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Assessment of Fracture Risk and its Application to Screening for Postmenopausal Osteoporosis: Synopsis of a WHO Report

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Abstract. The criteria required for an effective screening strategy for osteoporosis are largely met in Caucasian women. The disease is common and readily diagnosed by the measurement of bone mineral with single- or dual-energy absorptiometry. Such measurements have high specificity but lower sensitivity, so that the value of the technique is greater for those identified as being at higher risk. Against this background there is little evidence that osteoporosis can usefully be tackled by a public health policy to influence risk factors such as smoking, exercise and nutrition. This suggests that it is appropriate to consider targetting of treatment with agents affecting bone metabolism to susceptible individuals. Since the main benefits of the use of hormone replacement therapy (HRT) are probably on cardiovascular morbidity, the major role for selective screening is to direct non-HRT interventions. An appropriate time to consider screening and intervention is at the menopause, but screening at later ages is also worthy of consideration. Since the cost of screening is low and that of bone-active drugs is high, the selective use of screening techniques will improve the cost–benefit ratio of intervention.

Keywords: Bone mineral measurement; Fractures; Osteoporosis; Screening

Introduction

In the past decade osteoporosis has been widely recognized as a major health issue by both the medical profession and the general public. Public awareness has increased the demands on healthcare agencies, particularly in the areas of hormone replacement therapy (HRT) and women's health. The response of the medical profession, however, has been variable [1,2]. On the one hand, medical interest among experts in bone disease is very high, and the number of papers, congresses and journals devoted to the subject is growing rapidly. On the other hand, many general practitioners remain unaware of the problem; in one survey in the United Kingdom 20% of general practitioners had 'never seen a case' [3]. Others are reluctant either to assess patients or to prescribe interventions. Nonetheless, attitudes seem to be changing, as indicated by the growing number of consultations to general practitioners for osteoporosis and by the prescription of bone-specific agents, which is continuing to rise in many countries.

The views of bone experts are not, however, consistent. In the past few years several consensus development conferences have reviewed these problems [4–7]. Although partly a reflection of the increasing awareness of the problem, such conferences also indicate the difficulties that experts have on matters of substantial importance. The areas of disagreement apply less to the efficacy of interventions available for prevention or treatment than to the question of whom to treat [8–12]. In the case of HRT, for example, some advocate universal screening of postmenopausal women to identify those who would most benefit from HRT [11]. Others advocate the universal use of HRT in postmenopausal women, while a minority hold the view that the risks outweigh any benefits and that few, if any, women

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should receive HRT. Yet others argue that screening for fracture risk is either uneconomic or impractical [8,12]. Inevitably, such widely differing attitudes (the evangelists and the snails) [13] have a significant impact on the use of healthcare resources for screening or interventions, or both.

For these reasons the World Health Organization, in collaboration with the European Foundation for Osteoporosis and Bone Disease, convened a Study Group Meeting on the assessment of fracture risk and its application to screening for postmenopausal osteoporosis [14]. This paper reviews the major findings of the Study Group.

Osteoporosis

Osteoporosis is a skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture [7]. For women, osteoporosis can be diagnosed when a value for bone mineral density (BMD) or bone mineral content (BMC) is 2.5 standard deviations or more below the mean of the young adult reference range [14,15]. Utilizing this cut-off point, the prevalence of osteoporosis varies from 16% to 30% in Caucasian women, depending upon the number of sites measured (Table 1).

Table 1. Percentage of white women by age with osteoporosis defined as a bone mass below 2.5 SD of the young adult reference mean at the spine, hip or mid-radius

Age range (yr)	Osteoporosis of:	
	Any site (%)	Hip alone (%)
30–39	0	0
40–49	0	0
50–59	14.8	3.9
60–69	21.6	8.0
70–79	38.5	24.5
80+	70.0	47.5
≥50	30.3	16.2

From WHO [14].

The clinical significance of osteoporosis lies in the fractures which occur. Most occur at the spine, wrist and hip, but many fractures at other sites are also associated with a low bone mass independently of age, and should be considered to be osteoporotic [16]. Women are at particular risk for fracture, and the incidence in women is twice that in men in many countries [11,17,18]. Reasons include the lower bone mass of women at the time of maturity (peak bone mass), the accelerated loss of bone that occurs after the menopause and the greater likelihood of falls amongst elderly women [19]. Women also live significantly longer than men, so that women account for 75% of osteoporotic fractures in most Western countries. The remaining lifetime risk of osteoporotic fractures in women at the menopause is at least 30% and probably closer to 40% [20–22] (Table 2).

Table 2. Estimated lifetime fracture risk in women (95% confidence intervals) at the age of 50 years

Fracture site	Women	Men
Proximal femur	17.5 (16.8–18.2)	6.0 (5.6–6.5)
Vertebra[a]	15.6 (14.8–16.3)	5.0 (4.6–5.4)
Distal forearm	16.0 (15.7–16.7)	2.5 (2.2–3.1)
Any of the above	39.7 (38.7–40.6)	13.1 (12.4–13.7)

From Melton et al. [20].
[a]Clinically diagnosed fractures

Fractures of the hip incur the greatest morbidity and direct costs for health services [11,23,24]. A tenth of women who sustain a hip fracture become functionally dependent in the activities of daily living (taking functional status before fracture into account) and 19% require long-term care in a nursing home as a direct result of fracture. These figures, derived from the United States [25], are similar to those from many other countries [26,27]. Deaths attributable to hip fracture increase with age, in part related to the high comorbidity associated with this fracture. About 20% of patients with hip fracture will die within 1 year of fracture, often after an extended hospital stay. Osteoporotic fractures of the vertebrae and forearm are of less economic significance, but also give rise to significant morbidity [28–32]. There are, however, problems in identifying the frequency of vertebral fracture and its attendant morbidity [31,33].

The total costs of osteoporosis are difficult to assess because they include acute hospital care, loss of working days and long-term care in the home or nursing homes. Cost estimates are based on many assumptions that are difficult to test. The cost of osteoporotic fractures in the United States are estimated at $7–10 billion annually for a population of 250 million [34], in England and Wales at £614 million annually for a population of 50 million [35] and FF3.7 billion in France [36], excluding vertebral fractures.

The frequency of osteoporotic fractures is certain to increase in both men and women as a result of the aging of populations. Of the 1.7 million hip fractures which are estimated to have occurred world-wide in 1990 [37], demographic changes alone could cause the annual number of hip fractures to more than double by the year 2040. However, the elderly population in the United States has been growing even faster than predicted by the most optimistic assumptions about improving life expectancy. If these trends continue the number of hip fractures could be more than tripled over this period [38]. The major increase will occur in countries outside Europe and the United States (Fig. 1). Such projections assume that race-specific hip fracture incidence rates will not change. However, rates have increased substantially in all areas of the world, though age-adjusted rates

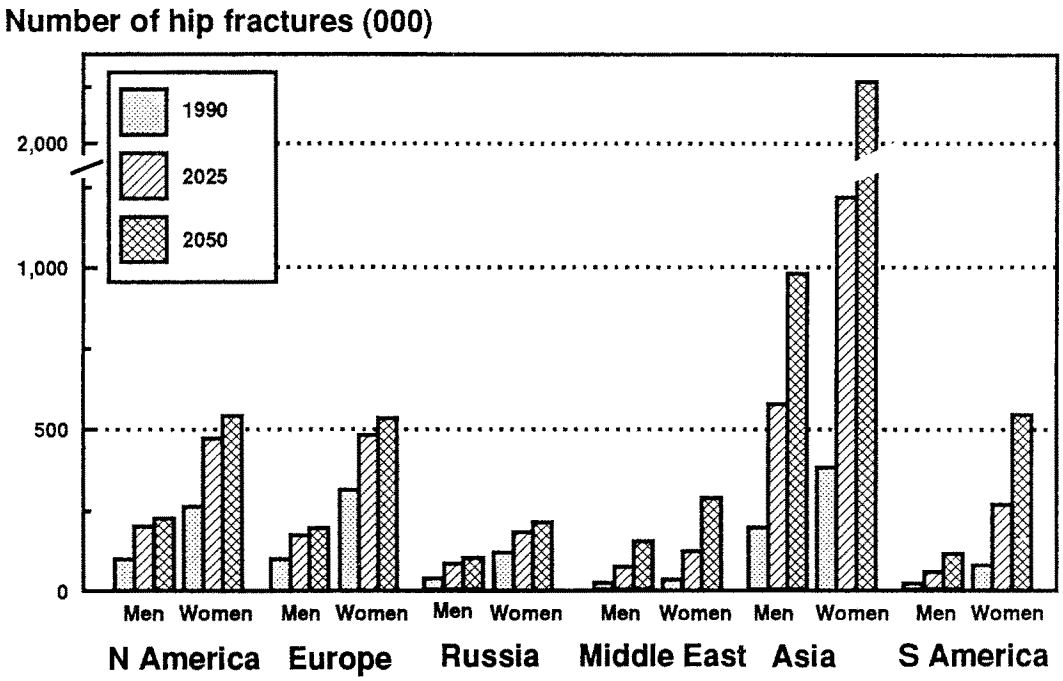

Fig. 1. Estimated number of fractures (in thousands) for men and women in different regions of the world in 1990, 2025 and 2050. (Modified from Cooper et al. [37].)

appear to have levelled off somewhat in Sweden, the United Kingdom and the United States [39–42].

Elderly women represent the major problem in terms of numbers of fractures, which suggests that screening and prevention would be most effective if aimed at this segment of the population. Although the problem is also significant in men and likely to increase in the future, the effects of intervention are less certain. From a healthcare viewpoint, what constitutes an acceptable or unacceptable risk of fracture in different countries is somewhat arbitrary and is likely to be determined largely by the priorities that must compete for healthcare resources.

Bone Mass and Bone Loss

BMD in the postmenopausal years is a function of peak bone mass and postmenopausal losses. Bone mass and bone loss in women are continuously distributed in the general population and appear to vary from site to site in the skeleton. A most important cause of osteoporosis is the bone loss that occurs after the menopause. A great deal of evidence indicates that postmenopausal bone loss is causally related to gonadal deficiency at the time of the menopause. The pattern of bone loss has been derived largely from cross-sectional population studies which are difficult to interpret accurately, and may underestimate the degree of loss with age [43]. Prospective studies show that the rate of postmenopausal bone loss varies, not only from site to site but also from one woman to another, ranging from less than 1% to more than 5% per year. On this basis, postmenopausal women have been stratified into two populations, with 25%–30% belonging to a group of particularly fast bone losers who may be especially vulnerable to osteoporotic fractures in later life [44]. Such observations provide the rationale for including assessments of bone loss in screening programmes. There is, however, no compelling evidence to suggest that the distribution of bone loss is bimodal [45–47].

Postmenopausal bone loss is also associated with a disruption of skeletal microarchitecture which appears to be irreversible [48–50]. The selective destruction of trabecular elements leads to a loss of mechanical competence that is disproportionate to the amount of material removed. At present there is no widely applicable method of restoring skeletal strength once it has been lost, and this argues for assessment and intervention as early as possible in the natural history of the disorder.

These skeletal abnormalities (Table 3) do not reflect all the factors relating to fracture risk. Density-independent components of fracture risk are clearly important for hip fracture, but have also been shown in other

Table 3. Pathogenesis of osteoporotic fracture

Skeletal
Bone mass
Spatial organization of bone
Turnover of bone
Quality of bone (plasticity)
Extraskeletal
Falls: frequency, type and severity
Response to trauma: neuromuscular coordination
Soft tissue cushion

fractures [51–60]. These determinants of skeletal competence assume greater importance with advancing years [54,61]. This does not imply that the prevention of early bone loss would have less impact on the elderly since the contribution of low bone density to fracture risk is not decreased with age [62]. Of the various contributing factors, only bone mass can currently be measured as a predictor of future fracture risk, and only bone mass can be manipulated in mid-life in the hope of preventing fractures decades later.

Assessment of Bone Mass

Many methods of assessing BMD or BMC are available. These include single-photon and X-ray absorptiometry (SPA and SXA) of the forearm and the heel, dual-energy X-ray absorptiometry (DXA) and dual-photon absorptiometry (DPA) of the lumbar spine, proximal femur, whole body or particular regions thereof, and quantitative computed tomography (QCT) of the spine or appendicular sites. All these techniques have sufficient specificity and sensitivity for the diagnosis of low bone mass. Measurements of ultrasound and radiographic photodensity are additional techniques which may be of value in screening, but they have been less well validated.

The requirements for a single screening test of BMD are the ability to predict fractures, low error of accuracy, reliability, rapidity and low radiation dose. These requirements are largely met by SPA, SXA and DXA and less adequately by DPA and QCT as described below.

Accuracy (the ability to measure bone mineral in the region studied) is of importance in the correct stratification of individuals within the population reference range of BMD. The accuracy error of SPA in cadaveric studies varies from 2% to 5% [63,64], and for DPA from 6% to 12% when compared with ash weight [65]. There have been no formal estimates of accuracy in cadaveric studies with DXA, but comparative data suggest a comparable accuracy [66]. The errors of accuracy of the various techniques that are commonly utilized for screening (Table 4) must be considered in parallel with the variance of BMD in the population to be examined, which ranges from 10% to 50% depending upon the technique used and any normalization procedure applied [68]. Of the candidates for a screening test, the accuracy performance in relation to the population variance is highest in the case of SPA by a factor of about 2. This might suggest that SPA should be the technique of choice for a screening test utilizing a single estimate of bone density, but this is counterbalanced by the fact that an appendicular measurement (e.g. at the wrist) is less accurate than DXA in predicting osteoporotic events [69].

In the context of screening the ultimate index of accuracy is the ability to predict from bone assessment at one site the probability of future osteoporotic fracture. This contrasts with the use of bone mineral measurements to diagnose osteoporosis, where accuracy is the ability to measure bone mineral density at that site. There are now many studies which have examined future fracture risk in cohorts of women at varying ages for up to 20 years with different techniques [54–57,69–79]. Estimates consistently show a gradient of risk between 1.5 and 3.1 for each standard deviation decrease in bone mineral density with all the absorptiometric techniques (Fig. 2).

Table 4. Characteristics of the healthy female population and the accuracy of bone density measured by single- and dual-photon absorptiometry (SPA, DPA), dual-energy X-ray absorptiometry (DXA) and quantitative computed axial tomography (QCT)

	SPA	DPA	DXA	QCT
A. Population coefficient of variation (%)	13.3	12.1	14.0	17.9
B. Accuracy (%)	2–5	8–10	?5–8	5–10
A/B	2.6–6.7	1.2–1.5	1.8–2.8	1.8–3.6

From Kanis et al. [67].
The ratio A/B provides an index of the relative power of each technique to position correctly a single estimate of bone density within a population reference range.

The gradient of risk of fracture with low mineral measurements is somewhat steeper than those reported for the risk of coronary artery disease with elevated serum cholesterol or hypertension [80] (Fig. 3). The gradient of risk is also similar to that reported in women for systolic blood pressure and the risk of stroke-associated mortality [81].

The gradient of risk for each standard deviation difference in initial BMD is broadly similar between fracture types and between measurement sites. There is, however, a higher gradient of risk when the technique measures the specific site of future fractures [69,77]. Thus, if the goal is to predict any type of osteoporotic fracture, SPA and DXA perform comparably well at many sites. If the goal is to predict hip fractures, DXA of the hip currently provides the best estimate.

Traditional concepts of sensitivity and specificity are

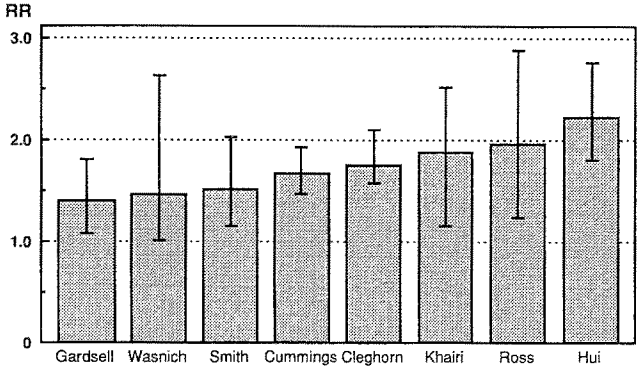

Fig. 2. The gradient of risk (change in relative risk) for each standard deviation decrease in bone mineral density derived from prospective cohort studies (From WHO [14].)

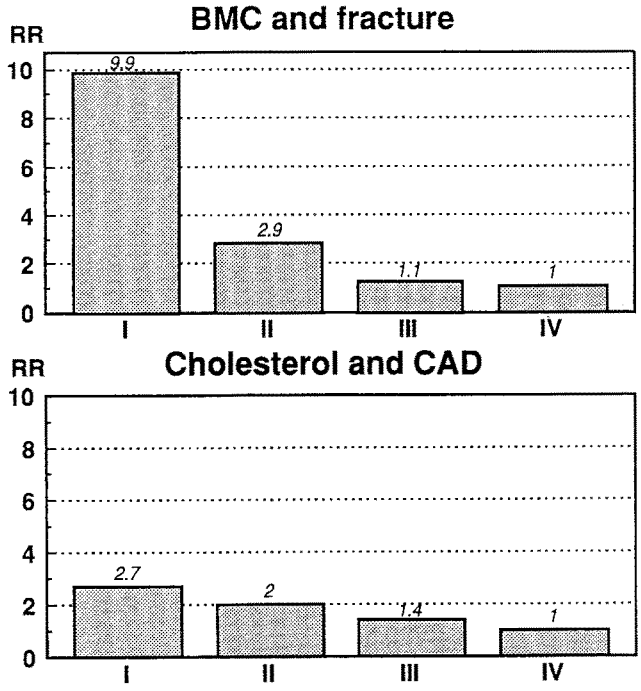

Fig. 3. Relative risk (RR) of hip fracture estimated from forearm bone mineral content (BMC) in a cohort of 399 women aged 40–70 years followed up for 10 years. The relative risks in the population are shown by quartiles of BMC. The *lower panel* shows the change in relative risk for coronary artery disease according to quartiles of serum cholesterol in women (From WHO [14].)

not appropriate when continuous variables such as bone mass are considered [82]. In the context of a lifetime risk rather than the presence of fracture, sensitivity is defined as the proportion of individuals who would in their lifetime sustain a fracture with a bone mineral value below a defined cut-off value. Specificity is defined as the proportion of subjects who would not fracture in their lifetime with BMD values above the cut-off. It should be noted that the terms 'sensitivity' and 'specificity' used in this way do not denote the presence or absence of fractures in individuals at the time of the test (the diagnosis of established osteoporosis is clinically obvious); instead they reflect the proportion who do or do not suffer fractures in the future.

Table 5 provides estimates of such sensitivity and specificity under a number of different conditions. The gradient of future fracture for each standard deviation shift in BMD is modelled at 1.5, 2.0 or 2.5, i.e. within the range identified in prospective studies. The average lifetime risk of fracture is modelled at 15% and 30%; the former is an accurate assessment of hip fracture risk in many Western countries and the latter a very conservative estimate of the risk of any osteoporotic fracture. The specificity and sensitivity are calculated assuming the high-risk category to include either 6.5% or 30% of the perimenopausal population (i.e. the range over which intervention might be contemplated). When considered in this way the false positive rate is close to zero, indicating that the specificity of bone mineral measurements is high since the lifetime risk of fracture is close to 100% using the 6.5% cut-off. When a 30% cut-off is used, the specificity remains high over all ranges of relative risk. In contrast, the test lacks sensitivity (29%–80% depending upon the assumptions made). The relatively low sensitivity indicates that a substantial proportion of fractures will occur in women who lie in the lower-risk groups (i.e. higher values for BMD) when BMD is used as a single test to assess fracture risk over a lifetime.

The inability of a single test to identify all individuals at risk reduces the impact of screening on the total incidence of osteoporotic fracture. However, effectiveness of a screening programme in the general community has to be balanced against its effectiveness in a subgroup at very high risk. In a screening programme for women it is suggested that the risk should be quantified as a lifetime risk of all fractures or hip fractures, depending upon the goals of screening. If the goal is to identify those at risk from any fracture, a high-risk group comprises the highest fifth of the distribution of risk (the lowest quintile of BMD). An intermediate risk group comprises the next fifth if subsequent screen-

Table 5. Estimates of sensitivity and specificity of a single measurement of bone mass to predict hip fracture (15% lifetime risk) or any osteoporotic fracture (30% risk) in postmenopausal women

		High risk category (% population)					
		6.5			30		
Gradient of risk	Lifetime risk (%)	Sensitivity (%)	Specificity (%)	Accuracy (%)	Sensitivity (%)	Specificity (%)	Accuracy (%)
1.5	15	38	98	89	65	75	74
	30	29	100	79	58	78	72
2	15	47	100	92	75	77	77
	30	31	100	79	68	80	76
2.5	15	52	100	93	81	77	78
	30	35	100	81	74	80	78

From Kanis [83].
Values are given where the risk of fracture is assumed to increase by 1.5, 2.0 or 2.5 for each standard deviation decrease in bone mineral density.

ing or biochemical testing is contemplated to help in the assessment of rates of bone loss (see below).

The accuracy of the test depends on the cut-off value chosen, which in turn depends on the goal of screening. If the goal is solely to prevent hip fracture more rigorous cut-offs should be selected to attain high specificity than if the goal is to prevent all types of osteoporotic fractures.

Assessment of Bone Loss

Individuals who lose bone at faster rates after the menopause are more likely to reach a threshold of bone density below which the risk of fracture is unacceptably high [67]. Techniques appropriate to screening involve the repeated estimation of bone mass. In addition, there is some evidence to indicate that rates of loss can be predicted from biochemical estimates of bone formation and resorption in the early postmenopausal years.

The additional requirements of bone density techniques for assessment of bone loss are low errors of reproducibility and evidence that such measurements improve the prediction of fracture risk. For the measurement of bone loss in individuals the estimate of reproducibility should be determined in vivo in healthy individuals or patients with osteoporosis. In healthy individuals the precision errors for SPA vary from 1.1% to 2.2% [84–88]. For DXA of the lumbar spine estimates vary from 0.8 to 1.3 [66,88]. In osteoporotic patients with a reduced BMC the coefficients of variation are higher. These precision errors must be judged against the rates of bone loss expected in a population, which vary from site to site. The ratio of loss to precision error is more favourable in the case of DXA than SPA, but an interval of 5 years is more than adequate to assess rates of loss in the majority of individuals with any of the techniques. This time interval may be appropriate for screening programmes but is less than optimal for clinical purposes such as the assessment of responses to treatment.

The contribution of bone loss to fracture risk (compared with bone mass at the menopause) increases with time. The influence of initial bone mass on current bone mass is generally greater than that of bone loss in women up to the age of 70 years [74,79,89]. In other words, fracture may be more accurately predicted from assessment of bone mass rather than from the rate of bone loss. However, the more appropriate consideration is the extent to which the combined assessment increases accuracy. Twelve years after the menopause approximately 30% of the variance in density measurements may be explained on the basis of differential rates of bone loss. If rates of bone loss vary markedly between individuals thereafter, the rate of loss would assume progressively greater importance with time. The longer the interval between menopause and a second assessment, the larger the effect of bone loss. Thus, assessments of loss become progressively more important with advancing years, in parallel with the increasing

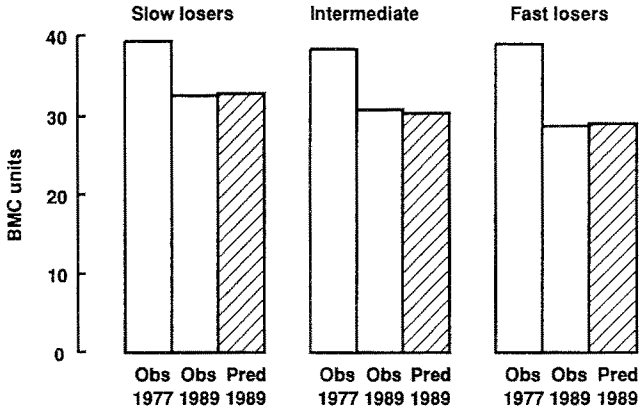

Fig. 4. Observed (Obs) bone mineral content at baseline (1977) and 12 years later (1989) compared with values predicted (Pred) by baseline bone mass and biochemical tests for slow, intermediate and fast losers of bone in the postmenopausal period. (Modified from Hansen et al. [44].)

risk of fracture. By the age of 70 years the contributions of initial mass and rates of bone loss approach statistical equality [90], but the errors of repeated measurements are greater, so that a minority of the variance is accounted for by bone loss.

A number of biochemical markers of bone turnover have been evaluated in the context of postmenopausal bone loss [91–95]. The sensitivity and specificity of each of the markers of bone loss is variable but low. However, multivariate analysis of a panel of markers offers greater accuracy than a single measurement [44,46,96,97]. Prospective studies over a 12-year period [44] suggest that 80% of women can be correctly characterized as fast or slow bone losers (true positives, true negatives) (Fig. 4). The biochemical tests have 50% efficiency or more compared with direct methods of assessment by repeated measurements of bone loss. The convenience, but lower accuracy of these biochemical tests must be balanced against the inconvenience of repeated measurements of bone mineral in any screening strategy.

The present evidence suggests that knowledge of losses over the first 5 years after the menopause will improve the estimate of ultimate bone density by about 50% [44]. Similar conclusions are derived from mathematical models [98]. It is likely that the power of tests to predict fracture risk can be improved still further by the development of more accurate assessment of bone mass and more specific biochemical markers.

Clinical Assessment of Risk

Surveys of risk factors for osteoporosis have focused largely on patients with fractures [21,58,99–104] or low bone density [105–109]. Many of the factors implicated in the causation or aggravation of bone loss are derived from retrospective epidemiological studies comparing individuals where the effect of confounding variables is uncertain. A good example is caffeine consumption,

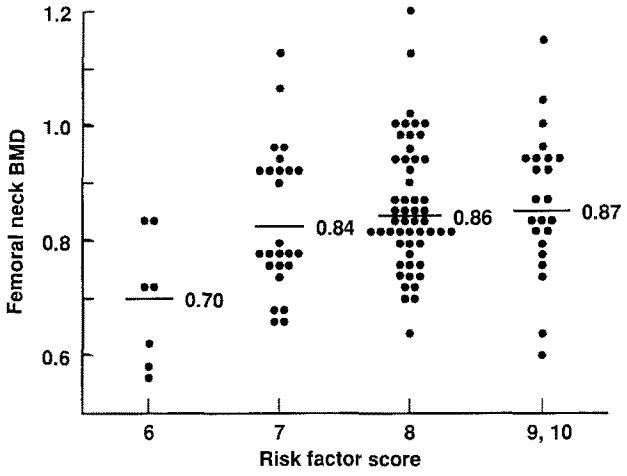

Fig. 5. Observed femoral neck bone mineral density plotted against risk factor score. (From Slemenda et al. [113].)

where causality is inferential [110]. Apart from age, sex and race, many of the risk factors identified are comparatively rare and their value for use in screening is correspondingly low. In a large retrospective survey of hip fracture cases the impact of all identifiable risk factors including height and weight was comparatively high, but not better than BMD (the MEDOS Study, unpublished results). One important predisposing factor, however, is a prior fragility fracture [70,111]. Nonetheless, fracture occurrence is a late indicator of risk and may not be optimal for use in a screening programme if this were to be targetted at the time of the menopause.

Several studies have found that such information does not predict bone mass with sufficient precision to be useful in the management of individuals [44,112,113]. For mineral density of the femoral neck, the best predictive model accounts for only 17% of the variability in bone mineral measurements of the hip and correctly classifies only 65% of perimenopausal women whose bone mass was in the lowest tertile (Fig. 5) [113]. This level of precision is not adequate for patient care nor for screening since BMD can be measured directly with fewer errors of misclassification [89,105,112,114–116]. In contrast, the risk of falls contributes to fracture risk independently of BMD [117], but has uncertain value at the time of the menopause.

Risks and Benefits of Intervention

The assessment of osteoporotic fracture risk needs to be placed in the context of the power of therapeutic intervention. It is possible that peak bone mass in early adult life can be maximized by factors such as adequate nutrition, exercise and avoidance of smoking. However, the extent to which lifestyle changes in childhood or early adult life will alter peak bone mass and the subsequent risk of fracture is unknown. Regular exercise appears to have the greatest effect, but the elements required for a successful programme are not well quantified. For this reason, a population-based approach to shifting the distribution of bone mass by means of a public health campaign is of uncertain value. Nevertheless, since lifestyle factors are known to be important for general health, avoidance of smoking, regular exercise and good nutrition can justifiably be promoted as part of a general health strategy.

Because the ability to modify peak bone mass is limited at present and since the causal impact of putative risk factors on fracture frequency is uncertain, the assessment of bone mineral before or at the time of skeletal maturity is not worthwhile at present, but is an important area for research.

In contrast, there is now good evidence that pharmacological intervention can decrease substantially the risk of fractures in later life. HRT is an effective method of reducing bone loss, and much epidemiological evidence and more direct studies suggest that the incidence of all osteoporotic fractures is substantially reduced by 30%–50% with an exposure of 3–10 years [118–121]. There is uncertainty whether the effects of HRT persist or whether 'catch-up' bone loss occurs [8,9,122]. This is an important issue since HRT is commonly recommended for up to 10 years but the vast majority of fractures occur after the age of 70 years, 20 years or more after the menopause. Most direct evidence suggests that bone that has been preserved is not rapidly lost when oestrogen treatment is stopped and that loss occurs at the same rate as it did immediately before therapy was instituted [113,123–125]. The epidemiological data from case–control or observational studies in the elderly take no account of deaths. In view of the increased comorbidity and the higher death rate of osteoporotic individuals [126,127] it is to be expected that the relative risk of hip fracture among oestrogen users would be lower the more elderly the population. The case for a transient effect of oestrogens thus appears to be weak, but is an important area for further research.

Oestrogen replacement therapy is probably safe but there are concerns that it may increase the risk of some forms of cancer. In women with intact uteri, added progestogen avoids the increased risk of endometrial cancer. There is a plausible association between oestrogen exposure and breast cancer, but no evidence of a significant increase in risk, particularly in terms of mortality, above that expected in fertile women of the same age [128–131]. The effect of added progestogens on the risk of breast cancer is unknown.

The greatest single potential benefit of HRT is on cardiovascular morbidity and mortality which, largely on the basis of epidemiological studies, appears to be substantially reduced by oestrogens [120,132–135]. The effects of added progestogens are less certain [136,137]. Studies suggest that the risk of coronary heart disease is reduced among women taking oestrogen plus progestogen, but there are inadequate data to determine whether this protective effect is as great as that of oestrogen alone. These effects of HRT on ischaemic heart disease have significant implications for screening

Table 6. The net change in life expectancy for a 50-year-old woman (USA) treated with long-term HRT (15 years) according to the presence of risk factors

	Life expectancy (yr)	Change in life expectancy (yr)		
		E	E+P[a]	E+P[b]
No risk factors	82.8	+0.8	+0.9	+0.1
With hysterectomy	82.8	+1.0	–	–
History of coronary heart disease	76.0	+1.8	+1.8	+0.9
Risk of coronary heart disease	79.6	+1.3	+1.4	+0.5
At risk of breast cancer	81.8	+0.4	+0.4	−1.0
At risk of hip fracture	82.4	+0.9	+1.0	+0.2

From Grady et al. [120].
E, treatment with oestrogen alone; E+P, the combination of oestrogen with progestins.
[a] Assumes that P decreases all risk of endometrial cancer.
[b] Assumes that P additionally decreases cardiovascular benefit (RR=0.8) by one-third, increases the relative risk of breast cancer from 1.3 to 2.0, but has no effect on fracture frequency (RR=0.7).

strategies. The greater are the benefits of HRT for cardiovascular risk, the poorer is the case for targetting intervention on the basis of BMD.

Under most assumptions the perceived benefits of HRT outweigh the risks [138–140] (Table 6).

Alternative therapies for the prevention of osteoporosis are used in most countries. Widely approved treatments include calcium, calcitonin and the bisphosphonates. In older women there is some evidence for the efficacy of anabolic steroids and various forms of vitamin D. In some countries, particularly in north-western Europe, vitamin D deficiency is common in the elderly and there is evidence for the preventive efficacy of vitamin D supplements in such patients [141].

Calcium is widely available throughout the world and is the major non-HRT intervention used in osteoporosis. The effects on bone mass are less complete than those of oestrogens, but several studies suggest that bone loss may be halved [84,91,142,143]. A large retrospective case–control study has shown a significant effect of calcium supplements on hip fracture risk [144]. A controlled prospective study in elderly women in sheltered accommodation showed that calcium and vitamin D significantly reduced the risk of hip fracture [141]. Calcitonin and bisphosphonates are currently used more in the treatment of established osteoporosis, but they may be acceptable for prevention in the foreseeable future [145–149]. The effect of these interventions on fracture frequency has been less well studied but a decrease in vertebral fracture frequency has been reported with the bisphosphonates [145,146] and with calcitonin [150,151]. In a retrospective case–control study [144] calcitonin has also been shown to reduce the risk of hip fracture.

Other interventions which appear to benefit patients include the vitamin D derivatives such as alfacalcidol and calcitriol [152,153], thiazide diuretics [154–156], anabolic steroids [157] and sodium fluoride [158–161]. Some of these agents might be considered for use in screening strategies if the strategies included an assessment of risk in the elderly and the identification of those with osteoporosis.

In addition to effects on fracture frequency, several other aspects of non-HRT treatment are of interest in the context of screening. The first relates to the cost of treatment, which represents a substantial proportion of the cost of screening [9,122]. The more expensive the intervention the stronger the case for directing its use in a rational manner, i.e. targetting individuals at high risk and with a known decrease in bone mass. A second important difference relates to the extraskeletal risks and benefits, which are negligible in the case of calcium and calcitonin and probably also the bisphosphonates. Thus, the indications for use of these non-HRT interventions are almost exclusively related to osteoporosis. This strengthens the argument for using bone density measurements for targetting these treatments, in contrast to the case for oestrogens. A third important difference is that non-HRT interventions are generally more acceptable later in life. Their side-effects are fewer and their uptake by patients and patient compliance are known to be much greater than that of HRT [143]. Since there is evidence for their efficacy in individuals even with established bone loss, there is a case to be made for late intervention. Finally, some of these agents, for example, calcium and vitamin D, can be given safely for prolonged periods, indeed over a lifetime, which is less certain and not currently recommended for HRT. These considerations significantly affect screening strategies, particularly the ages at which screening might be offered.

Screening

There is little evidence that osteoporosis can usefully be tackled by a public health policy to influence risk factors such as smoking, exercise and nutrition. Although exercise at all ages and nutritional factors after the menopause are particularly important, the effectiveness of population-based strategies to reduce fracture incidence by altering these lifestyle characteristics on a large scale is not known. The evidence that peak bone mass can be improved is also weak. Thus, the most practical time to assess fracture risk in women is at or after the menopause when several treatments in addition to HRT are available for the prevention or treatment of osteoporosis. Their use is increasing markedly and strengthens the case for targetting them appropriately to those most in need so that unnecessary treatment is avoided. The cost of preventive measures may possibly outstrip the savings made by preventing fractures. However, if preventive measures are to be used, effective screening will improve the cost–benefit ratio of intervention.

Bone mass measurements, with or without an assessment of bone loss, meet many of the essential criteria of a screening test. The test correctly identifies individuals at high risk and the number of individuals identified as being at high risk who do not sustain a fracture is very low. However, many individuals who subsequently fracture will not have been correctly identified. Thus, the value of screening is greater for those individuals identified as being at high risk, but less for those identified as low risk.

Since the major benefit of HRT is likely to lie elsewhere than its effects on bone, measurement of density as a central component of a screening policy involving a treatment with HRT is inappropriate. BMD measurements do have a role, however, in the assessment of individuals who would accept HRT if results showed them to be in a high-risk category. Since HRT is a major intervention utilized and its use is increasing, the argument for screening all women is poor.

Non-HRT interventions are increasingly used and available in many countries. Whereas some are probably less effective than oestrogen, they have fewer extraskeletal risks and benefits and in some cases can be given for life. The more widespread their acceptance and use, the greater the justification for targetting intervention by screening. Conversely, the increasing use of HRT is likely to alter the requirements for screening tests and the design of a screening strategy. A clearly defined policy on use of HRT would, therefore, be advantageous to complement a screening strategy. The Study Group recommended that perimenopausal women should receive professional advice on the risks of osteoporosis and the risks and benefits of HRT.

Selective screening is worthwhile for women within 5 years of the menopause to stratify risk and offer intervention. There is, however, no requirements for testing women who elect to take long-term HRT, nor is there a requirement where the results of the test will not change the decision to accept an intervention. In women the optimum time for using many interventions is at the time of the menopause. This does not necessarily suggest that this is the optimum time for a screening test since many women who elect to take HRT are likely to do so for relatively short periods. Indeed, there is a good case for screening women in older age groups. An alternative age is at 65 years, at which time bone loss has had a substantial influence on bone mass, the risk of hip fracture is still low, effective interventions are available and the cost-effectiveness is favourable. Analyses of cost-effectiveness [138] suggest that screening programmes might be financially more attractive than universal prescription of non-HRT interventions where the compliance to treatment is higher in the screened group than in the unscreened and treated group.

In addition to the costs of intervention [9,122,138] the cost of a screening programme depends upon a number of additional factors including the cut-off point used to target treatment, the age of the individual and the efficacy and duration of treatment. When direct medical costs for acute hip fracture care, screening and treatment are considered, the cost per fracture prevented increases with age irrespective of the cut-off point (Table 7). When a more stringent cut-off is used, the cost is lower (but more fractures would be missed). There have been relatively few detailed assessments of cost-effectiveness and these have principally been concerned with the use of HRT [9,138,162]. It is particularly interesting that targeting interventions appears to be more cost-effective at the age of 65 years than at the age of 50 years when the costs of long-term nursing home care are considered in addition to direct medical costs. However, it is less cost-effective to target interventions at the age of 70 than at 65 years. This is largely because of the higher costs of long-term nursing home care in the more elderly population. This suggests that selective screening strategies at the age of 65 years or thereabouts are worthy of further consideration.

Table 7. The effect of age, cut-off point and treatment on the costs of preventing fractures

Age (yr)	Cut-off (%)[a]	Lifetime probability of fracture[b]	No. of fractures prevented[c]	Cost per fracture prevented (£)[d]
50	38	2.5	1.43	2080
	8	5	2.58	776
60	38	1.5	0.73	3000
	8	3.15	1.38	1600
70	38	0.86	0.32	4700
	8	1.9	0.63	2380

From WHO [14].
[a] Perimenopausal reference range.
[b] All fractures.
[c] Fifty per cent decrease in bone loss.
[d] Assumes an annual cost of £100.

The uptake of screening is likely to be high (70%). The long-term compliance with non-HRT interventions is unknown but, depending on the type of agent, the side-effects and the perceived advantages, is likely to be higher than for HRT. Variations in uptake and compliance rates markedly affect the impact of screening, though not the costs, and may be amenable to change by education.

The lowest quintile of BMD is considered to be an appropriate cut-off point where the aims of treatment and subsequent intervention are to reduce the risk of all osteoporotic fractures. More stringent cut-offs are appropriate if the aim were solely to prevent hip fractures. Moreover, if hip fractures were the only concern it would be more appropriate to measure risk at the hip where the gradient of risk is greater, which would identify a larger proportion of individuals at risk. It is important to recognize that the foregoing considerations may not be applicable worldwide since there is no universally agreed definition of acceptable risk in the community and since the incidence of osteoporotic fractures varies markedly (more than enfold in different European countries) [18]. The choice of intervention thresholds in most elderly women can be based on

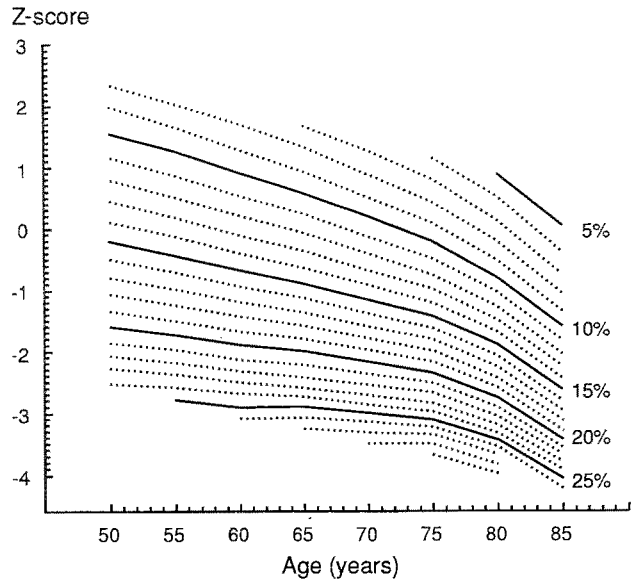

Fig. 6. Estimated lifetime risk of hip fracture in white women according to age and bone mineral density (BMD) at the wrist. The gradient of risk is set at a 1.65 increase in risk for every standard deviation decrement in BMD. Mean BMD at age 50 years is 0.44 g/cm^2 (Z-score = 0), with a standard deviation of 0.085g/cm^2 (each SD = a score of 1). (From Suman et al. [164].)

considerations similar to those applied to younger women. The remaining lifetime risk of fractures of the wrist and hip are similar at all ages after the menopause [21,22,98]. At all ages the risk of osteoporotic fractures increases as BMD decreases. Thus, chosing the lowest quintile for BMD of an appropriate age-matched population will have a similar specificity. An alternative approach is to set an intervention threshold more closely related to a given lifetime risk [71,163] (Fig. 6).

Conclusions

Various sets of criteria for the evaluation of screening programmes have been proposed [82,164,165]. These differ in their emphasis but the major criteria are summarized in Table 8. They include consideration of the disease, the test, the intervention and the complete programme. The principles for screening are to a large extent met in relation to osteoporosis. Suggested criteria for selection of women for screening are that they are of perimenopausal or postmenopausal status, not receiving long-term HRT for other reasons, and are willing to accept HRT or a non-HRT intervention depending on the test result. Techniques suitable for selective screening include the measurement of bone mineral by single- and dual-energy absorptiometry, which have high specificity at all ages after the menopause. Where the goal is to prevent any osteoporotic fracture measurements may be made at one of many sites. Where the aims are to prevent hip fracture, measurements at that site have greater predictive value. The use of clinically derived risk factors are an inappropriate screening test. An appropriate intervention threshold for bone mineral measurement in Caucasian populations is to target intervention at the lowest quintile of BMD, except where hip fractures are the only concern, when it is more appropriate to measure risk at the hip and select perhaps a lower proportion for intervention.

Table 8. Major criteria for the evaluation of screening programmes

The disease	An important social problem
	Natural history adequately understood
The test	Simple and safe
	Acceptable to the population
	Effective: sensitive and specific
The intervention available	Accepted and effective treatment
	Agreed policy on whom to treat
The programme	Facilities for diagnosis and treatment
	Cost-effective

In theory the optimal time for intervention in women is at the time of the menopause, but screening the intervention at later ages is justified. The cost of screening is low compared with the costs of the intervention used. In many countries that treat osteoporosis the proportion of the population treated would still be comparable to the current situation in the United States and most European countries but screening would redirect interventions to those at greatest risk. The major use of bone density measurements is with the non-HRT interventions where the extraskeletal benefits and risks are less. The uptake of screening is likely to be high and long-term compliance with non-HRT interventions, although unknown, is likely to be higher than for HRT.

The conclusions for screening are based largely on clincial considerations but have many logistic and economic consequences which should be addressed. Of particular importance is a formal assessment of the costs of any proposed strategy with sensitivity analyses to determine the effect of differences in any assumptions used. In addition, a policy on the use of HRT is lacking in many countries, but is required where the use of screening tests is contemplated.

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References

1. Grisso JA, Baum CR, Turner BJ. What do physicians in practice do to prevent osteoporosis? J Bone Miner Res 1990;5:213–9.
2. Wilkes HC, Meade TW. Hormone replacement therapy in general practice: a survey of doctors in the MRC's general practice research framework. BMJ 1991;302:1317–20.
3. Griffin J, Robinson R. Hormone replacement for osteoporosis. Lancet 1990;335:1163.
4. Peck WA, Barrett-Connor E, Buckwalter JA, et al. Osteoporosis: NIH Consensus Development Conference statement. JAMA 1984;252:799–802.
5. Anonymous. Consensus development conference: prophylaxis and treatment of osteoporosis. BMJ 1989;295:914–17.
6. Anonymous. Consensus development conference: prophylaxis and treatment of osteoporosis. Am J Med 1991;90:107–10.
7. Anonymous. Consensus development conference: diagnosis, prophylaxis and treatment of osteoporosis. Am J Med 1993;94:646–50.
8. Law MR, Wald NJ, Meade TW. Strategies for prevention of osteoporosis and hip fracture. BMJ 1991;303:453–9.
9. Pitt FA, Lloyd-Jones M, Brazier JE, McGrother CW, Kanis JA, Wallace WA, Jones K. The costs and benefits of screening and preventing postmenopausal osteoporosis in the Trent Region. Report of the Trent Osteoporosis Working Group 1990.
10. Cooper C, Shah S, Hand DJ, Adams J. Compston J, Davie M, Woolf A. Screening for vertebral osteoporosis using individual risk factors. Osteoporosis Int 1991;2:48–53.
11. Hoffenberg R, James OFW, Brocklehurst JC, Green ID, Horrocks P, Kanis JA, et al. Fractured neck of femur: prevention and management. J R Coll Physicians Lond 1989;23:8–12.
12. Freemantle N. Screening for osteoporosis to prevent fractures. In: Effective health care no. 1. School of Public Health, Leeds, 1992.
13. Sackett DL, Holland WW. Controversy in the detection of disease. Lancet 1975;2:357–9.
14. World Health Organization. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. WHO technical report series. Geneva: WHO, 1994.
15. Kanis JA, Melton LJ III, Christiansen C, Johnston CC, Khaltaev N. The diagnosis of osteoporosis. J Bone Miner Res, in press, 1994.
16. Seeley DG, Browner WS, Nevitt MC, Genant HK, Scott JC, Cummings SR. Which fractures are associated with low appendicular bone mass in elderly women? Ann Intern Med 1991;115:837–42.
17. Melton LJ. Epidemiology of fractures. In: Riggs BL, Melton LJ III, editors. Osteoporosis: etiology, diagnosis, and management. New York: Raven Press, 1988:133–54.
18. Johnell O, Gullberg B, Allander E, Kanis JA. The apparent incidence of hip fracture in Europe: a study of national register sources. Osteoporosis Int 1992;2:298–302.
19. Winner SJ, Morgan CA, Evans JG. Perimenopausal risk of falling and incidence of distal forearm fracture. BMJ 1989;298:1486–8.
20. Melton LJ, Chrischilles EA, Cooper C, Lane AW, Riggs BL. How many women have osteoporosis? J Bone Miner Res 1992;7:1005–10.
21. Cummings SR, Kelsey JL, Nevitt MC, O'Dowd KJ. Epidemiology of osteoporosis and osteoporotic fractures. Epidemiol Rev 1985;7:178–208.
22. Lauritzen JB, Schwarz P, Lund B, McNair P, Transbol I. Changing incidence and lifetime risk of common osteoporosis related fractures: Hvidovre Osteoporosis Study. Osteoporosis Int 1993;3:127–32.
23. Versluysen M. How elderly patients with femoral fracture develop pressure sores in hospital. BMJ 1986;292:1311–3.
24. Miller CW. Survival and ambulation following hip fracture. J Bone Joint Surg [Am] 1978;60:930–4.
25. Chrischilles EA, Butler CD, Davis CS, Wallace RB. A model of lifetime osteoporosis impact. Arch Intern Med 1991;151:2026–32.
26. Phillips S, Fox N, Jacobs J, Wright WE. The direct medical costs of osteoporosis for American women aged 45 and older, 1986. Bone 1988;9:271–9.
27. Nydegger V, Rizzoli R, Rapin C-H, Vasey H, Bonjour J-P. Epidemiology of fractures of the proximal femur in Geneva: incidence, clinical and social aspects. Osteoporosis Int 1991;2:42–7.
28. de Bruijn HP. The Colles' fracture: review of literature. Acta Orthop Scand 1987;58 (Suppl 223):7–25.
29. Wadsworth TG. Colles' fracture: failure in management may cause permanent disability. BMJ 1990;301:192–4.
30. Atkins RM, Duckworth T, Kanis JA. The features of algodystrophy following Colles' fracture. J Bone Joint Surg [BR] 1990;72:105–10.
31. Melton LJ, Lane AW, Cooper C, Eastell R, O'Fallon WM, Riggs BL. Prevalence and incidence of vertebral deformities. Osteoporosis Int 1993;3:113–9.
32. Ettinger B, Black DM, Nevitt MC, Rundle AC, Cauley JA, Cummings SR, Genant HK and the Study of Osteoporotic Fractures Research Group. Contribution of vertebral deformities to chronic back pain and disability. J Bone Miner Res 1992;7:449–56.
33. Kanis JA, McCloskey EV. Epidemiology of vertebral osteoporosis. Bone 1992;13:S1–10.
34. Peck WA, Riggs BL, Bell NH, Wallace RB, Johnston CC Jr, Gordon SL, Shulman LE. Research directions in osteoporosis. Am J Med 1988;84:275–82.
35. Kanis JA, Pitt F. Epidemiology of osteoporosis. Bone 1992;31(Suppl 1):S7–15.
36. Levy E. Cost analysis of osteoporosis related to untreated menopause. Clin Rheumatol 1989;8(Suppl 2):76–82.
37. Cooper C, Campion G, Melton LJ III. Hip fractures in the elderly: a world-wide projection. Osteoporosis Int 1992;2:285–9.
39. Melton LJ, O'Fallon WM, Riggs BL. Secular trends in the incidence of hip fractures. Calcif Tissue Int 1987;41:57–64.
39. Schneider EL, Guralnik JM. The aging of America: impact on health care costs. JAMA 1990;263:2335–40.

40. Naessen T, Persson I, Adami H-O, Bergstrom R, Berqvist L. Hormone replacement therapy and the risk for first hip fracture. Ann Intern Med 1990;113:95–103.
41. Rehnberg L, Nungu S, Olerud C. The incidence of femoral neck fractures in women is decreasing [Abstract]. Acta Orthop Scand 1992;63(Suppl 248):92–3.
42. Spector TD, Cooper C, Fenton Lewis A. Trends in admissions for hip fracture in England and Wales, 1968–1985. BMJ 1990;300:173–4.
43. Kanis JA, Adami S. Bone loss in the elderly. Osteoporosis Int 1994 (in press).
44. Hansen M, Overgaard K, Riis B, Christiansen C. Role of peak bone mass and bone loss in postmenopausal osteoporosis: 12 year study. BMJ 1991;303:961–4.
45. Falch JA, Sandvik L. Perimenopausal appendicular bone loss: a ten-year prospective study. Bone 1990;11:425–8.
46. Christiansen C, Riis BJ, Rodbro P. Prediction of rapid bone loss in postmenopausal women. Lancet 1987;1:1105–8.
47. Hui SL, Wiske PS, Norton JA, Johnston CC J. A prospective study of change in bone mass with age in postmenopausal women. J Chron Dis 1982;35:715–25.
48. Aaron JE, Makins NB, Sagreiya K. The microanatomy of trabecular bone loss in normal ageing men and women. Clin Orthop 1987;215:260–71.
49. Parfitt AM, Mathews CHE, Villaneuva AR, Kleerkoper M, Frame B, Rao DS. Relationships between surface volume and thickness of iliac trabecular bone in ageing and osteoporosis. J Clin Invest 1983;72:1396.
50. Parfitt AM. Trabecular bone architecture in the pathogenesis and prevention of fracture. Am J Med 1987;82:68–72.
51. Krolner B, Pors Nielsen S. Bone mineral content of the lumbar spine in normal and osteoporotic women: cross-sectional and longitudinal studies. Clin Sci 1982;62:329–36.
52. Firooznia H, Sloutskis D, Anderson JJ, Anthony JM, Kiel DP. Quantitative computed tomography assessment of spinal trabecular bone. II. In osteoporotic women with and without vertebral fractures. J Comput Assist Tomogr 1984;8:99–103.
53. Chevalley T, Rizzoli R, Nydegger V, Slosman D, Tkatch L, Rapin CH, Vasey H, Bonjour J-P. Preferential low bone mineral density of the femoral head in patients with a recent fracture of the proximal femur. Osteoporosis Int 1991;1:147–54.
54. Hui SL, Slemenda CW, Johnston CC. Age and bone mass as predictors of fracture in a prospective study. J Clin Invest 1988;81:1804–9.
55. Cummings SR, Black DM, Nevitt MC, Browner WS, Cauley JA, Genant HK, et al. and the Study of Osteoporotic Fractures Research Group. Appendicular bone density and age predict hip fracture in women. JAMA 1990;263:665–8.
56. Wasnich RD, Ross PD, Davis JW, Vogel JM. A comparison of single and multi-site BMC measurements for assessment of spine fracture probability. J Nucl Med 1989;30:1166–71.
57. Wasnich RD, Ross PD, Davis JW, Vogel JM. Prediction of postmenopausal fracture risk with use of bone mineral measurements. Am J Obstet Gynecol 1985;153:745–51.
58. Wasnich RD, Ross PD, MacLean CJ, Davis JW, Vogel JM. The relative strengths of osteoporotic risk factors in a prospective study of postmenopausal osteoporosis. In: Christiansen C, Johansen JS, Riis BJ, editors. Osteoporosis vol. 1. 1984, Glostrup Hospital, Glostrup, Denmark, 394–5.
59. Wasnich RD, Ross PD, Vogel JM, Davis JW. Osteoporosis: critique and practicum. Honolulu, Hawaii: Banyan Press, 1989.
60. Lips P, Obrant KJ. The pathogenesis and treatment of hip fractures. Osteoporosis Int 1991;1:218–31.
61. Cooper C, Barker DJP, Morris J, Briggs RSJ. Osteoporosis, falls, and age in fracture of the proximal femur. BMJ 1987;295:13–5.
62. Cummings SR. Bone mass and bone loss in the elderly: a special case. In: Christiansen C, Riis B, editors. Fourth International Symposium on Osteoporosis. Redovre, Denmark, 1993:499–500.
63. Cameron JR, Mazess RB, Sorenson MS. Precision and accuracy of bone mineral determination by direct photon absorptiometry. Invest Radiol 1968;3:141–50.
64. Chestnut CH. Noninvasive techniques in the diagnosis of osteoporosis. Presented at the NIH Consensus Development Conference on Osteoporosis, 1984.
65. Gotfredsen A, Harsager C, Christiansen C. Total and regional bone mass in healthy and osteoporotic women. In: Yakamura S, editor. Advances in *in vivo* body composition studies. New York; Pleum Press 1990: 101–6.
66. Hansen MA, Hassager C, Overgaard K, Marslew U, Riis BJ, Christiansen C. Dual-energy X-ray absorptiometry: a precise method of measuring bone mineral density in the lumbar spine. J Nucl Med 1990;31:1156–62.
67. Kanis JA, McCloskey EV, Eyres KS, O'Doherty DV, Aaron JE. Screening techniques in the evaluation of osteoporosis. In: Drife JO, Studd JWW, editors. HRT and osteoporosis. Berlin: Springer, 1990:135–47.
68. Kanis JA, Caulin F, Russell RGG. Problems in the design of clinical trials in osteoporosis. In: Dixon A St J, Russell RGG, Stamp TCB, editors. Osteoporosis: a multidisciplinary problem. Royal Society of Medicine International Congress Symposium Series 55, Royal Society of Medicines, London 1983:205–22.
69. Cummings SR, Black DM, Nevitt MC, Browner W, Cauley J, Ensrud K, et al. and the Study of Osteoporotic Fractures Research Group. Bone density and hip fractures in older women: a prospective study. Lancet 1992;341:72–5.
70. Ross PD, Davis JW, Epstein RS, Wasnich RD. Pre-existing fractures and bone mass predict vertebral fracture incidence in women. Ann Intern Med 1991;114:919–23.
71. Black DJ, Cummings SR, Melton LJ III. Appendicular bone mineral and a woman's lifetime risk of hip fracture. J Bone Miner Res 1992;7:639–46.
72. Smith DM, Khairi MRA, Johnston CC. The loss of bone mineral with aging and its relationship to risk fracture. J Clin Invest 1975;56:311–8.
73. Cleghorn DB, Polley KJ, Bellon MJ, Chatterton J, Baghurst PA, Nordin BEC. Fracture rates as a function of forearm mineral density in normal postmenopausal women: retrospective and prospective data. Calcif Tissue Int 1991;49:161–3.
74. Hui SL, Slemenda CW, Johnston CC. Baseline measurement of bone mass predicts fracture in white women. Ann Intern Med 1989;111:355–61.
75. Nordin BEC, Need AG, Chatterton BE, Horowitz M, Cleghorn DB. Bone density screening for osteoporosis. Lancet 1990;336:1327–8.
76. Ross PD, Wasnich RD, Heilbrun LK, Vogel JM. Definition of a spine fracture threshold based upon prospective fracture risk. Bone 1987;8:271–8.
77. Melton LJ, Atkinson EJ, O'Fallon WM, Wahner HW, Riggs BL. Long-term fracture prediction by bone mineral assessed at different skeletal sites. J Bone Miner Res 1993;8:1227–33.
78. Gardsell P, Johnell O, Nilsson BE. Predicting fractures in women by using forearm bone densitometry. Calcif Tissue Int 1989;44:235–42.
79. Gardsell P, Johnell O, Nilsson BE. The predictive value of bone loss for fragility fractures in women: a longitudinal study over 15 years. Calcif Tissue Int 1991;49:90–4.
80. Neaton JD, Wentworth D, for the Multiple Risk Factor Intervention Trial Research Group. Serum cholesterol, blood pressure, cigarette smoking and death from coronary artery disease: overall findings and differences by age for 316099 white men. Arch Intern Med 1992;152:56–64.
81. Khaw K, Barrett-Connor E, Suarez L, Crique MH. Predictors of stroke associated mortality in the elderly. Stroke 1984;15:244–8.
82. Wilson JMG, Jungner G. Principles and practice of screening for disease. WHO Public Health Paper no. 34. Geneva: World Health Organization, 1968.
83. Kanis JA. Screening for postmenopausal osteoporosis: a review for the Department of Health, UK, 1992.
84. Dawson-Hughes B, Dallal GE, Krall EA, Sadowski L, Sahyoun N, Tannenbaum S. A controlled trial of the effect of calcium supplementation on bone density in postmenopausal women. N Engl J Med 1990;323:878–83.
85. Geusens P, Dequeker J, Verstraeten A, Nijs J. Age, sex and menopause related changes of vertebral and peripheral bone:

population study using dual and single photon absorptiometry and radiogrammetry. J Nucl Med 1986;27:1540–9.
86. Nilas L, Gotfredsen A, Riis BJ, Christiansen C. The diagnostic validity of local and total bone mineral measurements in postmenopausal osteoporosis and osteoarthritis. Clin Endocrinol 1986;25:711–20.
87. Devogelaer JP, Depresseux G, Nagant de Deuxchaisnes C. Reproducibility of single photon absorptiometry by rectilinear forearm scanning at three sites. In: Dequeker J, Geusens P, Wahner HW, editors. Bone mineral measurement by photon absorptiometry. Leuven: Leuven University Press, 1988:215–9.
88. Kollerup G, Sorensen HA. Bone mass in the forearm by dual photon energy X-ray absorptiometry. In: Christiansen C, Overgaard K, editors. Osteoporosis 1990. Copenhagen: Osteopress, 1990:736–8.
89. Garn SM, Sullivan TV, Decker SA, Larkin FA, Hawthorne VM. Continuing bone expansion and increasing bone loss over a two-decade period in men and women from a total community sample. Am J Hum Biol 1994 (in press).
90. Hui SL, Slemenda CW, Johnston CC. The contribution of bone loss to postmenopausal osteoporosis. Osteoporosis Int 1990;1:30–4.
91. Stepan JJ, Pospichal J, Schreiber V, Kanka J, Mensik J, Presl J, Pacovsky V. The application of plasma tartrate-resistant acid phosphatase to assess changes in bone resorption in response to artificial menopause and its treatment with estrogen and norethisterone. Calcif Tissue Int 1989;45:273–80.
90. Crilly RG, Jones MM, Horsman A, Nordin BEC. Rise in plasma alkaline phosphatase at the menopause. Clin Sci 1980;58:341–2.
93. Christiansen C, Riis BJ, Nilas L, Rodbro P, Deftos L, Uncoupling of bone formation and resorption by combined oestrogen and progestagen therapy in postmenopausal osteoporosis. Lancet 1985;2:800–1.
94. Stepan JJ, Pospichal J, Presl J, Pacovsky V. Bone loss and biochemical indices of bone remodelling in surgically induced postmenopausal women. Bone 1987;8:279–84.
95. Delmas PD. Biochemical markers of bone turnover for the clinical assessment of metabolic bone disease. Endocrinol Metab Clin North Am 1990;19:1–18.
96. Johansen JS, Riis BJ, Delmas PD, Christiansen C. Plasma BGP: an indicator of spontaneous bone loss and of the effect of oestrogen treatment in postmenopausal women. Eur J Clin Invest 1988;18:191–5.
97. Uebelhart D, Schlemmer A, Johansen JS, Gineyts E, Christiansen C, Delmas PD. Effect of menopause and hormone replacement therapy on the urinary excretion of pyridinium cross-links. J Clin Endocrinol Metab 1991;72:367–73.
98. Horsman A, Birchall MN. Assessment and modification of hip fracture risk: predictions of a stochastic model. In: DeLuca HF, Mazess R, editors. Osteoporosis: physiological basis, assessment and treatment. New York: Elsevier, 1990:45–50.
99. Trotter MN, Broman GE, Peterson RR. Densities of bones of white and negro skeletons. J Bone Joint Surg [Am] 1960;42:50–8.
100. Nordin BEC, MacGregor J, Smith DA. The incidence of osteoporosis in normal women: its relation to age and the menopause. Q J Med 1966;137:25–8.
101. Sowers MR, Wallace RD, Lemke JH. Correlates of mid-radius bone density among postmenopausal women: a community study. Am J Clin Nutr 1985;41:1045–53.
102. Evers SE, Orchard JW, Haddad RG. Bone density in postmenopausal North American Indians and caucasian females. Hum Biol 1985;57:719–26.
103. Dequeker J, Tobing L, Rutten V, Geusens P, Medos Study Group. Relative risk factors for osteoporotic fracture: a pilot study of the MEDOS questionnaire. Clin Rheumatol 1991;10:49–53.
104. Ray WA, Griffin MR, Schaffner W, Baugh DK, Melton LJ. Psychotropic drug use and the risk of hip fracture. N Engl J Med 1987;316:363–9.
105. Stevenson JC, Lees B, Devenport M, Cust MP, Ganger KF. Determinants of bone density in normal women: risk factors for future osteoporosis. BMJ 1989;298:924–8.
106. Laitinen K, Valimaki M, Keto P. Bone mineral density measured by dual-energy X-ray absorptiometry in healthy Finnish women. Calcif Tissue Int 1991;48:224–31.
107. Krall EA, Dawson-Hughes B. Smoking and bone loss among postmenopausal women. J Bone Miner Res 1991;6:331–8.
108. Aloia JF, Vaswani AN, Yeh JK, Ross P, Ellis K, Cohn SH. Determinants of bone mass in postmenopausal women. Arch Intern Med 1983;143:1700–4.
109. Bauer DC, Browner WS, Cauley JA, Orwoll ES, Scott JC, Black DM, et al. for the Study of Osteoporotic Fractures Research Group. Factors associated with appendicular bone mass in older women. Ann Intern Med 1993;118:657–75.
110. Cooper C, Atkinson EJ, Wahner HW, O'Fallon WM, Riggs BL, Judd HL, Melton LJ III. Is caffeine consumption a risk factor for osteoporosis? J Bone Miner Res 1992;7:465–71.
111. Elliott CA, Price VH, Wallace WA. The predictive value of radial and hip fracture for further fracture risk in Nottingham. In: Christiansen C, Overgaard K, editors. Osteoporosis 1990. Copenhagen: Osteopress, 1990:216–7.
112. Johnston CC, Melton LJ, Lindsay R, Eddy DM. Clinical indications for bone mass measurements. Report of scientific advisory committee of the National Osteoporosis Foundation. Bone Miner Res 1989; 4 (Suppl 2):1–28.
113. Slemenda CW, Hui SL, Longscope C, Wellman H, Johnston CC. Predictors of bone mass in perimenopausal women: a prospective study of clinical data using photon absorptiometry. Ann Intern Med 1990;112:96–101.
114. van Hemert AM. Epidemiology of osteoporosis and prediction of fractures: a nine-year population based follow up. Thesis, Erasmus University of Rotterdam, 1989.
115. Citron JT, Ettinger B, Genant HK. Prediction of peak premenopausal bone mass using a scale of weighted clinical variables. In: Christiansen C, Johansen JS, Riis BJ, editors. Osteoporosis 1987, vol. 1. Denmark: Norhaven, 1987:146–9.
116. Elders PJM, Netelenbos JC, Lips P, Khoe E, van Ginkil FC, Hulshof KFAM, van der Stelt PV. Perimenopausal bone mass and risk factors. Bone Miner 1989;7:289–99.
117. Nguyen T, Sambrook P, Kelly P, Jones G, Lord S, Freund J, Eisman J. Prediction of osteoporotic fractures by postural instability and bone density. BMJ 1993;307:1111–5.
118. Kiel DP, Felson DT, Anderson JJ, Wilson PWF, Moskovitz MA. Hip fracture and the use of estrogens in postmenopausal women: the Framingham Study. N Engl J Med 1987;317:1169–74.
119. Paganini-Hill A, Ross RK, Gerkins VR, Henderson BE, Arthur M, Mack TM. Menopausal estrogen therapy and hip fractures. Ann Intern Med 1981;95:28–31.
120. Grady D, Rubin SM, Petitti DB, Fox CS, Black D, Ettinger B, et al. Hormone therapy to prevent disease and prolong life in postmenopausal women. Ann Intern Med 1992;117:1016–37.
121. Naessen T, Parker R, Persson I, Zack M, Adami H-O. Time trends in incidence rates of first hip fracture in the Uppsala health care region, Sweden, 1965–1983. Am J Epidemiol 1989;130:289–99.
122. Daly E, Roche M, Barlow D, Gray A, McPherson K, Vessey M. Hormone replacement therapy in the menopause: an analysis of benefits, risks and costs. Report to the Department of Health, UK, 1991.
123. Lindsay R, Hart DM, MacLean A, Clark AC, Kraszewski A, Garwood J. Bone response to termination of oestrogen treatment. Lancet 1978;1:1325–7.
124. Christiansen C, Christensen MS, Transbol I. Bone mass in postmenopausal women after withdrawal of oestrogen/gestagen replacement therapy. Lancet 1981;1:459–61.
125. Stevenson JC, Kanis JA, Christiansen C. Bone density measurement. Lancet 1992;339:370–1.
126. Browner WS, Seeley DG, Vogt TM, Cummings SR. Non-trauma mortality in elderly women with low bone mineral density. Lancet 1991;338:355–8.
127. Johansson C. Osteoporosis in the elderly. MD thesis, University of Goteborg, 1993.
128. Dupont WD, Page DL. Menopausal estrogen replacement therapy and breast cancer. Arch Intern Med 1991;151:67–72.

129. Steinberg KK, Thacker SB, Smith SJ, Stroup DF, Zank MM, Flanders WD, Berkelman RL. A meta-analysis of the effect of estrogen replacement therapy on the risk of breast cancer. JAMA 1991;265:1985–90.
130. Brinton LA, Hoover R, Fraumeni JF. Menopausal oestrogens and breast cancer risk: an expanded case–control study. Br J Cancer 1986;54:825–32.
131. Bergkvist L, Adami HO, Persson I, Bergstrom R, Krusemo UB. Prognosis after breast cancer diagnosis in women exposed to estrogen and estrogen–progesterone replacement therapy. Am J Epidemiol 1989;130:221–8.
132. Barrett-Connor E, Bush TL. Estrogen and coronary heart disease in women. JAMA 1991;265:1861–7.
133. Cauley J, Cummings SR, Black DM, Mascioli SR, Seeley DG, Prevalence and determinants of estrogen replacement therapy in elderly women. Am Obstet Gynecol 1990;163:1438–44.
134. Egeland G, Kuller L, Matthews K, Kelsey S, Cauley J, Guzick D. Premenopausal determinants of menopausal estrogen use. Preventive Med 1991;20:343–9.
135. Vandenbroucke JP. Postmenopausal oestrogen and cardioprotection. Lancet 1991;337:833–4.
136. Nachtigall L, Nachtigall RH, Nachtigall RD, Beckman EM, Estrogen replacement therapy. II. A prospective study in the relationship in carcinoma and cardiovascular and metabolic problems. Obstet Gynecol 1979;54:74–9.
137. Persson I, Falkeborn M, Lithell H. The effect of myocardial infarction (MI) risk of estrogens and estrogen–progestin combinations. In: Sixth international congress on the menopause. Bangkok: Parthenon Publishing Group, 1990:223.
138. Tosteson ANA, Rosenthal DI, Melton LJ, Weinstein MC. Cost effectiveness of screening perimenopausal white women for osteoporosis: bone densitometry and hormone replacement therapy. Ann Intern Med 1990;113:594–603.
139. Henderson BE, Paganini-Hill A, Ross RK. Decreased mortality in users of estrogen replacement therapy. Arch Intern Med 1991;151:75–8.
140. Hillner BE, Hollenberg JP, Pauker SG. Postmenopausal estrogens in prevention of osteoporosis. Am J Med 1986;80:1115–27.
141. Chapuy MC, Arlot ME, Duboeuf F, Brun J, Cronzet B, Arnaud S, Delmas PD, Meunier PJ. Vitamin D_3 and calcium to prevent hip fractures in elderly women. N Engl J Med 1992;327:1637–42.
142. Dawson-Hughes B. Calcium supplementation and bone loss: a review of controlled clinical trials. Am J Clin Nutr 1991;54:274S–280S.
143. Elders PJM, Netelenbos JC, Lips P, van Ginkel FC, Khoe E, Leeuwenkamp OR, Hackeng WHL, van der Stelt PF. Calcium supplementation reduces vertebral bone loss in perimenopausal women: a controlled trial in 248 women between 46 and 55 years of age. J Clin Endocrinol Metab 1991;73:533–40.
144. Kanis JA, Johnell O, Gullberg B, Allander E, Dilzen G, Gennari C, et al. Evidence for the efficacy of bone active drugs in the prevention of hip fracture. BMJ 1992;305:1124–8.
145. Storm T, Thamsborg G, Steiniche T, Genant HK, Sorensen OH. Effect of intermittent cyclical etidronate therapy on bone mass and fracture rate in postmenopausal osteoporosis. N Engl J Med 1990;322:1265–71.
146. Watts NB, Harris ST, Genant HK, Wasnich RD, Miller PD, Jackson RD, et al. Intermittent cyclical etidronate treatment of postmenopausal osteoporosis. N Engl J Med 1990;323:73–9.
147. Reginster JY, Denis D, Albert A, et al. One-year controlled randomised trial of prevention of early postmenopausal bone loss by intranasal calcitonin. Lancet 1987;2:1481–3.
148. Reginster JY, Lecart MP, Deroisy R, Sarlet N, Denis D, Ethgen D, Collette J, Franchimont P. Prevention of postmenopausal bone loss by tiludronate. Lancet 1989;2:1469–71.
149. Overgaard K, Hansen MA, Nielsen V-AH, Riis BJ, Christiansen C. Discontinuous calcitonin treatment of established osteoporosis: effects of withdrawal of treatment. Am J Med 1990;89:1–6.
150. Peyron R, Serrurier D, Edouard C, Ghozlan R, Mayoux-Benhamou A, Meunier PJ. Treatment of high remodelling vertebral osteoporosis with human calcitonin: a two-year double blind placebo-controlled trial in 93 patients. In: Christiansen C, Overgaard K, editors. Osteoporosis 1990. Copenhagen: Osteopress, 1990:1430–2.
151. Overgaard K, Hansen MA, Jensen SB, Christiansen C. Effect of salcatonin given intranasally on bone mass and fracture rates in established osteoporosis: a dose–response study. BMJ 1992;305:556–61.
152. Orimo H, Shiraki M, Hayashi T, Nakamura T. Reduced occurrence of vertebral crush fractures in senile osteoporosis treated with 1(OH)-vitamin D_3. Bone Miner 1987;3:47–52.
153. Tilyard M, Spears GFS, Thomson J, Dovey S. Treatment of postmenopausal osteoporosis with calcitriol or calcium. N Engl J Med 1992;326:357–62.
154. Felson DT, Sloutskis D, Anderson JJ, Anthony JM, Kiel DP. Thiazide diuretics and the risk of hip fracture. JAMA 1991;265:370–3.
155. LaCroix AZ, Wienpahl J, White LR, Wallace RB, Scherr PA. George LK, et al. Thiazide diuretic agents and the incidence of hip fracture. N Engl J Med 1990;322:286–90.
156. Ray WA. Long term use of thiazide diuretics and the risk of hip fracture. Lancet 1989;1:687–90.
157. Kanis JA, Beneton MNC, Gennari C, Gullberg B, Johnell O, Mazzuoli GF, Passeri M. Effects of anabolic steroids on cortical bone and fractures. In: Christiansen C, Riis B, editors. Fourth international symposium on osteoporosis. Redovra: Denmark, 1993:308–10.
158. Riggs BL, Hodgson SF, O'Fallon WM, Chao Eys, Wahner HW, Muhs JM, et al. Effect of fluoride treatment on the fracture rate in postmenopausal women with osteoporosis. N Engl J Med 1990;22:802–9.
159. Pak CY, Sakhaee K, Zerwekh JE, Parcel C, Peterson R, Johnson K. Safe and effective treatment of osteoporosis and intermittent slow release sodium fluoride: augmentation of vertebral bone mass and inhibition of fractures. J Clin Endocrinol Metab 1989;68:150–9.
160. Kanis JA, Meunier PJ, Should we use fluoride to treat osteoporosis? Q J Med 1984;53:145–64.
161. Mamelle N, Meunier PJ, Dusan R, Guilaume M, Martin JL, Gaucher A, et al. Risk–benefit ratio of sodium fluoride treatment in primary vertebral osteoporosis. Lancet 1988;2:361–5.
162. Cummings SR, Black D. Should perimenopausal women be screened for osteoporosis? Ann Intern Med 1986;104:817–23.
163. Suman VJ, Atkinson EJ, O'Fallon WM, Black DM, Melton LJ. A nomogram for predicting lifetime hip fracture risk from radius bone mineral density and age. Bone 1993;14:843–6.
164. Cuckle HS, Wald NJ. Principles of screening. In: Wald N, editor. Antenatal and neonatal screening. Oxford: Oxford University Press, 1984:1–22.
165. Cadman D, Chambers L, Feldman W, Sackett D. Assessing the effectiveness of community screening programmes. JAMA 1984;251:1580.

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