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ORIGINAL ARTICLE

The use of multiple sites for the diagnosis of osteoporosis

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Abstract *Introduction:* It has been suggested that bone mineral density (BMD) measurements should be made at multiple sites, and that the lowest T–score should be taken for the purpose of diagnosing osteoporosis. *Purpose:* The aim of this study was to examine the use of BMD measurements at the femoral neck and lumbar spine alone and in combination for fracture prediction. *Methods:* We studied 19,071 individuals (68% women) from six prospective population-based cohorts in whom BMD was measured at both sites and fracture outcomes documented over 73,499 patient years. BMD values were converted to Z-scores, and the gradient of risk for any osteoporotic fracture and for hip fracture was examined by using a Poisson model in each cohort and each gender separately. Results of the different studies were merged using weighted β-coefficients. *Results:* The gradients of risk for osteoporotic fracture and for hip fracture were similar in men and women. In men and women combined, the risk of any osteoporotic fracture increased by 1.51 [95% confidence interval (CI)= 1.42–1.61] per standard deviation (SD) decrease in femoral-neck BMD. For measurements made at the lumbar spine, the gradient of risk was 1.47 (95% CI= 1.38–1.56). Where the minimum of the two values was used, the gradient of risk was similar (1.55; 95% CI=1.45–1.64). Higher gradients of risk were observed for hip fracture outcomes: with BMD at the femoral neck, the gradient of risk was 2.45 (95% CI=2.10–2.87), with lumbar BMD was 1.57 (95% CI= 1.36–1.82), and with the minimum value of either femoral neck and lumbar spine was 2.11 (95% CI=1.81–2.45). Thus, selecting the lowest value for BMD at either the femoral neck or lumbar spine did not increase the predictive ability of BMD tests. By contrast, the sensitivity increased so that more individuals were identified but at the expense of specificity. Thus, the same effect could be achieved by using a less stringent T–score for the diagnosis of osteoporosis. *Conclusion:* Since taking the minimum value of the two measurements does not improve predictive ability, its clinical utility for the diagnosis of osteoporosis is low.

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Introduction

The internationally agreed upon description of osteoporosis is a progressive systemic skeletal disease characterised by low bone mass and micro-architectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture [1]. This description identifies low bone mineral density (BMD) as a central component but recognises the contribution of other skeletal and non-skeletal factors in the pathogenesis of fracture.

In 1994, the World Health Organisation (WHO) [2] provided an operational definition of osteoporosis in terms of BMD since this can be measured with some accuracy and precision whereas this is not the case for other determinants of osteoporotic fracture risk. Osteoporosis was defined as a decrease in BMD in postmenopausal women that was equal to or greater than 2.5 standard deviations (SD) below the average value for young healthy women (i.e. a T–score <−2.5 SD). The same criteria for osteoporosis are also applied to men [3]. With the development of more densitometry technologies, a reference standard has been proposed using dual energy X-ray absorptiometry (DXA) at the proximal femur. The reference value for computing the T–score is based on young healthy women (aged 20–29 years) using the National Health and Nutrition Examination Survey (NHANES) III reference base [4, 5].

There is still some ambiguity over the region of the hip to be used (femoral neck or total hip) although the femoral neck may be preferred since most data are available for this site and meta-analyses have characterised carefully the gradient of fracture risk provided at this site [6, 7]. A view has recently emerged that BMD should be measured not only at the hip but also at the lumbar spine in all patients for the purpose of diagnosing osteoporosis; where there are technical problems at any of these sites, the forearm should be additionally measured. The position statements of the International Society for Clinical Densitometry (ISCD) [8, 9] recommend that osteoporosis be diagnosed on the basis of the lowest T–score for BMD found at the spine, total hip, femoral neck or trochanter (or distal one third of the radius). The reason for recommending assessment of multiple regions is not clear but may relate to an assumption that the combined use of two or more sites may improve the prognostic value of the BMD test to predict fractures. The aim of this study was to test this assumption.

Methods

We studied 19,071 men and women from six prospectively studied, population-based cohorts in whom BMD measurements were available at the femoral neck and lumbar spine. Details of the cohorts studied have been previously published [5] but are summarised below and in Table 1.

Canadian Multicentre Osteoporosis Study (CaMos)

The Canadian Multicentre Osteoporosis Study (CaMos) is an on-going prospective age-stratified cohort. The study is documenting the incidence of fractures and risk factors in a random sample of 9,424 men and women aged 25 years or more selected by telephone listings. The sampling frame is from nine study centres in seven provinces [10]. Characterisation of individuals was by interview. BMD was measured by DXA at the femoral neck and lumbar spine (Hologic QDR 1000) in 8,307 individuals.

Dubbo Osteoporosis Epidemiology Study (DOES)

The Dubbo Osteoporosis Epidemiology Study (DOES) is a population-based study with multiple assessments of skeletal status in men and women aged 60 years or more from Dubbo, Australia [11, 12]. Participation in the study was 56% of the population. Baseline measurements included BMD at the femoral neck and lumbar spine assessed using DXA (GE–Lunar, DPX and Prodigy). Fractures are identified through radiologists' reports from the two centres servicing the region. Measurements of BMD at the femoral neck and lumbar spine were available in 2,038 of 2,071 individuals.

European Vertebral Osteoporosis Study (EVOS)

The European Vertebral Osteoporosis Study (EVOS) comprised age- and gender-stratified random samples

Table 1 Details of cohorts studied. *CaMos* Canadian Multicentre Osteoporosis Study, *EVOS* European Vertebral Osteoporosis Study, *EPOS* European Prospective Osteoporosis Study, *DOES* Dubbo Osteoporosis Epidemiology Study

Cohort	Sample size	% women	Person-years	Mean age (years)	Any fracture	Osteoporotic fracture	Hip fracture
CaMos	8,307	69	23,678	60.9	508	261	27
EVOS/EPOS	3,391	52	9,850	63.9	179	179	13
DOES	2,038	61	15,634	70.3	506	398	104
Hiroshima	2,593	69	9,793	65.1	186	89	31
Kuopio	1,750	100	8,360	52.2	177	–	–
Rochester	992	65	6,182	56.7	285	240	42
Totals	19,073	68	73,499	62.0	1,841	1,167	217

from 36 centres in 19 European countries [13]. Equal numbers of men and women were drawn in each centre within six 5–year age bands (50–54 up to 75–79 years). BMD was measured in 3,391 men and women from 13 centres by DXA at the lumbar spine and femoral neck using pencil beam machines that were cross-calibrated using the European spine phantom. The sample provided the framework for the European Prospective Osteoporosis Study (EPOS) where repeated assessment was undertaken in 29 of the centres [14, 15].

Hiroshima

The Adult Health Study (AHS) was established to document the 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% throughout this period. BMD at the spine and femoral neck was measured at each examination using DXA (Hologic QDR–2000) in 1994. Trained nurses interviewed the subjects about fracture at each examination [16, 17].

Kuopio

The Kuopio Osteoporosis Risk Factor and Prevention (OSTPRE) study in Finland comprised a postal enquiry sent to all 14,220 women aged 47–56 who were residents of Kuopio province in 1989 [18]. Of those women, 13,100 responded to the enquiry, of whom 938 were excluded for incomplete information. This left a study population of 12,162 women. A random stratified sample of 1,750 women underwent bone densitometry at the femoral neck and lumbar spine using the Lunar DPX [19].

Rochester

The Rochester cohort was recruited from two random population samples stratified by decade of age, one comprising women who were subsequently followed for up to 20 years [20] and another sample of women and men followed for 8 years [21]. BMD of the right femoral neck and lumbar spine was measured by dual photon absorptiometry in the first cohort (cross-calibrated to DXA) and by DXA (Hologic QDR 2000) in the second group. Fractures were ascertained by periodic interview combined with review of the inpatient and outpatient medical records of all local care providers.

Baseline and outcome variables

Since BMD was assessed by multiple techniques, the Z-score of BMD at each site for each gender and each cohort was computed from the regression of BMD by age. The variance of BMD by age was homogenous. Fracture ascertainment was undertaken by self-report (Kuopio, EVOS/EPOS, Hiroshima) and/or verified from hospital or central databases (CaMos, DOES, Kuopio, EVOS/EPOS, Rochester). The EPOS study also included sequential systematic radiography to define incident vertebral deformities, but only reports of clinical fractures were used. In addition, fractures considered to be due to osteoporosis were analysed, and finally, hip fracture alone was considered separately. An osteoporotic fracture was one considered to be due to osteoporosis by the investigator. For the EVOS/EPOS study, osteoporotic fractures comprised hip, forearm, humeral or limb fractures. For the CaMos study, they comprised fractures of the spine, pelvis, ribs, distal forearm, forearm and hip. In the other cohorts, fractures at sites considered to be characteristic for osteoporosis [22] were extracted by the authors.

Statistical methods

The risk of fracture was estimated by the use of Poisson regression applied to each cohort and each gender separately. Covariates included time since the start of follow-up and current age. We additionally tested interactions with age and BMD Z-scores in the model. The β-values for each coefficient are age dependent, $\beta_k\beta_k$.age. The estimated value of $\beta_k\beta_k$.age was determined for each age from 50–85 years, together with the variance. The results of each analysis and the two genders were weighted according to the variance and merged to determine the weighted mean and standard deviation. The risk ratios at different BMD Z-scores are then given by $e^{(\text{weighted mean coefficient})}$ and expressed as a risk ratio per SD decrease in BMD where the SD was gender specific. We additionally computed a risk ratio per unit change in BMD (0.1 g/cm^2) so that the gradient of fracture risk in men and women could be compared using the same denominator.

We used a fixed-effects model rather than a random-effects model since the latter gives undue weight to the effects of smaller cohorts. In addition, the fixed-effect model generally gives a more conservative (i.e. lower) point estimate for the risk ratio, albeit with wider confidence estimates. Heterogeneity in outcome variables between cohorts was tested by means of the I^2 statistic [23], and where more than moderate heterogeneity was found (>50%), risk ratios were re-computed using the random-effects model to determine whether the significance of estimates had changed.

The effect of measuring two sites and selecting the lowest Z-score value on the proportion of the population selected was computed from the correlation coefficient

between the femoral-neck BMD and lumbar spine BMD, as given in the Appendix.

Results

Details of the cohorts are provided in Table 1. The total sample studied was 19,071 men and women who were followed for 73,499 person years. During this time, there were 1,841 fractures, 1,167 of which were considered to be due to osteoporosis, and 217 hip fractures. For hip fracture outcomes, there was a low degree of heterogeneity (I^2=11% 95% CI=0–53), but heterogeneity was more marked for all osteoporotic fractures (I^2=51%; 95% CI=5–75) and for any fracture (I^2=58%; 95% CI=14–79). When current age was used with BMD Z-score as an interaction term (age x BMD), there was low heterogeneity for any fracture (I^2=10%; 95% CI=0–50; p >0.3), osteoporotic fracture (I^2=0%; 95% CI=0–63; p >0.3) and for hip fracture outcomes and BMD (I^2=0%; 95% CI=0–98; p >0.3), and the interaction term was retained in all analyses.

Gender

The gradients of risk determined by BMD at the femoral neck for the prediction of any fracture, any osteoporotic fracture and hip fracture alone are shown in Table 2. Relative risk per SD decrease in BMD were highest for hip fracture, lowest for any fracture and intermediate for osteoporotic fracture. For measurements at the lumbar spine, gradients of risk were similar to those noted at the femoral neck for any fracture and for any osteoporotic fracture but somewhat lower for the prediction of hip fracture. There was no difference in the gradient of risk between men and women at any site for any fracture outcome although relative risk per SD change was marginally higher in men than in women for hip fracture. These differences were even less apparent when gradients of risk were examined by unit change (0.1 g/cm^2) in BMD (Table 3).

Table 3 Relative risk (RR) per unit (0.1 g/cm^2) decrease in bone mineral density (BMD) in men and women. *CI* confidence interval

Outcome		Femoral neck		Lumbar spine	
Fracture	Gender	RR/unit	95% CI	RR/unit	95% CI
Any	Men	1.36	1.26–1.48	1.21	1.15–1.28
	Women	1.27	1.22–1.33	1.22	1.18–1.26
	Combined	1.29	1.25–1.34	1.22	1.18–1.25
Osteoporotic	Men	1.45	1.31–1.59	1.27	1.19–1.35
	Women	1.31	1.24–1.38	1.23	1.18–1.28
	Combined	1.34	1.28–1.40	1.24	1.20–1.28
Hip	Men	1.98	1.57–2.51	1.37	1.18–1.59
	Women	1.90	1.66–2.17	1.27	1.15–1.39
	Combined	1.92	1.70–2.16	1.29	1.19–1.40

Combining measurements

The Z-score at the lumbar spine was lower than that at the hip in 34% of cases, a fraction that was constant irrespective of whether or not a fracture event occurred. Five percent of individuals had a Z-score for BMD of −2.5 or less at either the lumbar spine or femoral neck, and 0.7% had a Z-score of ≤−2.5 at both sites. When the lowest value of BMD at the lumbar spine and femoral neck was taken, gradients of risk for any fracture and for any osteoporotic fracture were similar to those afforded by measurement at the femoral neck or lumbar spine alone. For hip fracture risk, mid-point estimates lay intermediate between the gradients of risk provided by each of the techniques alone (see Table 2). Thus, there was no increase in predictive ability by selecting the lowest Z scores from the femoral neck and lumbar spine BMD measurements.

Where the best linear combination of femoral neck and lumbar spine BMD was modelled, the combination gave a gradient of risk of 2.47 (95% CI=2.12–2.89/SD) for hip fracture risk, which is not an improvement on the use of femoral-neck BMD alone (see Table 2). The same conclusion was reached for the prediction of osteoporotic fracture [relative risk (RR)=1.59/SD] and for any fracture (RR=1.48/SD).

Table 2 Relative risk (RR) per standard deviation (SD) decrease in Z-score of bone mineral density (BMD) in men and women. *CI* confidence interval

Outcome		Femoral neck		Lumbar spine		Combined minimum Z-score of the two sites	
Fracture	Gender	RR/SD	95% CI	RR/SD	95% CI	RR/SD	95% CI
Any	Men	1.52	1.36–1.69	1.45	1.31–1.62	1.48	1.33–1.64
	Women	1.42	1.34–1.49	1.41	1.34–1.49	1.45	1.37–1.53
	Combined	1.43	1.37–1.51	1.42	1.35–1.49	1.45	1.38–1.52
Osteoporotic	Men	1.67	1.46–1.91	1.61	1.41–1.84	1.64	1.44–1.88
	Women	1.47	1.37–1.57	1.43	1.34–1.54	1.52	1.52–1.63
	Combined	1.51	1.42–1.61	1.47	1.38–1.56	1.55	1.45–1.64
Hip	Men	2.54	1.83–3.52	1.92	1.42–2.60	2.13	1.58–2.87
	Women	2.43	2.03–2.90	1.48	1.26–1.74	2.10	1.77–2.50
	Combined	2.45	2.10–2.87	1.57	1.36–1.82	2.11	1.81–2.45

Table 4 Proportion of the population identified as osteoporotic on one or two tests according to the correlation coefficient between tests

Prevalence of osteoporosis Percent[a]	Correlation coefficient[b]		
	0.40	0.64	0.80
	(This study)		
1.0	2.1	1.9	1.7
10.0	16.8	15.4	14.0
20.0	34.1	31.1	28.6
50.0	68.5	64.1	60.3
75.0	90.0	86.6	83.8
90.0	97.5	96.0	94.6

[a]The left-hand column gives a range of prevalences of osteoporosis with one test

[b]The correlation coefficients between bone mineral density (BMD) at the lumbar spine and femoral neck was 0.64. The effect of a lower and higher correlation coefficients is also shown

Impact on selection of patients

The correlation coefficient between measurements made at the lumbar spine and femoral neck was 0.638. From the correlation coefficient, if 10% of individuals in a population were characterised as having osteoporosis on the basis of BMD at the femoral neck alone, the prevalence of osteoporosis would increase to 15.3% with the addition of lumbar spine measurements and taking the minimum value to dichotomise the population. Further examples are shown in Table 4. The effect is more marked the lower the correlation coefficient.

Impact on relative risk

Individuals were characterised as having 'low' or 'high' BMD according to a T-score of ≤−2.5 or >−2.5. For men, 95% had a T-score >−2.5 at both the lumbar spine and femoral neck, and 0.7% had a T-score of <−2.5 at both sites. For women, the frequencies were 81% and 5.5%, respectively. The relative risk of fracture increased with the number of low BMD sites (Table 5). For hip fracture prediction, for example, the RR was 7.3 in men and 3.0 in women in the presence of one low BMD site. The RR was increased still further to 17.5 and 4.5, respectively, with two abnormal sites. Thus, the greater the number of low sites, the higher the RR but the lower the prevalence in the population.

In the presence of two low sites, the prevalences were 0.7% and 5.5% in men and women, respectively. In the case of femoral-neck measurements alone, prevalences of 0.7% and 5.5% are equivalent to T-scores of −3.22 and −2.94 in men and women, respectively. At these T-scores, the relative risk for hip fracture was 22.3 in men and 6.1 in women. Thus, the relative risks using hip BMD alone were similar or higher than those provided by both lumbar spine and femoral-neck BMD combined at the same prevalence.

Table 5 Risk ratio (RR) [±95% confidence interval (CI)] for fractures at the sites shown in men and women according to the number of bone mineral density (BMD) sites (lumbar spine or femoral neck) with a T-score of ≤–2.5

Number of abnormal BMD sites	Outcome fracture	Men		Women	
		RR	95% CI	RR	95% CI
0	Any	1.0	–	1.0	–
1		3.3	2.4–4.4	1.9	1.7–2.1
2		6.5	3.5–12	2.2	1.8–2.5
0	Osteoporotic	1.0	–	1.0	–
1		3.7	2.5–5.4	2.1	1.8–2.4
2		9.9	4.8–20	3.0	2.5–3.7
0	Hip	1.0	–	1.0	–
1		7.3	3.5–15	3.0	2.1–4.3
2		18	5.9–52	4.5	3.0–6.8

Discussion

The present analysis derives similar values as found in previous meta-analyses [4, 5] that examined the gradients of risk for hip fracture or for osteoporotic fracture from BMD measurements at the femoral neck or lumbar spine. An advantage of the present study is that the meta-analysis is based on individual data from each cohort and not on published values with summary statistics. The homogeneity of the data further suggests that these findings can be applied generally. The present analysis also indicates that the gradients of fracture risk in men and women are broadly similar for BMD measurements at the hip or lumbar spine, as shown in other population-based studies [24–29] and in a previous meta-analysis for femoral-neck measurement using a larger number of cohorts [5]. Thus, if there are differences in fracture risk prediction between men and women using DXA at either site, these differences are small.

The principal aim of the present study was to determine whether the incorporation of more than one site would improve the gradient of risk for fracture prediction. The results suggest that combining BMD at the lumbar spine and femoral neck and selecting the lowest value does not increase predictive ability compared with a measurement from either site alone, as predicted by Blake et al. [30]. Indeed, for hip fracture prediction, the combination had a somewhat lower predictive value than measurements made at the hip alone. The same may hold true for vertebral fracture risk: an independent study examined the risk of vertebral fracture in the placebo arm of a large multinational study [31]. When patients in this latter study were categorised according to the presence or absence of osteoporosis, as judged by the T-score, the risk ratio for vertebral fracture was 2.47 (95% CI=1.79–3.42) using the T-score at the femoral neck, 1.84 (95% CI=1.19–2.85) at the lumbar spine, and 1.75 (95% CI=1.23–2.49) using the minimum T-score at either site.

The lack of additive value in the example given in this paper may relate to progressive osteoarthrosis at the lumbar spine with age. Sclerosis will contribute to the BMD result but is unlikely to strengthen the bones of the spine or to be

associated with stronger bones at another site. Irrespective of any mechanism, BMD tests at the lumbar spine may be of more value for monitoring treatment since the spine is considered to be the most responsive site to pharmacologic intervention.

The use of the minimum Z-score did have an important effect on the number of individuals considered to have osteoporosis, an effect that depended upon the correlation coefficient between the two BMD measurements. Since the gradient of risk is not improved (gradient of risk is proportional to the area under the ROC curve), the sensitivity of the technique is improved but at the expense of specificity. Thus, the net effect is to use a less stringent criterion for diagnostic purposes. The effect would be more marked the more sites used for diagnostic purposes. The same effect can be achieved by the use of a single BMD measurement and using a less stringent diagnostic criterion, say a T-score of −2.0 SD. This strategy erodes, therefore, the WHO concept of an international reference standard for diagnosis since the prevalence of osteoporosis and the risk associated therewith will vary according to the number of sites measured. It is for this reason that the International Osteoporosis Foundation has recommended that diagnostic criteria should be confined to DXA at a single site (the femoral neck) using a single reference base [3].

The results should not be interpreted to mean that there is no value in combining indices of fracture risk. Indeed, the converse is true. There are, in principle, two considerations; the first where the combined gradient of risk is equal to that of either measurement, and the second where there is an improved gradient of risk.

In the present study, the former situation applies. For example, the gradient of risk for the production of osteoporotic fractures was approximately a 1.5/SD decrease in Z-score for BMD, irrespective of the site or combination used (see Table 2). If the prevalence of osteoporosis were 10% in a given population with the use of one test, the prevalence increases to 15.4% when two tests are used (see Table 5). The risk in the former population compared with that of the general population (PRR) is 1.91, and the PRR in the latter is lower at 1.75. This is the expected trade-off between sensitivity and specificity. However, in that population with osteoporosis at both sites (approximately 3%), then the PRR is 2.33. Thus, the presence of two abnormal tests gives a higher PRR because a smaller proportion of the population is selected. Indeed, when the proportion of the population was fixed, the use of femoral-neck BMD alone gave risk ratios that were similar to those found with the use of the two BMD sites.

A somewhat different situation pertains to the combination of risk factors that improves the gradient of risk of the test. If it was desired to treat 10% of the population, a test with a gradient of risk of 1.5/SD would identify a population with a PRR of 1.91, as given above. With an improvement in gradient of risk from 1.5 to 1.8/SD by the addition of an independent risk factor, the PRR is 2.44. Thus, improvements in gradients of risk with the combination of BMD and independent risk factors [32] increases the risk in any selected population whereas in the first situation improvements in PRR are related to a decrease in the population selected. Further examples are given in Table 6.

Table 6 Population relative risk (PRR*, i.e. risk of a segment of the population compared with the general population) according to the proportion of the population selected and the gradient of risk/standard deviation (SD) change in risk score

Gradient of risk	Proportion of population selected (%)			
	10	20	30	40
1.5	1.91	1.66	1.51	1.40
2.0	2.78	2.20	1.89	1.67
2.5	3.57	2.65	2.17	1.87
3.0	4.27	3.01	2.39	2.00
3.5	4.89	3.30	2.56	2.10

$\mathrm{PRR} = \left(1 - \phi\left(\phi^{-1}(1-p) - 1n(GR)\right)\right)/p$

where ϕ is the standardised normal distribution function, p is the proportion of the population selected, and GR is the gradient of risk/SD

We conclude that BMD measurements at the lumbar spine predict any fracture and any osteoporotic fracture as well as measurements at the femoral neck. For hip fracture, the predictive value is less with lumbar-spine BMD than with femoral-neck BMD. No advantage is afforded by combining the values of femoral neck and lumbar spine and using the lowest of these two for the diagnosis of osteoporosis although they may be of value in the assessment of fracture risk.

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Appendix

The proportion of individuals with at least one type of BMD measurements below a cut off

Let Ai denote the event that the measurement of type i is below a cut off g. We use the symbols ∪ and ∩ for the union and the intersection of events, respectively. The probability that any of n measurements is below the cut off is

$$P(A_1 \cup A_2 \cup \ldots \cup A_n)$$

The following notations are used

$$S_1 = \sum P(A_i)$$

$$S_2 = \sum P(A_i \cap A_j)$$

$$S_3 = \sum P(A_i \cap A_j \cap A_k)$$

$$S_n = P(A_1 \cap A_2 \ \ldots \ \cap A_n)$$

Then the relationship below holds

$$P(A_1 \cup A_2 \cup \ldots \cup A_n) = \sum (-1)^{i+1} S_i$$

The argument $(-1)^{i+1}$ obviously can only take the values +1 or −1. This is because the first argument of the summation (S_1) double counts some combination areas of A_1 A_2 A_3 etc. Those probabilities have to be subtracted in the second argument, but since too much is subtracted, there needs to be some adding in the third argument and so on…

When only two sites of measurement are considered (e.g. BMD at lumbar spine and femoral neck), the relationship can be written

$$P(A \cup B) = P(A) + P(B) - P(A \cap B)$$

The last term of the above expression, P(A∩B), is the probability that both measurements are below the cut-off limit g. We assume that the scale of the measurements is standardised so their means and SDs are 0 and 1, respectively. If the correlation coefficient between the measurements is ρ, then the probability that both of two measurements, X and Z, are below the limit g and can be written

$$\begin{aligned} P(A \cap B) &= P(\{X < g\} \cap \{Z < g\}) \\ &= P(\{X < g\} \cap \{\rho \cdot X + Y < g\}), \end{aligned}$$

where X and Y are independent and X has a normal distribution with the mean 0 and the standard deviation 1, and Y has a normal distribution with the mean 0 and the variance $1-\rho^2$. Then the variance of $\rho \cdot X+Y$ is 1 and the covariance between X and $\rho \cdot X+Y$ is ρ, so the correlation coefficient is also ρ. Let Φ denote the standardised normal distribution function. We then obtain

$$P(A \cap B) = \int_{-\infty}^{g} \Phi\left(\frac{g - \rho \cdot x}{\sqrt{1-\rho^2}}\right) \cdot \frac{\exp(-x^2/2)}{\sqrt{2\pi}} dx$$

and

$$P(A) + P(B) = 2\ \Phi(g)$$

Thus, the probability that any of the two measurements is below the limit g, P(A ∪ B) can be calculated by the two last-mentioned relationships.

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