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 = 2.2×10^5 PY; male = 8.1×10^4 PY; female = 1.5×10^5 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

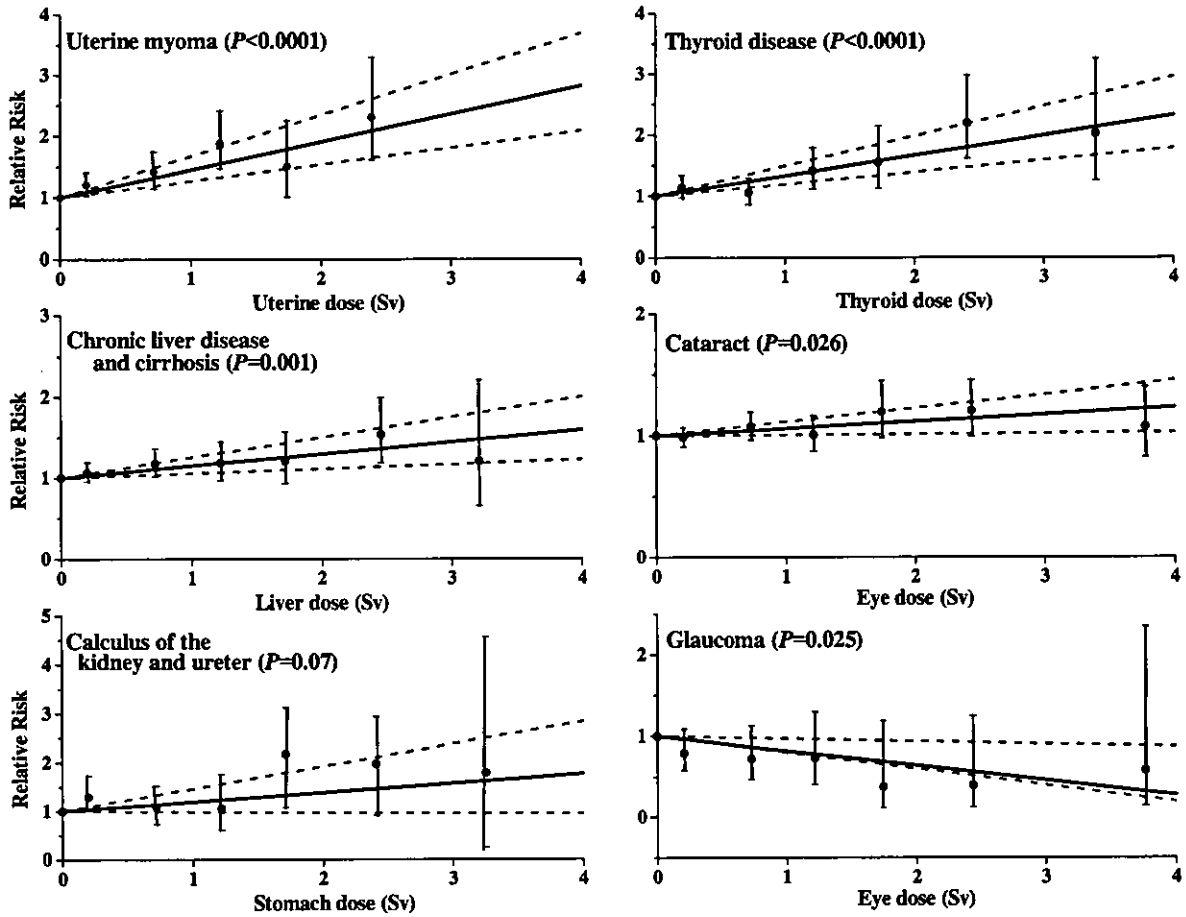

FIG. 1. Estimated linear dose response (solid line) for the incidence of six noncancer diseases with significant or suggestive radiation effects, 1958–1998. The 95% confidence bounds are shown as dotted lines. The estimated relative risks (•) and 95% confidence intervals are shown for each dose category.

(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*)

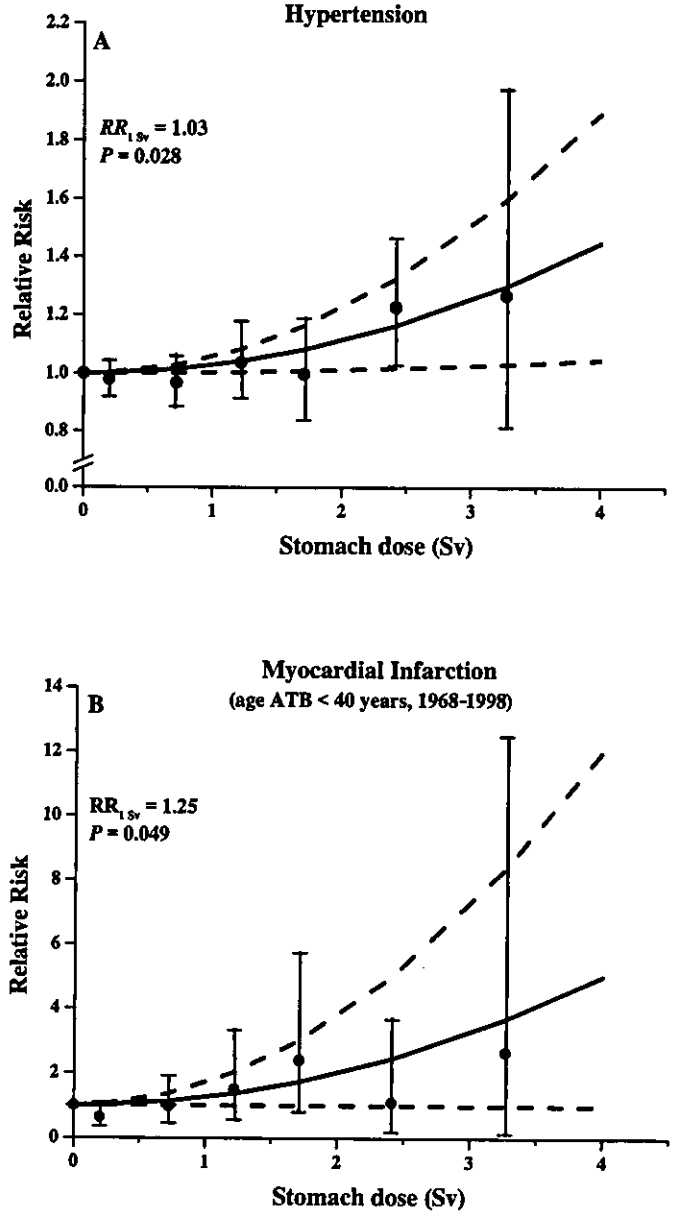

FIG. 2. Panel A: Estimated quadratic dose response for the incidence of essential hypertension, 1958–1998. Panel B: Estimated quadratic dose response for the incidence of myocardial infarction incident during 1968–1998 among AHS participants who were under 40 years ATB. The estimated relative risks (•) 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] χ^2 $df = 2$ test.
[e] χ^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

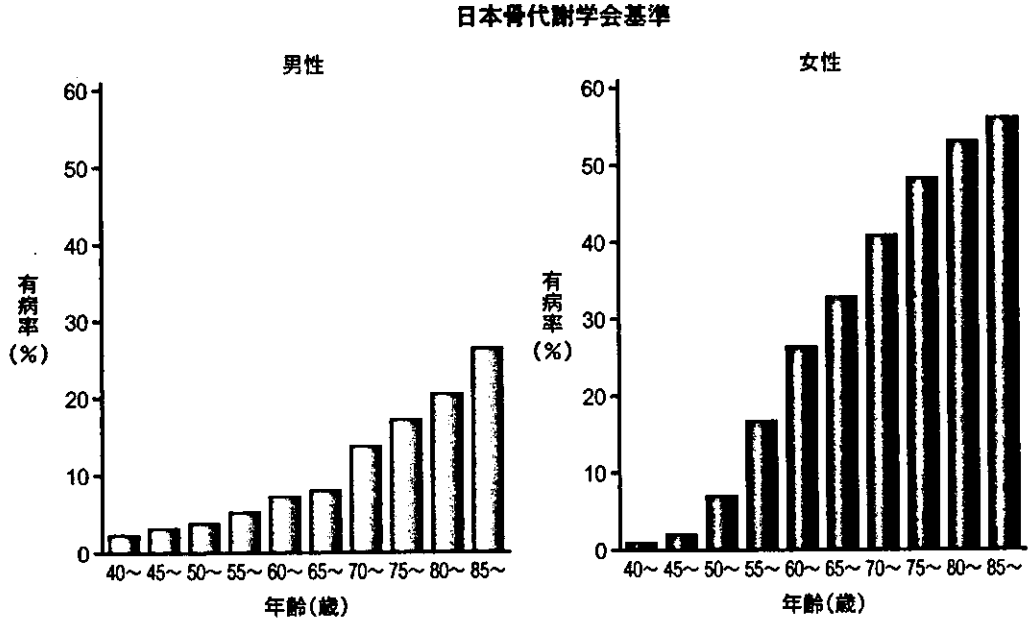

図1　骨粗鬆症の有病率

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)

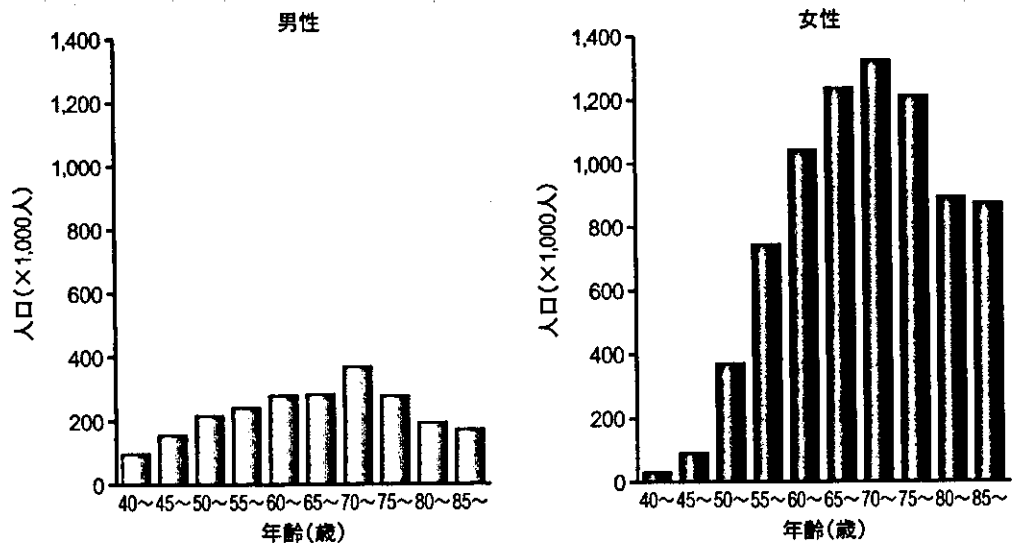

図2　骨粗鬆症人口の推定

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)

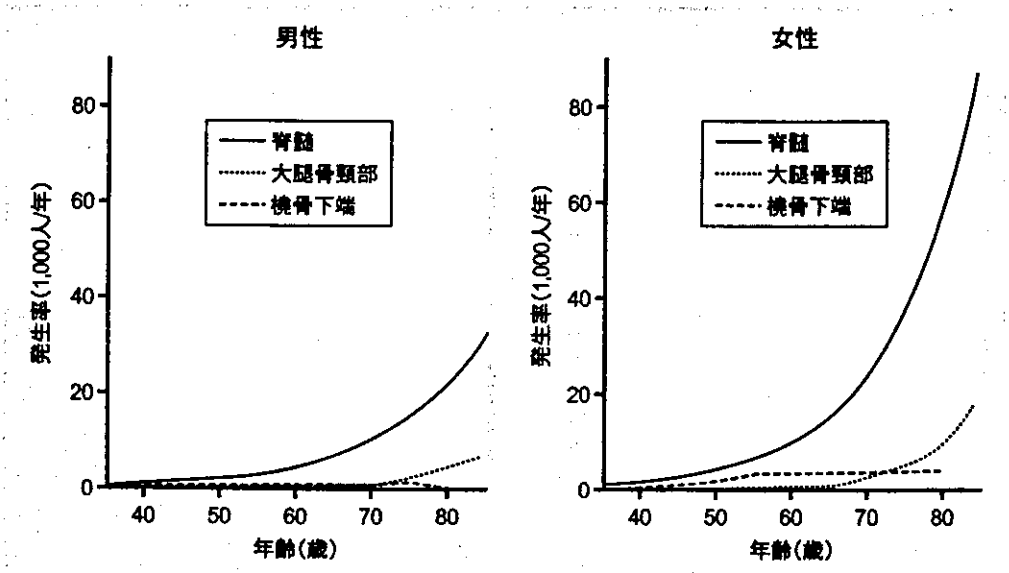

図3　骨粗鬆症性骨折の発生率の比較

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）

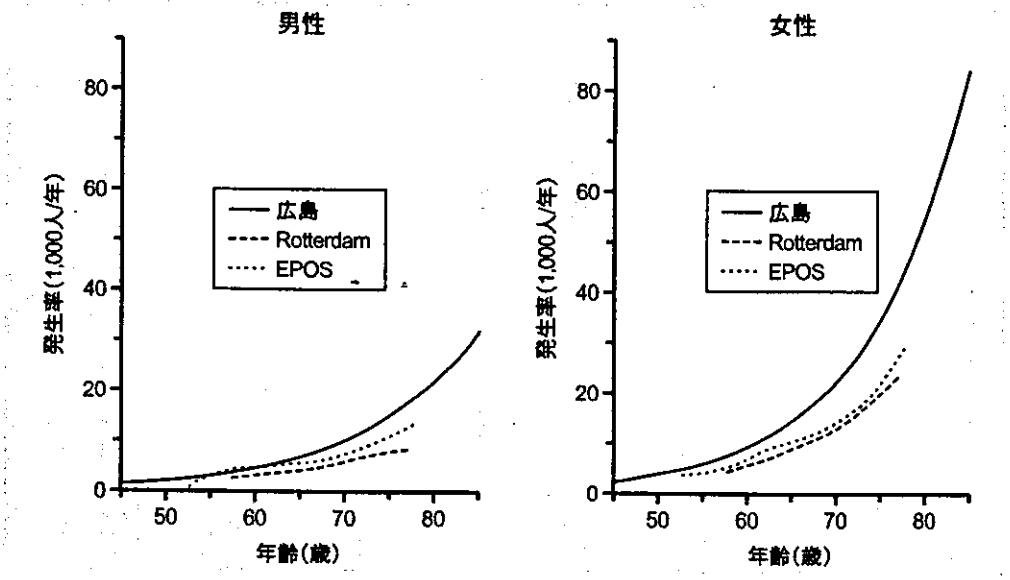

図4　脊椎骨折発生率の比較～広島コホートとヨーロッパコホートとの比較～

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）

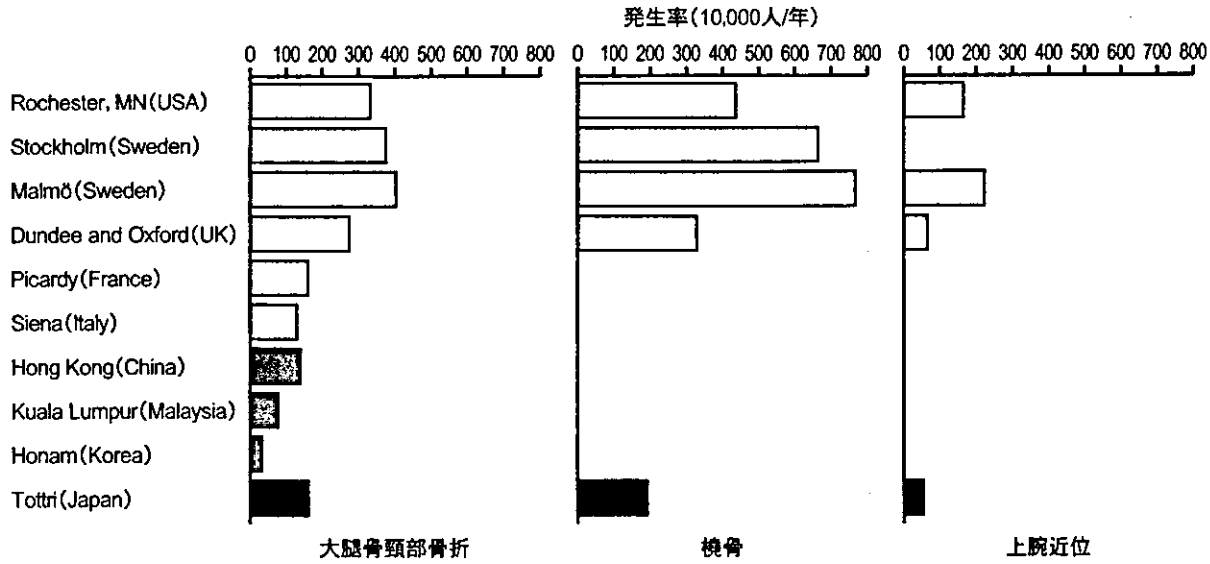

図5　骨折発生率の国際比較（女性）

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）

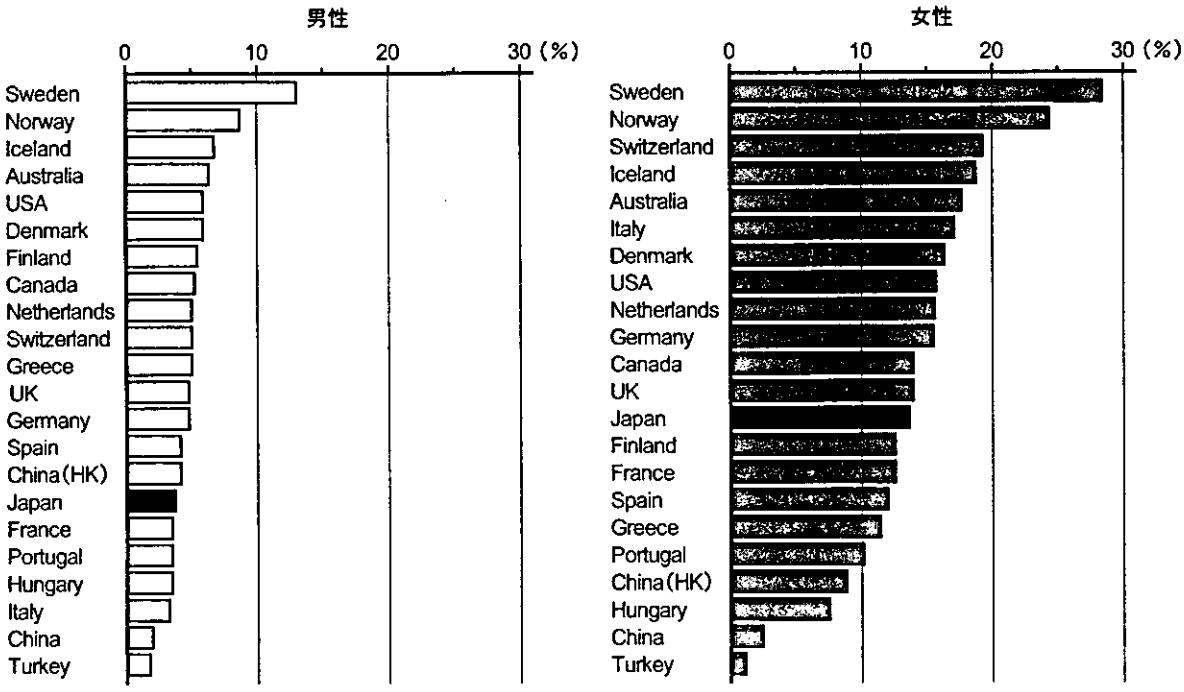

図6　国別の50歳における大腿骨頸部骨折のライフタイムリスク

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 β-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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nificantly increased risk of fracture compared with individuals with no smoking history, but the risk ratios were lower than for current smoking. We conclude that a history of smoking results in fracture risk that is substantially greater than that explained by measurement of BMD. Its validation on an international basis permits the use of this risk factor in case finding strategies.

Keywords Body mass index · Hip fracture · Meta-analysis · Osteoporotic fracture · Smoking

Introduction

It is well established that smoking is associated with a reduction in bone mineral density (BMD) in postmenopausal women and men [1]. A meta-analysis has suggested that the risk of hip fracture may also be markedly increased [2]. In current smokers, the risk of hip fracture compared with non-smokers was similar in women up to the age of 50 years. However, it increased thereafter, to a risk ratio (RR) of 1.17 at 60 years, 1.41 at 70 years and 1.71 at 80 years. In 90-year-old women the risk ratio was 2.08 [2]. In population-based samples, the risk of other osteoporotic fractures also appears to increase [3], but this is not an invariant finding [4]. The risk of forearm fractures does not appear to increase among smokers [3, 5 ,6].

Increased fracture risk may in part be due to the fact that patients who smoke have low BMD [1]. Studies adjusted for BMD suggest that the relative risk is only modestly adjusted downward [7]. In the meta-analysis of Law and Hackshaw [2], although the difference in bone density between smokers and non-smokers was not apparent at age 50, it became noticeable with increasing age, so that at age 80 bone mineral density at the hip was 0.45 SD lower in smokers, as compared with non-smokers. From the relationship between bone mineral density in the hip and hip-fracture risk, the risk ratio in smokers was estimated at 1.56, compared with a direct estimate of 1.71 for hip fractures. This led the authors to suppose that the majority of any risk was attributable to decreased bone density.

The association between smoking and subsequent fracture risk has led to the inclusion of current smoking as a risk factor in assessment guidelines in the United States and Canada [8, 9], if not in Europe [11, 12, 13]. Since smoking is considered a risk factor, partly independent of BMD, intervention is recommended in smokers with a *T*-score for BMD of −1.5, whereas in non-smokers the intervention threshold is set at −2.0 SD. Attention has focused recently on assessing fracture probability by using multiple risk factors, rather than BMD alone, to provide intervention thresholds [8, 14, 15]. This demands knowledge of the interrelationships between these risk factors. The aim of our study was to quantify, in an international setting, the risk associated with smoking for future fractures and to explore the dependence of this risk on age, sex, body mass index (BMI) and BMD.

Materials and methods

We studied 59,232 men and women, of whom 18% had a history of current smoking, taken from ten prospectively studied cohorts. Brief details of these cohorts appear below and are summarized in Table 1.

CaMos

The Canadian Multicentre Osteoporosis Study (CaMos) is a current, prospective age-stratified cohort. The study documents the incidence of fractures and risk factors in a random sample of 9,424 men and women aged 25 years or older, selected by telephone listings. The sampling frame is from nine study centers in seven provinces [16]. Individuals were characterized by interview. BMD was measured by DXA (Dual X-ray absorptiometry) at the hip, using the Hologic QDR in seven centers and the Lunar DPX Alpha in two centers.

Table 1 Details of cohorts studied

Cohort	Sample size	% Women	Person-years	Mean age (years)	Smoking history (%)		Any kind of fracture	Osteoporotic fracture	Hip fracture
					Current	Ever			
CaMos	9,401	69	26,656	62.1	-	54	586	316	42
DOES	2,163	61	16,333	70.7	8	41	532	418	107
EVOS/EPOS	13,841	52	41,429	63.8	20	52	731	731	50
Gothenburg I	2,320	61	16,255	78.7	15	41	424	424	332
Gothenburg II	7,012	100	29,335	58.9	25	49	433	438	29
Hiroshima	1,937	69	7,563	64.8	20	34	134	64	21
Kuopio	11,798	100	56,602	52.3	11	-	1,053	-	-
Rochester	998	65	6,212	56.8	-	47	289	244	42
Rotterdam	7,590	60	42,613	70.1	23	63	967	746	271
Sheffield	2,172	100	6,900	80.0	7	46	290	241	63
Totals	59,232	74	249,898	62.8	18	52	5,444	3,495	957

DOES

The Dubbo Osteoporosis Epidemiology Study (DOES) is a population-based study with multiple assessments of skeletal status in men and women from Dubbo, Australia, and at least 60 years old [17, 18]. Study participation was 56% of the population. Baseline measurements included BMD at the femoral neck, assessed using DXA (GE-Lunar, DPX and Prodigy). Fractures are identified through radiologists' reports from the two centers servicing the region.

EVOS/EPOS

The European Vertebral Osteoporosis Study (EVOS) comprised age- and sex-stratified random samples from 36 centers in 19 European countries [19]. Equal numbers of men and women were drawn in each center within six sequential 5-year age bands (from 50 to 79 years). A baseline radiograph for vertebral-fracture prevalence was undertaken in 15,570 men and women. BMD was measured in 3,461 men and women from 13 centers, by DXA at the femoral neck using pencil-beam machines cross-calibrated with the European spine phantom. The sample provided the framework for the European Prospective Osteoporosis study (EPOS), in which repeated assessment was undertaken in 29 of the centers [20, 21].

Gothenburg I

This study comprised four birth cohorts of 2,375 randomly sampled men and women aged at least 70, followed for up to 20 years in Gothenburg, [22, 23] after a baseline BMD measurement. Participants were drawn randomly from the Gothenburg population register by date of birth, to provide cohorts aged 70, 76, 79 and 85 years at the time of investigation. Bone mineral density was measured at the right heel using dual photon absorptiometry.

Gothenburg II

The Gothenburg study comprised a randomly drawn population cohort of approximately 7,000 women aged 21–89, followed for up to 7.9 years (mean = 4.2 years) [24]. Seventy percent of those invited participated in the study, which examined risk factors for osteoporosis through a standardized questionnaire. BMD was assessed at baseline at the distal forearm, using the Osteometer DTX 200.

Hiroshima

The Adult Health Study in Hiroshima (AHS) was established to document late health effects of radiation exposure among atomic-bomb survivors in Hiroshima and Nagasaki. The original AHS cohort consisted of about 15,000 atomic-bomb survivors and 5,000 controls selected from residents in Hiroshima and Nagasaki, using the 1950 national census supplementary schedules and the Atomic Bomb Survivors Survey. AHS subjects have been followed through biennial medical examinations since 1958, with a participation rate of approximately 80%. BMD at the lumbar spine and proximal femur has been measured at each biennial health examination using DXA (Hologic QDR-2000) since December 1993. At each examination, trained nurses interviewed subjects about fractures and measured height and weight [25, 26].

Kuopio

The Kuopio Osteoporosis Risk Factor and Prevention (OSTPRE) study in Finland was based on a postal enquiry sent to all of the 14,220 women aged 47–56 residing in Kuopio province in 1989. Of these, 13,100 responded, 1,214 of whom were excluded due to incomplete information. This left a study population of 11,886 women. A random stratified sample of 3,222 underwent bone mineral densitometry at the femoral neck, with DXA using the Lunar DPX [27].

Rochester

The Rochester cohort was recruited from two random population samples stratified by decade of age. One sample included women who were followed for up to 20 years [28], and the other was composed of women and men followed for 8 years [29]. BMD of the right femoral neck was measured—by dual photon absorptiometry for the first cohort (cross-calibrated to DXA), and by DXA (Hologic QDR 2000) for the second group. Fractures were ascertained by periodic interview combined with review of the inpatient and outpatient medical records of all local care providers.

Rotterdam

The Rotterdam study, begun in 1990, was a prospective cohort study that aimed to examine and follow up on all residents aged 55 years and older living in Ommoord, a district of Rotterdam [30]. By 1993, 7,983 residents had been included (response rate 78%). Bone mineral density was assessed at the femoral neck by DXA, using a Lunar DPX-L. Fracture follow-up was done using an automated link with general practitioner computer systems and hospital admission data [31]. Fracture data were collected and validated by two independent research physicians. For this analysis, validated fracture follow-up was available for 7,590 participants (3,012 men), with an average follow-up time of 6 years.

Sheffield

The Sheffield cohort comprised women aged 75 years or older, selected randomly from the population of Sheffield, UK, and surrounding districts, between 1993 and 1999. Approximately 35,000 women, identified from general practitioner listings, were contacted by letter and invited for assessment of their skeletal status. Of the 5,873 women agreeing to attend the screening visit, 281 were excluded. The remainder were randomly allocated after they gave informed consent to treatment with the bisphosphonate clodronate, or to an identical placebo. This study is still in progress. The material used for the present paper included 2,148 women allocated to treatment with placebo [32]. All women had baseline assessment of BMD at the femoral neck, using the Hologic 4500. Outcomes were assessed by home visits at 6-month intervals.

Baseline and outcome variables

A history of current or past smoking was obtained by self-report. For the EVOS/EPOS, Hiroshima and Gothenburg I cohorts, this was recorded as past or current use of tobacco. For the Gothenburg II cohort, the same data were collected, but use for 6 months qualified as past or current use. For Rotterdam, Sheffield and DOES, tobacco use was recorded as previous, current or never. Data on current smoking was not available for two cohorts (CaMos and Rochester). Height and weight were measured using standard techniques in all cohorts. BMI was calculated as weight in kg divided by height squared in m. Bone mineral density was assessed by multiple techniques as described above. For the purposes of this analysis, we utilized BMD assessed at the femoral neck by DXA, with the exception of the Gothenburg cohorts, for which BMD was assessed by DPA at the heel and DXA at the distal forearm.

Fractures were ascertained from self-reports (Sheffield, Kuopio, EVOS/EPOS, Hiroshima) and/or verified from hospital or central databases (Gothenburg, CaMos, DOES, Sheffield, EVOS/EPOS, Rochester, Rotterdam). The EPOS study also included sequential systematic radiography to define incident vertebral deformities, but the data were not used in this analysis. Our analysis used information on any kind of clinical fracture and on clinical fractures considered to be osteoporotic. In addition, hip fracture was considered separately. An osteoporotic fracture was one that the investigator considered to be due to osteoporosis, except as indicated below. For the EVOS/EPOS study, osteoporotic fractures comprised hip, forearm, humeral or spine fractures. For the CaMos study, they comprised fractures of the spine, pelvis, ribs, distal forearm, forearm and hip. In the other cohorts (Sheffield, Rotterdam, Rochester, Gothenburg I and II, Hiroshima) fractures at sites considered characteristic for osteoporosis were extracted [33]. Details about the number of participants, gender and fractures are provided in Table 1.

Statistical methods

The risk of fracture was estimated by Poisson regression, applied separately to each cohort and sex [32]. Covariates included time since start of follow-up, current age, history of smoking, and BMD. We also excluded BMD from the model. The beta coefficient for each sex in each cohort is age-dependent, $\text{beta}_k + \text{beta}_{k+1} \times \text{age}$. The estimated value of the βcoefficients and their variance was determined for each age within the range of 50 to 85 years. Results of each cohort and both sexes were weighted according to the variance and merged to determine the weighted mean and standard deviations. The risk ratio of those who currently smoked or ever smoked versus those without a smoking history was equal to weighted e^{mean}. In further models, we examined the effects including BMI with and without BMD. There was little heterogeneity between cohorts in the relationship between hip-fracture risk and smoking ($I^2 = 12\%$; 95% CI (confidence interval) = 0–53%), and a fixed-effect model was used [34].

The component of the risk ratio explained by BMD was computed from a meta-analysis of BMD and fracture risk [35]. The risk of any fracture was assumed to increase 1.6-fold for each SD decrease in BMD. For hip fracture, the gradient of risk was assumed to be 2.6 per SD. The proportion of risk attributed to a low BMD was computed as

$$\frac{[\log RRa/\log GR] - [\log RRb/\log GR]}{[\log RRa/\log GR]}$$

Where RR_a is the unadjusted risk ratio, RR_b is the risk ratio adjusted for BMD, and GR is the gradient of risk.

Results

Of 59,232 men and women studied, 867 men and 4,577 women were identified as having a subsequent fracture

Table 2 Prevalence of smoking history in men and women by age

Age (years)	Probability of smoking (%)		
	Men	Women	Combined
50	41.3	26.8	32.9
55	37.2	22.3	28.4
60	33.3	18.3	24.3
65	29.6	15.0	20.6
70	26.1	12.1	17.4
75	22.9	9.7	14.6
80	20.0	7.8	12.1
85	17.4	6.2	10.0

(any kind), of which 677 men and 2,817 women were characterized as osteoporotic. Of these, 207 men and 750 women sustained a hip fracture. The total follow-up in person years was 61,563 in men and 188,334 in women. BMD measurements were available in 36,550 individuals (64%) and BMI in 96%. The prevalence of smoking among the cohorts decreased almost linearly with age in men and women ($p < 0.001$; Table 2). At all ages, current smoking was higher in men than in women.

Current smoking

Current smoking was associated with a significantly increased risk of any kind of fracture, including osteoporotic or hip fractures taken alone, in both men and women (Table 3). For any kind of fracture and for osteoporotic fractures taken alone, the risk in smokers was significantly higher in men ($p = 0.015$) than in women ($p = 0.03$). For hip fractures taken alone, there was no difference in the risk ratio between men and women. For men and women combined, risk with current smoking was highest for hip fracture (RR = 1.84), lowest for fractures taken overall (RR = 1.25) and intermediate for osteoporotic fracture (RR = 1.29).

Risk ratio was adjusted downward somewhat when taking BMD into account (see Table 3). In women, for any fracture overall or osteoporotic fracture specifically, the associations between smoking and fracture were no longer significant. In men, the effect was less marked or not apparent. In men and women together, low BMD accounted for the minority of the risk associated with current smoking. For fractures overall, 45% of the risk was explained by BMD, whereas for osteoporotic fracture alone it was 40% and for hip fracture, only 23%.

BMI

The risk ratios for smokers were also adjusted downward when account was taken for BMI, though all ratios remained significantly increased (Table 4). The downward adjustment was less than the adjustment for BMD alone. When smoking, BMI and BMD were entered into the model, a further decrease in risk ratio was observed, although the risk ratios remained above unity, significantly so for the risk of (any) fractures overall and for hip fracture.

Table 5 Risk ratio (*RR*) and 95% confidence intervals (CI) for osteoporotic and hip fractures in current smokers for men and women combined

Age (years)	Without BMD		Adjusted for BMD	
	RR	95% CI	*RR*	95% CI
(a) Osteoporotic fracture				
50	1.05	0.80–1.37	0.82	0.57–1.18
55	1.06	0.86–1.30	0.85	0.65–1.12
60	1.08	0.92–1.26	0.88	0.72–1.08
65	1.14	1.00–1.30	0.91	0.76–1.09
70	1.27	1.12–1.45	1.01	0.85–1.20
75	1.45	1.28–1.65	1.20	1.01–1.43
80	1.54	1.34–1.77	1.30	1.08–1.57
85	1.52	1.28–1.80	1.28	1.00–1.63
(b) Hip fracture				
50	2.52	1.24–5.10	2.28	0.94–5.51
55	2.35	1.32–4.19	2.09	1.03–4.24
60	2.17	1.38–3.44	1.87	1.07–3.25
65	1.98	1.38–2.86	1.68	1.07–2.65
70	1.92	1.42–2.60	1.69	1.15–2.48
75	1.94	1.52–2.49	1.76	1.30–2.37
80	1.91	1.55–2.35	1.69	1.31–2.19
85	1.80	1.43–2.26	1.57	1.16–2.13

Table 3 Risk ratio of fracture (*RR*) and 95% confidence interval (CI) associated with current smoking by fracture outcome in men and women

Outcome	Sex	*RR*	95%CI	RR[a]	95%CI
Any kind of fracture	M	1.50	1.26–1.77	1.49	1.20–1.84
	F	1.18	1.07–1.30	1.02	0.90–1.16
	M+F	1.25	1.15–1.36	1.13	1.01–1.25
Osteoporotic Fracture	M	1.53	1.27–1.83	1.54	1.21–1.95
	F	1.20	1.06–1.35	1.01	0.87–1.17
	M+F	1.29	1.17–1.43	1.13	1.00–1.28
Hip fracture	M	1.82	1.34–2.49	1.69	1.16–2.48
	F	1.85	1.46–2.34	1.55	1.16–2.07
	M+F	1.84	1.52–2.22	1.60	1.27–2.02

[a]Risk ratio adjusted for BMD

Table 4 Risk ratio (*RR*) for fracture in current smokers (men and women combined) adjusted for age, BMD, BMI and both BMD and BMI. *CI* confidence interval

	Outcome fracture					
	Any		Osteoporotic		Hip	
Adjustment	*RR*	95% CI	*RR*	95% CI	RR	95% CI
Age	1.25	1.15–1.36	1.29	1.17–1.43	1.84	1.52–2.22
Age BMD	1.13	1.01–1.25	1.13	1.00–1.28	1.60	1.27–2.02
Age BMI	1.19	1.09–1.30	1.21	1.08–1.34	1.65	1.34–2.03
Age, BMI, BMD	1.12	1.01–1.25	1.11	0.98–1.26	1.55	1.23–1.96

Age

Risk ratios increased with age for any fracture and for osteoporotic fractures specifically, but they were significantly higher than unity at all ages (Table 5). With adjustment for BMD, current smoking was a significant risk only from the age of 70 years. In contrast, for hip fracture risk, the risk ratio decreased with age but was significantly higher than unity at all ages with or without adjustment for BMD.

Ever-smokers

A history of smoking (ever smoked) was also associated with a significant risk increase for any fracture, and, specifically, for an osteoporotic or hip fracture (Table 6). The risk ratios were lower than for current smoking (see Table 3), but, just as in that case, were highest for hip fracture. There was no significant difference in risk ratio between men and women, no difference when adjusted for BMD, and no significant effect of age on the risk ratio (data not shown). The exclusion of data from the Gothenburg cohorts (where BMD was assessed at the heel or forearm) had no material effect on these results (data not shown).

Discussion

The present study confirms that a history of smoking carries a modest but significant risk for future fractures. In addition, the effect of smoking is over and above that which can be explained by variations in BMD. The risk of subsequent fractures was greater in the case of hip fracture than for all fractures, and intermediate for osteoporotic fractures. For hip-fracture risk in women, the increase in risk ratio (1.85) was comparable to that described in the meta-analysis from Law and Hackshaw [2]. In their findings, risk ratios increased with age; however, in the present study risk ratios for hip fracture tended to decrease with age. In contrast, risk ratios for osteoporotic fractures (which included hip fractures) increased with age. The strength of the association we found was lower than for ever-smokers, consistent with the view that the effect of smoking appears to wane slowly after a person stops smoking [36].

A particular strength of the present study is that the estimate of risk is from an international setting, from randomly or quasi-randomly selected population cohorts, and the calculations were based on the primary data. This decreases the risk of publication and selection biases, which may have large effects. For example, in the large, prospective study from Kuopio, the risk of fracture for current smokers was 1.47 (95% CI = 1.05–2.06) when the sample included individuals selected on the basis of risk factors. From the random population sample used in the present study, the relative risk for fractures overall was 1.18 (95% CI = 0.70–2.00) [3]. Furthermore, the consistency of the association within cohorts indicates the generalizability of this risk factor's importance.

The large sample size studied permitted us to examine risk by age. For all fractures and for osteoporotic fractures specifically, the risk ratios were relatively constant with age. If anything, they tended to increase with age. In the case of hip fracture, risk ratios decreased with age, but this was not significant. Much larger samples would be needed to verify such an effect. A limitation of this study was that we were unable to examine the dose dependency of the association, due to differences in the way that smoking histories were obtained. In this regard, men tend to smoke more than women. This may account for the slightly higher risk ratios observed in men.

The present study also quantifies the independent contributions of low BMD or BMI to the risks associated with smoking. Low BMD explained a minority of the total risk, contradicting the findings of Law and Hackshaw [2] but agreeing with others [7]. With regard to BMD, there are several mechanisms whereby smoking might adversely affect fracture risk. Female smokers may have increased rates of bone loss after menopause [37], but this is not consistently found [38, 39]. Smoking women also have earlier menopause [37, 40, 41]. It has been suggested that smoking may enhance estrogen catabolism [42]. The effects of hormone replacement therapy (HRT) have in some, but not all, studies been attenuated among smokers [43, 44]. Smokers are also thinner and, hence, have lower body mass index [40, 45]. Consequently, the protective effect of adipose tissue and peripheral estrogen metabolism is impaired. Bone loss is reported to be higher in male smokers than in female smokers [38], perhaps due to men's higher exposure to cigarette smoking. We observed higher risk ratios for men than for women for any fracture and for osteoporotic fracture specifically. Such effects may explain the component of fracture risk that is attributable to low BMD or BMI. However, as shown in the present study, this represents a minority of the risk.

The mechanism for the BMD-independent increase in risk could not be determined from this study. Possibly, it results, in part, from lower levels of physical activity or

Table 6 Risk ratio (*RR*) associated with a smoking history by subsequent fracture outcome in men and in women. *RR* is not adjusted for BMD

Outcome	Sex	*RR*	95% confidence interval
Any fracture	M	1.27	1.07–1.51
	F	1.18	1.10–1.26
	M+F	1.19	1.12–1.27
Osteoporotic fracture	M	1.34	1.10–1.63
	F	1.15	1.07–1.25
	M+F	1.18	1.09–1.27
Hip fracture	M	1.11	0.67–1.83
	F	1.42	1.18–1.72
	M+F	1.38	1.15–1.65

to co-existing morbidity, which might in turn increase the risk of falls or impair protective responses to injury [46, 47, 48]. It is also possible that smoking-induced changes in the microarchitecture of cancellous bone would weaken the resistance to mechanical force out of proportion to any effect on BMD. Finally, errors in measurement of BMD [49] will result in the underestimation of bone's contribution to fracture risk.

Whatever the mechanism involved, these data indicate that the risk of fractures is greater for smokers and those with a history of smoking than it is for individuals of the same age, sex and BMD who do not or did not smoke. This has implications for intervention thresholds. Health economic analyses suggest that intervention is cost-effective when treatment is targeted to women with a *T*-score of −2.5 SD at the femoral neck [15]. Since smoking carries a risk over and above that provided by BMD alone, intervention thresholds for BMD can be less stringent in smokers and still yield the same cost-effectiveness. This approach has been incorporated into health economic analyses [8, 50]. However, a large number of additional and stronger independent risk factors for fracture have been identified. These include a history of fracture, corticosteroid exposure, a family history of fracture, secondary osteoporosis, and possibly the biochemical indices of bone turnover [15, 51, 52, 53, 54]. Before these risk factors can be readily used for assessing fracture risk in the general population, their interrelationships will need to be determined.

We conclude that a history of smoking results in a substantial risk for future fractures and that this risk is largely independent of BMD. The fact that this association holds up on an international scale provides a rationale for using this risk factor in case-finding strategies. Moreover, identified patients can be targeted for treatment at lower BMD thresholds than are non-smoking individuals of the same age who have osteoporosis .

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