Table 5. Hazard ratios for the incidence of cardiovascular disease due to mild or moderate-to-severe metabolic abnormalities and/or abdominal obesity, in 2,685 male participants over 11 years of follow-up (1996-2007).

	No metabolic abnormalitiy	Mild metabolic abnormalitiy	Moderate-to-severe metabolic abnormalitiy
Without abdominal obesity			
Participants	1,051	584	342
Total person-years of follow-up	10,739	5,821	3,399
Cardiovascular events	11	10	11
Crude rate per 1000 person-years	1.02	1.72	3.24
Age-adjusted HR (95% CI)*	1.00 reference	1.54 (0.65-3.63)	2.51 (1.08-5.82)
Multivariate-adjusted HR (95% CI)**	1.00 reference	1.49 (0.63-3.52)	2.52 (1.08-5.87)
With abdominal obesity			
Participants	202	264	242
Total person-years of follow-up	1,982	2,611	2,329
Cardiovascular events	5	8	13
Crude rate per 1000 person-years	2.52	3.06	5.58
Age-adjusted HR (95% CI)*	2.34 (0.81-6.74)	2.81 (1.13-7.00)	4.36 (1.94-9.82)
Multivariate-adjusted HR (95% CI)**	2.36 (0.81-6.82)	2.68 (1.07-6.73)	4.12 (1.80-9.43)

Abbreviations: HR, hazard ratio; CI, confidence interval.
Hazard ratios were calculated by a Cox proportional hazards regression model, with no metabolic abnormality without abdominal obesity acting as the reference; *adjusted for age; **adjusted for age, smoking habits, drinking habits, leisure-time physical activity and serum non-high-density lipoprotein cholesterol.

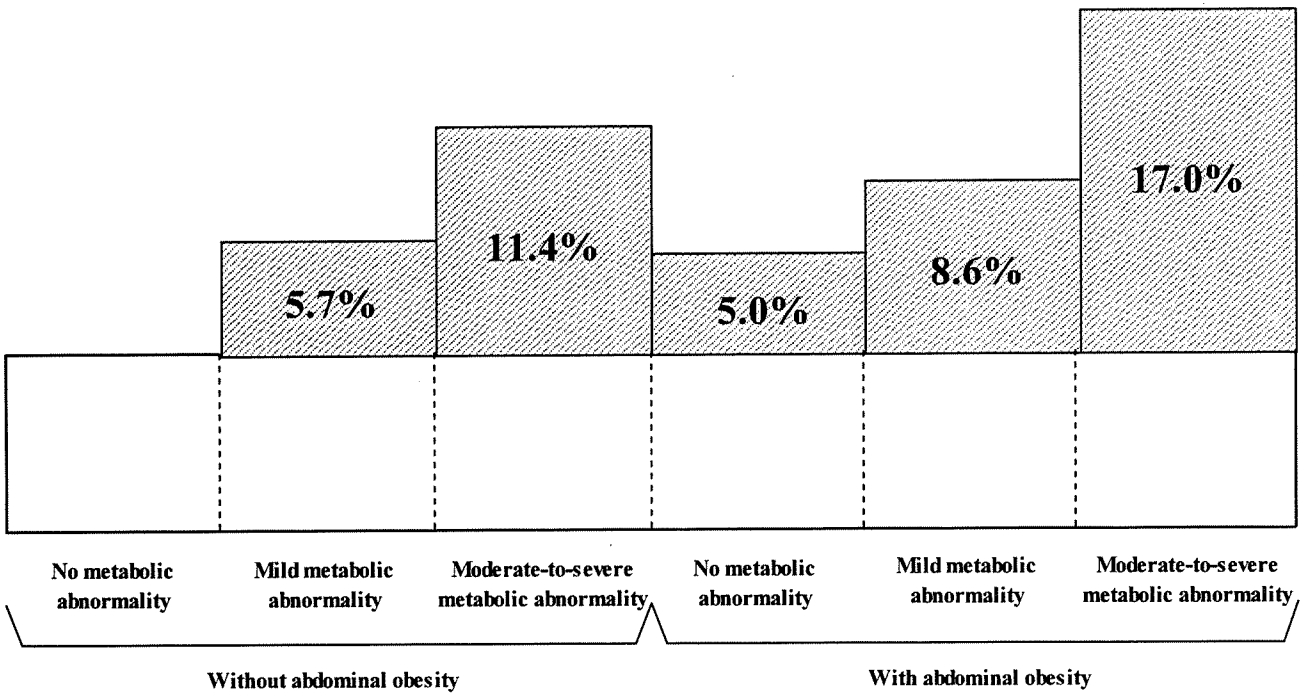

Figure 1: Population attributable fraction for the incidence of cardiovascular disease due to mild or moderate-to-severe metabolic abnormalities and/or abdominal obesity, in the study population over 11 years of follow-up (1996-2007).

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Biologic Score and Mortality Based on a 30-Year Mortality Follow-Up: Radiation Effects Research Foundation Adult Health Study

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This study aimed to test whether scored biologic functions can predict individual life expectancies and to investigate the disease-related and time-related differences in evaluated associations. A biologic score was defined as the first principal component score of the five physiological tests. Study participants were 4,871 people aged 35–74 years at baseline examination in 1970–1972 and followed until the end of 1999. We evaluated the prognostic value of the biologic score by Cox proportional hazard analysis. In all age and sex groups, increasing trends of mortality for all diseases by increment of biologic score were observed after adjustment for potential risk factors. The validity of the biologic score was significant throughout the entire study period. Each disease except cancer showed a significant association with biologic score at baseline examination. In conclusion, the biologic score is a valid predictor of life span in this large-scale prospective study of middle-aged and elderly Japanese.

Key Words: Biologic score—Cohort study—Mortality—Longitudinal study.

AGING is characterized by deterioration of biologic functions, resulting in increased morbidity and mortality. Although the effect of aging differs among organs, much effort has been devoted to develop a comprehensive biologic marker in human and animal studies that can be used to assess the global biologic function reflecting the aging process (1–7). Although various regression techniques have been used to calculate a comprehensive biologic marker representing biologic age (4,8,9), various problems such as the regression to sample mean age, that biologic age values calculated for persons younger than sample mean age tend to be too old and those for persons older than sample mean age, too young, have been described (10). Other techniques were also used to establish a comprehensive biologic marker (6,10). Nakamura and colleagues (11) applied principal component analysis for the assessment of a comprehensive biologic marker and proved the marker's validity. To evaluate the reliability and validity of candidate biologic markers of aging, the relationship between the biologic markers and consequent morbidity and mortality should be demonstrated. Relatively high biologic age has been observed in hypertensive patients (4), whereas low biologic age has been observed in people who survive or lead active daily lives (6,8,12,13). However, such studies are limited, follow-up periods are relatively short, or results are controversial (14).

A battery of age-related physiological functions devised by Hollingsworth and Jablon (9) were measured in participants of the Adult Health Study (AHS) cohort of the Atomic Bomb Casualty Commission (ABCC), during 1970–1972 (15,16). Five physiological tests, including handgrip strength, auditory acuity, vibration perception, skin elasticity, and reaction time, were administered in all AHS participants and the results correlated significantly with age (9). Using those five physiological tests, the "biologic score" was devised as "global biologic function" based on the first principal component identified by principal component analysis. Since then, the ABCC and its successor, the Radiation Effects Research Foundation (RERF), have been conducting a mortality survey. Using this data set, we investigated the association between biologic score and mortality for 30 years and evaluated the cause-related difference and time-related difference in the association.

Materials and Methods

Participants

The participants are members of the AHS cohort of the RERF. The AHS began in 1958 as a clinical cohort study to investigate the long-term medical effects of exposure to atomic bomb radiation among the survivors and unexposed controls in Hiroshima and Nagasaki. Approximately 20,000 persons were invited to participate in the biennial health examination program. A detailed description of the examinations, which included clinical evaluations and routine laboratory tests, is available elsewhere (17).

Physiological Tests

Current study participants were derived from 6,129 persons of the AHS cohort who underwent a battery of noninvasive

Table 1. Principal Component Analysis for Physiological Measurements

	Men		Women	
	1st Principal Component	2nd Principal Component	1st Principal Component	2nd Principal Component
Grip strength	−0.420	0.674	−0.420	0.711
Auditory acuity	0.405	0.560	0.427	0.041
Vibration perception	0.440	0.332	0.419	0.698
Skin elasticity	0.491	0.130	0.482	0.041
Reaction time	0.475	−0.323	0.481	−0.066
Proportion of variance	0.533	0.153	0.541	0.140

age-related physiological tests between July 1970 and June 1972 in Hiroshima. Physiological tests conducted for all participants included handgrip strength, auditory acuity, vibration perception, skin elasticity, and reaction time. Handgrip strength (in kilograms) was measured twice for both the left and right hands with the participant in a standing position using a dynamometer. Grip devices were calibrated with known weights. The maximum grip strength among all measurements was used for the present analysis. Auditory acuity (in decibels) was measured for each ear at 4,000 cycles/s. Vibration perception was measured as the minimal voltage intensity required for perception of a stimulus from an electric vibrometer applied at the ankle. Skin elasticity was measured as time (seconds) required for the skin to flatten to a normal level after a standard pinch on the back of the hand. Reaction time for a complex task was measured by the light extinction test. The task was to switch off randomly placed flashing lights, with each switch off activating the next light. Analysis was restricted to 4,871 participants (1,676 men and 3,195 women) who lived in Hiroshima, who were 35–74 years old at the time of examination, and who completed all five measurements in addition to providing other clinical information.

Biologic Score

Principal component analysis was applied to estimate the biologic score of each individual. In the analysis, each of the five physiological test measurements was initially standardized by dividing the value by its standard deviation, after log transformation of both skin elasticity and reaction time. Table 1 lists the coefficients of the first principal component and the second component, and the proportion of variance. The first principal component accounts for 53.3% of the total variation in the five measurements. Although the second principal component contained some information about the total variation, we defined the first component score as the biologic score for each individual. Because all coefficients for the first component are almost equal, the component could be interpreted as global biologic function.

Other Measurements

Clinical examinations included medical history, general physical examinations, height and body weight measurements, serum cholesterol concentration measurements, and self-administrated questionnaires. Body mass index (BMI) was calculated as body weight (kilograms) divided by the square of the height (meter). Blood pressure was measured by a sphygmomanometer at the right arm with the participant in the seated position. Information about smoking habits and alcohol intake was obtained from self-administrated questionnaires conducted during 1965–1968. Categories for smoking habits were "never," "former," and "current." For current smokers, a question was included about the number of cigarettes smoked. Categories for alcohol intake were "never" and "former/current." Individual radiation dose estimates were based on RERF's 2002 Dosimetry System.

Mortality Follow-Up

Mortality was followed up for the entire study sample from the time of physiological tests and examinations in 1970–1972 until the end of 1999. Deaths were routinely identified through Japan's *Koseki* (obligatory household registries) system, and ascertainment was essentially complete. Underlying causes of death were obtained from death certificates and classified as cancer (140–208 by International Classification of Diseases [ICD] 8th or 9th), heart disease (390–429 by ICD 8th or 9th), coronary heart disease (CHD; 410 by ICD 8th or 9th), stroke (430–438 by ICD 8th or 9th), cerebral infarction (433 and 434 by ICD 8th or 9th), cerebral hemorrhage (431 by 8th or 9th), and pneumonia (480–487 by ICD 8th or 9th). Pneumonia was chosen because it is one of the major causes of death in the elderly population in Japan.

Statistical Analysis

Relative risk (RR) of mortality associated with biologic score was adjusted multivariately for potentially confounding factors applying Cox proportional hazard analysis, in both men and women. The factors considered in the model were age at baseline, systolic blood pressure, BMI, smoking and drinking habits, serum cholesterol level, and radiation dose. Allowance for the effect of radiation dose was necessary because the study population included atomic bomb survivors exposed to radiation. When the RR of all causes of mortality, with the exception of externally caused deaths, was estimated according to the sex–age-specific quintile of biologic score, the third quintile was established as a reference. For the trend test, the mean value of the biologic score in each quintile category was assigned to the category. In the case of cause-specific mortalities, RR was calculated for each 1-score increment of biologic score. Analysis was carried out separately by sex. Deaths within the first 2 years after the baseline were excluded from analysis. Secular trends of multivariate-adjusted RR for all

Table 2. Characteristics of the Study Participants

	Men	Women
Number of participants	1,676	3,195
Age at baseline (y)	55.5 (11.1)	53.9 (10.7)
Systolic blood pressure (mmHg)	130.9 (23.6)	125.6 (23.4)
Diastolic blood pressure (mmHg)	81.9 (26.1)	78.7 (26.2)
Total cholesterol (mg/dL)	183.7 (34.3)	200.7 (37.6)
Body mass index (kg/m^2)	21.7 (3.1)	22.6 (3.6)
Current smoker (%)	68.4	13.9
Cigarettes smoked (per d)	18.6	10.1
Current alcohol drinker (%)	70.0	15.7
Grip strength (kg)	46.4 (9.0)	29.2 (6.3)
Auditory acuity (decibels)	41.8 (21.4)	32.0 (16.7)
Vibration perception (V)	28.7 (11.8)	25.3 (10.8)
Skin elasticity (s)	12.1 (17.9)	13.6 (19.8)
Reaction time (s)	9.1 (2.8)	9.3 (2.7)

Note: Continuous variables are shown as mean (*SD*).

causes of death, except external causes, were calculated by dividing the follow-up period from baseline examination (within 5 years, after 5 years, after 10 years, after 15 years, and after 20 years).

Results

The average age at baseline examination was 55.6 years for men and 53.9 years for women. The characteristics of the study participants by sex and age category are shown in Table 2. The biologic score ranged from –3.4 to 4.5 for men and –3.4 to 5.0 for women. Figure 1 shows plots of biologic score according to age at examination for both sexes. A gradual increase in biologic score with age is apparent for both sexes.

Over the 27-year follow-up period, 2,475 deaths were registered, in addition to those due to external causes, which included trauma and suicide. Table 3 lists the numbers of cause-specific deaths for both men and women. The crude mortality was 23.3 per 1,000 person-years. Figure 2 shows the crude mortality rates according to biologic score by sex and age category. In general, higher mortality rates were noted among participants with higher biologic scores at baseline, even in the same chronological age category in both sexes.

Multivariate-adjusted RR was compared among different biologic score categories divided into quintiles for each age and sex group, using the third quintile group as reference (Figure 3). In all age and sex groups, increasing trends of mortality by increment of biologic score were observed.

Multivariate-adjusted RR of all causes of death, with the exception of external causes, for each 1-score increment of biologic score in men was significantly high (RR 1.22, 95% confidence interval [95% CI], 1.14–1.31). Multivariate-adjusted RRs for heart disease, CHD, stroke, and pneumonia were significant and did not differ from the age-adjusted RR values (Table 4). Multivariate-adjusted RR of all causes of death, with the exception of external causes, for each 1-score increment of biologic score in women was significantly high (RR 1.27, 95% CI, 1.20–1.35). All multivariate-adjusted RRs except for cancer were significant, which were almost similar to the age-adjusted RR values (Table 4).

Secular trends of multivariate-adjusted RR of all causes of death except for external causes showed significantly higher mortality risks with higher biologic score in any follow-up period. Similar RR levels were observed after 5 years. Those observations were noted in both sexes (Table 5).

Discussion

The present analysis identified a significant relationship between biologic score based on five physiological tests performed in 1970–1972 and a subsequent 30-year mortality. The trend was observed in both sexes in each chronological age category, even after adjusting for covariates related to mortality. The advantages of the present study are its large number of participants including men and women with a wide range of age at the time of baseline examination and a long follow-up period. The confirmation of death in this cohort allowed us to evaluate the value of a "comprehensive biologic marker" in predicting life span, although death certificate accuracy for several disease categories in the study period was not fully examined.

There are a few longitudinal studies related to biologic age and clinical condition or mortality. In an aging study of 1,086 men aged 17–102 years, Borkan and colleagues (6) found that the individuals of the deceased group were biologically older than the survivors at the time of first examination. However, the Normative Aging Study reported by Costa (5) did not find a good correlation between biologic age (calculated with a weighted regression equation) and signs of aging over the course of 5 years. Uttley and colleagues (13) retrospectively analyzed the relationship between biologic age based on 38 variables and mortality 10 years later and reported that, in general, the participants who died had been estimated as older than the participants who had survived. Such studies did not cover a wide chronological age range for both sexes and the follow-up periods were relatively short. In addition, our analysis was performed by excluding deaths during the first 2 years of the follow-up period to avoid comorbidity.

In the Midwest Mennonite Study, functional–biologic age based on regression analysis did not accurately predict 10-year survival, although the independent variables were associated with mortality (13). In contrast, the relationship between biologic score and mortality was significant for all age categories for both sexes in our study based on principal component analysis. Grip strength, which is one component of the biologic score in this study, was an accurate and consistent predictor of mortality among the same cohort (18). The methodological differences between the Midwest Mennonite Study and our study might have contributed to the different statistical significances of the results (10).

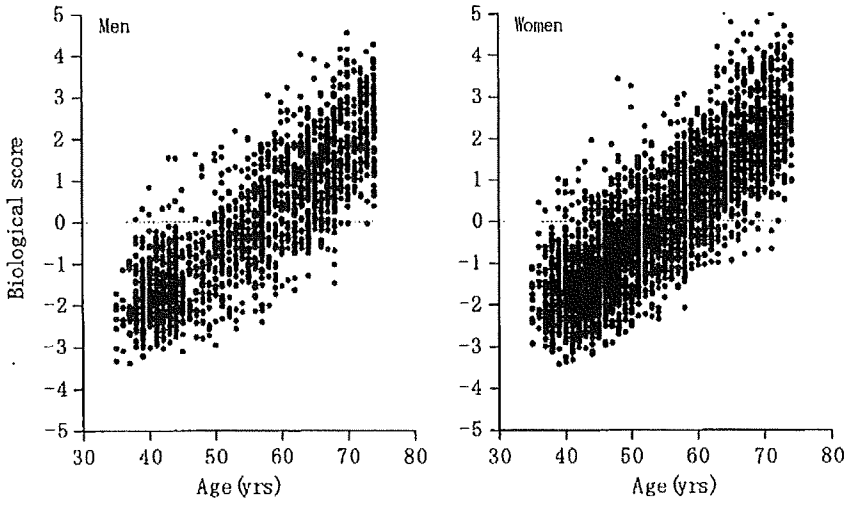

Figure 1. Biologic score according to age at examination.

We evaluated the RRs for specific causes of death, including cancer, heart disease, stroke, and pneumonia. It is interesting that the biologic score was strongly associated with cardiovascular disease (CVD) mortality and pneumonia mortality, but not cancer. The RRs for stroke and CHDs were almost similar. Those findings suggest that CVD and cancer relate differently to the aging phenomenon. A close relationship between the aging process and CVD, especially ischemic heart disease, has been observed in previous studies (19,20). Studies at the cellular level also showed that vascular disorders increase linearly with age (21). Age-related changes in vascular reactivity, which reflect cellular changes in, for example, endothelial cells, smooth muscle cells, platelets, and macrophages, as well as in environmental factors such as increasing hypertension and hyperlipidemia, relate to vascular disorders as well (22,23). Because these changes occur progressively in more or less every person, the development of atherosclerotic diseases is an important manifestation of the aging phenomenon in human beings. Although the biologic score in our study was not necessarily based on measurements related to the cardiovascular system, a strong relationship was observed with death from atherosclerotic disease. This may confirm the usefulness of biologic score as an aging marker, and the marker may predict aging-related disorders of the cardiovascular system.

Table 3. Number of Deaths by Cause During the Follow-Up Period (1970–1999)

	Men	Women	Total
Number of participants at baseline	1,676	3,195	4,871
Mean (±*SD*) age at baseline (y)	55.6 ± 11.1	53.9 ± 10.7	54.5 ± 10.8
All death except external causes	1,076	1,399	2,475
Cancer	388	392	780
Heart	183	332	515
CHD	87	121	208
Stroke	172	263	435
CI	74	105	179
CH	41	55	96
Pneumonia	82	109	191

Note: CH = cerebral hemorrhage; CHD = coronary heart disease; CI = cerebral infarction.

One of the criticisms concerning the use of an aging marker is that if it includes risk factors such as blood pressure and body weight, it may be too strongly associated with CVDs (5). The present score avoids that association because it does not use those risk factors in the equation. Bulpitt (24) pointed out that aging occurs at different rates in various organs, making it difficult to represent systemic aging as one index, suggesting that the use of measurements that include as many systems as possible is necessary for a comprehensive assessment of aging. From a clinical point of view, however, an aging marker based on a small number of simple noninvasive tests is likely to be of a more practical value. Biologic score as determined in the present study, and its dependence on only five variables, could predict mortality.

There was no significant difference in cancer mortality by biologic score within the same chronological group, and this result was not affected by covariates such as smoking habits and radiation exposure. This suggests that cancer is more weakly related than CVD to age-related changes in biologic function. We found no other report, longitudinal or cross-sectional, on the relationship between an aging marker and cancer. Whether development of cancer results from aging is still controversial. One hypothesis is that the incidence of cancer is higher among the elderly population simply because they have been exposed to carcinogens for a longer time and that aging itself does not promote carcinogenesis (25,26). But recent knowledge as to the mechanisms including DNA repair and telomere biology resulted in reevaluation of links between aging and cancer (27–29). Because aging is complex, investigation of relationship

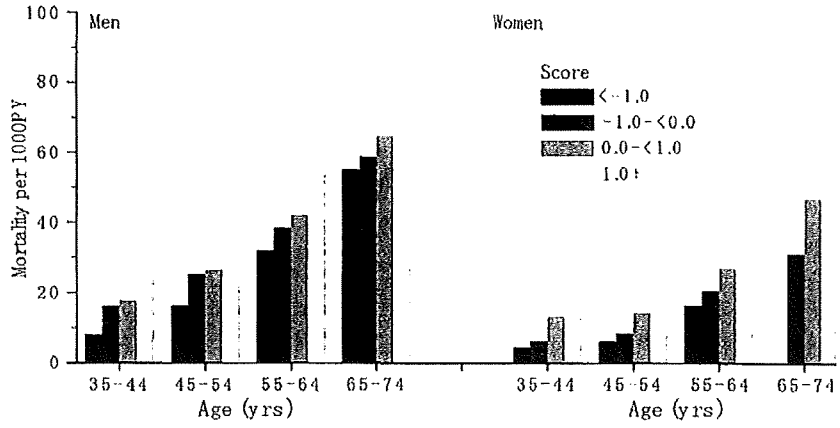

Figure 2. Crude mortality by biologic score.

between aging markers other than biologic functions and cancer is required.

The observation periods of other studies were all shorter than 10 years (6,13). The 30-year follow-up in our study allowed analysis of the time-dependent significance of biologic score by permitting us to divide the time into shorter periods. Review by time periods showed that a significant association was observed 2–30 years after initiation of the study. The RR at 5 years or less since baseline was highest. However, the RRs at any follow-up period more than 5 years since baseline were similar. This suggests that the score at one point in time predicted mortality 30 years later.

An attempt to formulate aging markers using physiological functions using an ABCC study population, consisting primarily of atomic bomb survivors and their controls, was started in the 1960s to test the hypothesis that ionizing radiation promotes aging (30,31). The results, however, did not reveal any association between radiation and such aging markers (16), in keeping with the theory of Strehler and colleagues that aging is a more complex phenomenon than radiation-related life shortening (32). In the present study population as well, biologic score did not correlate with the radiation dose. Furthermore, the association between biologic score and mortality was independent of the radiation dose. Hence, we think that the results of the present study can be extrapolated to the general population.

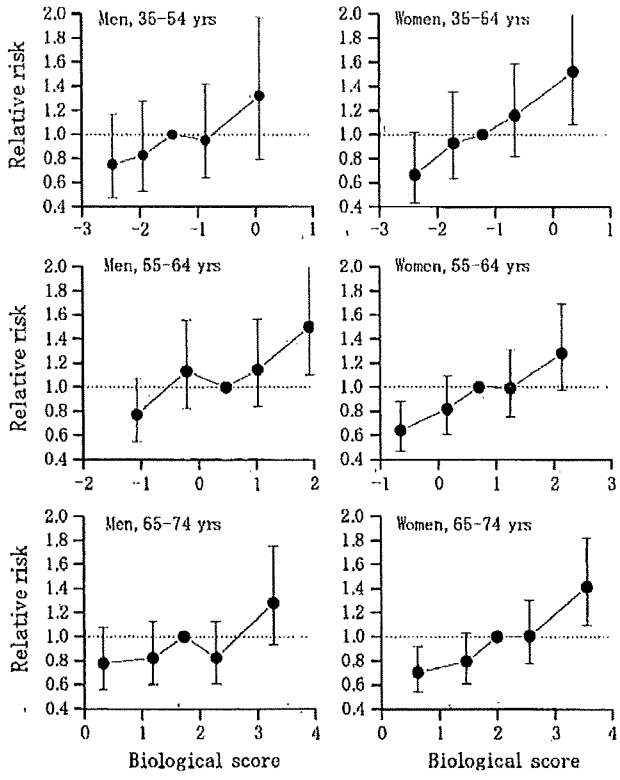

Figure 3. Multivariate-adjusted relative risk among different biologic score categories divided into quintiles in each age and sex group, using the third quintile group as reference.

Table 4. Relative Risk (RR) of Death for Each 1-Score Increment in Biologic Score

	Age-Adjusted RR (95% confidence interval)	Multivariate-Adjusted RR (95% confidence interval)
Men		
All death except external causes	1.23 (1.15–1.31)	1.22 (1.14–1.31)
Cancer	1.06 (0.95–1.18)	1.06 (0.94–1.18)
Heart	1.23 (1.05–1.44)	1.23 (1.04–1.44)
CHD	1.31 (1.04–1.64)	1.36 (1.07–1.72)
Stroke	1.24 (1.06–1.46)	1.24 (1.05–1.47)
CI	1.07 (0.83–1.37)	1.06 (0.82–1.37)
CH	1.22 (0.88–1.70)	1.25 (0.89–1.76)
Pneumonia	1.65 (1.30–2.08)	1.55 (1.22–1.97)
Women		
All death except external causes	1.27 (1.20–1.34)	1.27 (1.20–1.35)
Cancer	1.10 (0.99–1.23)	1.11 (0.99–1.23)
Heart	1.30 (1.16–1.46)	1.33 (1.18–1.49)
CHD	1.37 (1.13–1.65)	1.38 (1.14–1.67)
Stroke	1.38 (1.22–1.57)	1.39 (1.22–1.58)
CI	1.31 (1.06–1.59)	1.30 (1.06–1.60)
CH	1.53 (1.16–2.00)	1.56 (1.18–2.06)
Pneumonia	1.40 (1.15–1.71)	1.39 (1.13–1.69)

Note: RR was adjusted for age, systolic blood pressure, body mass index, total cholesterol, smoking habits, alcohol consumption, and radiation dose. CH = cerebral hemorrhage; CHD = coronary heart disease; CI = cerebral infarction.

Table 5. Secular Trend of Multivariate-Adjusted Relative Risk (RR) of All Deaths Except External Causes

	RR (95% CI)
Follow-up period for men (y)	
≤5 since baseline	1.52 (1.27–1.82)
>5	1.18 (1.10–1.27)
>10	1.15 (1.06–1.24)
>15	1.17 (1.06–1.28)
>20	1.20 (1.06–1.35)
Follow-up period for women (y)	
≤5 since baseline	1.46 (1.22–1.75)
>5	1.25 (1.18–1.33)
>10	1.21 (1.14–1.29)
>15	1.22 (1.13–1.31)
>20	1.19 (1.09–1.31)

Note: RR was estimated for each 1-score increment of biologic score. CI = confidence interval.

Conclusion

The biologic score at baseline predicted life span for a period of 30 years in the large-scale prospective study of middle-aged and elderly Japanese.

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Conflict of Interest

There is no apparent or potential conflict of interest with respect to the results reported in the article.

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Incidence of dementia among atomic-bomb survivors — Radiation Effects Research Foundation Adult Health Study

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ABSTRACT

Radiotherapy has been reported to cause neuropsychological dysfunction. Here we examined whether exposure to atomic bomb radiation affected the incidence of dementia among 2286 atomic bomb survivors and controls — all members of the Adult Health Study cohort. Study subjects were non-demented and aged ≥60 years at baseline examination and had been exposed in 1945 at ≥13 years of age to a relatively low dose (≤4 Gy), compared with total dose from radiotherapy. Dementia diagnoses were made during biennial health examinations with a two-phase procedure. DSM IV criteria were used for diagnosing dementia, NINCDS-ADRDA for Alzheimer disease, and NINDS-AIREN for vascular disease. To estimate the effect of radiation on the dementia incidence rate, we applied Poisson regression analysis. Incidence per 1000 person-years was 16.3 in the <5 mGy group, 17.0 in the 5–499 mGy group, and 15.2 in the ≥500 mGy group. Alzheimer disease was the predominant type of dementia in each dose category. After adjustment for potential risk factors, radiation exposure did not affect the incidence rate of either all dementia or any of its subtypes. No case of dementia had a history of therapeutic cranial irradiation. Although we found no relationship between radiation exposure and the development of dementia among atomic bomb survivors exposed at ≥13 years old in this longitudinal study, effects on increased risk of early death among atomic bomb survivors will be considered.

1. Introduction

Cranial and total body irradiation can lead to cognitive deficits [1–3], and the extent depends on both radiation and host factors[2]. The effects of therapeutic cranial irradiation are most pronounced in children[1]. Cognitive deficits have developed in children treated for leukemia[4,5] and brain tumors[6,7]. The radiation effects in adults treated prophylactically or for glioma, brain metastases, or primary CNS lymphoma vary with total dose, fractional dose, duration of therapy, and volume of brain irradiated[2,8–10]. In past studies, however, the small number of cases and relatively short follow-up time (≤10 years) did not allow evaluation of an association between *later-onset* dementia and radiotherapy. A retrospective case-control study using a general population sample in Rochester, MN (USA), did not show a significant association between therapeutic radiation exposure and Alzheimer disease[11]. The effect of workplace exposures to ionizing radiation on dementia mortality are inconsistent. Occupational exposure to radiation is associated with increased risk of death from dementia in female nuclear weapons workers, but not radiology technicians[12,13].

Regarding atomic bomb radiation, children who had been exposed *in utero* develop small heads and intellectual damage[14–16] while those who were exposed at ≥13 years of age do not differ from controls in cognitive function[17] or dementia prevalence[18]. Although a clinically assessed incidence study is critical to establishing cause, earlier studies were cross-sectional. Here we describe a prospective study by the Radiation Effects Research Foundation (RERF) in Hiroshima assessing the long-term neuropsychological effects of atomic bomb radiation in the Adult Health Study (AHS) cohort.

2. Methods

2.1. Subjects and radiation dose

The AHS consists of atomic bomb survivors and their age- and sex-matched non-exposed controls from Hiroshima and Nagasaki. It was initiated in 1958 to investigate the health effects of ionizing radiation

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from the atomic bombings. Biennial clinical examinations that include physical examinations and laboratory measurements have been conducted continuously with a relatively high participation rate (70 to 90% of eligible subjects)[19]. Approximately one-half of the AHS cohort died before 1992 and a smaller number moved away or refused to participate.

This study uses data from AHS participants in Hiroshima who were aged ≥60 years in September 1992 and who underwent a baseline examination for dementia between 1 September 1992 and 31 August 1996. At baseline, 2648 (89.8%) of the eligible subjects were assessed for cognitive impairment with the Cognitive Abilities Screening Instrument (CASI)[20] and/or the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)[21]. The most frequent reason for refusal of cognitive function assessment was that activities were not hampered and hence the cognitive function assessment was considered unnecessary by eligible subjects themselves. The reliability and validity of the Japanese version of CASI has been established[20]. Of those, 164 prevalent cases and 198 subjects who did not take the follow up assessments (66 deceased and 132 refused) were excluded, leaving 2286 participants for the incidence study. Details about the study subjects are described elsewhere[22]. The RERF institutional review boards (Research Protocol Review Committee and Human Investigation Committee) approved this study, and all participants provided written informed consent.

We estimated individual brain dose based on RERF's Dosimetry System 2002 (DS02), taking into account survivor location, shielding by terrain and body[23]. We used radiation dose as weighted sums of gamma ray and neutron components in Gy, giving the neutron component a weight of 10, since most radiation exposure was from gamma rays. Estimated brain doses were corrected for dose uncertainty and were assigned 4 Gy when dose estimates exceeded that value[24]. We divided radiation dose into three categories: <5 mGy (non exposed) (790 subjects), 5–499 mGy (713 subjects), and ≥500 mGy (541 subjects). DS02 doses had not been estimated for 242 subjects. There was no significant difference of dose distribution between participants for the incidence study and prevalent cases excluded from this study. We obtained information about therapeutic radiation received by study subjects prior to 1987 by hospital survey [25] and about radiation received after that by questionnaire.

2.2. Detection of incident dementia cases

We used a two-phase procedure to determine whether the participants were demented. The first phase consisted of screening based on CASI score, disease history, physical examination, and reported activities of daily living. Those with ≥5 errors compared with a previous CASI evaluation, those with complaints of forgetfulness, and those reported by family members to have declined in cognitive function received a second-phase examination that consisted of an IQCODE examination[21] and a neurological examination by a neurologist. About 15% of all participants underwent diagnostic CT or MRI examinations, and those were reviewed by neurologists. About 8% of participants who were unable to visit the outpatient clinic underwent the examination at home, in a hospital, or in their institutional residence. The validity of the two-phase procedure used in this study was established in the Ni-Hon-Sea dementia study[26].

The consensus panel included examining physicians and neurologists who independently evaluated the data, basing the diagnosis of dementia on the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM IV)[27], the diagnosis of Alzheimer disease (AD) (probable AD and possible AD) on the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA)[28], and the diagnosis of vascular disease (VaD) (probable VaD) on the National Institute for Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN)[29]. Diagnostic categories used for analyses were AD, VaD, and dementia (all types, including those other than AD and VaD).

3. Statistical methods

We calculated crude incidence rates by sex for each dose category for dementia, AD (probable and possible), and VaD (probable) by dividing the number of cases by the number of person-years at risk. Details about the statistical methods are described elsewhere[22]. Briefly, we calculated the number of person-years by time between the baseline examination and the last follow-up examination for subjects who had no dementia. For subjects with dementia, we calculated the number of person-years by time from the baseline examination to the onset date. The onset date was determined by caregiver information or as the midpoint between the disease diagnosis date and the date of the previous disease-free examination. We calculated 95% confidence intervals (CIs) for incidence rates assuming a Poisson distribution for the number of cases within each category.

To estimate the radiation effect on the incidence rate of all dementia, probable and possible AD, and probable VaD, we applied a Poisson regression analysis with a log-linear model as functions of dose, age, sex, education, body mass index (BMI), smoking, drinking, age at menopause, hypertension (401–404 by International Classification of Diseases [ICD] 9th), diabetes (250 by ICD 9th), and stroke (430–438 by ICD 9th) as potential risk factors, using AMFIT of the EPICURE package (Epicure User's Guide, HiroSoft International, Seattle, WA). The primary data for these analyses are based on tabulation of the data cross-classified by age at baseline examination (5-year categories from ages 60 through 89 and ≥90), dose (unknown, <5 mGy, 5 to 499 mGy, ≥500 mGy), years since baseline (2-year categories from years 0 through 9 and ≥10), and dichotomous variables of sex (male, female), education (≤6 years of education, ≥7 years of education), BMI (<24 kg/m^2, ≥24 kg/m^2), smoking (never and former, current), drinking (never and former, current), age at menopause (<50 years old, ≥50 years old), and disease history (presence, absence). Ages were entered into the model as their mean values in each cell in the cross-tabulation. We obtained information about education, smoking, drinking, and age at menopause from previously administered questionnaires and BMIs from the baseline examinations. Details about potential risk factors are described elsewhere[22,30]. We considered $P \leq 0.05$ as statistically significant.

4. Results

Table 1 shows the characteristics of the study subjects by radiation dose category at baseline. During the study period (mean, 5.9 years; SD, 2.8 years), 195 cases of dementia (42 men and 153 women) were newly diagnosed among the 2044 subjects whose radiation doses

Table 1
Characteristics of subjects at baseline by radiation dose category.

Radiation dose (mGy)	<5	5–499	≥500	unknown
No. of subjects	790	713	541	242
Male (%)	29.2	27.9	29.6	24.2
Mean age (S.D.)	70.3 (7.5)	71.9 (7.5)	69.9 (7.0)	68.8 (6.3)
Mean radiation dose (mGy)	0.5	186.4	1330	
Mean BMI (kg/m^2)	23.0	23.1	22.4	22.7
Current and past smoker (%)	30.7	30.2	36.1	26.0
Current and past drinker (%)	48.2	47.2	50.6	45.5
Education level ≤6 years (%)	43.1	43.6	40.8	33.9
Stroke history (%)	4.2	4.2	5.5	3.7
No. who received radiotherapy	19	21	19	9

Table 2
Incidence rates per 1000 person-years and 95% confidence intervals for dementia, AD, and VaD.

Radiation dose	(mGy)		<5	5–499	≥500
Person-years	Total		4659	4242	3091
	Men		1401	1107	916
	Women		3258	3135	2176
All dementia	Total	Case	76	72	47
		Incidence rate	16.3 (13.0–20.4)	17.0 (13.5–21.4)	15.2 (11.4–20.2)
	Men	Case	16	14	12
		Incidence rate	11.4 (7.0–18.7)	12.7 (7.5–21.4)	13.1 (7.4–23.1)
	Women	Case	60	58	35
		Incidence rate	18.4 (14.3–23.7)	18.5 (14.3–23.9)	16.1 (11.6–22.4)
AD*	Total	Case	50	43	30
		Incidence rate	10.7 (8.1–14.2)	10.1 (7.5–13.7)	9.7 (6.8–13.9)
	Men	Case	8	6	5
		Incidence rate	5.7 (2.9 – 11.4)	5.4 (2.4 – 12.1)	5.5 (2.3 – 13.1)
	Women	Case	42	37	25
		Incidence rate	12.9 (9.5–17.4)	11.8 (8.6–16.3)	11.5 (7.8–17.0)
VaD**	Total	Case	14	13	7
		Incidence rate	3.0 (1.8–5.1)	3.1 (1.8–5.3)	2.3 (1.1–4.8)
	Men	Case	4	5	3
		Incidence rate	2.9 (1.1–7.6)	4.5 (1.9–10.9)	3.3 (1.1–10.2)
	Women	Case	10	8	4
		Incidence rate	3.1 (1.7–5.7)	2.6 (1.3–5.1)	1.8 (0.7–4.9)

*Probable and possible cases.
**Probable cases.

were estimated. Table 2 shows the crude incidence rates and 95% CIs by radiation dose category. The number of cases diagnosed was 123 (19 men and 104 women) for AD, including 76 cases of probable AD (13 men and 63 women) and 47 cases of possible AD (6 men and 41 women), and 34 for probable VaD (12 men and 22 women).

Poisson regression analysis showed that after adjustment for potential risk factors, dementia incidence was not affected by radiation exposure (Table 3). The relative risks for all dementia among those exposed to relatively low doses (5–499 mGy) and those exposed to relatively high doses (≥500 mGy) compared with non-exposed subjects were 0.82 ($P=0.24$) and 0.94 ($P>0.5$), respectively. Neither the incidence rate of AD nor VaD was significantly associated with radiation exposure (Table 3). The significant risk factors for all dementia were age, education, and stroke history. Probable AD was associated with low education level and probable VaD was associated with hypertension and stroke history (data not shown)[30]. While 68 subjects had histories of radiotherapy before this incidence study, only two dementia cases were diagnosed among them (for thyroid benign disease in subject exposed to a100-mGy atomic bomb dose and prostatic cancer bone metastasis in subject exposed to a 1356-mGy atomic bomb dose).

Table 3
Results of Poisson regression analysis.

	Hazard ratio	95% CI	*P*-value
All dementia			
Dose 1	0.82	0.59–1.14	0.238
Dose 2	0.94	0.65–1.33	>0.5
Probable AD			
Dose 1	0.64	0.37–1.09	0.105
Dose 2	0.94	0.54–1.62	>0.5
Possible AD			
Dose 1	0.88	0.45–1.09	>0.5
Dose 2	0.87	0.40–1.81	>0.5
Probable VaD			
Dose 1	0.84	0.37–1.84	>0.5
Dose 2	0.77	0.32–1.77	>0.5

Dose 1: 5–499 mGy group vs <5 mGy group.
Dose 2: ≥500 mGy group vs <5 mGy group.
CI: confidence interval.
Model is adjusted for age, age^2, sex, education, BMI, smoking, drinking, menopausal age, and history of hypertension, diabetes, and stroke.

5. Discussion

In this prospective study, radiation exposure was not a risk factor for dementia among atomic bomb survivors exposed after they were 13 years old. The result reinforces our previous findings that cognitive function[17] and prevalence of dementia[18] ascertained by clinical assessment, and incidence of dementia ascertained by history-taking during 1958–1998[19], were not associated with radiation exposure in the AHS cohort. The dementia study in the AHS had some advantages: (a) the subjects were representative of the whole community, including hospitals and institutional populations, (b) this was a prospective study that maintained a relatively high rate of participation in biennial health examinations (88% in 1998 and 72% in 2002), and (c) dementia screening procedures established in the Ni-Hon-Sea dementia study[26] allowed us to catch even mild dementia cases.

Many studies show that adult radiotherapy results in rare long-term cognitive disability when relatively low fraction doses (≤2000 mGy) are used[2,3,8,10,31,32] with the exception of one case report in which a patient treated with 2000 mGy per fraction developed progressive dementia.[33] The previous results of studies on cognitive function in the AHS were compatible with those of studies on the effects of cranial radiotherapy in adults[17]. In the present study, 6 dementia cases developed in 110 subjects exposed to ≥2000 mGy and 113 developed in 1144 subjects exposed to <2000 mGy. Single whole body exposure to atomic bomb radiation did not show any significant effect on dementia occurrence even in those exposed to >2000 mGy. In the studies on the effects of cranial radiotherapy in adults, the number of cases and follow-up periods were limited. Although population-based studies can overcome such limitations, there are few population-based evaluations on the relationship between dementia and radiotherapy. Our findings are in agreement with those of a retrospective case-control study using a general population sample in Rochester, *MN*, in which there was no significant association between therapeutic radiation exposure and Alzheimer disease[11]. Another U.S. study did show an association between whole brain radiotherapy and dementia incidence, but the incidence was only 1.9 to 5.1%, although it may have been underestimated[34]. Our findings are also compatible with studies on the effects of relatively low occupational exposure in radiological technicians[12], although the underreporting of dementia in death certificates may have impaired the detection of an association.

In this study we investigated the association of dementia with not only atomic bomb irradiation but also therapeutic irradiation. The incidence rate of dementia among those who received radiation therapy was low. Only 2 of 68 patients who received radiotherapy on tissue other than brain developed dementia. The patients in our study who received radiotherapy for malignant disease, however, had a lower survival rate than those who did not, and it is possible that some of them would have developed dementia had they lived longer. Life expectancy decreased with atomic bomb radiation dose and median loss among members with estimated doses of 1 Gy or more was 2.6 years[35]. Selection bias due to censoring by death may results in underestimation of radiation risk among atomic bomb exposed subjects. Although brain tissue obtained at autopsy during 1961–1963 did not show any relationship between neuropathological changes and exposure to atomic bomb radiation[36], selection bias by early death may limit the generalizability of the results. Since evaluation of cognitive and non-cognitive functions using longitudinal observation may reveal radiation effects on neuropsychological dysfunction, further investigation will be required in the future.

Among prenatally exposed survivors, intelligence quotient and school performance of 10- to 11-year-olds were significantly lower for those exposed 8–25 weeks after ovulation[16]. Future examination will be required to determine neurological sequelae among atomic survivors exposed at <13 years of age. In interpretation of the results, this longitudinal study revealed no relationship between exposure to ionizing radiation and the development of dementia among atomic bomb survivors exposed at ≥13 years of age, but increased risk of early death among atomic bomb survivors should also be considered.

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Incidence and risks of dementia in Japanese women: Radiation Effects Research Foundation Adult Health Study

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ABSTRACT

Background: Although dementia has a great impact on public health, there are few reports on dementia incidence and risk factors for Asian populations.
Objectives: To determine incidence and risk factors of dementia, Alzheimer disease (AD), and vascular dementia (VaD) among Japanese women.
Methods: Between 1992 and 1996, 1637 non-demented women aged ≥60 years were followed for an average of 5.9 years in RERF's Adult Health Study. Dementia diagnoses were made during biennial health examinations using a two-phase procedure. DSM IV criteria were used for diagnosing dementia, NINCDS-ADRDA for AD, and NINDS-AIREN for VaD. Potential risk factors were analyzed using Poisson regression analysis.
Results: 161 cases of dementia (109 of AD and 56 of VaD, based on individual criteria) were newly diagnosed. Incidence increased dramatically with age, especially for AD. Probable AD decreased with increasing education level. Probable VaD was significantly associated with hypertension and stroke. Age at menopause did not show any effect on dementia. All dementia and probable AD were significantly associated with grip strength.
Conclusions: AD is predominant in dementia incidence among Japanese women. Modification of stroke risk factors and improvement of physical fitness may help prevent dementia.

1. Introduction

Although dementia has a great impact on public health in aging societies, few reports document its incidence and risk factors in Asian populations [1,2]. A prevalence study of the Adult Health Study (AHS) cohort of the Radiation Effects Research Foundation (RERF) reported a higher frequency of Alzheimer disease (AD) than vascular dementia (VaD) between 1992 and 1996, especially in women [3]. The study also demonstrated that the increase in estimated prevalence of AD with age was steeper for women than for men, which is similar to the prevalence and incidence findings for the very old in North America and Europe [4–9]. Since life expectancy in Japanese women is the longest in the world, dementia is likely to become an increasingly important national health problem; investigation of the risk factors is an essential first step in managing it.

US and European studies report a roughly similar age-specific incidence pattern [4–9]. Results regarding risk factors, however, have not been consistent [10–16]. Systemic recall bias among demented or cognitive-impaired subjects might have made risk factor analysis problematic. Since biennial clinical follow-up examinations have been conducted since 1958 in the AHS, the effect of any recall bias among the cohort would be minimal.

A collaborative study of dementia comparing Japanese Americans living in Seattle and Honolulu with Japanese living in Hiroshima (the AHS cohort) was initiated in the early 1990s. The purpose of the study–referred to collectively as the Ni-Hon-Sea study–is to identify whether prevalence, incidence, and cause of dementia are constant across cultures. The studies use similar designs and case ascertainment procedures [3,17,18].

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In the present study, we analyzed a prospective cohort study to determine incidence and risk factors of dementia, AD, and VaD among Japanese women.

2. Methods

2.1. Subjects

In 1958, the Atomic Bomb Casualty Commission, succeeded by the RERF, began the AHS to survey illnesses and changes in physiological and biochemical function resulting from exposure to atomic-bomb radiation. The AHS consisted of atomic-bomb survivors and their controls. The subjects were invited to participate in biennial health examinations that included physical examinations and laboratory assessments. A relatively high participation rate (70%–90% of eligible subjects) has been maintained throughout the study period. The population and methods have been described in detail elsewhere [19].

In the present study, we used data from AHS participants in Hiroshima who were aged ≥60 years in September 1992 and underwent initial dementia screening (baseline examination) between September 1992 and August 1996. Potential study subjects for incidence analysis were those who were dementia-free at baseline and were reassessed for dementia through September 2003. Subjects who did not agree to cognitive function screening and informant-based assessment were excluded.

2.2. Detection of incident dementia cases

We used the same two-phase procedure to determine whether the participants had dementia as we used in the prevalence study [3]. The first phase consisted of screening based on Cognitive Abilities Screening Instrument (CASI) score [17], disease history, physical exam, and reported activities of daily living (ADL). Those with five or more disparities compared with a previous CASI evaluation, those with complaints of forgetfulness, or those reported by family members to show cognitive decline were given in the second phase the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) [20], a neurological examination by a neurologist, a cognitive test other than CASI (such as Hasegawa's Dementia Scale or the Mini Mental State Examination), a Hachinski Ischemic Score, and a Clinical Dementia Rating (CDR) [21]. About 15% of participants underwent computed tomography and magnetic resonance imaging (CT/MRI) examinations to obtain further diagnostic information, which were reviewed by neurologists. About 8% of participants were unable to visit the outpatient clinic and underwent examinations at home, in the hospital, or in their institutional residence. The validity of the two-phase procedure in this study was established in the Ni-Hon-Sea study. Details about the standardization of the procedures are available elsewhere [18]. Neuropathological examinations were not done in our study. The RERF institutional review boards (Research Protocol Review Committee and Human Investigation Committee) reviewed and approved the study, and all participants provided written informed consent.

The consensus panel included examining physicians and neurologists who independently evaluated and determined the presence of dementia (based on the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM IV)) [22], AD (based on the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria) [23], and VaD (based on the National Institute for Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria) [24]. To minimize the number of false positive diagnoses, we classified cases with a CDR ≥1 as having dementia. For subjects who were suspected of having very mild dementia (CDR = 0.5) or dementia with CDR ≥1, the consensus panel reevaluated the clinical data at the next examination and changed the diagnosis and/or onset date retrospectively when necessary.

The multifactorial etiopathology of VaD causes difficulties in diagnosing VaD and mixed dementia [25,26]. Epidemiological studies demonstrate that vascular factors can contribute not only to VaD but also to AD [26]. When a vascular lesion and brain atrophy are observed simultaneously, it is difficult to judge which is contributing more to the cognitive decline. Such cases were diagnosed as possible AD in NINCDS-ADRDA and/or possible VaD in NINDS-AIREN.

2.3. Statistical methods

We calculated the age-specific incidence rates of dementia, AD (probable and possible based on NINCDS-ADRDA criteria), and VaD (probable and possible based on NINDS-AIREN) using the person-years approach by dividing the number of cases by the number of person-years at risk in 10-year age intervals starting at age 60 years. We calculated the number of person-years by time between the baseline examination and the last follow-up examination for subjects who had no dementia. For subjects with dementia, we calculated the number of person-years by time from the baseline examination to the onset date, which we based on caregiver information or calculated as the midpoint between the disease diagnosis date and the date of the previous disease-free examination. We calculated confidence intervals (CIs) for incidence rates assuming a Poisson distribution for the number of cases within each age interval.

To estimate the incidence rate of all dementia, probable AD, and probable VaD observed among the cohort members, we applied a Poisson regression analysis with a log-linear model using AMFIT of the EPICURE package (Epicure User's Guide, HiroSoft International, Seattle, WA). We analyzed neither possible AD nor possible VaD independently since consensus panel judgment of these types of dementia has not been consistent.

First, we depicted the estimated incidence curves for all dementia, probable AD, and probable VaD based on the model including age and age^2 (if it was significant). Next, we examined 1637 women for

Table 1
Baseline characteristics of subjects, dementia incidence study, 1992–1996.

Number of subjects	Total	Incidence study	Refused follow up	Prevalent cases	Refused enrollment
	2105	1637	140	122	206
Age, y (mean ± SD)	72.15 ± 8.02	70.95 ± 7.16	75.89 ± 8.18	82.71 ± 7.78	72.87 ± 9.03
BMI (mean ± SD)	22.89 ± 3.73	23.02 ± 3.64	22.64 ± 4.35	21.38 ± 3.47	22.34 ± 4.00
Hypertension (%)	40.1	38.2	47.1	51.6	43.2
Diabetes (%)	11.3	10.6	14.3	9.8	15.0
Stroke (%)	5.2	3.5	7.1	26.2	4.4
Current or ex drinker, %	34.3	36.2	23.6	18.9	35.4
Current or ex smoker, %	11.9	12.5	11.4	4.9	12.1
Menopause age, y (mean)	48.4	48.5	47.9	47.2	48.2
Grip, kg (mean)	20.1	20.4	18.9	13.5	19.5
Higher education, %[a]	53.5	56.5	47.9	32.8	45.6

[a] 7 years or more.

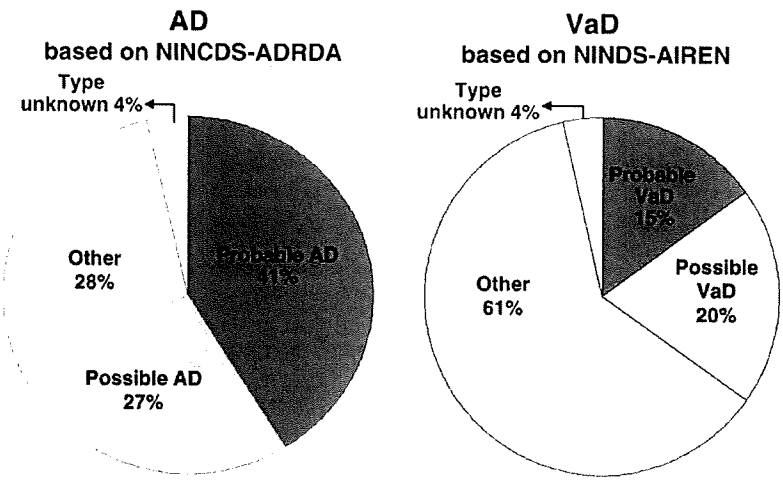

Fig. 1. Diagnoses of dementia cases based on NINCDS-ADRDA and NIKNDS-AIREN criteria.

dependency of incidence of dementia, probable AD, and probable VaD on various risk factors (age, education, body mass index (BMI), smoking, drinking, age at menopause, grip strength, hypertension, diabetes, and stroke). Information about education, smoking, drinking, and age at menopause was obtained from questionnaires conducted at previous surveys. Information about BMI and grip strength was measured at baseline examinations. We entered BMI and grip strength into the models as a continuous variable and education, smoking, drinking, age at menopause, and disease history as dichotomous variables. We categorized education level as lower ($\leq$6 years of education) or higher ($\geq$7 years of education) because 6 years of schooling was mandatory in the old Japanese education system. The categories for smoking and drinking were never and former/current. The categories for age at menopause were younger (<50 years old) or older ($\geq$50 years old). Since preliminary analysis showed that dementia incidence was not affected by radiation exposure (data not shown), as was the case in the prevalence study [3], we did not include radiation dose in the model as a covariate. We considered $P \leq 0.05$ as statistically significant.

3. Results

3.1. Subjects studied

Among the 2105 eligible subjects, 206 who did not agree to cognitive function screening and informant-based assessment were excluded. The remaining 1899 subjects were assessed for cognitive impairment with CASI and/or IQCODE [20]. Among those, 122 were diagnosed as having dementia [3].

After excluding the 122 prevalent cases and the 140 subjects who died before or refused to take the follow-up dementia examinations, 1637 subjects remained. Table 1 shows the characteristics of all potential study subjects. The incidence study participants were younger and more educated than the prevalent cases or those who refused assessment of dementia at baseline examination or follow-up examination. When education levels were stratified by baseline age category ($\leq$65 years, 66–75 years, $\geq$76 years), there was no difference in education level except that the prevalent cases were less educated (data not shown).

3.2. Cases

During the study period (mean $\pm$ SD of follow up, 5.9 $\pm$ 2.8 years), 161 cases of dementia were newly diagnosed. The mean number of dementia screening examinations was 3.3 for all subjects and 3.5 for those ultimately diagnosed with dementia. In 1998, 5% were censored by death and 6% by refusal; in 2002, 16% were censored by death and 11% by refusal. The incidence per 1000 person-years of dementia among subjects aged $\geq$60 years was 16.6; 109 cases were diagnosed with AD (66 probable and 43 possible) and 56 were diagnosed with VaD (24 probable and 32 possible) (Fig. 1). Eighteen subjects who showed insidious cognitive decline and had vascular brain damage and brain atrophy according to CT/MRI were diagnosed as having possible AD and possible VaD based on combined diagnoses of AD and VaD. Among 14 cases of non-AD and non-VaD based on combined diagnoses, 1 case was of substance-induced dementia, 7 were of dementia due to other medical conditions, and 6 were of dementia of unknown cause. Table 2 shows the age- and sex-specific incidence rates per 1000 person-years and 95% CIs for all dementia, AD, and VaD.

Fig. 2 shows the estimated incidence curves for all dementia, probable AD, and probable VaD based on the model that included age and age^2 (if it was significant). Incidence curves for men are shown for comparison. The upturn after age 80 years is steeper for women than for men. Table 3 shows the final results of Poisson regression of potential risk factors. For all dementia, age, education, stroke, and grip strength showed statistically significant effects. The estimated relative risk (RR) for higher education level to lower education level was 0.71. The RR with 5-kg increments in grip strength was 0.84. The incidence of dementia was 1.92 times higher among those with a stroke history than those without a history. For probable AD, the age effect was

Table 2
Age-specific incidence rates per 1000 person-years and 95% confidence intervals (CI) for all dementia, Alzheimer disease, and vascular dementia.

Age	Person-years	All dementia			Alzheimer disease[a]			Vascular dementia[a]		
		Number of cases	Incidence rate	95% CI	Number of cases	Incidence rate	95% CI	Number of cases	Incidence rate	95% CI
60–69	3193	3	0.9	0.3–2.9	2	0.6	0.2–2.5	1	0.3	0–2.2
70–79	4651	53	11.4	8.7–14.9	36	7.7	5.6–10.7	24	5.2	3.5–7.7
80–89	1674	82	49.0	39.4–60.8	57	34.0	26.3–44.1	27	16.1	11.1–23.5
$\geq$90	166	23	138.5	92.0–208.4	14	84.3	49.9–142.3	4	24.1	9.0–64.2

[a] Probable and possible cases.

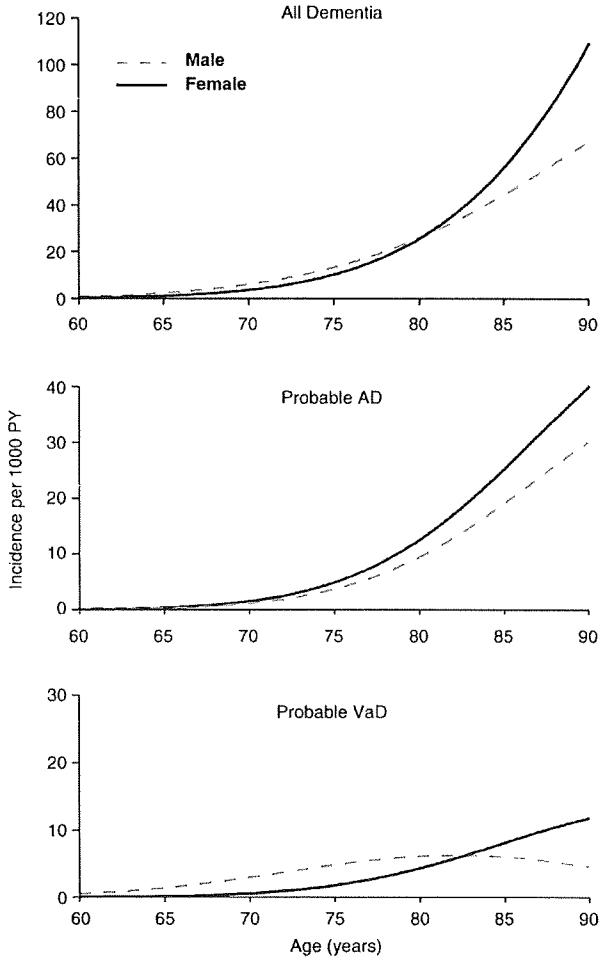

Fig. 2. Age- and sex-specific incidence rates of dementia, probable Alzheimer disease, and probable vascular dementia.

remarkable, showing the largest estimate for age. The RR for higher education level compared with lower education level was 0.54. Those with 5 kg more in grip strength showed a lower risk (RR = 0.79). The incidence of probable VaD increased with hypertension (RR = 3.67) and stroke (RR = 5.93). Age at menopause, BMI, smoking, and drinking did not show any effects on either type of dementia.

4. Discussion

In spite of methodological differences, the dementia incidence rates among Japanese women reported in this study are comparable to those reported in other cohort studies in the same time period (after the 1990s) in the US and Europe [4–9]. In Japan, incidence estimates are few. The Hisayama study conducted between 1985 and 1992 [12], and the Osaki-Tajiri project conducted between 1998 and 2005 [13] are perhaps the only comparable Japanese incidence studies to date. The age-specific incidence rates of total dementia that we found were quite similar to the rates in the other Japanese studies. Although we did not include individuals who died before a follow-up examination or those who refused assessment of dementia at baseline or follow up, the biennial follow-up examinations allowed us to diagnose dementia several years before death. A relatively high participation rate (89% in 1998 and 73% in 2002) was maintained throughout the study period. The follow-up examinations were conducted not only in the outpatient clinic but also in homes, hospitals, or institutional residences, allowing us to accurately detect overall dementia, including mild, moderate, and severe forms.

The Hisayama study, which shows a greater incidence of VaD than ours and a smaller incidence of AD, was conducted before the early 1990s [12]. Since that study showed a decline in stroke incidence during 1985 to 1992 [27], temporal differences between the present study and the Hisayama study may partially explain the difference in VaD incidence. On the other hand, in a recent incidence study in northern Japan (the Osaki-Tajiri project), MRI examinations revealed that possible AD (attributable in part to cerebrovascular disease) was more common than VaD [13,28]. The authors of the Osaki-Tajiri project noted that some cases in Japan previously diagnosed as VaD might have been better diagnosed as possible AD with cardiovascular disease because the vascular contribution to dementia was additive to the AD pathology, not primary. In our study, biennial health examinations and dementia screening using neuropsychological tests and/or questionnaires helped us to catch the temporal relationship between vascular brain damage and cognitive decline and to avoid over-diagnosis of VaD.

Our finding of a higher risk of probable AD among those with lower education levels is in agreement with findings of previous studies [6,29,30], although education levels differed by study cohort. Our results are also compatible with a recent meta-analysis showing that low education was a stronger risk factor for AD than for non-AD dementias [31].

We found that stroke was a major risk factor for VaD and overall dementia, as it was in our prevalence study [3] and other previous studies [32–34]. Our results support the idea that modification of stroke risk factors can help prevent dementia. Hypertension, the most important risk factor for stroke in Japanese in Japan and Hawaii [35], was a risk factor for vascular dementia. Hypertension is also a risk factor for silent brain infarction [36], which is also associated with dementia [26].

Cognitive and physical function impairment occur together, especially in aging [37,38]. Grip strength was an accurate and consistent predictor of mortality in a previous AHS study, suggesting that grip strength is a valid marker of biological age [39]. In the present study, poor grip strength was associated with a higher risk of dementia with an RR similar to that found in a US study [40].

The relationship of reproductive period duration, age at menopause, or hormone replacement therapy to dementia occurrence or progression is controversial [41–43]. Japanese women in this cohort

Table 3
Final results of Poisson regression analysis of potential risk factors.

	Estimate	standard error	*P*
All dementia			
Constant	−36.18	8.951	<0.001
Age	0.653	0.219	0.003
Age^2	−0.003	0.001	0.021
Education[a]	−0.349	0.168	0.038
Stroke	0.656	0.297	0.027
Grip (1 kg increment)	−0.036	0.014	0.007
Probable AD			
Constant	−53.74	17.45	0.002
Age	1.069	0.428	0.013
Age^2	−0.006	0.003	0.032
Education[a]	−0.626	0.278	0.025
Grip (1 kg increment)	−0.047	0.023	0.035
Probable VaD			
Constant	−10.82	0.5165	<0.001
Age	0.056	0.028	0.047
Hypertension	1.301	0.481	0.007
Stroke	1.780	0.517	<0.001

Model is adjusted by age, age^2, education, grip strength, BMI, smoking status, drinking status, menopausal age, and history of hypertension, diabetes, or stroke.
[a] 0 for ≤6 years, 1 for ≥7 years.

showed low rates of postmenopausal hormone therapy (<5%). We found no effect of age at menopause in this study.

Results regarding smoking, drinking, diabetes, and elevated BMI are inconsistent [10,11,16]. We found no association between those potential risk factors and dementia incidence.

The number of persons with dementia is expected to increase as the population ages. The predominant form of dementia in older Japanese women is AD, which showed a remarkable increase with age, especially extreme old age. Measures to deal with dementia are therefore essential, especially since life expectancy in Japanese women is the longest in the world. The AHS has been providing extensive data on a prospective basis since 1958 and will continue to offer a unique opportunity for the long-term study of aging and dementia.

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Low-Density Lipoprotein Cholesterol Concentrations and Death Due to Intraparenchymal Hemorrhage

The Ibaraki Prefectural Health Study

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Background—Few studies have examined the association between low levels of low-density lipoprotein (LDL) cholesterol and risk of intraparenchymal hemorrhage.

Methods and Results—A total of 30 802 men and 60 417 women, 40 to 79 years of age with no history of stroke or coronary heart disease, completed a baseline risk factor survey in 1993 under the auspices of the Ibaraki Prefectural Health Study. Systematic mortality surveillance was performed through 2003, and 264 intraparenchymal hemorrhage deaths were identified. LDL cholesterol levels were calculated with the Friedewald formula. Persons with LDL cholesterol ≥140 mg/dL had half the sex- and age-adjusted risk of death due to intraparenchymal hemorrhage of those with LDL cholesterol <80 mg/dL. After adjustment for cardiovascular risk factors, the multivariable hazard ratio compared with persons with LDL cholesterol <80 mg/dL was 0.65 (95% CI 0.44 to 0.96) for those with LDL cholesterol 80 to 99 mg/dL, 0.48 (0.32 to 0.71) for 100 to 119 mg/dL, 0.50 (0.33 to 0.75) for 120 to 139 mg/dL, and 0.45 (0.30 to 0.69) for ≥140 mg/dL. These inverse associations were not altered substantially after the exclusion of persons with hypertriglyceridemia, after analysis with a Cox proportional hazard model with time-dependent covariates, or in sensitivity analysis for the potential effect of competing risks.

Conclusions—Low LDL cholesterol levels are associated with elevated risk of death due to intraparenchymal hemorrhage. (***Circulation.*** **2009;119:2136-2145.)**

Key Words: cholesterol ■ arteriosclerosis ■ intraparenchymal hemorrhage ■ follow-up studies

Intraparenchymal hemorrhage, which has a low survival rate and a high risk of disability,[1] has unique pathological and epidemiological characteristics that distinguish it from coronary heart disease.[2] This type of stroke is caused primarily by hypertension and possibly by low concentrations of low-density lipoprotein (LDL) cholesterol.[3,4]

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An association between low total cholesterol levels and increased risk of intraparenchymal hemorrhage was reported among Japanese men and women[5–9] and among Japanese American,[10–12] American,[13–15] Finnish,[16] and Swedish men,[17] whereas a U-shaped association was found for Japanese men and women,[18–20] and no association was found for Swedish women[17] or Korean men.[21] Recent prospective studies have shown an inverse association primarily among hypertensive persons or usual drinkers or with high levels of γ-glutamyl transferase[22,23]; however, no study has examined the association between LDL cholesterol and risk of intraparenchymal hemorrhage. For this reason, we looked for an association between LDL cholesterol levels and risk of death due to intraparenchymal hemorrhage in a large Japanese population–based cohort study.

Methods

Study Cohort and Population

The Ibaraki prefectural government initiated a community-based cohort study, known as the Ibaraki Prefectural Health Study, in 1993 to obtain information on health status for the purpose of health education and policy making.[24] Participants in the cohort were 98 196 individuals (33 414 men and 64 782 women) 40 to 79 years of age living in Ibaraki Prefecture who underwent an annual health checkup in 1993, which included an examination of blood lipids for 96 610 individuals (32 984 men and 63 626 women).

We excluded 5391 persons (2182 men and 3209 women) from the analysis because of a history of stroke or coronary heart disease at

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the time of baseline inquiry. Thus, a total of 91 219 individuals (30 802 men and 60 417 women) were enrolled in the present study.

Informed consent was obtained from community representatives to conduct an epidemiological study based on guidelines of the Council for International Organizations of Medical Science.[25] The Ethics Committee of Ibaraki Prefecture approved this study.

Measurement of Risk Factors

Serum total cholesterol and triglycerides were measured by enzymatic methods with an RX-30 device (Nihon Denshi, Tokyo, Japan), and high-density lipoprotein (HDL) cholesterol levels were measured by phosphotungstic acid magnesium methods with an MTP-32 (Corona Electric, Ibaraki, Japan). These measurements were performed on the premises of the Ibaraki Health Service Association and were standardized by the Osaka Medical Center for Health Science and Promotion under the aegis of the US National Cholesterol Reference Method Laboratory Network. The laboratory of the Osaka Medical Center for Health Science and Promotion has been standardized since 1975 by the CDC-NHLBI Lipid Standardized Program provided by the Centers for Disease Control and Prevention (Atlanta, Ga) and has met all criteria for both precision and accuracy of lipid measurements.[26] LDL cholesterol was calculated with the Friedewald formula as follows: LDL cholesterol (mg/dL)=total cholesterol (mg/dL)−HDL cholesterol (mg/dL)−0.2×triglycerides (mg/dL).[27] A previous study showed no bias related to LDL cholesterol levels among persons with triglycerides <802 mg/dL (<8.8 mmol/L).[28] We also calculated non-HDL cholesterol as follows: Non-HDL cholesterol (mg/dL)=total cholesterol (mg/dL)−HDL cholesterol (mg/dL).

Mild hypertension was defined as systolic blood pressure 140 to 159 mm Hg or diastolic blood pressure 90 to 99 mm Hg; the corresponding values for moderate hypertension were 160 to 179 mm Hg or 100 to 109 mm Hg, and for severe hypertension, they were ≥180 or ≥110 mm Hg. Diabetes mellitus was defined as a fasting plasma glucose level ≥126 mg/dL (≥7.0 mmol/L) or ≥200 mg/dL (≥11.1 mmol/L) during nonfasting or as use of medication for diabetes, and impaired glucose tolerance was defined as a fasting plasma glucose level 110 to 125 mg/dL (6.1 to 6.9 mmol/L) or a nonfasting level of 140 to 199 mg/dL (7.8 to 11.0 mmol/L) and no use of medication for diabetes. Kidney dysfunction was defined as serum creatinine levels ≥1.2 mg/dL (≥110 μmol/L) for men or ≥1.0 mg/dL (≥90 μmol/L) for women and/or as a history of kidney disease. Height in stocking feet and weight in light clothing were measured, and body mass index was calculated as weight (kg)/height (m)^2. An interview was conducted to ascertain smoking status, number of cigarettes smoked per day, usual weekly intake of alcohol in *go* units (a Japanese traditional unit converted to grams of ethanol per day by 23 g of ethanol per *go* unit), and histories of stroke and heart disease. Current drinkers were defined as occasional and habitual drinkers.

Follow-Up Surveillance

To ascertain deaths in the cohort, the investigators conducted a systematic review of death certificates, which in Japan are forwarded to the local public health center in each community. It is believed that all deaths that occurred in the cohort were ascertained, except for subjects who died after they had moved from their original community, in which case the subject was treated as a censored case. Data on death rates are centralized at the Ministry of Health and Welfare, where the underlying causes of death are coded for the National Vital Statistics according to the International Classification of Diseases, 9th (1993–1994) and 10th (1995–2004) revisions. Cause-specific mortality was determined by total deaths due to intraparenchymal hemorrhage (International Classification of Diseases, 10th revision, code I61), hemorrhagic stroke (I60 to I61), subarachnoid hemorrhage (I60), ischemic stroke (I63), and coronary heart disease (I20 to I25).

To confirm the validity of the death certificate diagnoses for stroke and its subtypes in the Ibaraki Prefectural Health Study, a validation study was conducted in community-based samples (6004 persons 40 to 79 years of age) from Ibaraki prefecture, where a community-based stroke registry was conducted,[29] between 1993 and 1997. In this stroke registry, the information for stroke cases (eg, episodes of symptom onset and imaging data of CT/MRI) was collected, and a final diagnosis was made by a panel of 3 or 4 physicians. We used 25 fatal cases (deaths within 28 days of symptom onset) in this stroke registry as the "gold standard" of stroke death and compared these with 94 stroke cases based on death certificate diagnoses. The sensitivity and specificity of death certificate diagnoses, respectively, were 80% and 100% for intraparenchymal hemorrhage, 71% and 100% for subarachnoid hemorrhage, 63% and 99% for ischemic stroke, and 76% and 99% for total stroke.

The follow-up inquiry for the present study was conducted until the end of 2003, and the median length of follow-up was 10.3 years. Only 3.2% of the subjects had moved out of the communities and were treated as censored. Whereas 0.3% of the subjects had died of intraparenchymal hemorrhage, 7.5% had died of other causes and were treated as censored.

Statistical Analysis

Statistical analysis was based on death rates from intraparenchymal hemorrhage divided by clinical categories of LDL cholesterol (<80, 80 to 99, 100 to 119, 120 to 139, and ≥140 mg/dL [<2.06, 2.06 to 2.57, 2.58 to 3.09, 3.10 to 3.61, and ≥3.62 mmol/L]) and other lipid profiles, that is, total cholesterol, HDL cholesterol, and triglycerides. Person-years of follow-up were calculated from the date of the baseline survey in 1993 to the date of death due to intraparenchymal hemorrhage or other causes, exit from the community, or the end of 2003, whichever occurred first.

Sex- and age-adjusted means and proportions of selected cardiovascular risk factors at baseline survey were presented among the categories of LDL cholesterols. Differences from the lowest category of LDL cholesterol in sex- and age-adjusted mean values and proportions of baseline characteristics were examined by ANCOVA and Mantel-Haenszel χ^2 tests. Multivariable hazard ratios (HRs) and 95% CIs were calculated after adjustment for sex, age, and potential confounding factors by use of the Cox proportional hazards model. These potential confounding factors included body mass index (sex-specific quintiles), blood pressure categories (normal, mild hypertension, moderate hypertension, or severe hypertension), antihypertensive medication use (yes or no), lipid medication use (yes or no), diabetes status (normal, impaired glucose tolerance, or diabetes mellitus), γ-glutamyl transferase (sex-specific quintiles), kidney dysfunction (yes or no), smoking status (never, ex-smoker, and current smokers of 1 to 19 or ≥20 cigarettes/d), alcohol intake category (never or ex-drinkers, occasional drinkers, and habitual drinkers of <69 and ≥69 g of alcohol per day).

We tested the assumption of proportional hazards according to lipid profiles and found no violation for proportionality. Tests for effect modification by sex or other variables were conducted with an interaction term generated by multiplying the variables of lipids by sex or other variables. Because the Friedewald formula introduces biased data for LDL cholesterol,[28] we additionally conducted our analysis after the exclusion of persons with hypertriglyceridemia (triglycerides ≥300 mg/dL) at baseline survey (2025 men and 2360 women).

We further analyzed the data with the time-dependent covariate Cox proportional hazard model using the additional data of lipid profiles and confounding factors for 80 578 persons (88.3% of the participants) who had undergone examination of blood lipids more than twice. The median duration between the date of the latest examination and the date of the end of follow-up was 0.7 years. We used blood pressure categories, antihypertensive medication use, diabetes mellitus, lipid medication use, body mass index, γ-glutamyl transferase, smoking status, alcohol consumption, and kidney dysfunction as time-dependent covariates.

Because the presence of competing risks may lead to biased results, we also conducted sensitivity analysis in several models. We used a stratified Cox proportional hazard model with interaction terms of competing risks,[30] a proportional hazards model for the subdistribution of competing risks,[31] and 2 types of "worst-case" scenarios: (1) All subjects censored because of disease other than intraparenchymal hemorrhage or because they moved out of the

Table 1. Baseline Characteristics According to LDL Cholesterol Categories

	LDL Cholesterol Categories					Overall Population
	(Lower)				(Higher)	
Range, mg/dL	<80	80–99	100–119	120–139	≥140	
Range, mmol/L	<2.06	2.06–2.57	2.58–3.09	3.10–3.61	≥3.62	
Median, mmol/L	1.81	2.35	2.84	3.34	4.03	3.04
No. of persons	8788	16 776	22 840	20 357	22 458	91 219
Men, %	53.3	41.2‡	35.5‡	29.6‡	22.5‡	33.8
Age, y	57.3	57.6	58.2‡	59.2‡	59.8‡	58.6
Systolic blood pressure, mm Hg	133.6	132.5‡	132.8‡	133.4	134.6‡	133.4
Diastolic blood pressure, mm Hg	78.2	77.9*	78.3	79.2‡	80.1‡	78.9
Hypertensive medication use, %	20.0	19.0*	19.0*	19.7	20.4	19.6
Diabetes, %	5.8	4.7‡	4.6‡	5.2*	5.9	5.2
Body mass index, kg/m^2	22.7	22.9‡	23.4‡	23.7‡	24.1‡	23.5
γ-Glutamyl transferase, U/L	33.7	22.0‡	21.7‡	22.6‡	25.2‡	24.0
Kidney dysfunction, %	9.1	9.1	9.6	10.3†	11.4‡	10.1
Current smoker, %	25.5	21.5‡	19.9‡	19.2‡	19.7‡	20.5
Heavy drinkers, %	6.0	2.9‡	2.1‡	1.9‡	1.9‡	2.5
Lipid medication use, %	1.5	1.4	2.0*	2.3‡	4.4‡	2.5
Total cholesterol, mmol/L	4.05	4.50‡	4.98‡	5.47‡	6.32‡	5.24
HDL cholesterol, mmol/L	1.47	1.46	1.44‡	1.42‡	1.39‡	1.43
Non-HDL cholesterol, mmol/L	2.58	3.04‡	3.53‡	4.05‡	4.92‡	3.81
Triglycerides, mmol/L	1.89	1.50‡	1.50‡	1.54‡	1.62‡	1.58

ANCOVA and Mantel-Haenszel χ^2 tests were used to compare sex- and age-adjusted mean values and percentages for cardiovascular risk factors and lipid profiles. Test for difference vs the lowest category: *P<0.05, †P<0.01, ‡P<0.001.

communities were assumed to have died of intraparenchymal hemorrhage instead, and (2) all subjects censored because of disease other than intraparenchymal hemorrhage or who moved out of the communities were assumed to have survived as long as the longest survival time observed in the present study.

All statistical tests were 2-sided, and P<0.05 was regarded as statistically significant. All statistical analyses except for the proportional hazard model for the subdistribution of competing risks were conducted with SAS, version 9.13 (SAS Institute, Inc, Cary, NC). R version 2.6.1 (R Foundation for Statistical Computing, Vienna, Austria) was used for calculations pertaining to the proportional hazard model for the subdistribution of competing risks.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

A total of 91 219 persons (30 802 men and 60 417 women) were followed up for a median of 10.3 years, during which time 264 subjects (125 men and 139 women) died of intraparenchymal hemorrhage. The crude death rate was 29 per 100 000 person-years for intraparenchymal hemorrhage and 795 per 100 000 person-years for all-cause death.

Table 1 shows selected cardiovascular risk factors by LDL cholesterol concentration category. Compared with persons who had the lowest levels of LDL cholesterol (<80 mg/dL [<2.06 mmol/L]), those who had the highest levels (≥140 mg/dL [≥3.62 mmol/L]) were older, more likely to be female and to use medication for a lipid abnormality, and less likely to smoke or drink heavily. They also tended to have kidney dysfunction; higher means of systolic and diastolic blood pressure, body mass index, and total and non-HDL cholesterol levels; and lower means of γ-glutamyl transferase, HDL cholesterol, and triglycerides.

Sex- and age-adjusted death due to intraparenchymal hemorrhage was half as low for the highest category of LDL cholesterol as for the lowest category, whereas there was a weak inverse association with total cholesterol and no association with HDL cholesterol or triglycerides (Table 2). Adjustment for known cardiovascular risk factors did not alter these associations materially. The multivariable HR (95% CI) for the highest versus lowest lipid levels was 0.45 (0.30 to 0.69; P<0.001) for LDL cholesterol, 0.55 (0.33 to 0.91; P=0.02) for total cholesterol, 0.98 (0.62 to 1.53; P=0.91) for HDL cholesterol, 0.42 (0.26 to 0.68; P<0.001) for non-HDL cholesterol, and 1.13 (0.63 to 2.02; P=0.69) for triglycerides.

These inverse associations were not altered substantially after we excluded persons with hypertriglyceridemia or when we analyzed with the time-dependent covariate Cox proportional hazard model. The HR (95% CI) for highest versus lowest LDL cholesterol was 0.48 (0.31 to 0.74; P=0.001) after the exclusion of persons with hypertriglyceridemia and 0.53 (0.34 to 0.81; P=0.003) when we used the time-dependent covariate Cox proportional hazard model.

To identify the confounding effect of lipid-lowering medication use, we also calculated the HR of death due to intraparenchymal hemorrhage. The HR for users versus nonusers of lipid-lowering medication was 0.39 (0.12 to 1.21; P=0.10) after sex and age adjustment, 0.41 (0.13 to 1.28; P=0.13) after multivariable adjustment, and 0.48 (0.25 to