 7.7 to 6.4 g. Under these conditions, the Keys equation predicts that total cholesterol concentrations should decrease by 6.5 mg/dL (0.17 mmol/L). The actual difference observed between age-adjusted total cholesterol concentrations in the 1-egg/d category and those in the 1–2-eggs/wk category was 5.8 mg/dL (0.15 mmol/L). In men, a similar calculation yields a predicted reduction in total cholesterol concentrations of 5.4 mg/dL (0.14 mmol/L) (assumed total energy and dietary cholesterol intakes of 2400 kcal and 400 mg, respectively), but the actual observed difference in age-adjusted total cholesterol was only 0.8 mg/dL (0.02 mmol/L). Thus, differences in age-adjusted total cholesterol concentration between categories conformed to the Keys equation in the women but not in the men. Why is the relation between egg consumption and total cholesterol different between women and men? Ueshima et al (13) observed a high-order relation in several groups of Japanese men, with large differences between groups in both dietary intake and total cholesterol. However, only a weak, although significant, correlation was noted between the dietary lipid score and serum total cholesterol for subjects within a culturally homogeneous population in which intraindividual variability is large compared with interindividual variability. In the study by Dawber et al (11), the distribution of daily dietary cholesterol intake was examined by tertile of egg consumption, and significant differences in total daily cholesterol intake between subjects within each egg consumption tertile were found in both women and men. However, markedly greater variability was seen in men. Therefore, men appear to consume dietary cholesterol from a greater variety of sources (ie, sources other than eggs) than do women.

A population with a low mean cholesterol concentration, such as the population in Japan, has a much lower IHD mortality rate than do Western populations (22). However, cholesterol has been shown to have predictive value for IHD mortality in Japan (18). Women in the 1–2-eggs/wk group had the lowest age-adjusted total cholesterol concentrations, and their relative risk of all-cause death was significantly lower than that of the women in the 1-egg/d group. The women in the 1–2-eggs/wk group also tended to have lower mortality due to stroke, IHD, and cancer than did the 1-egg/d group. Because of the relatively high participation rate in the present study (76.6%), generalization of the present results in Japan may be warranted.

Limitations of the study

We surveyed essential nutritional components by using the food-frequency method. Therefore, we have no data on total calorie intake or total dietary intakes of cholesterol or saturated and polyunsaturated fatty acids. To obtain this information, detailed food records or 24-h dietary recalls are needed. However, because of the large amount of effort required to collect and process multiple days of food records or recalls, these methods are impractical and seldom used as the primary method for estimating usual intakes in large-scale epidemiologic studies.

Another limitation is that we used mortality data as endpoints, which may have led to misclassification of the cause of death. However, the death-certificate diagnosis of stroke and cancer in Japan has been reported to be quite accurate (23, 24). However, it has also been reported that most cases of cardiac sudden death

tended to be described on Japanese death certificates as "coronary heart disease," "heart failure," or "unknown cause" (25, 26). Furthermore, mortality statistics for IHD may have been underestimated with the use of ICD9 by the end of 1994 because deaths coded as "heart failure" may have hidden some coronary events (25–28). Nevertheless, our results mainly focused on all-cause mortality, and thus the data were thought to be correct.

Finally, the consumption of only 1–2 eggs/wk by women may simply reflect a more health-conscious attitude that eventually results in a better outcome. We did not measure variables related to health consciousness, such as exercise or participation in sports; however, the percentage of women who smoked in the 1–2-eggs/wk category (10.6%) was not lower than that in the 1-egg/d category (7.5%) (Table 1). This suggests that the women in the 1–2-eggs/wk category did not have more health-conscious attitudes.

Conclusions

Dose-response relations of egg consumption to total cholesterol and age-adjusted total cholesterol concentrations were noted in the women, and all-cause mortality was affected by egg consumption. Among the women, tendencies for lower mortality due to stroke, IHD, and cancer in the 1–2-eggs/wk group than in the 1-egg/d group may have resulted in significantly fewer all-cause deaths. However, no such relations were noted in the men. Sources other than eggs may contribute to total cholesterol intake in men. These results suggest that limiting egg consumption may have some health benefits, at least in women in geographic areas where egg consumption makes a relatively large contribution to total dietary cholesterol intake.

For a list of the investigators and members of the NIPPON DATA80 Research Group, please see the appendix of reference 18.

YN participated in designing and conducting the study, analyzing and interpreting the data, and writing and preparing the manuscript. TO and AO participated in conducting the study and analyzing and interpreting the data. ST and TK participated in managing and interpreting the data. TH and YK participated in managing the data and conducting the study. HU was the principal investigator and participated in designing and conducting the study and analyzing and interpreting the data. None of the authors had any conflicts of interest.

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研究成果の要約

血清アルブミン値、総コレステロール値と総死亡の関連

Okamura T, Hayakawa T, Kadowaki T, et al. A combination of serum low albumin and above-average cholesterol level is associated with excess mortality. J Clin Epidemiol 2004; 57: 1188-1195.

【研究の目的】欧米の追跡調査では、血清アルブミンの低値が、循環器疾患や総死亡の危険因子とされているが、本邦での調査は少ない。また一般に血清アルブミン値が高い者は、総コレステロール値も高いが、両者の死亡への影響を同時に検討した研究はほとんどない。

【研究方法】全国から無作為抽出された300地区に居住する1980年の循環器疾患基礎調査受診者を14年間追跡した(NIPPON DATA80)。このうち30～59歳の受検者のうち循環器疾患既往歴のない6,957人(男性;3,062人、女性;3,895人)を分析対象とした。1980年当時のアルブミン値で、男性は≦43、44-46、≦47、女性は≦42、43-45、≦46(g/L)の3グループに分けて、14年間の死亡との関連を検討した。アルブミンが最も高い群を1とした時の各グループの死亡確率を、高血圧、糖尿病、喫煙などを統計学的に補正して求めた。

【結果】男性では、血清アルブミン値が高いと、総死亡、悪性新生物死亡、非がん非循環器疾患死亡が低くなる傾向を示した。総コレステロールの中央値(真ん中の値、男性:185 mg/dl、女性:185 mg/dl)で対象者を2グループに分けると、アルブミンによる死亡低下作用は総コレステロールが高いグループでのみ認められた(下表参照)。

表. 総コレステロール中央値以上の集団における血清アルブミン値と総死亡、循環器疾患死亡の関連

	血清アルブミン値	総死亡			循環器疾患死亡		
	(Stratum mean, g/L)	RR	95% C.I.	P-values	RR	95% CI	P-values
男性	47- (48.1)	1.00			1.00		
	44-46 (45.0)	2.37	1.13, 4.97	0.02	4.09	0.92, 18.1	0.06
	-43 (41.8)	3.37	1.53, 7.42	<0.01	5.04	1.04, 24.5	0.04
	2.6-g/liter (1SD) の増加	0.68	0.53, 0.87	<0.01	0.68	0.45, 1.03	0.07
女性	46- (47.0)	1.00			1.00		
	43-45(44.0)	1.54	0.81, 2.91	0.41	1.63	0.52, 5.16	0.40
	-42 (40.9)	1.97	0.97, 4.02	0.06	1.67	0.43, 6.55	0.46
	2.4-g/liter (1SD) の増加	0.81	0.68, 0.98	0.03	0.82	0.60, 1.11	0.19

注)RRは相対危険度。アルブミンが最も高いグループの死亡率を1として計算している。

上の表に示した関連は総コレステロールが中央値未満の集団では明らかではなかった。

【メッセージ】高めの総コレステロール値を持ち、かつ血清アルブミン値が低い場合、壮年期日本人の総死亡上昇を予測する要因であった。血清アルブミンは、コレステロールの酸化を防ぐことによって循環器疾患死亡に対する防御作用を示していると推測される。両者とも安価で簡便な検査であるが、組み合わせによって死亡予測に有用な指標となり得る。

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A combination of serum low albumin and above-average cholesterol level was associated with excess mortality

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Abstract

Background: There is no population-based prospective study concerning the relation between serum albumin and mortality in a non-Western population, and few previous studies included the subgroup analysis stratified by serum cholesterol level.

Methods: A 13.7-year cohort study was conducted on 6,957 males and females aged 30–59 years from 300 randomly selected areas throughout Japan, who participated in the National Survey on Circulatory Disorders in 1980.

Results: In the group with median and above of total cholesterol, one standard deviation (SD) increment of serum albumin (2.6 g/L for males and 2.4 g/L for females) was inversely associated with all-cause mortality for both males and females (relative risk RR = 0.68 and 0.81; 95% confidence interval CI = 0.53–0.87 and 0.68–0.98), and with cancer mortality for females (RR = 0.74; 95% CI = 0.57–0.96); and the lowest category of serum albumin (≤43 g/L) showed the highest cardiovascular mortality for males (RR = 5.04; 95% CI = 1.04–24.5) among the three albumin categories. These relationships were not evident in the group with total cholesterol level below median.

Conclusion: A combination of a low albumin level and above average cholesterol level, even both within the clinical normal range, is associated with excess mortality in the Japanese general population.

Keywords: Serum albumin; Cholesterol; Mortality; Cohort studies

1. Introduction

Several studies have reported higher mortality from all causes [1–8] and higher mortality or morbidity from coronary heart disease [2–4,6,8–13], stroke [14] and cancer [2,4] with decreasing concentrations of serum albumin, a measure of nutritional or acute inflammatory status. To our knowledge, however, there is no prospective study concerning the relation between serum albumin and mortality in a non-Western population. In the meantime, it is well established that a high level of serum total cholesterol (TC) is an important causal risk factor for coronary heart disease and all-cause mortality [15].

Both serum albumin and TC are included in routine serum biochemistry measurement because of convenience and low cost. Furthermore, serum albumin is thought to be an antioxidant because it has binding capacities for free radicals and protects oxidization of serum low-density lipoprotein [16,17]. Few studies have examined the joint and interaction effects of serum TC and serum albumin in identifying persons who are at increased risk of subsequent mortality, and the results of previous studies were controversial [6,10].

Our working hypothesis was that, as with Western populations, serum albumin is a predictor for excess mortality and the relation would be different according to serum TC level, even in a population with low TC levels, such as the Japanese. To investigate this hypothesis, we examined data from a prospective survey of 7,894 persons in the Japanese general population.

2. Materials and methods

2.1. Populations

We used data from the National Integrated Project for Prospective Observation of Non-communicable Diseases

[1] Investigators and members of the research group are listed in references 18, 19, and 20.

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Table 1
Age and age-adjusted means or prevalences of base line characteristics stratified by albumin level at the baseline survey

Risk characteristics	Baseline serum albumin level (stratum mean), g/L						P-value
Male	≤43 (41.8)		44–46 (45.0)		≤47 (48.1)		
Number of participants	806		1,382		874		
Age, years	48.3	(7.5)	43.9	(8.0)	39.6	(7.5)	$P < 0.01$
Cholesterol, mmol/L	4.5	(0.03)	4.9	(0.02)	5.1	(0.03)	$P < 0.01$
Glucose, mmol/L	7.3	(0.07)	7.1	(0.05)	6.9	(0.07)	$P < 0.01$
Systolic BP, mmHg	132.4	(0.66)	134.1	(0.48)	137.1	(0.63)	$P < 0.01$
Diastolic BP, mmHg	80.9	(0.44)	83.0	(0.32)	85.3	(0.42)	$P < 0.01$
BMI, kg/m2	22.4	(0.11)	22.7	(0.08)	23.2	(0.11)	$P < 0.01$
Hypercholesterolemia, %	3.0		6.2		9.5		$P < 0.01$
Diabetes, %	1.5		1.0		0.3		0.05
Hypertension, %	44.4		42.1		39.9		0.18
Daily drinker, %	53.1		48.3		48.1		0.06
Current smoker, %	69.2		64.2		65.0		0.05
Female	≤42 (40.9)		43–45 (44.0)		≥46 (47.0)		
Number of subjects	1,001		1,995		899		
Age, years	45.1	(8.2)	44.0	(8.6)	43.2	(8.9)	$P < 0.01$
Cholesterol, mmol/L	4.6	(0.03)	4.8	(0.02)	5.1	(0.03)	$P < 0.01$
Glucose, mmol/L	7.0	(0.05)	7.0	(0.04)	7.0	(0.06)	0.50
Systolic BP, mmHg	126.7	(0.55)	129.1	(0.39)	133.4	(0.58)	$P < 0.01$
Diastolic BP, mmHg	77.0	(0.35)	78.5	(0.25)	80.9	(0.37)	$P < 0.01$
BMI, kg/m2	23.0	(0.10)	22.8	(0.07)	22.9	(0.11)	0.52
Hypercholesterolemia, %	5.6		6.1		10.9		$P < 0.01$
Diabetes, %	0.9		0.5		0.2		0.10
Hypertension, %	28.2		29.0		35.9		$P < 0.01$
Daily drinker, %	2.0		3.0		1.9		0.10
Current smoker, %	7.3		8.0		9.6		0.18

Abbreviations: BMI, body mass index; BP, blood pressure.
Numbers in parentheses are standard deviation for age and standard error for the other variables.

and Its Trends in the Aged, 1980 (NIPPON DATA80), a national cohort study based on the National Survey on Circulatory Disorders in 1980. Details of the study have been described elsewhere; membership of the research group was as previously published [18–20]. A total of 7,894 community based individuals (3,477 males and 4,417 females) aged 30 to 59 in 300 randomly selected districts were enrolled in the present study, which included a clinical examination and a questionnaire about drinking and smoking. Follow-up was until 1994.

2.2. Mortality data

We used the National Vital Statistics of Japan to determine the cause of death. Permission to use the National Vital Statistics was obtained from the Management and Coordination Agency, Government of Japan. All death certificates issued by physicians were forwarded centrally to the Ministry of Health and Welfare via the public health centers in the area of residency. The underlying causes of death were coded according to the 9th International Classification of Disease. We confirmed those who died in each district by matching data from the National Vital Statistics, using the area, gender, and dates of birth and death as key codes.

2.3. Baseline examination

Nonfasting blood samples were drawn and centrifuged within 60 minutes of collection in 1980. Serum albumin and TC were analyzed in an autoanalyzer (SMA12/60; Technicon, Tarrytown, NY, USA) with the bromcresol green method for albumin and the Lieberman–Burchard direct

Table 2
The number of deaths according to underlying cause of death

Cause of death	ICD9 code	Numbers of death		
		Male	Female	Total
Cardiovascular	393–459	53	32	85
All heart disease	393–398, 410–429	27	18	45
Coronary heart disease	410–414	13	5	18
Stroke	430–438	22	14	36
Other		4	0	4
Cancer	140–208	84	59	143
Stomach	151	20	12	32
Lung	162	21	8	29
Liver	155, 199.1c	15	3	18
Pancreas	157	12	1	13
Breast	174,175	—	9	9
Other		16	24	40
Noncardiovascular, noncancer		54	36	90
Liver disease	570–573	7	3	10
Accident, poisoning, and suicide	800–999	23	14	37
Other		24	19	43
Total		191	127	318

Abbreviations: ICD9, 9th International Classification of Disease.
Among 3,062 males and 3,895 females aged 30–59 years old at baseline during the 13.7-year follow-up. Cause of death: at least five cases in either males or females.

Table 3
The number of deaths and multivariate-adjusted RR (95% CI) for major causes of deat0h according to serum albumin level

Albumin levels (Stratum mean, g/L)	No. of persons	Person-years	All causes: Deaths, no.	RR	95% CI	*P*-value
Male						
Albumin categories[a]						
≥47 (48.1)	874	11,978	23	1.00		
44–46 (45.0)	1,382	18,829	75	1.41	0.88–2.27	0.16
≤43 (41.8)	806	10,806	93	1.95	1.19–3.19	0.01
P-value, difference between two models[b]						0.14
2.6 g/L (1 SD) increase[c]				0.72	0.61–0.84	<0.01
P-value, difference between two models[d]						0.04
Female						
Albumin categories[a]						
≥46 (47.0)	899	12,394	24	1.00		
43–45 (44.0)	1,995	27,485	64	1.13	0.70–1.81	0.62
≤42 (40.9)	1,001	13,683	39	1.27	0.75–2.14	0.37
P-value, difference between two models[b]						0.07
2.4 g/L (1 SD) increase[c]				0.88	0.74–1.04	0.14
P-value, difference between two models[d]						0.84

[a] The relative risk (RR) was adjusted for age, body mass index, hypertension, diabetes, smoking, drinking, and serum total cholesterol category.
[b] The difference between models with or without categorical interaction term of albumin and cholesterol is compared based on the logarithm likelihood.
[c] The relative risk (RR) was adjusted for age, body mass index, hypertension, diabetes, smoking, drinking, and serum total cholesterol level.
[d] The difference between models with/without linear interaction term of serum albumin and cholesterol is compared based on the logarithm likelihood.
Abbreviations: CI, confidence interval; RR, relative risk.

method for TC at one laboratory (formerly Center for Adults diseases, Osaka; present name, Osaka Medical Center for Health Science and Promotion). Measurement precision and accuracy for serum TC were certified in the Lipid Standardization Program administered by the U.S. Centers for Disease Control and Prevention, Atlanta, GA [21]. Hypercholesterolemia was defined as serum TC being 6.21 mmol/L or greater.

Baseline blood pressures were measured by trained observers using a standard mercury sphygmomanometer on the right arm of seated subjects. Hypertension was defined as systolic blood pressure 140 mmHg or higher, diastolic blood pressure 90 mmHg or higher, use of antihypertensive agents, or any combination of these. Serum glucose was measured by the cupric–neocuproine method [22]. Diabetes was defined as a serum glucose of 11.1 mmol/L or greater, a history of diabetes, or both. Height in stocking feet and weight in light clothing were measured. Body mass index was calculated as weight (kg) divided by the square of height (m). Public health nurses obtained information on smoking and drinking habits, and present and past medical histories.

2.4. Statistical analysis

Because previous studies reported that the relation between serum albumin and mortality varied by gender [4,8,14], gender-specific analyses were performed in the present study. The value of serum albumin was distributed within a narrow range, and cut-points were chosen to give an approximately symmetric distribution across three categories: ≤43 g/L, 44–46 g/L, and ≥47 g/L for males, ≤42 g/L, 43–45 g/L, and ≥46 g/L for females.

Person-years were calculated as the sum of individual follow-up periods until the occurrence of death or to November 15, 1994. Age-adjusted mean values or prevalence of covariates were calculated in each group according to albumin category, and the differences were tested by analysis of covariance or chi-square tests. The association of all-cause and cause-specific mortality to serum albumin was calculated using Cox's proportional hazard model adjusting for age, TC category (below median vs. median and above), hypertension, diabetes, body mass index (BMI), smoking status (never, ex, and current) and drinking status (never, former, occasional, and daily). The highest category was defined as a standard. The model with continuous serum albumin value instead of albumin categories was also examined. The significance of the interaction of serum albumin and TC was tested with an interaction term for either continuous or categorical variables (three albumin categories and the median of serum TC: 4.78 mmol/L for males and 4.76 mmol/L for females) in the multivariate models. A test for difference between two models with or without interaction was performed based on the logarithm likelihood.

Analyses of mortality in relation to serum albumin were also done in the subgroups stratified by the median of serum TC level. Further analyses were repeated excluding deaths within the first 5 years of follow-up. In this analysis, we dealt with early deaths as censored. This analysis could not be performed meaningfully for cause-specific mortality because of the small numbers of each cause-specific death after excluding early deaths. The Statistical Package for the Social Sciences (SPSS Japan, version 10.0J, Tokyo) was used for analysis. All probability values were two-tailed and all confidence intervals were estimated at the 95% level.

Cardiovascular				Cancer				Noncancer, noncardiovascular			
Deaths, no.	RR	95% CI	*P*-value	Deaths, no.	RR	95% CI	*P*-value	Deaths, no.	RR	95% CI	*P*-value
7	1.00			7	1.00			9	1.00		
26	1.55	0.66–3.63	0.31	30	1.50	0.65–3.46	0.34	19	1.20	0.53–2.70	0.66
20	1.32	0.52–3.39	0.56	47	2.04	0.87–4.77	0.10	26	2.40	1.05–5.52	0.04
			0.02				0.27				0.93
	0.84	0.62–1.14	0.27		0.77	0.61–0.98	0.03		0.58	0.44–0.77	<0.01
			0.75				0.66				<0.01
9	1.00			9	1.00			9	1.00		
17	1.30	0.51–3.33	0.58	30	1.34	0.63–2.84	0.44	17	0.79	0.35–1.78	0.57
9	1.35	0.47–3.90	0.58	20	1.57	0.70–3.51	0.27	10	0.86	0.34–2.18	0.75
			0.77				0.08				0.39
	0.81	0.62–1.07	0.14		0.87	0.67–1.14	0.87		1.00	0.72–1.41	0.99
			0.61				0.85				0.74

Of 7,894 participants, a total of 937 were excluded for the following reasons: past history of coronary heart disease or stroke, $n = 123$; missing information at the baseline survey, $n = 131$; and lost to follow-up, $n = 683$, leaving 6,957 participants (3,062 males and 3,895 females) for the analysis.

Approval for the study was obtained from the Institutional Review Board of Shiga University of Medical Science (No. 12-18, 2000).

3. Results

Table 1 shows age-adjusted means or prevalence of the baseline characteristics of all subjects in each albumin group. There were significant differences in the mean values for serum TC and systolic and diastolic blood pressure, with higher values in the higher albumin groups in both genders; the prevalence of hypercholesterolemia was also highest in the highest albumin category. BMI in males, and the prevalence of hypertension in females, also reached statistical significance; they were higher in the higher albumin groups. Mean serum glucose showed an inverse relation across albumin group in males. There was no relation between albumin category and smoking or drinking status.

Total person-years were 95,175 and mean follow-up period was 13.7 years. During the follow-up, there were 318 deaths (191 males and 127 females). The number of cause-specific deaths is shown in Table 2. In this table, numbers of deaths are shown for specific causes where there are at least five deaths: there were 85 deaths from cardiovascular disease (including 18 from coronary heart disease and 36 from stroke), 143 deaths from cancer, and 90 from noncancer, noncardiovascular diseases (including 10 deaths from liver disease and 37 from accident, poisoning, or suicide).

Table 3 shows gender-specific relative risks of cause-specific mortality according to serum albumin level. For males, compared with the highest albumin group, the lowest albumin group showed a significant excess risk of all-cause and noncancer, noncardiovascular mortality (relative risk RR = 1.95 and 95% confidence interval CI = 1.19–3.19; RR = 2.40 and 95% CI = 1.05–5.52, respectively) and, as a continuous variable, the serum albumin level showed a significantly inverse association with all-cause, cancer, and noncancer, noncardiovascular mortality (RR for 1 SD increment of serum albumin = 0.72, 0.77, and 0.58; 95% CI = 0.61–0.84, 0.61–0.98, and 0.44–0.77, respectively) and the differences between two models with or without linear interaction term of serum albumin and TC reached statistical significance ($P = 0.04$ and $P < 0.01$, respectively). There were no significant findings for females. There was no association between serum albumin and subcategories of cardiovascular disease mortality (coronary heart disease, all heart disease, and stroke) in either gender (data not shown in the table).

Table 4 shows gender-specific relative risks of all-cause and cause-specific mortality according to serum albumin level stratified by the median of serum TC. In the group at median and above of TC, for males, the relative risk for all-cause mortality for the lowest albumin group compared with the highest was 3.37 (95% CI = 1.53–7.42) and for the middle group, it was 2.37 (95% CI = 1.13–4.97). In both genders, there was a significant linear inverse association between serum albumin and all-cause mortality; for cardiovascular mortality in males, relative risk for the lowest albumin group compared with the highest was 5.04 (95% CI = 1.04–24.5); serum albumin was not associated with stroke mortality; however, the lowest group of serum albumin compared with the highest shows significant positive

Table 4
The number of deaths and multivariate-adjusted RRs (95% CIs) for major causes of death according to serum albumin stratified by the median of total cholesterol[a]

			All-cause				Cardiovascular			
Albumin levels (Stratum mean, g/L)	No. of persons	Person-year	Deaths, no.	RR	95% CI	*P*-value	Deaths, no.	RR	95% CI	*P*-value
Male										
Below the median of total cholesterol										
Albumin categories[a]										
≥47 (48.1)	350	4,756	14	1.00			5	1.00		
44–46 (45.0)	668	9,048	35	0.80	0.43–1.52	0.50	9	0.55	0.18–1.72	0.31
≤43 (41.8)	498	6,636	62	1.02	0.54–1.94	0.95	10	0.35	0.10–1.21	0.10
2.6 g/L (1 SD) increase[b]				0.77	0.62–0.94	0.01		1.08	0.68–1.74	0.74
P-value, difference between two models[c]						0.09				0.22
Median and above of total cholesterol										
Albumin categories[a]										
≥47 (48.1)	524	7,222	9	1.00			2	1.00		
44–46 (45.0)	714	9,781	40	2.37	1.13–4.97	0.02	17	4.09	0.92–18.1	0.06
≤43 (41.8)	308	4,171	31	3.37	1.53–7.42	<0.01	10	5.04	1.04–24.5	0.04
2.6 g/L (1 SD) increase[b]				0.68	0.53–0.87	<0.01		0.68	0.45–1.03	0.07
P-value, difference between two models[c]						0.05				0.65
Female										
Below the median of total cholesterol										
Albumin categories[a]										
≥46 (47.0)	352	4,822	11	1.00			2	1.00		
43–45 (44.0)	1,005	13,858	27	0.72	0.36–1.46	0.36	5	0.82	0.16–4.31	0.82
≤42 (40.9)	590	8,067	19	0.68	0.32–1.46	0.33	4	0.95	0.16–5.50	0.95
2.4 g/L (1 SD) increase[b]				1.11	0.83–1.47	0.50		0.88	0.47–1.65	0.70
P-value, difference between two models[c]						0.04				<0.01
Median and above of total cholesterol										
Albumin categories[a]										
≥46 (47.0)	547	7,571	13	1.00			4	1.00		
43–45 (44.0)	990	13,627	37	1.54	0.81–2.91	0.41	8	1.63	0.52–5.16	0.40
≤42 (40.9)	411	5,616	20	1.97	0.97–4.02	0.06	5	1.67	0.43–6.55	0.46
2.4 g/L (1 SD) increase[b]				0.81	0.68–0.98	0.03		0.82	0.60–1.11	0.19
P-value, difference between two models[c]						0.17				0.89

Abbreviations: RR, relative risk; 95% CI, 95% confidence interval.

[a] The relative risk (RR) was adjusted for age, body mass index, hypertension, diabetes, smoking, drinking, and serum total cholesterol category.

[b] The relative risk (RR) was adjusted for age, body mass index, hypertension, diabetes, smoking, drinking, and serum total cholesterol level.

[c] The difference between models with/without linear interaction term of serum albumin and cholesterol is compared based on the logarithm likelihood. Median of total cholesterol was 4.78 mmol/L for males and 4.76 mmol/L for females.

association with all heart disease mortality for males (RR = 8.94; 95% CI = 1.01–78.7; data not shown in the table); the relative risk for coronary heart disease was not calculated because of small numbers. In addition, in females, there was a significantly linear inverse association with cancer mortality (RR = 0.74; 95% CI = 0.57–0.96). In the group with median and above of TC, there was no significant difference between two models with or without linear interaction term of serum albumin and TC for each cause of death.

In the group below median TC, serum albumin level showed significantly inverse association with all-cause and noncancer, noncardiovascular mortality for males (RR = 0.77 and 0.52; 95% CI = 0.62–0.94 and 0.35–0.77, respectively), although these relationships disappeared after excluding deaths due to liver disease (RR = 0.85 and 0.76; 95% CI = 0.69–1.06 and 0.47–1.22, respectively; data not shown in the table). For females, in the analysis of all-cause and cardiovascular mortality, the difference between two models with or without linear interaction term of serum albumin and TC reached statistical significance ($P = 0.04$ and $P < 0.01$, respectively).

Further analysis was performed after excluding deaths within the first five years of follow-up. The results were similar to those shown in Table 4. In the group with median