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Abstract

The aim of this prospective study was to identify clinical risk factors (CRFs) for a major osteoporotic (OP) fracture and to assess whether a risk score combining these factors to BMD or the FRAX score improve the ability to identify women at high risk of fracture in early postmenopausal women. The study population included 2,651 peri- and early post-menopausal women (mean age (± SD): 54 ± 4 yr) with a mean follow-up period of 13.4 years (± 1.4 years). At baseline, a large set of CRFs was recorded and vertebral BMD was measured (Lunar, DPX) in all women. Femoral neck BMD was also measured in 1,399 women in addition to spine BMD. Women with current or past OP treatment >3 months at baseline (n=454) were excluded from the analyses. Over the follow-up period, 415 women sustained a first low-energy fracture including 145 major OP fractures (108 wrist, 44 spine, 20 proximal humerus, 13 hip). In Cox multivariate regression models, only 3 CRFs were significant predictors of a major OP fracture independently of BMD and age: a personal history of fracture, 3+ pregnancies and current postmenopausal hormone therapy. When combining spine BMD and CRFs, the area under receiver operating characteristics curve (AUC) of the model-based risk score (0.69) was somewhat higher than the AUC of spine BMD alone (0.65) (p=0.007). However, the sensitivity of the score remained moderate: to identify 80% of women who subsequently sustained a fracture, the cut-off for high risk had to be set above 50%. When combining hip BMD and CRFs, the AUC of the model-based risk score (0.70) and of the FRAX score (0.66) were not significantly different from the AUC of hip BMD alone (0.69).

Only a limited number of clinical risk factors were found associated with the risk of major OP fracture in early postmenopausal women. In this population, the FRAX tool had a poor sensitivity for fracture prediction and did not significantly improve the discriminant value of hip BMD alone.

MESH Keywords Bone Density ; Female ; Fractures, Bone ; etiology ; Humans ; Middle Aged ; Osteoporosis, Postmenopausal ; complications ; Postmenopause ; Prospective Studies ; Risk Factors ; Sensitivity and Specificity

The 1994 WHO definition of osteoporosis (1), i.e. a bone mineral density (BMD) value less than 2.5 standard deviations from the young adult normal value (T score < −2.5) represents the landmark which has been used in most clinical trials as a major inclusion criteria (2) and consequently remains often used as an intervention threshold by a lot of practitioners (3). However, and even though a low BMD is strongly associated with the risk of fracture, it is well recognized that different risk factors, such as age, history of a prior fragility fracture, steroid use and many others are independent contributors to the risk of fracture and improve the sensitivity of BMD measurement to identify patients at high risk of fracture (4 ,5). Current guidelines have thus emphasized the usefulness of combining BMD and clinical risk factors to determine an absolute risk of fracture and decide which patient has to be treated and which patient has a sufficiently low fracture risk to be observed without treatment. In this regard, the fracture risk assessment tool (FRAX), which has just been launched during this last year, allows to calculate the 10-year probability of fractures in men and women from several clinical risk factors (CRFs) with or without the measurement of femoral neck BMD (6 ,7). The performance characteristics of the FRAX tool have been validated in independent cohorts with over a million of person-years of observation. However, most if not all of these cohorts concern elderly women, usually over the age of 65 and have mainly focussed on hip fractures. There is some uncertainty as to whether this screening tool would have the same performances in early postmenopausal women where risk factors for fracture and fracture locations are likely different than in older women. Using data from a large cohort of peri- and early post-menopausal women, we aimed 1/ to identify significant risk factors for fracture, independent of age and BMD, 2/ to assess and compare the sensitivity and specificity of FRAX and BMD for fracture prediction, and 3/ to assess whether adding new risk factors to FRAX or using a different combination of CRFs and BMD would improve the ability to identify women at high risk of fracture.

Materials and Methods

Study population

This study is part of the “Menopause et Os” (MENOS) cohort study which was conducted in the Menopause Center of the Toulouse University Hospital (8). The primary objective of that study was to determine whether bone mass measurement at menopause together with other various clinical characteristics could be a predictor of different postmenopausal diseases such as osteoporotic fractures, cardiovascular diseases and gynaecological cancers i.e. breast, uterus and ovarian cancers. The program was initiated in all women aged more than 45 years who were consecutively referred to the Menopause Center during the years 1988 to 1991 for a systematic “menopause check-up”. This study was approved by the Ethical Committee (CPP) of the Toulouse University Hospital and all women gave written informed consent. At baseline, all women were evaluated through the same procedure of the menopause unit, which included personal interview and medical examination, fasting blood sample drawing (for hormonal and biochemical measurements) and bone densitometry measurements. Women were considered postmenopausal if they had not menstruated within the last 12 months before the examination, associated with serum FSH levels above 30 IU/l and serum E2 levels below 20 pg/ml.

Between 2002 – 2004, all women were invited back again for a medical visit (follow-up visit) and further bone mass measurements. Of the 4,024 women who were initially included, 2,651 (65.9%) attended the follow-up visit. Of the 1,373 non-respondents, 109 had died, 424 refused to participate in the follow-up visit and 840 were lost to follow-up.

Methods

Clinical risk factors data collection

At baseline, all women answered a computer-assisted standardized questionnaire that has been extensively described elsewhere (9 –11), recorded by the same trained research nurse. The following clinical and historical data were extracted for each subject: age, weight, height, body mass index (kg/m^2), reproductive history (age of menarche, prior use of oral contraceptive (OC) pills, number of live births, age and type of menopause, hysterectomy, bilateral oophorectomy, postmenopausal hormone therapy (PHT) use), self-reported personal history of low-trauma fractures (i.e., those occurring after a fall from standing height or less) after age 45 as well as a history of hip or vertebral fracture either in the mother or in the father. History of medical conditions and use of medications known to interfere with bone mass (including steroids, sodium fluoride, calcitonin, bisphosphonates) as well as L-thyroxine (L-T4) treatment were recorded. Women with past/current osteoporosis treatment > 3 months (with the exception of PHT and calcium/vitamin D supplementation) at baseline (n= 455) were excluded from the analyses, which left us with 2,196 women.

The smoking and drinking status was also determined. Each woman was asked whether she smoked or had ever smoked and the number of glasses of wine or alcohol she used to consume per day or week. Dietary calcium intake was assessed by using Fardellone's questionnaire (12). The woman's overall level of physical activity (low, moderate, high) was determined by asking whether she practiced a sport or leisure physical activity regularly (at least once a week), what type of professional activity she had and how much time she spent in home-based physical activity. Each woman then underwent a medical examination where all recorded data were reviewed and completed when necessary.

At the follow-up visit, anthropometric measurements were taken and all women answered the MENOS epidemiological standardized questionnaire. For the current analysis, information on prior and current PHT use, total duration of PHT use, years since menopause, history and age of hysterectomy and/or oophorectomy were used to determine the age at menopause (for those who were not menopausal at baseline) as well as PHT use throughout the course of the study.

Fracture ascertainment

At the follow-up visit, women were asked whether they had suffered a fracture after baseline (incident fracture) and the type, mechanism and circumstances of the fracture were recorded. We only considered incident fractures that occurred with minimal or no trauma (fall from standing height or less) at the level of the spine, hip, distal forearm and proximal humerus. Fractures of fingers, toes or skull and face were excluded. All incident fractures were confirmed by radiographs or by medical/surgical reports. Systematic radiographs of the spine were not performed and we considered only symptomatic (clinical) spine fractures.

Bone mineral density measurements

Bone mineral density (BMD, g/cm^2) of the lumbar spine (L2–L4) was determined in all women using dual energy X-ray absorptiometry (DXA) (DPX-IQ, Lunar GE, Madison, WI, USA) following conventional procedures as previously described (13). Due to changes in the bone mass measurements protocol that occurred in the Menopause Center during the baseline examination period, femoral neck BMD was also measured in those 1,399 women who were included in the study from 1989 onwards. Therefore, in our sample, 797 women had only vertebral BMD measurements whereas 1,399 women had both vertebral and femoral neck BMD measurements at baseline. T-scores (SD from young normals) for each measurement site were calculated based on the comparison of measured BMD values with our own normative database at age 25–35 (n = 110, mean spine BMD = 1.18 g/cm^2 ± 0.12 g/cm^2 ; mean FN BMD = 0.990 g/cm^2 ± 0.11 g/cm^2 ; personal data).

Statistical analyses

The first major osteoporotic fracture (wrist, clinical spine, upper arm and hip) during the follow-up period was taken as the endpoint event. We used Student t tests and chi-square tests to compare baseline characteristics of women with and without incident fracture. Variables significantly associated with fracture ($p \leq 0.10$) were retained for the multivariate analysis. We used Cox proportional hazards models to model age to first fracture. Selection of the most predictive factors took place in two steps. First, we examined each variable separately and selected those that were significantly associated with the risk of fracture ($p \leq 0.10$) after adjustment for time since menopause that was introduced into the model as a time dependent variable (time set to zero for women before menopause). We then performed manual backward stepwise Cox regression ($p \leq 0.05$; Wald test) to determine the best set of independent predictors of fracture. Use of postmenopausal hormone therapy (PHT) (never; past; current use) was introduced into the model as a time dependent variables since we had information on the age at which women started PHT and on the number of months they used it during follow up. We report hazard ratios as relative risks with 95% confidence intervals.

We conducted separate analyses for women who had a spine BMD measurement and for those who had a hip BMD in complement of spine BMD measurement. Hence, we present 2 separate models: one with spine BMD and the other one with hip BMD.

In the second part of the analysis, we assessed and compared the discriminatory value for fracture of FRAX and BMD in the subgroup of women who had a hip BMD measurement. We used the algorithm available at www.shef.ac.uk/FRAX to calculate individual FRAX values based on each woman's hip BMD measurement value and clinical characteristics at baseline. Although PHT may be prescribed for many different reasons, it is well established that its use decreases bone loss and results in a significant protection against fractures (xxx refxx). Since FRAX is not intended to be used in subjects receiving pharmacologic treatment for osteoporosis, we excluded from this analysis women who were current users of PHT at baseline, which left a sample of 956 women (and 76 fractures). We also assessed whether adding new CRFs to FRAX or constructing a risk score based on the best prediction model in our population would improve the ability to identify women at high risk of fracture. We used Cox models with time to fracture as the endpoint and baseline characteristics (FRAX or hip BMD, plus CRFs) as independent variables to calculate individual score values (parametric part of the risk function) and rank women by their predicted risk of fracture. We assessed the overall discriminative value of the different risk scores considered by calculating the areas under the ROC curve (AUC). We also assessed the sensitivity (proportion of women with fracture who had been classified as high risk) and specificity (proportion for women without fracture who had not been classified as high risk) of each risk score for various definitions of the high-risk group based on percentiles of the score distribution in the study population.

All statistical analyses were conducted using SAS 9.1 and STATA v9.

Results

During the mean follow-up period of 13.4 (± 1.4) years, 415 women sustained a first low-energy fracture including 145 (6.6%) major OP fractures (108 wrist, 44 spine, 20 proximal humerus, 13 hip). Baseline characteristics of women with and without incident major OP fracture are given in table 1 and 2 . Women with fracture were significantly older and had lower BMD values. They were more likely to have a history of fracture after the age of 45, a family history of hip fracture, a lower number of pregnancies and a higher age at puberty. However, they were less likely to have ever used OC and to be using PHT at baseline.

In Cox regression models adjusting for time since menopause, individual variables that remained significantly associated with the risk of fracture were: spine BMD, PHT use throughout follow-up, a personal history of fracture and the number of pregnancies. In stepwise Cox regression, all these variables were retained into the model; hence, they represent the best set of fracture predictors. The hazard ratios and corresponding 95% confidence intervals associated with each of these variables are presented in table 3 .

We conducted a separate analysis on the subset of women who had also a hip BMD measurement at baseline, and ended up with the same selection of predictors. Hazard ratio estimates in the model with hip BMD are approximately of the same magnitude than those in the model with spine BMD (table 3). The second part of the analysis focused on the 956 women who had a hip BMD measurement and were not current PHT users at baseline. Their mean FRAX value (average probability of having a major OP fracture over the next 10 years) was 3.8% (± 2.4). Based on FRAX, the total number of major OP fractures expected during the first 10 years of follow-up (sum of the individual FRAX probabilities) was 36, whereas the observed number of fractures during the same period was 42.

We then compared the sensitivity for fracture of FRAX and hip BMD for various definitions of the high risk group based on percentile of their distribution in the study population (table 4). If the cut-off for high risk is set, for instance, at 30% (i.e., the 30% of women with the highest FRAX values or with the lowest BMD values are classified as being “at high risk”), the sensitivity is approximately equal to 49 % and 55%, respectively for FRAX and hip BMD. To have a sensitivity around 80%, the cut-off has to be raised to 60% for both measures, which means that 60% of the women have to be classified as being at “high risk”. Noteworthy, given the low incidence of fracture (around 0.5%), the specificity of any measure is approximately equal to the percentage of women who are not classified at high risk. For instance, at the 30% cut-off, the specificity was approximately equal to 70% for both FRAX and hip BMD. The overall discriminant value for

fracture, as measured by the area under the ROC curve (AUC), is equal to 0.63 (95% CI: 0.56 – 0.69) and 0.66 (0.60 – 0.73), respectively for FRAX and hip BMD.

The first part of the analysis revealed that parity was a significant predictor of fracture, independent of age, BMD and history of fracture. This factor is not taken into account in FRAX calculation. Hence, we examined whether adding parity to the predictive model including FRAX would significantly improve the ability to identify women at high risk of fracture. The AUC of the new score 'FRAX + parity' (0.65; 95% CI: 0.58 – 0.71) is not significantly better than the AUC of FRAX or hip BMD alone.

Finally, we examined the discriminative value of a simple risk score including the four factors - age, hip BMD, history of fracture, and parity - that best predicted fracture in our study population. The AUC of this model-based risk score is equal to 0.69 (0.63 – 0.72), which is statistically significantly better than the AUC of FRAX ($p = 0.01$), but not significantly better than the AUC of hip BMD alone ($p = 0.16$). The ROC curves of the 4 risk assessment tools considered in this analysis are shown in figure 1 .

In the study population, a significant number of women (357 out of 956) started PHT during follow-up (on average, 3.1 years after baseline). Fracture risk may be overestimated in these women, which might affect the overall predictive value of the screening tools. Hence, we re-run the analysis after exclusion of women who started PHT after baseline. We found the same set of predictors than in the overall population and the AUC of the different screening tools were of the same magnitude than before (0.64 for FRAX, 0.69 for hip BMD, 0.63 for the score 'FRAX plus parity', and 0.63 for the model-based risk score). Noteworthy, there were no significant difference in mean hip BMD and percentage of osteoporotic ($T < -2.5$) women between the subgroup of women who started PHT during follow-up and those who did not.

Discussion

This prospective study involving 2,196 early postmenopausal women (mean age at baseline: 54 ± 4 years) revealed that there were only a few clinical risk factors for major osteoporotic (OP) fractures independent of BMD and age. Moreover, the FRAX risk assessment tool did not have a better discriminative value for fracture than BMD alone. Adding new CRFs to FRAX or using a combination of CRFs and BMD based on the best predictive model in our population did not significantly improve fracture prediction compared to BMD alone.

Out of the 38 potential CRFs examined, only 3 - a history of fracture, current use of PHT, and parity - were significant and independent predictors of fracture after age and BMD level are taken into account. Using BMD measured either at the spine or the hip to generate two different multivariate models did not modify the set of predictors, nor their gradient of risk.

As already reported (14 –16) and not surprisingly, our study confirms that a history of a fragility fracture is a powerful predictor of future fracture independent of BMD. The multivariable- and BMD-adjusted risk of a major OP fracture was 2.3 fold to 2.5 fold higher in women who had reported a prior low trauma fracture after the age of 45 years compared to women without a prior fracture history. In agreement with previous studies (17), we also found that use of postmenopausal hormone therapy (PHT) resulted in a significant protection against fractures: current PHT users had a 50 to 60% reduced risk of major OP fractures compared with never users.

These results are consistent with those reported in Huppio's study (18), which to our knowledge is one of the few that concerned a large population of 3,000 perimenopausal women who had been followed over 3.6 years and whose mean age at baseline (53 yrs) was very similar to that in our study. In this cohort, only 2 majors CRFs were identified in addition to low BMD that is previous fracture history and no use of PHT.

In the present study, we found an additional significant and independent predictor of fracture, that is parity: compared to nulliparous women, women with 3 children or more had a 48% to 56% decreased risk of major fragility fracture independent of BMD and other clinical risk factors. Interestingly there was a monotonal relationship between increasing parity and the risk of fracture, as the probability of fracture decreased with increasing number of children. Such relationship has already been reported in most (but not all) prior studies that examined the association between parity and fracture risk (19 –21).

Several CRFs included in FRAX (in particular, familial history of fracture, current use of systemic glucocorticoids, low BMI, current smoking, high intake of alcohol and rheumatoid arthritis) were not significantly associated with the risk of fracture in our population. This may be interpreted as a true lack of predictive power in peri- and early post-menopausal women. Alternatively, the lack of association between some factors and fracture risk may be due to a lack of statistical power. This may be the case, in particular, for a family history of fracture that showed a non-significant trend towards an increased risk of fracture in exposed women. Indeed, we have calculated that, with a frequency of exposure of 10% (238 women out of 2196 reported having a family history of fracture), and an incidence of fracture of 5 per 1000 person-years in unexposed women (as observed in our population), the statistical power was only about 20% to show a RR of 1.3 (RR estimate for family history in Kanis' meta-analysis (22)). Lack of power is also evident for CRFs such as exposure to systemic glucocorticoïds, high intake of alcohol and rheumatoid arthritis, whose prevalence is very low in our sample. For instance, only 29 (1.3%) women were using glucocorticoid in our population of young and relatively healthy postmenopausal women.

One of the main differences between our cohort and the cohorts used to develop the FRAX tool (5) is that our cohort is on average 10 years younger (53 vs 63 years in the FRAX cohorts). The mix of fracture is different in early postmenopausal women where wrist fractures are the most frequent than in elderly women where hip fractures become predominant. Hence, it seems logical to think that the nature or strength of risk factors for fracture may vary according to the women' age and/or the type of fracture. Noteworthy, in the meta-analyses using data from the FRAX cohorts, all CRFs except a personal history of fracture were more strongly associated with the risk of hip fracture than with the risk of other OP fractures (5). In accordance with this finding, Kanis et al found that the CRFs were most useful in enhancing the performance of BMD in the prediction of hip fracture (5). At the age of 50 years, the gradient of risk with BMD alone was 3.7/SD, but with the addition of CRFs increased to 4.2/SD. For other major OP fractures, the gradient of risk with BMD alone was lower and adding CRFs only modestly improved it. At the age of 50 years, it was 1.2/SD with hip BMD alone, whereas it was 1.4/SD with the combination of BMD and CRFs, which translates in an AUC around 0.6, that is very similar to what we found. The use of FRAX in our study population did not significantly improve the sensitivity of BMD assessment, which remained low under most reasonable assumptions that avoid unnecessary treatment. If the cut-off for high risk is set at 30%, for instance, the sensitivity is equal to 49% and 55 %, respectively for FRAX and hip BMD. To identify the majority (i.e., around 80%) of the women who will suffer a fracture, the cut-off has to be raised to 60% (i.e., 60% of the population has to be classified as being at high risk). Noteworthy, other investigators reported the lack of sensitivity of FRAX in elderly women (23 –25) and in some male populations (26).

We found that parity, which is not included in the FRAX algorithm, was a significant predictor of the risk of major OP fracture, independent of BMD and of the other CRFs. This risk factor may be more specific of early post-menopausal women than of older women. Hence, we assessed whether adding parity to FRAX would improve the ability to identify young postmenopausal women at high risk of fracture. We found that the new score combining parity and FRAX did not significantly improve the sensitivity of FRAX, and did not have a better discriminant value than hip BMD alone. Even a score based on the best predictive equation in our population (best fit of our data) was not significantly more discriminant than hip BMD alone.

Our study has several strengths and limitations. An extensive amount of data were collected for each woman at the baseline and follow-up visits, including the use of osteoporosis medications and PHT throughout the follow-up, which allowed to examine a large set of potential CRFs for fracture. All incident fractures were confirmed through either medical records or X-ray radiographs and we have been very careful to record the circumstances of each fracture through medical personal interview. A large number of participants (almost 60%) used PHT at some point of the study and about 36% were still current users by the end of the follow-up. Such a high frequency of PHT was very common in the French population before the publication of the WHI results, whatever the underlying reasons, mainly to resume climacteric symptoms but also to prevent osteoporosis. However, we have rerun the analysis after exclusion of women who took PHT at some point over the course of the study. We found the same set of CRFs for fracture, and the discriminative value of FRAX and of hip BMD remained unchanged. Women included in the MENOS cohort were all referred to our center by their personal physician for a " menopause check-up". Reasons for referral are not known but may include a higher risk of osteoporosis. Accordingly, the prevalence of a T-score < −2.5 was slightly higher than expected for this age range which could suggest a selection bias and could thus not permit to generalize our results to the general population. Nevertheless, they may broadly apply to women likely to seek medical care and advice at the time of menopause or in the few years after.

In conclusion, only a limited number of CRFs were found associated with the risk of major OP fracture in this population of early postmenopausal women. Combining CRFs and BMD did not significantly improve prediction of fracture over BMD alone, and sensitivity remained low under most reasonable assumptions that avoid unnecessary treatment.

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Figure 1

Receiver operating characteristic curves for the FN BMD, the FRAX score and the FRAX score with parity and the score issued from our model for major osteoporotic fracture prediction in early postmenopausal women

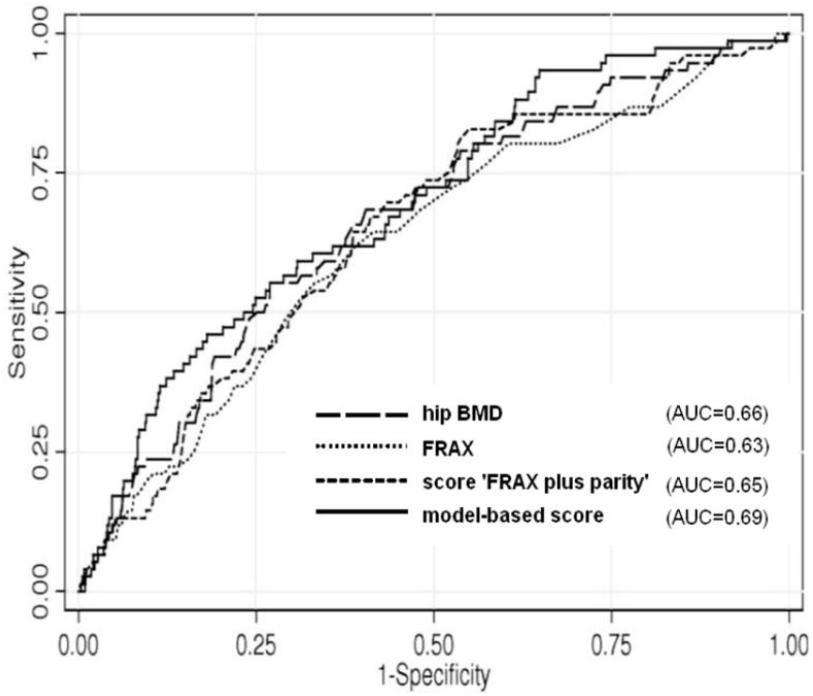

Table 1

Baseline characteristics of women with and without incident major osteoporotic fracture

	Women with fracture (n = 145)	Women without fracture (n = 2,051)	p value[$]
Age (years)	54.8 ± 4.3	53.4 ± 4.2	<0.0001
BMI (kg/m^2)	22.9 ± 2.99	23.1 ± 3.10	0.44
Age at menarche (years)	13.3±1.5	13.1±1.5	0.08
Age at menarche (years)			
<10	0	6(0.3%)	0.31
[10; 15[	115 (79.3%)	1,712 (83.51%)	
≥15	30 (20.7%)	332 (16.2%)	
Ever use of oral contraceptive (n)	36 (24.8%)	707(34.5%)	0.0177
Parity (n)	1.8 ± 1.3	2.0 ± 1.2	0.013
Number of pregnancies			
0	23 (15.9%)	212 (10.3%)	0.0248
1	38 (26.2%)	429 (20.9%)	
2	54 (37.2%)	807 (39.4%)	
≥ 3	30 (20.7%)	603 (29.4%)	
Numbers of breastfed children			
0	85 (58.6%)	1,069 (52.1%)	0.22
1	31 (21.4%)	448 (21.8%)	
≥ 2	29 (20.0%)	534 (26.1%)	
Total duration of breastfeeding (month)	7.1 ± 7.2	8.0 ± 7.8	0.36
Menopause status (yes/no)	129 (89.0%)	1,766 (86.1%)	0.33
Early Menopause (< 40 years) (n)	5 (2.7%)	56 (3.5%)	0.61
PHT use			0.0097
Never	104 (71.7%)	1,296 (63.2%)	
Past	11 (7.6%)	98 (4.8%)	
Current	30 (20.7%)	657 (32.0%)	
Prior breast cancer (n)	5 (3.5%)	37 (1.8%)	0.16

[$] chi2 or t test

Table 2

Baseline BMD and clinical risk factors for fracture in women with and without incident major osteoporotic fracture

	Women with fracture (n=145)	Women without fracture (n=2,051)	p value
Vertebral BMD (g/cm^2)	0.96 ± 0.126	1.03 ± 0.148	<0.0001
T-score			
> −1	32 (22.2%)	858 (42.1%)	<0.0001
]−2.5; −1]	73 (50.7%)	888 (43.5%)	
≤ −2.5	39 (27.1%)	293 (14.4%)	
Femoral neck BMD(1) (g/cm^2)	0.77 ± 0.104	0.84 ± 0.115	<0.0001
T-score			
> −1	13 (13.3%)	423 (32.5%)	<0.0001
]−2.5; −1]	57 (58.2%)	713 (54.8%)	
≤ −2.5	28 (28.5%)	165 (12.7%)	
BMI < 19 kg/m^2	10 (6.9%)	110 (5.4%)	0.43
Previous fracture history (after 45 years) (y/n)	12 (8.3%)	43 (2.1%)	<0.0001
Maternal/paternal hip fracture history (y/n)	22 (15.2%)	216 (10.5%)	0.08
Corticosteroid use (y/n)	2(1.4%)	27(1.3%)	0.95
Tobacco use			
Never	121 (88.3%)	1,565 (80.1%)	0.055
Past	7 (5.1%)	199 (10.2%)	
Current	9 (6.6%)	191 (9.7%)	
Alcohol use			
1+ drink of wine	21 (14.5%)	392 (19.1%)	0.17
1+ drink of alcohol	22 (15.2%)	39 (19.3%)	0.22
Rheumatoid arthritis (y/n)	0	1	0.79
Secondary osteoporosis (y/n)	2 (1.4%)	48 (2.3%)	0.10
Calcium daily intake (mg)	764.0 ± 492.14	774.7 ± 472.87	0.80
Calcium/vit D supplements (y/n)	11 (7.6%)	135 (6.6%)	0.64
Physical activity			0.18
Low	69 (47.6%)	817(39.9%)	
Moderate	68 (46.9%)	1,084 (53.0%)	
High	8 (5.5%)	146 (7.1%)	

(1) n = 1,399 women

$ chi2 or t test

Table 3

Predictors of major osteoporotic fracture

Predictive factors	Model including spine BMD[1] Hazard Ratio (95% CI)	Model including hip BMD[2] Hazard Ratio (95% CI)
Years since menopause (/5 years)	1.09 (0.91–1.31)	1.11 (0.91–1.36)
BMD (/1 SD decrease)	1.41 (1.18–1.69)	1.70 (1.35–2.14)
Prior history of fracture (> 45 yrs)	2.54 (1.39–4.62)	2.28 (1.04–5.03)
PHT throughout follow-up:		
Never	1	1
Past	0.87 (0.58–1.32)	0.95 (0.57–1.58)
Current	0.49 (0.32–0.76)	0.58 (0.34–0.96)
Parity (n)		
0	1	1
1	0.87 (0.52–1.47)	1.02 (0.54–1.95)
2	0.68 (0.42–1.11)	0.66 (0.36–1.22)
3+	0.44 (0.26–0.76)	0.52 (0.27–1.00)

(1) Final Cox regression model in 2,183 women with vertebral BMD and a complete set of data

(2) Final Cox regression model in 1,399 women with hip BMD and a complete set of data

Table 4

Sensitivity and corresponding cut-offs of the risk score issued from the Hip T-score and FRAX model for the prediction of major OP fractures

% of women in the high risk group	Hip T-score		FRAX model[1]	
	Cut-off	Sensitivity	Cut-off	Sensitivity
90%	−0.1	96.5%	2.1 %	98.7%
80%	−0.6	92.1%	2.3 %	86.8%
70%	−0.9	86.8%	2.5 %	82.9%
60%	−1.3	80.3%	2.8 %	80.3%
50%	−1.5	72.4%	3.1 %	72.4%
40%	−1.7	64.5%	3.5 %	61.8%
30%	−2.0	55.3%	4.1 %	48.7%
20%	−2.3	40.8%	4.9 %	31.6%
10%	<−2.6	22.4%	> 6.2 %	19.7%

(1) 10-year probability of major osteoporotic fracture