identified can be targeted for treatment at a higher BMD than individuals of the same age without a fracture history.

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# Noncancer Disease Incidence in Atomic Bomb Survivors, 1958–1998

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**Yamada, M., Wong, F. L., Fujiwara, S., Akahoshi, M. and Suzuki, G. Noncancer Disease Incidence in the Atomic Bomb Survivors, 1958–1998. *Radiat. Res.* 161, 622–632 (2004).**

**We examined the relationships between the incidence of noncancer diseases and atomic bomb radiation dose using the longitudinal data for about 10,000 Adult Health Study (AHS) participants during 1958–1998. The current report updates the analysis we presented in 1993 with 12 additional years of follow-up. In addition to the statistically significant positive linear dose–response relationships detected previously for the incidence of thyroid disease ($P < 0.0001$), chronic liver disease and cirrhosis ($P = 0.001$), and uterine myoma ($P < 0.00001$), we also found a significant positive dose response for cataract ($P = 0.026$), a negative linear dose–response relationship for glaucoma ($P = 0.025$), and significant quadratic dose–response relationships for hypertension ($P = 0.028$) and for myocardial infarction among survivors exposed at less than 40 years of age ($P = 0.049$). Significant radiation effects for calculus of the kidney and ureter were evident for men but not for women (test of heterogeneity by sex: $P = 0.007$). Accounting for smoking and drinking did not alter the results. Radiation effects for cataract, glaucoma, hypertension, and calculus of the kidney and ureter in men are new findings. These results attest to the need for continued follow-up of the aging A-bomb survivors to fully elucidate the effects of radiation exposure on the occurrence of noncancer diseases.** ©


## INTRODUCTION

The Adult Health Study (AHS) was begun in 1958 by the Atomic Bomb Casualty Commission (ABCC), succeeded in 1975 by the Radiation Effects Research Foundation (RERF), as biennial clinical examinations of a subset of the Life Span Study (LSS) cohort to examine the late effects of atomic bomb exposure. The 1993 report (*1*) showed for the first time that the incidence of uterine myoma, chronic liver disease and cirrhosis, and thyroid disease increased with radiation dose during 1958–1986, confirming some of the impressions from an earlier prevalence study (*2*). The current report, covering 40 years between 1958–1998, updates the first incidence study results with 12 additional years of follow-up and two more diseases. Cigarette smoking and alcohol consumption were also examined as potential confounders and as dose–response modifiers.

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## MATERIALS AND METHODS

### *Study Population*

The AHS was established in 1958 as a subset of the LSS cohort, comprising 19,961 Hiroshima and Nagasaki subjects. The AHS biennial health examinations presented clinical information complementary to the LSS death and tumor registries data. To enhance detection of radiation effects, the AHS included disproportionately more individuals exposed at higher doses than were present in the LSS: about half were within 2 km of the hypocenter (proximal exposure), a quarter were at distances over 3 km (distal exposure), and a quarter were not in city (NIC) at the time of bombing (ATB).

The study subjects attended at least two examinations between July 1, 1958 and June 30, 1998. This report uses data from 10,339 subjects ($2.2 \times 10^5$ person-years of follow-up), which is the original cohort reduced by 5,000 NIC subjects, 2,064 who lacked Dosimetry System 86 (DS86) dose estimates (*3*), and 2,558 who attended fewer than two examinations. Compared to the 1993 report (*1*), an additional 698 subjects and $3 \times 10^4$ person-years (15.8%) are represented here. Since case identification relied on the biennial health examinations, the AHS data are qualitatively different from those of the LSS mortality and tumor registry program.

Sixty-three percent of the subjects were women and 73% were Hiroshima residents (Table 1). About 50% of the AHS subjects had died by July 1998. The proportion of participants who were under 20 years of age ATB increased from 1/3 in 1958–1960 to 60% in 1996–1998, reflecting age-related mortality. Conversely, those over 40 years ATB decreased from 29% in 1958–1960 to 2% in 1996–1998. A high participation rate (75 to 90%) was maintained throughout the examinations for study subjects living in Hiroshima and Nagasaki and their neighboring towns. More than half had attended 11 or more examinations.

A subject's follow-up began at the initial AHS visit and ended on the earlier of the date of the last disease-free visit or the date of the disease onset. The disease onset date was estimated as the midpoint between the first disease diagnosis date and the date of the previous disease-free examination. For each disease, cases present at the initial visit were excluded.

### *Clinical Procedures and Selection of Diseases for Study*

The biennial health examinations, conducted with informed consent, consist of history-taking, physical examination, and laboratory tests. Details are available elsewhere (*1, 2*). Incident cases were ascertained by scanning for the first occurrence of the three-digit International Classification of Diseases (ICD) (*4*) codes stored in the AHS database. The ICD codes of the 21 diseases examined are listed in the Appendix. At each examination, the first three digits of the ICD codes, up to six diagnoses

**TABLE 1**
**Distribution of the 10,339 AHS Participants by DS86 Weighted Total Shielded Kerma Categories (Sv)**

| | | DS86 categories (RBE = 10) in Sv | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Total | 0.0 | 0.001–0.49 | 0.5–0.99 | 1.0–1.49 | 1.5–1.99 | 2.0–2.49 | 2.5–2.99 | 3.0+ |
| Hiroshima | 7575 | 2750 | 2541 | 941 | 454 | 252 | 193 | 131 | 314 |
| Men | 2698 | 1004 | 823 | 335 | 174 | 102 | 77 | 48 | 136 |
| Women | 4877 | 1746 | 1718 | 606 | 280 | 150 | 116 | 83 | 178 |
| Mean dose | 0.57 | 0 | 0.21 | 0.72 | 1.23 | 1.75 | 2.24 | 2.75 | 4.14 |
| Mean age ATB | 30.6 | 30.4 | 31.2 | 31.3 | 30.7 | 31.2 | 29.0 | 29.2 | 27.2 |
| Nagasaki | 2764 | 1205 | 532 | 345 | 338 | 166 | 76 | 35 | 67 |
| Men | 1111 | 514 | 192 | 125 | 129 | 75 | 32 | 14 | 30 |
| Women | 1653 | 691 | 340 | 220 | 209 | 91 | 44 | 21 | 37 |
| Mean dose | 0.58 | 0 | 0.22 | 0.76 | 1.23 | 1.74 | 2.18 | 2.70 | 3.83 |
| Mean age ATB | 24.5 | 24.2 | 26.5 | 24.5 | 24.1 | 23.8 | 23.3 | 22.4 | 22.1 |
| Total | 10,339 | 3954 | 3073 | 1286 | 792 | 418 | 269 | 166 | 381 |

per person, were stored before June 1986; four-digit codes, up to 12 per person, were stored thereafter. Medical charts and death certificates were not reviewed for case validation.

*Radiation Dosimetry*

We used individual estimates of kerma and organ-specific dose in which survivor location and shielding by terrain and the body are taken into account based on the DS86. Kerma and organ doses, both expressed in sieverts, were calculated as weighted sums of their γ-ray and neutron components in grays, giving the neutron component a weight of 10. Before weighted sums were calculated, DS86 kerma estimates were truncated to 4 Gy, in consideration of the imprecision in dose assessment for proximal survivors (*5*). The estimated organ doses were adjusted for random dosimetry error, generally thought to be about 35%, to reduce bias in risk estimates (*5–7*). We used thyroid dose for the analysis of thyroid diseases, eye dose for eye diseases, liver dose for liver disease, uterine dose for gynecological diseases, bladder dose for prostate disease, and stomach dose for all others. Our 1993 report (*1*) used unweighted organ-specific doses for thyroid diseases, eye diseases, liver disease, gynecological diseases, prostate disease, and gastrointestinal diseases, and unweighted shielded kerma for residual diseases, with truncation to 6 Gy instead of 4 Gy and without adjustment for random dosimetry errors. As a result, the individual dose estimates used here were generally lower compared to those of the previous report.

Table 1 shows the distribution of the AHS participants by DS86 categories. Nearly 20% of the cohort had exposure doses of 1 Sv or more. The mean weighted shielded kerma was 0.57 Sv ± 0.94 [standard deviation of the mean (SD)]. The unexposed category (doses = 0) includes 38.2% of the study cohort. Among the exposed (doses > 0), the mean weighted shielded kerma was 0.92 Sv ± 1.06.

*Cigarette Smoking and Alcohol Consumption*

Cigarette smoking history was abstracted from four LSS mail surveys (administered to men in 1965, to women in 1969–1970, to both men and women in 1979–1980 and in 1991) and one survey administered during the AHS examinations of 1965–1966. All AHS participants were part of the pre-1991 surveys, but only about 15% were part of the 1991 survey. The response rate was over 95% for all surveys. Smoking and drinking statuses were considered as time-varying covariates. Follow-up time was classified as "never smoked", "smoke currently" or "smoked in the past" according to changes in smoking status. We also used composite classification of "never smoked" and "ever smoked" for descriptive purposes. Among men, 11% never smoked, 79% smoked at some time, and 10% had no smoking information. Among women, 72% never smoked, 18% smoked at some time, and 10% had no smoking information.

We obtained alcohol intake information from two LSS mail surveys in 1979–1980 and 1991 and from the AHS epidemiological survey of 1965–1966. The classification scheme used for smoking was applied to alcohol. Among men, 16% never drank, 70% drank at some time, and 14% had no data. Among women, 63% never drank, 26% had drunk at some time, and 11% had no data. Due to lack of timely information, nonsmoking and nondrinking groups most likely included actual smokers and drinkers.

There was no significant difference in dose among the smoking and drinking classes except for smoking in women: The mean dose was significantly higher by 15% for ever-smokers than for never-smokers ($P < 0.01$).

The background disease incidence rates were significantly higher for "ever smoked" than for "never smoked" subjects for cardiovascular disease, gastric ulcer, chronic liver disease, and cholelitiasis. However, the background risk of cataract was significantly lower among the "ever smoked". Alcohol-related increase in risk was found for chronic liver disease, and protective effects were observed for hyperplasia of the prostate and Parkinson's disease.

*Statistical Methods*

We applied Poisson regression methods for the longitudinal analysis of incidence data, using AMFIT of the EPICURE program package (*8*). We stratified disease incidence rates by city (Hiroshima, Nagasaki), sex (male, female), age ATB in years (upper bounds: 10, 20, 30, 40, 50, 60, 60+), age at examination (age ATE) in years (upper bounds: 20, 30, 40, 50, 60, 70, 80, 80+), calendar time (July 1, 1958–December 31, 1967; January 1, 1968–December 31, 1977; January 1, 1978–December 31, 1987; January 1, 1988–June 30, 1998), and DS86 total weighted organ dose in sieverts (upper bounds: 0, 0.5, 1.0, 1.5, 2.0, 3.0, 3.0+). For some analyses, cigarette smoking (never smoked, smoke currently, smoked in the past) and alcohol intake (never drank, drink currently, drank in the past) were also included as time-varying covariates in disease rate stratification. The number of disease cases in each stratum was assumed to be an independent Poisson variate with mean $PY_{ij}\gamma_{ij}$, where $PY_{ij}$ is person-years and $\gamma_{ij}$ is disease incidence rate in the $j$th dose category and the $i$th category defined by other cross-classifications. $\gamma_{ij}$ may also be represented by $\gamma_{ij} = \gamma_{i0}\,RR_{ij}$, where $\gamma_{i0}$ is the incidence rate in stratum $i$ in the absence of radiation exposure and $RR_{ij}$ is the relative risk due to radiation dose associated with the $j$th exposure level. We assumed an additive linear dose–response model: $RR_{ij} = 1 + \beta d_{ij} \exp[\alpha_k(Z_k)]$, where $d_{ij}$ is the $j$th dose level in stratum $i$, $\beta$ is the excess risk per sievert averaged over all strata, and $z_k$ represents the effect modifiers. We used the mean dose in each $ij$th stratum for $d_{ij}$. For diseases with a significant linear dose effect ($\beta$), the presence of curvature was assessed by the significance of $\eta$ in the linear-quadratic model, $RR_{ij} = 1 + \beta d_{ij} + \eta d_{ij}^2$. We also examined purely quadratic effects for all diseases by testing the significance of $\eta$ in the model $RR_{ij} = 1 + \eta d_{ij}^2$. We used a two-sided type I error of 0.05.

**TABLE 2**
**Number of Disease Cases and Observed Background Incidence**

| Disease | No. of cases | | Background incidence per 10,000 PY | | | | |
|---|---|---|---|---|---|---|---|
| | | | Crude rates | | | Standardized rates[a] | |
| | Male | Female | Total | Male | Female | Male | Female |
| Hypertension | 1792 | 3243 | 286.44 | 304.33 | 276.92 | 178.2 | 185.2 |
| Hypertensive heart disease | 585 | 1301 | 80.73 | 80.13 | 81.06 | 38.0 | 42.3 |
| Ischemic heart disease | 600 | 946 | 63.40 | 76.10 | 56.67 | 31.5 | 27.3 |
| Myocardial infarction | 65 | 52 | 5.36 | 9.88 | 2.94 | 4.0 | 1.3 |
| Occlusion, stenosis | 232 | 208 | 17.69 | 27.46 | 12.47 | 9.9 | 5.5 |
| Aortic aneurysm | 74 | 110 | 6.78 | 9.88 | 5.12 | 3.8 | 2.4 |
| Stroke I | 272 | 259 | 20.79 | 30.76 | 15.47 | 11.3 | 6.9 |
| Stroke II | 356 | 373 | 27.98 | 41.01 | 21.04 | 15.7 | 9.6 |
| Thyroid disease | 182 | 782 | 36.99 | 19.82 | 46.66 | 12.9 | 48.5 |
| Cataract | 975 | 2509 | 154.25 | 123.01 | 171.98 | 53.8 | 97.9 |
| Gastric ulcer | 476 | 454 | 37.45 | 60.23 | 25.81 | 37.2 | 15.5 |
| Duodenal ulcer | 219 | 152 | 14.46 | 25.96 | 8.47 | 22.3 | 6.3 |
| Chronic liver disease and cirrhosis | 785 | 989 | 71.66 | 93.72 | 60.32 | 59.2 | 35.2 |
| Cholelithiasis | 271 | 688 | 40.64 | 35.59 | 43.38 | 16.3 | 22.6 |
| Calculus of kidney and ureter | 170 | 153 | 11.02 | 16.47 | 8.1 | 8.8 | 5.0 |
| Uterine myoma | — | 922 | 51.68 | — | 51.68 | — | 37.7 |
| Cervical polyp | — | 281 | 15.48 | — | 15.48 | — | 11.8 |
| Hyperplasia of prostate | 461 | — | 60.68 | 60.68 | — | 22.7 | — |
| Dementia | 79 | 237 | 11.32 | 6.36 | 13.99 | 2.3 | 6.7 |
| Parkinson's disease | 35 | 62 | 3.12 | 4.05 | 2.63 | 1.5 | 1.3 |
| Glaucoma | 52 | 159 | 10.16 | 6.67 | 12.03 | 2.9 | 5.4 |

[a] Directly standardized to the Japanese population of 1985.

The reference group consisted of 3954 persons with DS86 dose estimates of zero.

We evaluated the significance of the effect modifiers (city, sex, age ATB, age ATE, calendar time, smoking and drinking) for the diseases for which the main effects of radiation were significant or suggestive. Generally, covariates were treated as categorical except for age ATB and age ATE, for which we used the cell-specific means. We used the likelihood ratio method for significance testing and for computing the 95% confidence intervals.

## RESULTS

The number of disease cases and the background incidence rates for the 21 diseases are shown in Table 2. We estimated the background rates using the unexposed subjects. We calculated the standardized rates using the Japanese population of 1985 (*9*), as in the previous report (*1*). The standardized rates increased for only dementia and Parkinson's disease, in spite of the aging of the population and implementation of more specific diagnostic procedures such as ultrasonography.

Table 3 shows the estimated relative risk at 1 Sv ($RR_{1Sv}$), the average excess disease per $10^4$ PY Sv, and the attributable risk based on the linear model. Attributable risk is the percentage of the disease cases due to over 0.001 Sv of exposure. The last two columns also show the significance level and the $RR_{1Sv}$ obtained by further stratifying the background rates by smoking and drinking. Between 1958–1998, a significant linear increase with radiation dose ($P < 0.05$) was detected for the incidence of thyroid diseases, chronic liver disease and cirrhosis, uterine myoma, and cataract and was suggested for calculus of the kidney and ureter ($P = 0.07$). A significant linear decrease was detected for the incidence of glaucoma. There was no indication of a curvilinear increase/decrease in risk at high doses for these diseases. The fitted linear models and the estimated relative risks are shown in Fig. 1. The relative risk estimate for uterine myoma at over 3 Sv was omitted, since only three women had that exposure level. A nonlinear dose–response relationship was evident for hypertension (Fig. 2A). Significant radiation effects were not detected for other cardiovascular diseases, including MI. However, in accord with our previous results (*1*), MI incidence during 1968–1998 for survivors under 40 years ATB ($MI^{<40}$, 78 cases) showed a significant curvilinear dose–response relationship (Fig. 2B). Adjustment for smoking and drinking only slightly affected the significance level of the linear dose response for hypertension and calculus of the kidney and ureter. The results of the examination of city, sex, age ATB, age ATE, and calendar time as modifiers of the dose–response relationship are shown in Table 4; significant or suggestive evidence of radiation effects is shown in the results for each disease.

### *Thyroid Disease*

The relative risk at 1 Sv ($RR_{1Sv}$) for thyroid disease was 1.33 ($P < 0.0001$, 95% CI: 1.19–1.49). The average number of excess disease cases per $10^4$ PY Sv was 12, and the attributable risk was 18%. These estimates are similar to

those obtained previously (*1*), which were based on 13.5% fewer cases.

Radiation risk was higher for subjects exposed at younger ages and for subjects examined at younger ages. With age ATB included as the most significant effect modifier, age ATE was not additionally significant ($P = 0.58$), indicating age ATB as the stronger factor. In fact, increased radiation risk was apparent for survivors exposed at less than 20 years of age ($P < 0.0001$, $RR_{1Sv} = 1.54$, 95% CI: 1.33–1.81) but not for those exposed at older ages ($P = 0.18$, $RR_{1Sv} = 1.11$, 95% CI: 0.96–1.30).

*Chronic Liver Disease and Cirrhosis*

$RR_{1Sv}$ for liver disease was 1.15 ($P = 0.001$, 95% CI: 1.06–1.25). The average excess risk was 11 cases per $10^4$ PY Sv and the attributable risk was 8%. Similar estimates were obtained in our previous report, with 42% fewer cases. The effect modifiers were not significant.

The ICD code for chronic liver disease (571) includes alcoholic liver disease (571.1–571.3), chronic hepatitis (571.4), cirrhosis without mention of alcohol (571.5), biliary cirrhosis (571.6), and other chronic nonalcoholic liver disease (571.8). The use of the four-digit ICD after June 1986 resulted in a large increase in cases after June 1986, due mainly to nonalcoholic fatty liver (571.8) detected by ultrasonography, comprising 69% of the incident cases. Ultrasonography began to be used in the Hiroshima laboratory in 1981 and in the Nagasaki laboratory in 1984. Participation in ultrasonography was voluntary before 1991, raising the possibility of dose-related bias. Ultrasonography has been performed routinely since 1991, resulting in a dramatic rise in fatty liver diagnoses, but diagnoses of other chronic liver diseases did not change noticeably.

We examined radiation effects for fatty liver alone and for all other chronic liver diseases occurring after 1986. For all liver diseases, there was significant linear dose response ($P = 0.054$, $RR_{1Sv} = 1.14$, 95% CI: 1.0–1.32). No significant heterogeneity in the risk estimates was observed before and after June 1986 ($P = 0.76$). For fatty liver alone (445 cases), a linear dose response was suggested ($P = 0.073$, $RR_{1Sv} = 1.16$, 95% CI: 0.99–1.37). For 199 cases of other chronic liver diseases, radiation effects were nonsignificant ($RR_{1Sv} = 1.06$, $P = 0.64$, 95% CI: 0.84–1.40).

*Uterine Myoma*

$RR_{1Sv}$ for uterine myoma was 1.46 ($P < 0.00001$, 95% CI: 1.27–1.67). There were 25 excess cases per $10^4$ PY Sv, and the attributable risk was 19%. Similar estimates were obtained previously (*1*), with 23% fewer cases. Much of the increase in cases could be attributed to the use of ultrasonography.

Radiation risk varied significantly by calendar time or, equivalently, time since exposure ($P = 0.015$) and by age ATB ($P = 0.042$). The risk decreased steadily in the first three decades of follow-up ($RR_{1Sv} = 2.0, 1.7, 1.1$), which was noted in our previous report (*1*), then increased slightly in the fourth decade ($RR_{1Sv} = 1.3$).

Years since exposure was the most significant effect modifier compared to age ATB and age ATE. Neither age ATB ($P = 0.75$) nor age ATE ($P = 0.75$) was additionally significant with years since exposure included as dose–effect modifier.

We also found that radiation risk was elevated for the exposed nondrinkers ($P < 0.0001$, $RR_{1Sv} = 1.62$, 95% CI: 1.36–1.94), but not for exposed drinkers ($P < 0.50$, $RR_{1Sv} = 1.09$, 95% CI: 0.86–1.40) (test of heterogeneity, $P = 0.011$).

*Cataract*

We detected a significant positive linear dose–response relationship ($P = 0.026$, $RR_{1Sv} = 1.06$, 95% CI: 1.01–1.11). The estimated number of excess cataract cases per $10^4$ PY Sv was 8, and the attributable risk was 4%. Radiation risk varied significantly by age ATE ($P < 0.001$) and possibly by follow-up period ($P = 0.09$). A decreasing trend for the first three decades was observed here as well as in the previous report, although $RR_{1Sv}$ increased to 1.08 in the most recent decade. Considered simultaneously with age ATE as effect modifier, follow-up period was also significant ($P = 0.012$), but their interaction was not ($P = 0.78$). Since lens opacities surge after age 60 years (*11*), we looked for heterogeneity in the dose response between age ATE $\leq 60$ and $>60$ years. Radiation effects were significant for the younger group ($P = 0.009$, $RR_{1Sv} = 1.16$, 95% CI: 1.04–1.32) but not for the older group ($P = 0.24$, $RR_{1Sv} = 1.03$, 95% CI: 0.98–1.09) (test of heterogeneity: $P = 0.08$).

*Glaucoma*

Examined for the first time in this report, glaucoma showed a significant negative dose–response relationship ($P = 0.025$, $RR_{1Sv} = 0.82$, 95% CI: 0.80–0.97). The lower 95% confidence bound was the lowest value feasible before RR became negative. There was a deficit of $-1.5$ glaucoma cases per $10^4$ PY Sv, and rates were reduced by 15% for subjects exposed to over 0.001 Sv. The dose–response relationship was not modified by the covariates considered.

Since rural/urban variation in baseline disease rates could bias radiation risk estimates (*12*), distal/proximal exposure indicator was used as a surrogate for adjustment. This resulted in a lack of dose response ($P = 0.14$), with $RR_{1Sv}$ essentially unchanged.

*Hypertension*

Radiation effects were not evident under the linear dose–response model ($P = 0.15$), but they were significant under the purely quadratic model ($P = 0.028$, $RR_{1Sv} = 1.03$, 95% CI: 1.00–1.06) (Fig. 2A). Based on the quadratic model, there were seven excess hypertension cases per $10^4$ PY Sv, and 2% were attributed to radiation exposure. Incident cases increased by 16% since the previous report. There was

**TABLE 3**
**Linear Dose Response for Noncancer Disease Incidence between 1958 and 1998 in Hiroshima and Nagasaki Men and Women, Stratified by City, Sex, Age ATB, Age ATE, and Calendar Time**

| Disease | No. cases | Without smoking and drinking in stratification | |
|---|---|---|---|
| | | *P* | Estimated RR at 1 Sv |
| Hypertension | 5035 | 0.14 | 1.04 (0.99, 1.09)[b] |
| *Hypertension*[f] | 5035 | 0.028 | 1.03 (1.00, 1.06) |
| Hypertensive heart disease | 1886 | 0.86 | 1.01 (0.92, 1.10) |
| Ischemic heart disease | 1546 | 0.47 | 1.04 (0.94, 1.14) |
| Myocardial infarction[d] | 117 | 0.38 | 1.11 (0.90, 1.46) |
| *Myocardial Infarction*$^{<40}$[g] | 78 | 0.05 | 1.25 (1.00, 1.69) |
| Occlusion, stenosis | 440 | 0.61 | 1.05 (0.88, 1.27) |
| Aortic aneurysm | 184 | 0.74 | 1.05 (0.88, 1.44) |
| Stroke I | 531 | 0.52 | 1.05 (0.90, 1.25) |
| Stroke II | 729 | 0.43 | 1.06 (0.92, 1.23) |
| Thyroid disease | 964 | 0.0000 | 1.33 (1.19, 1.49) |
| Cataract | 3484 | 0.026 | 1.06 (1.01, 1.11) |
| Gastric ulcer | 930 | 0.98 | 1.00 (0.89, 1.13) |
| Duodenal ulcer | 371 | 0.54 | 0.95 (0.81, 1.14) |
| Chronic liver disease and cirrhosis | 1774 | 0.0010 | 1.15 (1.06, 1.25) |
| Cholelithiasis | 959 | 0.93 | 1.00 (0.89, 1.12) |
| Calculus of kidney and ureter | 323 | 0.07 | 1.19 (0.98, 1.46) |
| Uterine myoma (females) | 922 | 0.0000 | 1.46 (1.27, 1.67) |
| Cervical polyp (females) | 281 | 0.29 | 1.14 (0.90, 1.48) |
| Hyperplasia of prostate (males) | 461 | 0.26 | 0.91 (0.79, 1.07) |
| Dementia | 316 | 0.22 | 1.17 (0.91, 1.52) |
| Parkinson's disease | 97 | 0.98 | 1.00 (0.72[c], 1.55) |
| Glaucoma | 211 | 0.025 | 0.82 (0.80[c], 0.97) |

[a] Average PY: total = $2.2 \times 10^5$ PY; male = $8.1 \times 10^4$ PY; female = $1.5 \times 10^5$ PY (actual numbers depend on the disease).
[b] 95% confidence interval.
[c] Minimum feasible value.
[d] Incidence after June 30, 1964, since no ICD codes for MI were available before 1964.
[e] Based on Wald's confidence interval; no feasible likelihood-based upper bound could be estimated.
[f] Based on the quadratic dose–response model.
[g] Based on the quadratic dose–response model, for incidence during 1968–1998 and age ATB under 40 years.

suggestive evidence ($P = 0.07$) for increased hypertension risk for exposed nonsmokers ($RR_{1Sv} = 1.04$) but not for exposed smokers ($RR_{1Sv} = 1.00$). The dose response was not modified significantly by other covariates.

### *Cardiovascular Diseases*

None of the cardiovascular diseases showed a significant relationship with radiation dose. The linear dose response was not significant for overall MI ($P = 0.38$) and MI$^{<40}$ incidence ($P = 0.10$), but a significant quadratic relationship was evident for MI$^{<40}$ ($P = 0.05$, $RR_{1Sv} = 1.25$, 95% CI: 1.00–1.69) (Fig. 2B). Under the quadratic model, the number of excess MI$^{<40}$ cases per $10^4$ PY Sv is one and 16% were attributed to radiation exposure.

### *Calculus of the Kidney and Ureter*

An overall linear dose response was suggestive ($P = 0.07$): It was significant for men ($RR_{1Sv} = 1.47$, 95% CI: 1.13–1.96) but not for women ($RR_{1Sv} = 0.86$, 95% CI: 0.73–1.17) (test of heterogeneity: $P = 0.007$). The dose response disappeared after adjustment for smoking and drinking ($P = 0.13$), but radiation effects remained significant for men even after adjustment. Subjects exposed at an early age ($P = 0.0008$, $df = 2$) and examined at a younger age ($P = 0.019$, $df = 2$) showed higher radiation risks. Age ATB was the most significant effect modifier in the overall analysis as well as in the male-specific analysis.

## DISCUSSION

### *Thyroid Disease*

Radiation-related thyroid abnormalities continued to occur in the extended follow-up period. Although malignant and benign thyroid tumors increased with A-bomb radiation dose (*10, 11*), radiation effects on specific thyroid disorders could not be assessed here because a large percentage of cases had multiple thyroid abnormalities, and thyroid function tests and ultrasonography were not administered routinely.

The latest AHS thyroid disease prevalence study in Nagasaki applying uniform diagnostic criteria (ultrasonography, thyroid function test, and autoimmune antibody) revealed a significant dose response for solid nodules in women, especially those exposed at young ages, and a con-

**TABLE 3**
**Extended**

| Without smoking and drinking in stratification | | With drinking and smoking in stratification | |
|---|---|---|---|
| Average excess disease × $10^4$ PY Sv[a] | Attributable risk (%) | *P* | Estimated RR at 1 Sv |
| 10.59 (−3.41, 24.63) | 2.2 (−0.7, 5.0) | 0.08 | 1.05 (0.99, 1.10) |
| 7.26 (0.76, 14.06) | 1.8 (0.2, 3.6) | 0.01 | 1.03 (1.01, 1.06) |
| 0.61 (−5.92, 7.48) | 0.42 (−4.2, 5.2) | 0.87 | 0.99 (0.91, 1.09) |
| 2.13 (−3.47, 8.10) | 1.5 (−3.2, 6.5) | 0.33 | 1.05 (0.95, 1.16) |
| 0.57 (−0.59, 1.64) | 8.5 (−8.8, 24.5) | 0.48 | 1.12 (0.84, 1.60) |
| 1.03 (0.01, 13.84) | 15.6 (0.03, 30.8) | 0.14 | 1.17 (0.97, 1.56) |
| 0.76 (−2.00, 3.82) | 2.5 (−6.6, 12.6) | 0.52 | 1.06 (0.89, 1.30) |
| 0.34 (−1.41, 2.49) | 2.5 (−11.0, 18.9) | 0.90 | 1.02 (0.78, 1.41) |
| 1.05 (−2.02, 4.50) | 2.8 (−5.4, 12.1) | 0.41 | 1.08 (0.90, 1.31) |
| 1.57 (−2.21, 5.84) | 3.0 (−4.2, 11.2) | 0.40 | 1.07 (0.92, 1.24) |
| 11.99 (7.43, 16.32) | 18.5 (11.5, 25.2) | <0.0001 | 1.38 (1.22, 1.57) |
| 7.98 (0.95, 15.16) | 3.8 (0.4, 7.2) | 0.004 | 1.11 (1.03, 1.19) |
| −0.038 (−4.44, 4.76) | −0.06 (−6.5, 7.0) | 0.89 | 1.00 (0.88, 1.12) |
| −0.89 (−3.38, 2.09) | −3.4 (−12.7, 7.8) | 0.69 | 0.96 (0.82, 1.16) |
| 10.90 (4.25, 17.79) | 8.1 (3.2, 13.2) | 0.0087 | 1.12 (1.03, 1.22) |
| −0.19 (−4.43, 4.31) | −0.3 (−6.6, 6.4) | 0.94 | 1.00 (0.89, 1.12) |
| 2.41 (−0.21, 5.39) | 9.8 (−0.9, 21.9) | 0.13 | 1.16 (0.96, 1.43) |
| 25.02 (15.68, 34.66) | 18.9 (11.8, 26.2) | <0.0001 | 1.39 (1.22, 1.60) |
| 2.48 (−1.97, 7.41) | 6.8 (−5.4, 20.4) | 0.31 | 1.13 (0.90, 1.45) |
| −4.76 (−11.95, 3.58) | −5.8 (−14.6, 4.4) | 0.21 | 0.90 (0.78, 1.06) |
| 1.64 (−0.91, 4.63) | 7.1 (−4.0, 20.1) | 0.18 | 1.20 (0.92, 1.59) |
| 0.020 (−1.06[c], 1.68) | 0.3 (−14.2[c], 22.6) | 0.95 | 0.99 (0.73, 1.58) |
| −1.47 (−1.74[c], −0.19) | −15.4 (−17.8[c], −2.0) | 0.012 | 0.73 (0.72[c], 0.89[c]) |

cave dose response for autoimmune hypothyroidism (*12*). However, no significant radiation risk was detected for other thyroid disease (*12*).

Thyroid abnormalities also occur after exposure to other sources of ionizing radiation, including external (*13*) and internal radiation (*14*). Although the prevalence of hypothyroidism or thyroiditis increased in patients who received radiation therapy (*15, 16*), the effects of relatively low doses of external radiation exposure are equivocal (*17*). The ongoing AHS thyroid study in Hiroshima and Nagasaki initiated in 2000 should help to examine radiation effects on specific thyroid diseases and to confirm the recent AHS findings for hypothyroidism and autoimmune thyroid disease (*12*).

*Chronic Liver Disease and Cirrhosis*

The significantly increased incidence of chronic liver disease and cirrhosis with radiation dose in the AHS is consistent with the LSS finding (*18*). In Japan, the predominant causes of chronic hepatitis and cirrhosis are HCV or HBV infection and excessive alcohol intake (*19*). The prevalence of anti-HBV surface antigen increased among the high-dose AHS subjects in 1975–1977 (*20*). Although the AHS study of anti-HCV antibody prevalence in 1993–1995 showed no dose response (overall prevalence was 9%), a possible radiation-associated increase in chronic liver diseases was found among anti-HCV antibody-positive individuals (*21*). The dose-related increase in the incidence of chronic liver disease and cirrhosis in our study might be partially explained by the persistent HBV infection or acceleration of active HCV infection among the heavily exposed survivors. On the other hand, an analysis of the risk factors for cirrhosis based on pathological review of about 1100 survivors who died between 1954–1997 did not show that A-bomb radiation increased the risk of liver cirrhosis (G. Sharp, personal communication). Additional studies including the measurement of HCV-RNA should help clarify the etiology of the dose-associated increase in chronic liver disease and cirrhosis. The dose response suggested in this report for fatty liver after 1986 should be confirmed in a more comprehensive future study that includes laboratory measurements such as of cholinesterase.

*Uterine Myoma*

Radiation risk for uterine myoma decreased with time since exposure. The higher radiation risk in the earlier follow-up period might be attributed to higher incidence in the older exposed female cohort, since uterine myoma is a hormone-dependent disease with peak incidence in the perimenopausal period.

To examine whether the significant radiation effects were due to bias from more frequent gynecological examinations of exposed women, especially early in the follow-up, a prevalence study of uterine nodules using ultrasonography was conducted during 1991–1993 in Hiroshima (*22*). That study demonstrated a significant dose–response relationship

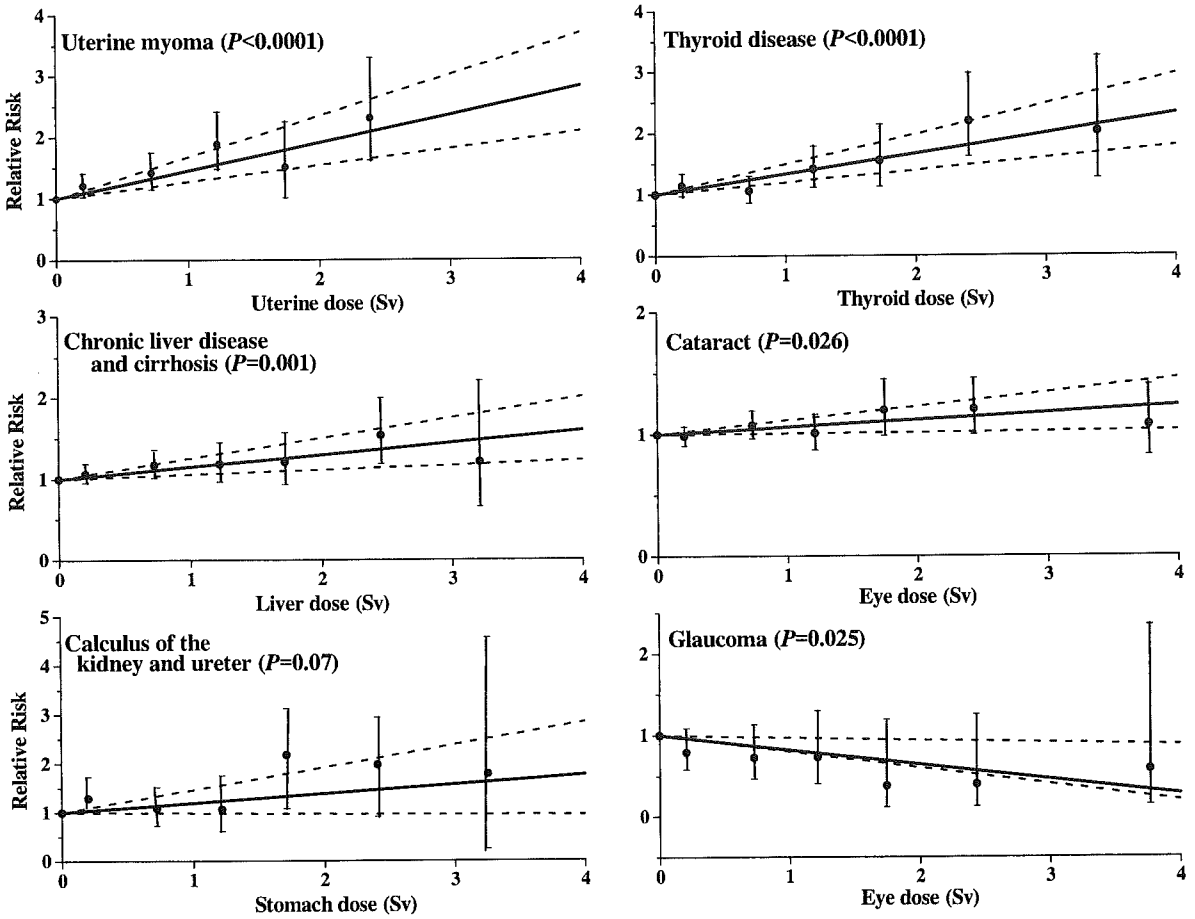


**FIG. 1.** Estimated linear dose response (solid line) for the incidence of six noncancer diseases with significant or suggestive radiation effects, 1958–1998. The 95% confidence bounds are shown as dotted lines. The estimated relative risks (●) and 95% confidence intervals are shown for each dose category.

(odds ratio estimate of 1.61 at 1 Sv), and the postulated bias was refuted.

The development of endometrial cancer or uterine sarcoma, but not benign nodules, many years after radiation therapy has been reported (*23, 24*). No significant risk for uterine carcinoma has been reported in the LSS (*25*). Since the pathogenesis of uterine myoma remains obscure, further studies are needed to elucidate the mechanism of the development of uterine myoma after A-bomb radiation exposure.

### *Cataracts*

A previous AHS ophthalmological study revealed an increased prevalence of posterior subcapsular opacities in the high-dose group, especially among younger survivors (*26*), but an early AHS ophthalmological study (*27*) and our previous AHS noncancer incidence study for 1958–1986 (*1*) revealed no additional radiation effects on cataracts. However, 12 additional years of follow-up has revealed that the overall incidence of cataract was significantly increased with radiation dose. The cataract cases under 60 years of age at incidence in the most recent follow-up period may have enhanced detection of radiation effects. In recent studies, much-delayed lenticular changes were detected after radiotherapy (*28*), exposure to cosmic radiation among astronauts (*29*), and exposure from radiation-contaminated buildings in Taiwan (*30*). Our findings of a more elevated radiation risk for lens opacities among the younger participants and an increased RR with long latency are compatible with these findings (*28–30*).

### *Glaucoma*

Glaucoma cases in this study were ascertained through self-reporting. Recent population surveys on glaucoma prevalence conducted in Singapore and the United States showed that prevalence rates were underestimated in the absence of detailed ophthalmological examination (*31, 32*). Since no other reports of a relationship between glaucoma and radiation were found in the literature, additional studies of cases ascertained through uniform application of tonometry and gonioscopy are warranted.

### *Hypertension*

The incidence of hypertension increased with radiation dose, particularly for those with over 2 Sv of exposure. Although no human studies directly link radiation exposure with hypertension (*33*), radiation-induced nephropathy (*34*)

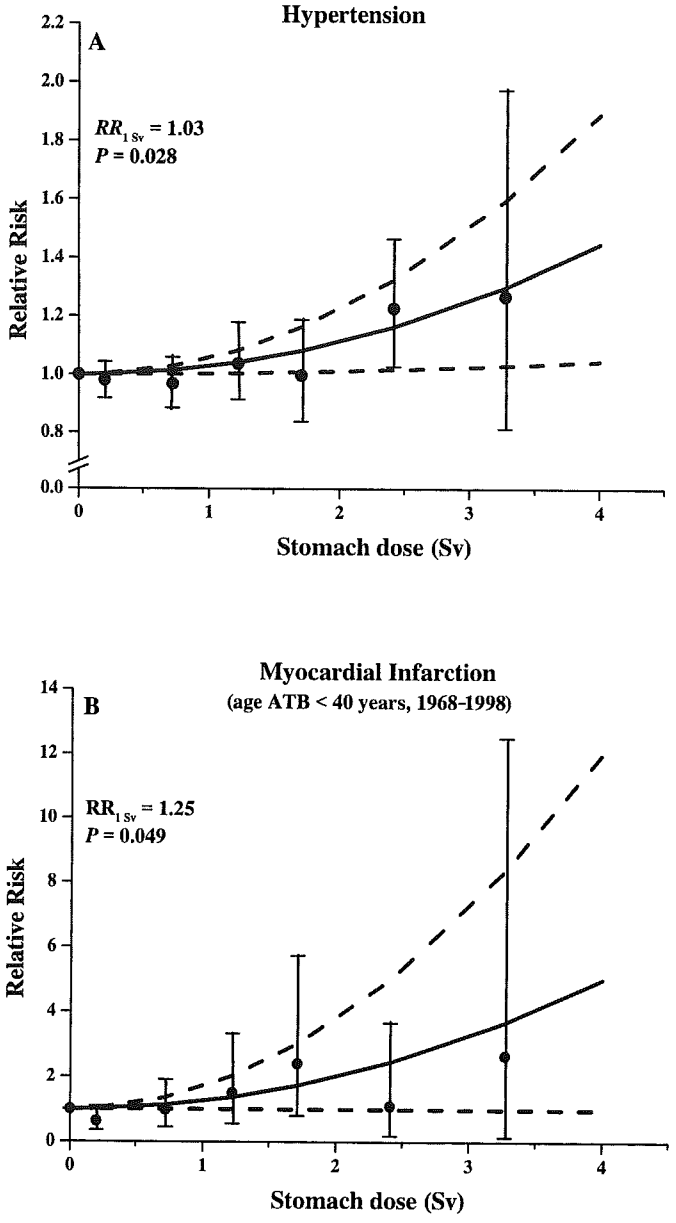


**FIG. 2.** Panel A: Estimated quadratic dose response for the incidence of essential hypertension, 1958–1998. Panel B: Estimated quadratic dose response for the incidence of myocardial infarction incident during 1968–1998 among AHS participants who were under 40 years ATB. The estimated relative risks (●) and the 95% confidence intervals are shown for each dose category.

and arterial hypertension (*35*) were reported, which may be relevant to current findings.

The AHS longitudinal analysis of blood pressure for 1958–1986 showed a small but statistically significant elevation in blood pressure levels in exposed survivors under 16 years of age (*36*). The trend, however, was reversed in the older cohort. Our present results are consistent with those of the longitudinal blood pressure trends for younger survivors. The discrepancy in the older cohort might be due in part to possible modification by medication and co-morbidity after the onset of hypertension.

*Cardiovascular Disease*

An increase in atherosclerosis and radiation-induced heart diseases has been reported in animal experiments and in humans after radiotherapy in the 1960s and 1970s and for occupational exposure before 1950 (*37–39*). Decreased risk of myocardial infarction by the use of modern techniques suggested that a relatively high dose of radiation may be involved in the induction of atherosclerotic lesions (*37, 40*).

An AHS longitudinal analysis of total serum cholesterol showed that the cholesterol levels of the irradiated subjects were significantly higher than those of the unirradiated subjects (*41*), and the same tendency was shown for the blood pressure trends among the younger cohort (*36*). These increases may partially explain the elevated incidence of myocardial infarction among the younger exposed subjects in this study.

One limitation of our study is that fatal MI and asymptomatic MI were not included. The ongoing AHS cardiovascular disease incidence study, which applies stringent criteria for case definition, including lethal heart attack cases, and measurements of atherosclerotic parameters such as carotid artery thickness, should provide additional information to improve our ability to elucidate the relationship between cardiovascular disease and radiation.

*Calculus of the Kidney and Ureter*

An increased risk with radiation dose was suggested for the first time for calculus of the kidney and ureter ($P$ = 0.07), with the effects significantly evident for men. Although the prevalence of hyperparathyroidism (*42*) and the level of calcium (*43*) were increased with radiation dose in the AHS, the small number of hyperoparathyroid cases cannot fully explain the findings for nephrolithiasis. Also, the observed sex difference in radiation effects cannot be explained by calcium metabolism. The development of calculus of the kidney and ureter in the AHS participants merits further investigation.

In summary, this updated analysis examining the relationship between exposure to A-bomb radiation and the incidence of noncancer diseases between 1958 and 1998 showed a statistically significant linear positive dose–response relationship for thyroid disease, chronic liver disease and cirrhosis, and uterine myoma, which is consistent with our previous results (*1*). Our new findings include a positive linear dose–response relationship for cataract, a negative linear dose–response relationship for glaucoma, a quadratic dose–response relationship for hypertension and for MI in the younger cohort, and a suggested positive dose–response relationship for calculus of the kidney and ureter. In this study, we examined smoking and drinking as effect modifiers and found their effects to be minimal. Despite some limitations, such as restricted case ascertainment and necessary exclusion of nonparticipants, the results of this study offer important clues to the late effects of A-bomb radiation on the development of certain noncancer diseases.

**TABLE 4**
**Estimated RR at 1 Sv ($RR_{1Sv}$) by Effect Modifiers for the Diseases with Evidence for Radiation Effects**

| Disease | Overall $RR_{1Sv}$ | City | | | Sex | | | Age ATB (years) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Hiroshima | Nagasaki | *P* | Male | Female | *P* | 10 | 25 | 40 | *P* |
| Thyroid disease | 1.33 | 1.40 | 1.25 | 0.31 | 1.26 | 1.35 | 0.61 | 1.64 | 1.15 | 1.03 | 0.0005 |
| Liver disease | 1.15 | 1.15 | 1.13 | 0.85 | 1.10 | 1.19 | 0.39 | 1.20 | 1.12 | 1.07 | 0.20 |
| Uterine myoma | 1.46 | 1.42 | 1.55 | 0.55 | — | — | — | 1.36 | 1.63 | 2.10 | 0.042 |
| Cataract | 1.06 | 1.05 | 1.10 | 0.47 | 1.11 | 1.04 | 0.24 | 1.12 | 1.07 | 1.04 | 0.29 |
| Glaucoma | 0.82 | 0.80 | 0.88 | 0.55 | 0.97 | 0.80 | 0.21 | 0.85 | 0.83 | 0.80 | 0.49 |
| Calculus of the kidney and ureter | 1.19 | 1.18 | 1.20 | 0.20[d] | 1.47 | 0.86 | 0.007[d] | 1.46 | 1.03 | 1.00 | 0.008[d] |
| Hypertension[b] | 1.03 | 1.02 | 1.04 | 0.68 | 1.03 | 1.02 | 0.65 | 1.03 | 1.03 | 1.02 | 0.91 |
| Myocardial infarction[c] | 1.25 | 1.27 | 1.02 | 0.62 | 1.22 | 1.30 | 0.84 | 1.27 | 1.24 | 1.22 | 0.92 |

| Disease | Overall $RR_{1Sv}$ | Age at examination | | | | | | Calendar time[a] | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 30 | 40 | 50 | 60 | 70 | *P* | I | II | III | IV | *P* |
| Thyroid disease | 1.33 | 1.88 | 1.53 | 1.32 | 1.19 | 1.12 | 0.002 | 1.50 | 1.23 | 1.24 | 1.57 | 0.36 |
| Liver disease | 1.15 | 1.26 | 1.21 | 1.16 | 1.13 | 1.10 | 0.25 | 1.05 | 1.15 | 1.24 | 1.10 | 0.60 |
| Uterine myoma | 1.46 | 1.57 | 1.50 | 1.44 | 1.38 | 1.34 | 0.72 | 2.00 | 1.71 | 1.10 | 1.32 | 0.015 |
| Cataract | 1.06 | 2.09 | 1.67 | 1.21 | 1.07 | 1.02 | 0.0005 | 1.17 | 1.04 | 1.00 | 1.08 | 0.086 |
| Glaucoma | 0.82 | 0.92 | 0.90 | 0.88 | 0.85 | 0.82 | 0.41 | 0.80 | 0.90 | 0.83 | 0.85 | 0.88 |
| Calculus of the kidney and ureter | 1.19 | 2.30 | 1.53 | 1.21 | 1.09 | 1.04 | 0.019 | 0.72 | 1.09 | 1.31 | 1.29 | 0.13[e] |
| Hypertension[b] | 1.03 | 1.04 | 1.04 | 1.03 | 1.02 | 1.02 | 0.59 | 1.02 | 1.03 | 1.04 | 1.00 | 0.71 |
| Myocardial infarction[c] | 1.25 | 2.56 | 1.83 | 1.44 | 1.24 | 1.12 | 0.37 | — | 1.36 | 1.31 | 1.12 | 0.78 |

*Note.* Background stratified by city, sex, age ATB, age ATE, and calendar time.
[a] Calendar time: July 1958–June 1968 (I), July 1968–June 1978 (II), July 1978–June 1988 (III), July 1988–June 1998 (IV).
[b] Based on the quadratic dose–response model.
[c] Based on the quadratic dose–response model, for incidence during 1968–1998 and age ATB under 40 years.
[d] $\chi^2$ $df = 2$ test.
[e] $\chi^2$ $df = 4$ test.

**APPENDIX**
**Twenty-one Noncancer Diseases and their International Classification of Disease (ICD) Codes over Time**

| Disease | ICD edition | | |
|---|---|---|---|
| | 7th | 8th | 9th |
| Hypertension | 444, 445 | 400, 401 | 401 |
| Hypertensive heart disease | 440–443 | 402, 404 | 402, 404 |
| Ischemic heart disease | 420 | 410–414 | 410–414 |
| Myocardial infarction | — | 410 | 410 |
| Occlusion, stenosis | 332 | 433, 434 | 433, 434 |
| Aortic aneurysm | 451, 452 | 441, 442 | 441, 442 |
| Stroke I | 330–332 | 430, 431, 433, 434 | 430, 431, 433, 434 |
| Stroke II | 330–332, 334 | 430, 431, 433, 434, 436 | 430, 431, 433, 434, 436 |
| Thyroid diseases | 250–254 | 240–245 | 226, 240–245 |
| Cataract | 385 | 374 | 366 |
| Gastric ulcer | 540 | 531 | 531 |
| Duodenal ulcer | 541 | 532 | 532 |
| Chronic liver disease and cirrhosis | 581, 583 | 571, 573 | 571 |
| Cholelithiasis | 584 | 574 | 574 |
| Calculus of kidney and ureter | 602 | 592 | 592 |
| Uterine myoma | 214 | 218 | 218 |
| Cervical polyp | 215 | 219 | 216, 622 |
| Hyperplasia of prostate | 610 | 600 | 600 |
| Dementia | 304, 305 | 290 | 290 |
| Parkinson's disease | 350 | 342 | 332 |
| Glaucoma | 387 | 375 | 365 |

*Note.* Myocardial infarction was identified after June 1964.

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# 骨粗鬆症・骨折の疫学

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骨粗鬆症は加齢とともに増加し，有病率は70歳後半の女性で約50%，男性で約20%となる。わが国の骨粗鬆症人口は，1,000万人以上と推計されている。脊椎骨折は頻度が高く，日本人50歳女性のライフタイムリスクは37%で，比較的早い老年期から発生率は高くなる。大腿骨頸部骨折は70歳以降急激に増加し，50歳女性の大腿骨頸部骨折のライフタイムリスクは約14%で，70歳女性の10年間の発生確率は3%，80歳で約10%である。

## *Epidemiology of osteoporosis and fracture*

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Prevalence of osteoporosis is increasing with age. And it reached about 50% for women in their late seventies and about 20% for men of the same age. In Japan, osteoporosis population is estimated at over ten million people. Spine fracture is very common in the elderly, with a lifetime risk of 37% for Japanese women aged 50. Incidence of spine fracture increased at relatively early stages of old age. Hip fracture rapidly increases among those at ages over 70, with a lifetime risk of about 14% for women aged 50 and 10-year fracture probability of 3% and 10% for women aged 70 and those aged 80, respectively.

## はじめに

高齢社会の到来とともに，わが国では寝たきりや高齢者の介護が問題となっている。国民生活基礎調査によると，介護が必要になった原因として，女性では，「脳血管障害」，「高齢による衰弱」に続いて，「骨折・転倒」が第3位であり，男性においても5位の原因となっている。大腿骨頸部骨折後だけでなく脊椎骨折後においても，死亡率が高まり，歩行困難など日常生活動作(ADL)が低下する。

骨粗鬆症およびそれに伴う骨折の予防は，高齢社会を迎えたわが国において重要な課題である。

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本稿では，骨粗鬆症・骨折の頻度など疫学的な面から，「国民の健康問題としての骨粗鬆症」について言及したい。

## 1．骨粗鬆症の有病率

骨粗鬆症の有病率は，どの診断基準を使うか，どの部位の骨密度で判定するかによって違ってくる。日本骨代謝学会の基準，すなわち成人女性骨密度（腰椎）平均値から70%未満のものを使って，日本人の骨粗鬆症の有病率を求めると，40歳代においては，男女とも数パーセントであるが，加齢とともに増加し，70歳代後半では，男性の約20%，女性の約50%となる（図1）[1]。

年齢別に骨粗鬆症人口をみると，最も多いのは男女とも70～74歳である（図2）。これからわが国の骨粗鬆症人口を推計すると，40歳以上の女性で約780万人，男性では約230万人，男女合わせると1,000万人以上となる。

## 2．骨粗鬆症性骨折の発生率

### （1）年齢と発生率

骨粗鬆症性骨折の中で最も発生率が高いのは，脊椎骨折である。脊椎骨折発生率は，70歳代の女性では大腿骨頸部骨折の5倍以上である（図3）[2][3]。

脊椎骨折，大腿骨頸部骨折の発生率は，加齢とともに指数関数的に増加するが，脊椎骨折は比較的早い老年期から高く，大腿骨頸部骨折は70歳以降に急激に増加する。脊椎骨折，大腿骨頸部骨折ともに，女性の発生率は，男性に比べて約2倍である。橈骨下端骨折は，女性では，40～50歳代にかけて発生率が増加して，その後はプラトーになる。

### （2）年次推移

日本人の脊椎骨折発生率は，近年低下している[4]が，大腿骨頸部骨折発生率，橈骨下端骨折は増加傾向にある[3]。脊椎骨折発生率は，男女ともに出生年が10年若いと，発生率は約半分に低下する[4]。脊椎骨折は，大きな外力が加わらなくても発生し，低骨密度との関連が強い。第二次世界大戦後，日本人の食生活は急激に欧米化し，体格は向上し，初経年齢は早く，閉経年齢は遅くなった。それによって，近年生まれの人ほど，骨密度は増加し，その結果，脊椎骨折発生率は低下したと考えられる。一方，大腿骨頸部骨折は，転倒で発生することがほとんどで，転倒しやすくなる状態，転倒時の状況などの骨密度以外の要因の影響も強く受ける。近年の運動量の低下，和式生活様式の変化などによって，大腿骨頸部骨折発生率は増加していると考えられる。

### （3）欧米との比較

脊椎骨折の発生率を，広島[2]とヨーロッパ（European Prospective Osteoporosis Study（EPOS））[5]を比較すると，広島が高い（図4）。広島，EPOSは，新規骨折発生の診断基準として，追跡前後の椎体高を比較して，「20%以上低下」を使っているが，より小さな椎体高の変化を骨折としている「カットオフ値15%以上」を使っているRotterdam研究[6]の発生率と比較しても，広島の発生率は高い。

日本人の大腿骨頸部骨折，橈骨末端，上腕骨頸部の発生率は，スウェーデン，米国，イギリスに比べると低い（図5）。しかし，大腿骨頸部骨折については，ヨーロッパの中でもフランス，イタリアとはほぼ同じ発生率で，香港ともほぼ同じであった[3]。

### （4）ライフタイムリスク

ある年齢の人々が，生涯に骨折を起こす確率を「ライフタイムリスク」という。ライフタイムリスクは，平均余命と発生率から計算されるため，平均余命が長く，発生率が高い国のライフタイムリスクは高くなる。日本人女性の50歳における脊椎骨折のライフタイムリスクは37%，大腿骨頸部骨折のライフタイムリスクは13.6%と推計され

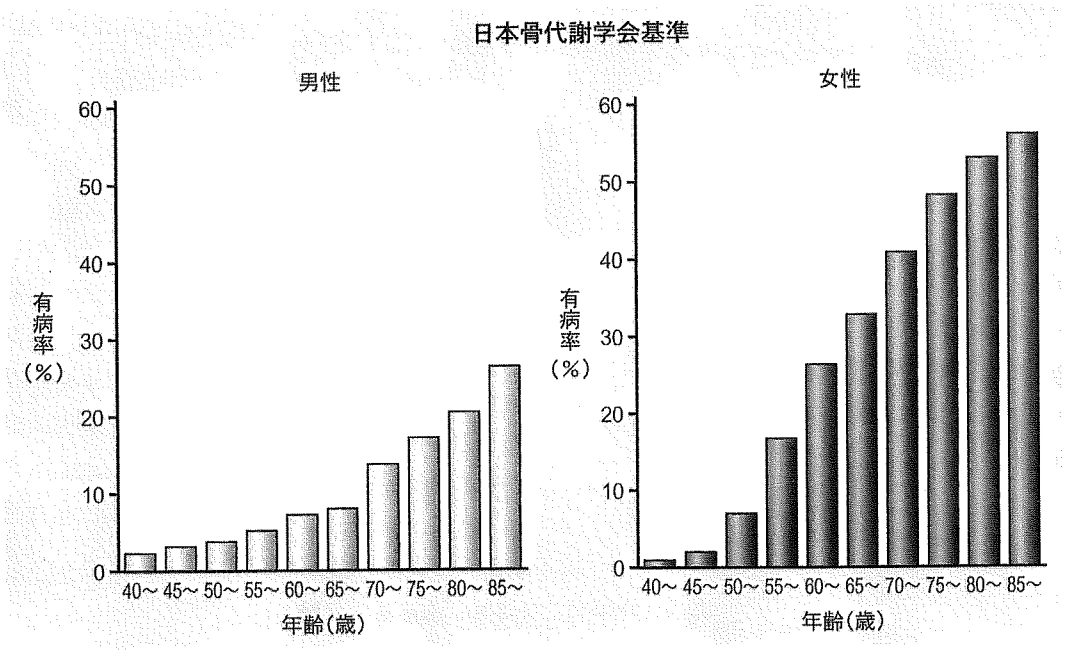


図1　骨粗鬆症の有病率

骨粗鬆症の有病率は加齢とともに上昇し，女性の 70 歳後半では約 50%となる。

（文献 1 より改変）

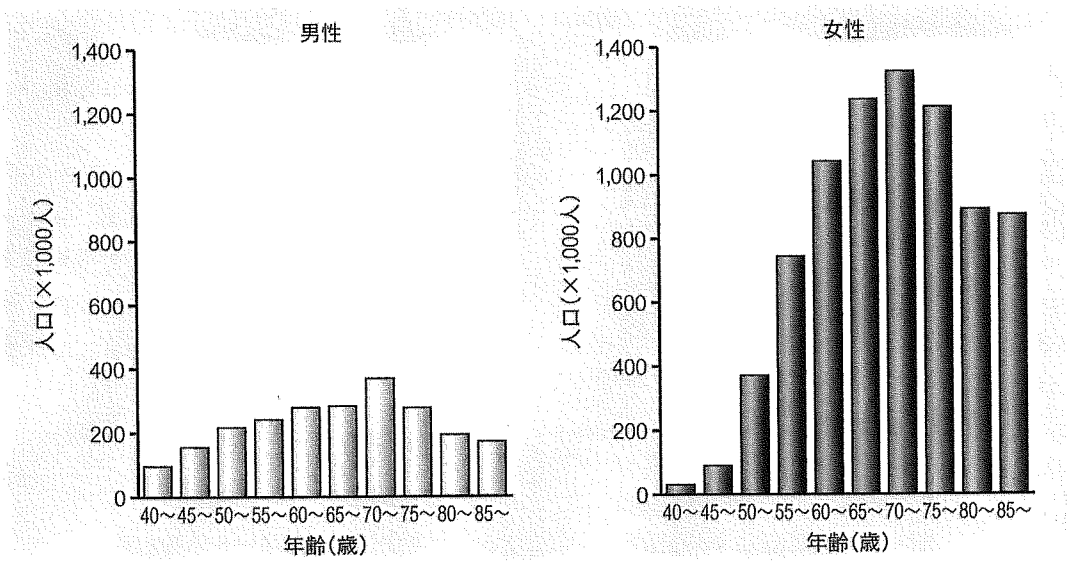


図2　骨粗鬆症人口の推定

40 歳以上の骨粗鬆症人口は 1,000 万人以上で，骨粗鬆症人口が最も多いのは，男女とも 70 歳前半である。

（文献 1 より改変）

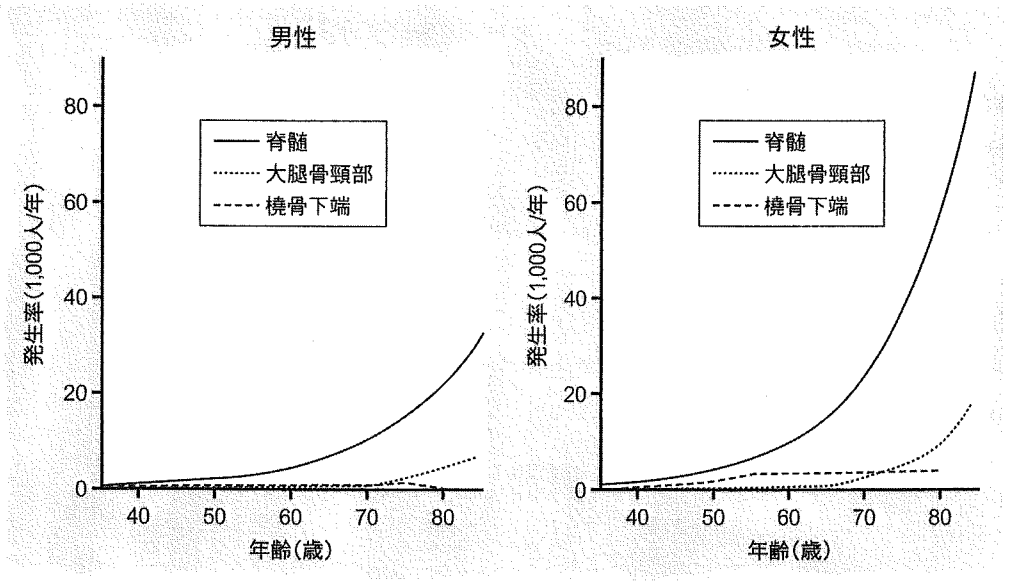


図3　骨粗鬆症性骨折の発生率の比較

骨粗鬆症性骨折の中で最も発生率が高いのは脊椎骨折で，比較的若い老年期から増加する。

（文献2，3より改変）

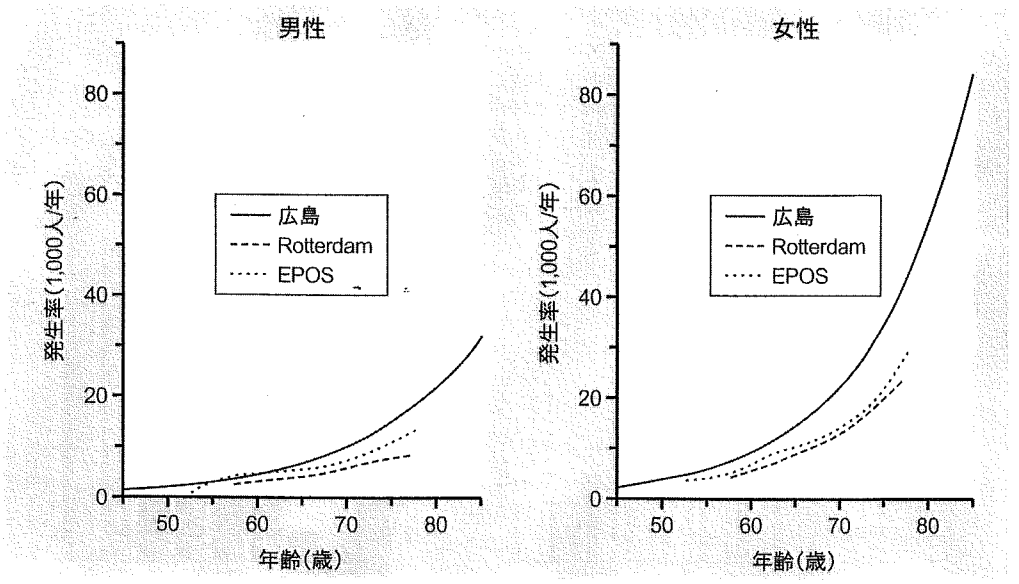


図4　脊椎骨折発生率の比較～広島コホートとヨーロッパコホートとの比較～

日本人の脊椎骨折発生率は，ヨーロッパコホートに比べて約2倍である。

EPOS：European Prospective Osteoporosis Study

（文献2，5，6より改変）

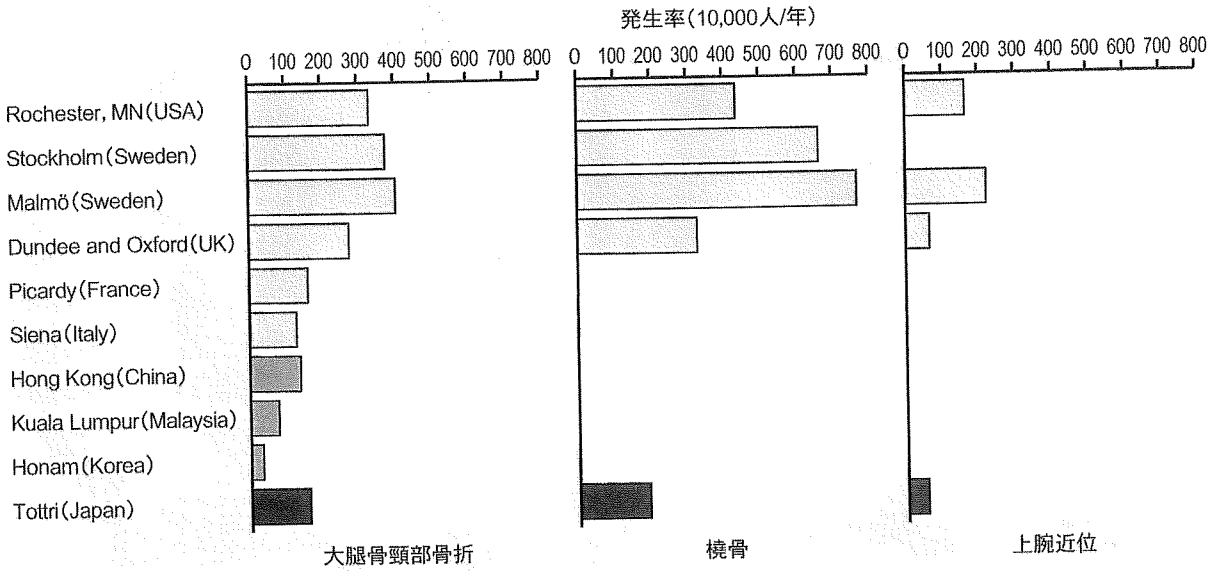


図5　骨折発生率の国際比較（女性）

大腿骨頸部、橈骨末端，上腕骨頸部骨折の発生率は国間で差があり，日本人の大腿骨頸部骨折発生率は北欧に比べて低く，香港とほぼ同じである。

（文献3より改変）

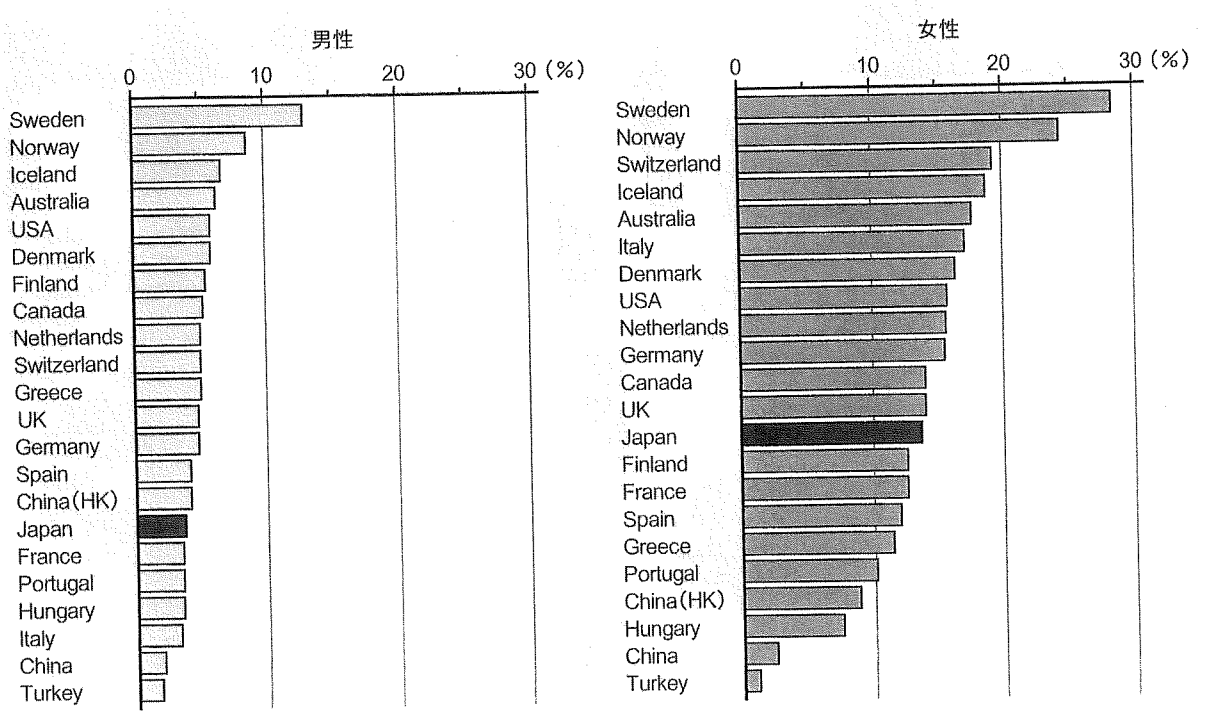


図6　国別の50歳における大腿骨頸部骨折のライフタイムリスク

大腿骨頸部骨折のライフタイムリスクが高い国は北欧で，日本人女性のライフタイムリスクは約14%である。

（文献7より改変）

表1　日本人における大腿骨頸部骨折の10年間の発生確率

大腿骨頸部骨折の10年間の発生確率は，50歳，60歳では男女あまり差は無いが，70歳以降の女性は男性の約3倍となり，80歳女性では9.6%である。

| 年齢（歳） | 10年間の発生確率　（%） | |
|---|---|---|
| | 男 | 女 |
| 50 | 0.2 | 0.2 |
| 60 | 0.5 | 0.8 |
| 70 | 1.3 | 3.2 |
| 80 | 3.3 | 9.6 |

（文献7より改変）

ている。大腿骨頸部骨折のライフタイムリスクが，最も高い国はスウェーデン（28.5%）で，次いでノルウェー，最も低い国はトルコ（1%）であった（**図6**）[7]。また，10年間に大腿骨頸部骨折発生する確率は，日本人70歳女性では3.2%，80歳では9.6%と推計されている。（**表1**）[7]。

## おわりに

骨粗鬆症の有病率および骨折のライフタイムリスクは高く，閉経後あるいは老年期に誰でも，骨折する可能性を持っている。このように頻度の高い疾患については，国民の健康問題としてとらえ，骨粗鬆症，骨折の予防対策に取り組むことが必要である。

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ORIGINAL ARTICLE

# Smoking and fracture risk: a meta-analysis

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**Abstract** Smoking is widely considered a risk factor for future fracture. The aim of this study was to quantify this risk on an international basis and to explore the relationship of this risk with age, sex and bone mineral density (BMD). We studied 59,232 men and women (74% female) from ten prospective cohorts comprising EVOS/EPOS, DOES, CaMos, Rochester, Sheffield, Rotterdam, Kuopio, Hiroshima and two cohorts from Gothenburg. Cohorts were followed for a total of 250,000 person-years. The effect of current or past smoking, on the risk of any fracture, any osteoporotic fracture and hip fracture alone was examined using a Poisson model for each sex from each cohort. Covariates examined were age, sex and BMD. The results of the different studies were merged using the weighted $\beta$-coefficients. Current smoking was associated with a significantly increased risk of any fracture compared to non-smokers (RR = 1.25; 95% Confidence Interval (CI) = 1.15–1.36). Risk ratio (RR) was adjusted marginally downward when account was taken of BMD, but it remained significantly increased (RR = 1.13). For an osteoporotic fracture, the risk was marginally higher (RR = 1.29; 95% CI = 1.13–1.28). The highest risk was observed for hip fracture (RR = 1.84; 95% CI = 1.52–2.22), but this was also somewhat lower after adjustment for BMD (RR = 1.60; 95% CI = 1.27–2.02). Risk ratios were significantly higher in men than in women for all fractures and for osteoporotic fractures, but not for hip fracture. Low BMD accounted for only 23% of the smoking-related risk of hip fracture. Adjustment for body mass index had a small downward effect on risk for all fracture outcomes. For osteoporotic fracture, the risk ratio increased with age, but decreased with age for hip fracture. A smoking history was associated with a sig-

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