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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

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

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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References

1. Nelson HD, Morris CD, Kraemer DF, Mahon S, Carney N, Nygren P, Helfand M (2002) Osteoporosis in postmenopausal women: diagnosis and monitoring. In: Oregon Health and Science University Evidence-Based Practice Center (eds) Evidence report/technology assessment No. 28. Agency for Healthcare Research and Quality, Rockville, MD
2. Law MR, Hackshaw AK (1997) A meta-analysis of cigarette smoking, bone mineral density and risk of hip fracture; recognition of a major effect. Br Med J 315:841–846
3. Huopio J, Kroger H, Honkanen R, Saarikoski S, Alhava E (2000) Risk factors for perimenopausal fractures: a prospective study. Osteoporos Int 11:219–227
4. Bohannon AD, Hanlon JT, Landerman R, Gold DT (1999) Association of race and other potential risk factors with non-vertebral fractures in community-dwelling elderly women. Am J Epidemiol 149:1002–1009
5. Mallmin H, Ljunghall S, Persson I, Bergstrom R (1994) Risk factors for fractures of the distal forearm: a population-based case-control study. Osteoporos Int 4:298–304
6. Kelsey JL, Browner WS, Seeley DG, Nevitt MC, Cummings SR (1992) Risk factors for fracture of the distal forearm and proximal humerus. Am J Epidemiol 135:477–489
7. Cummings SR, Nevitt MC, Browner WS, Stone K, Fox KM, Ensrud KE, Cauley J, Black D, Vogt TM (1995) Risk factors for hip fracture in white women. New Engl J Med 332:767–773
8. National Osteoporosis Foundation (1998) Osteoporosis: review of the evidence for prevention, diagnosis and treatment and cost-effectiveness analysis. Osteoporos Int [Suppl 4] 8:1–88
9. National Osteoporosis Foundation (1998) Physicians guide to prevention and treatment of osteoporosis. National Osteoporosis Foundation, Washington DC, pp 1–38
10. Brown J, Josse RG for the Scientific Advisory Council of the Osteoporosis Society of Canada (2002) Clinical practice guidelines for the diagnosis and management of osteoporosis in Canada. Canad Med Assoc J [Suppl 10] 167:S1-S34
11. Kanis JA, Delmas P, Burckhardt P, Cooper C, Torgerson D on behalf of the EFFO (1997) Guidelines for the diagnosis and management of osteoporosis. Osteoporos Int 7:390–406
12. Royal College of Physicians (1999) Osteoporosis: clinical guidelines for prevention and treatment. Royal College of Physicians, London
13. Royal College of Physicians (2000) Osteoporosis: clinical guidelines for prevention and treatment. Update on pharmacological interventions and an algorithm for management. Royal College of Physicians, London
14. Kanis JA, Black D, Cooper C, Dargent P, Dawson-Hughes B, De Laet C, Delmas P, Eisman J, Johnell O, Melton J, Oden A, Papapoulos S, Pols H, Rizzoli R, Silman A, Tenenhouse A (2002) A new approach to the development of assessment guidelines for osteoporosis. Osteoporos Int 13:527–536
15. Kanis JA (2002) Diagnosis of osteoporosis and assessment of fracture risk. Lancet 359:1929–1936
16. Kreiger N, Tenenhouse A, Joseph L et al (1999) The Canadian Multicenter Osteoporosis Study (CaMos): background, rationale, methods. Can J Aging 18:376–387
17. Jones G, Nguyen TV, Sambrook PN, Kelly PJ, Gilbert C, Eisman JA (1994) Symptomatic fracture incidence in elderly men and women. The Dubbo Osteoporosis Epidemiology Study (DOES). Osteoporos Int 4:277–282
18. Nguyen TV, Eisman JA, Kelly PJ, Sambrook PN (1996) Risk factors for osteoporotic fractures in elderly men. Am J Epidemiol 144:255–263
19. O'Neill TW, Felsenberg D, Varlow J, Cooper C, Kanis JA, Silman AJ (1996) The prevalence of vertebral deformity in European men and women: European vertebral osteoporosis study. J Bone Miner Res 11: 1010–1017
20. Felsenberg D, Silman AJ, Lunt M, Ambrecht G, Ismail AA, Finn JD, Cockerill WC, Banzer D, Benevolenskaya LI, Bhalla A, Bruges Armas J, Cannata JB, Cooper C, Dequeker J, Eastell R, Ershova O, Felsch B, Gowin W, Havelka S, Hoszowski K, Jajic I, Janot J, Johnell O, Kanis JA, Kragl G, Lopez Vaz A, Lorenc R, Lyritis G, Masaryk P, Matthis C, Miazgowski T, Parisi G, Pols HAP, Poor G, Raspe HH, Reid DM, Reisinger W, Scheidt-Nave C, Stepan J, Todd C, Weber K, Woolf AD, Reeve J, O'Neill TW (2002) Incidence of vertebral fracture in Europe: results from the European Prospective Osteoporosis Study (EPOS). J Bone Miner Res 17:716–724
21. Ismail AA, Pye SR, Cockerill WC, Lunt M, Silman AJ, Reeve J, Banzer D, Benevolenskaya LI, Bhalla A, Bruges Armas J, Cannata JB, Cooper C, Delmas PD, Dequeker J, Dilsen G, Falch JA, Felsch B, Felsenberg D, Finn JD, Gennari C, Hoszowski K, Jajic I, Janott J, Johnell O, Kanis JA, Kragl G, Lopez Vaz A, Lorenc R, Lyritis G, Marchand F, Masaryk P,

Matthis C, Miazgowski T, Naves-Diaz M, Pols HAP, Poor G, Rapado A, Raspe HH, Reid DM, Reisinger W, Scheidt-Nave C, Stepan J, Todd C, Weber K, Woolf AD, O'Neill TW (2002) Incidence of limb fracture across Europe: results from the European Prospective Osteoporosis Study (EPOS). Osteoporos Int 13:565–571
22. Svanborg A (1977) 70-year-old people in Gothenburg. A population study in an industrialised Swedish city II. Journal Presentation of Social and Medical Conditions. Acta Med Scand [Suppl] 611:5
23. Johansson C, Black D, Johnell O, Oden A, Mellstrom D (1998) Bone mineral density is a predictor of survival. Calcif Tissue Int 63:190–196
24. Stenstrom M, Olsson JO, Mellstrom D (2000) Thyroid hormone replacement is not related to increased risk of osteoporosis. Osteoporos Int [Suppl 2] 11:S144.
25. Fujiwara S, Kasagi F, Yamada M, Kodama K (1997) Risk factors for hip fracture in Japanese cohort. J Bone Miner Res 12:998–1004
26. Fujiwara S, Fumiyoshi K, Masunari N, Naito K, Suzuki G, Fukunage M (2003) Fracture prediction from bone mineral density in Japanese men and women. J Bone Miner Res 18:1547–1553
27. Honkanen R, Kroger H, Tuppurainen M, Alhava E, Saarikoski S (1995) Fractures and low axial bone density in perimenopausal women. J Clin Epidemiol 48:881–888
28. Melton LJ 3rd, Crowson CS, O'Fallon WM, Wahner HW, Riggs BL (2003) Relative contributions of bone density, bone turnover and clinical risk factors to long-term fracture prediction. J Bone Miner Res 18:312–318
29. Melton LJ 3rd, Atkinson EJ, O'Connor MK, O'Fallon WM, Riggs BL (1998) Bone density and fracture risk in men. J Bone Miner Res 13:1915–1923
30. Hofman A, Grobbee DE, De Jong PT, van den Ouweland FA (1991) Determinants of disease and disability in the elderly: the Rotterdam study. Eur J Epidemiol 7:403–422
31. De Laet CE, Van Hout BA, Burger H, Hofman A, Weel AE, Pols HAP (1998) Hip fracture prediction in elderly men and women: validation of the Rotterdam study. J Bone Miner Res 13:1587–1593
32. Johansson H, Oden A, Johnell O, Jonsson B, De Laet C, Oglesby A, McCloskey EV, Kayan J, Jalava T, Kanis JA (2003) Optimisation of BMD measurements to identify high-risk groups for treatment—a test analysis. J Bone Miner Res (in press)
33. Kanis JA, Oden A, Johnell O, Jonsson B, De Laet C, Dawson A (2001) The burden of osteoporotic fractures: a method for setting intervention thresholds. Osteoporos Int 12:417–427
34. Higgins JPT, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. Br Med J 327:557–560
35. Marshall D, Johnell O, Wedel H (1996) Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. Lancet 312:1254–1259
36. Cornuz J, Feskanich D, Willett WC et al (1999) Smoking, smoking cessation and risk of hip fracture in women. Am J Med 106:311–314
37. Sowers MR, Clark MK, Hollis B, Wallace RB, Jannausch M (1992) Radial bone mineral density in pre- and perimenopausal women: a prospective study of rates and risk factors for loss. J Bone Miner Res 7:647–657
38. Hannan MT, Felson DT, Dawson Hughes B, Tucker KL, Cupples LA, Wilson PWF, Keil DP (2000) Risk factors for longitudinal bone loss in elderly men and women. The Framingham Osteoporosis Study. J Bone Miner Res 15:710–720
39. Burger H, De Laet C, Van Daele P, Weel A, Witteman J, Hofman A, Pols H (1998) Risk factors of increased bone loss in an elderly population. The Rotterdam Study. Am J Epidemiol 147:871–879
40. Hermann AP, Brot C, Gram J, Kolthoff N, Mosekilde L (2000) Premenopausal smoking and bone density in 2,015 perimenopausal women. J Bone Miner Res 15:780–787
41. McKinlay SM, Bifano NL, McKinley JB (1985) Smoking and age at menopause in women. Ann Intern Med 103:350–356
42. Seeman E (1996) The effects of tobacco and alcohol use on bone. In: Marcus R, Feldman D, Kelsey J (eds) Osteoporosis 1996. Academic, San Diego, pp 577–597
43. Kiel DP, Baron JA, Anderson JJ, Hannan MT, Felson DT (1992) Smoking eliminates the potential effects of oral estrogens on the risk for hip fractures among women. Ann Intern Med 116:716–721
44. Hoidrup S, Gronbaek M, Pedersen AT, Lauritzen JB, Gottschau A, Schroll M (1999) Hormone replacement therapy and hip fracture risk: effects of modifications by tobacco smoking, alcohol intake, physical activity and body mass index. Am J Epidemiol 150:1085–1093
45. Johnell O, Gullberg B, Kanis JA, Allander E, Elffors L, Dequeker J, Dilsen G, Gennari C, Lopez Vaz A, Lyritis G, Mazzuoli G, Miravet L, Passeri M, Perez Cano R, Rapado A, Ribot C (1995) Risk factors for hip fracture in European women: the MEDOS study. J Bone Miner Res 10:1802–1815
46. Gunnes M, Mellstrom D, Johnell O (1998) How well can a previous fracture indicate a new fracture? A questionnaire study of 29,802 postmenopausal women. Acta Orthop Scand 69:508–512
47. Ensrud KE, Nevitt MC, Yunis C, Cauley JA, Seeley DG, Fox KM et al (1994) Correlates of impaired function in older women. J Am Geriatr Soc 42:481–489
48. Nelson HD, Nevitt ME, Scott JC, Stone KL, Cummings SR (1994) Smoking, alcohol and neuromuscular and physical function of older women. JAMA 272:1825–1831
49. Svendsen OL, Hassager C, Skodt T, Christiansen C (1995) Impact of soft tissue on in vivo accuracy of bone mineral measurements in the spine, hip and forearm: a human cadaveric study. J Bone Miner Res 10:868–873
50. Kanis JA, Johnell O, Oden A, De Laet C, Jonsson B (2001) Intervention thresholds for osteoporosis. Bone 31:26–31
51. Van Staa TP, Leufkens HGM, Cooper C (2002) Does a fracture at one site predict later fractures at other sites? A British cohort study. Osteoporos Int 13:624–629
52. Klotzbeucher CM, Ross PD, Landsman PB, Abbot TA, Berger M (2000) Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. J Bone Miner Res 15:721–739.
53. Guidelines Writing Group (2002) Glucocorticoid-induced osteoporosis. Guidelines for prevention and treatment. Bone and Tooth Society of Great Britain, National Osteoporosis Society and Royal College of Physicians. Royal College of Physicians, London
54. Delmas PD, Eastell R, Garnero P, Seibel MJ, Stepan J (2000) The use of biochemical markers of bone turnover in osteoporosis. Osteoporos Int [Suppl 6] 11:S2-S17