

## BONE MASS AND THE RISK OF BREAST CANCER AMONG POSTMENOPAUSAL WOMEN

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### ABSTRACT

**Background** Recent studies have shown a direct relation between serum estrogen levels assessed at a single point in time and the risk of breast cancer, but no evidence links estrogen levels assessed repeatedly over an extended interval to the risk of breast cancer. Bone mass has been proposed as a marker of cumulative exposure to estrogen in women. We therefore studied the association between bone mass and the incidence of breast cancer.

**Methods** Between 1967 and 1970, 1373 women who were 47 to 80 years old and had no history of breast cancer underwent posteroanterior hand radiography in the Framingham Study. We used radiogrametry to measure the cortical width of each woman's second metacarpal. Participants were followed until the end of 1993. All incident cases of breast cancer were confirmed by pathological reports. We used a Cox proportional-hazards model to examine the relation of metacarpal bone mass to the risk of postmenopausal breast cancer.

**Results** Postmenopausal breast cancer developed in 91 subjects. Incidence rates per 1000 person-years increased from 2.0 among the women in the lowest age-specific quartile of metacarpal bone mass to 2.6, 2.7, and 7.0 among the women in the second, third, and highest quartiles, respectively. After adjustments for age and other potential confounding factors, the rate ratios for the risk of breast cancer were 1.0, 1.3, 1.3, and 3.5 from the lowest quartile to the highest (P for trend, <0.001).

**Conclusions** Women in the highest quartile of bone mass are at higher risk for postmenopausal breast cancer than those in the lowest quartile. The mechanisms underlying this relation are not understood, but cumulative exposure to estrogen may play a part. (N Engl J Med 1997;336:611-7.)

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**H**IGH levels of estrogen are considered to be a risk factor for breast cancer,<sup>1-3</sup> but it has been difficult to assess this association. Measurement of estrogen levels in blood or urine poses many methodologic and logistic problems, including fluctuations in estrogen levels during the menstrual cycle,<sup>4-6</sup> the high costs of storing specimens for long periods, and variations in assay methods over time and among studies.<sup>7</sup> In addition, it is unclear whether a single measurement of serum or urinary estrogen indicates a woman's cumulative exposure to estrogen.

Assessment of the effects of exogenous estrogens, such as postmenopausal estrogen replacement, is also complex.<sup>3</sup> Many women take replacement estrogens for only a few years, making it difficult to study long-term exposure to estrogen. Furthermore, many factors associated with estrogen therapy are also related to breast cancer,<sup>8,9</sup> thus requiring careful adjustment for potential confounding effects.

Since estrogens are important determinants of bone mineral density, several investigators have proposed that bone mineral density may serve as a marker of cumulative estrogen exposure in women.<sup>10-14</sup> Two studies<sup>12,13</sup> have reported that women with fractures had a low risk of breast cancer. However, many factors other than bone density can influence the risk of fracture, and not all the women with fractures necessarily had low estrogen levels. Cauley et al. recently reported that during four years of follow-up, the risk of breast cancer was two to two and a half times higher among women with bone mineral density above the lowest quartile than among women with bone mineral density in the lowest quartile.<sup>14</sup>

We used data from the Framingham Study to examine the relation of metacarpal bone mass to the subsequent risk of postmenopausal breast cancer.

### METHODS

The Framingham Study began in 1948 in Framingham, Massachusetts. The original cohort included 2873 women who were 28 to 62 years old at the first examination. The subjects have been examined approximately biennially since then. At each examination, a medical history is taken, and a physical examination and a series of laboratory tests are performed.

#### Assessment of Bone Mass

Between 1967 and 1970, at the time of biennial examination 10 or 11, a posteroanterior radiograph of the right hand was taken as part of a study of osteoporosis. Of the 1760 women seen at those visits, 1394 underwent posteroanterior hand radiography. We used radiogrametry to measure the bone mass of the second metacarpal.<sup>15</sup> We chose the second metacarpal because it is one of the largest bones of the hand, has a more constant shape

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than the other metacarpals,<sup>16</sup> and is approximately circular at the midshaft, with the medullary cavity nearly centered in the tubular bone cylinder.<sup>16,17</sup>

Two readers, who were unaware of the status of the study participants with respect to breast cancer, assessed bone mass according to a standard protocol. Hand radiographs were placed flat on a lighted viewing box, and measurements of cortical external width (R) and medullary width (r) were made halfway up the second metacarpal with a digital caliper. Calipers were calibrated to the nearest 0.01 mm, and measurements were recorded to the nearest 0.1 mm. To assess intraobserver and interobserver reliability in the measurement of cortical width, we gave 25 hand radiographs to each of the two readers twice for blinded readings. The intraobserver correlation coefficients for external and medullary width were 0.99 and 0.94, respectively; the corresponding interobserver correlation coefficients were identical. We used the relative metacarpal cortical area, calculated as  $100 \times (R^2 - r^2) \div R^2$ , as an indicator of bone mass.

### Identification of Breast-Cancer Cases

Methods used to identify cases of breast cancer in the Framingham Study cohort have been described in detail by Kreger et al.<sup>18</sup> Briefly, cases were identified by self-report at each biennial examination, by surveillance of admissions to the only local hospital, and by a review of all death records obtained from state health departments. Cohort members who missed a biennial examination were contacted by telephone or mail to obtain information about medical events during the two years since their last examination. In addition, for the nonrespondents and the subjects whose vital status was unknown, we searched the National Death Index to identify those who had died and to determine the cause of death. The entire Framingham Study file for each suspected case of cancer was then reviewed to determine the date of the diagnosis, the location of the tumor in the breast, and the histopathological details. Pathology reports were available for all cases identified in this analysis. All cases of breast cancer were coded according to the *International Classification of Diseases for Oncology*<sup>19</sup> (topography code 174).

### Other Variables

Information on other risk factors for breast cancer, including age, number of years of education, height, weight, age at first pregnancy, parity, and age at menopause, was obtained. For the 115 women whose menstrual periods had stopped because they had undergone hysterectomy without bilateral oophorectomy, we used the median age at menopause for the entire cohort (50 years) as their age at menopause. At examinations 2 (1951 to 1954) and 7 (1960 to 1964), the women were asked to estimate the number of drinks of beer, wine, or spirits consumed each month. Total alcohol consumption was computed by multiplying the average amount of alcohol in a single drink of beer, wine, or spirits by the average of the numbers of drinks reported at examinations 2 and 7. Cigarette smoking has been recorded at each examination for the past 45 years. We used the mean number of cigarettes smoked per day before the date of hand radiography as the base-line variable for smoking. Habitual physical activity was assessed at the fourth examination (between 1954 and 1958) with use of the Framingham Physical Activity Index.<sup>20</sup> Postmenopausal estrogen use has been assessed at each biennial examination since 1960. For each woman, the total number of years of postmenopausal estrogen use was summed from the time of hand radiography to either the date of a diagnosis of breast cancer or the date on which the data were censored (the date of the last contact, for women lost to follow-up, or December 31, 1993, when the study was closed).

### Statistical Analysis

Since age is an important determinant of breast cancer and the women with lower bone mass were older on average than those

**TABLE 1. CHARACTERISTICS OF 1373 WOMEN IN THE FRAMINGHAM STUDY, ACCORDING TO THE PRESENCE OR ABSENCE OF BREAST CANCER DIAGNOSED BETWEEN 1969 AND 1993.**

CHARACTERISTIC	WOMEN WITH BREAST CANCER (N=91)	WOMEN WITHOUT BREAST CANCER (N=1282)
	mean $\pm$ SD	
Age at time of radiography (yr)	61.1 $\pm$ 8.0	61.5 $\pm$ 8.1
Height at time of radiography (in.)*	62.3 $\pm$ 2.1	62.4 $\pm$ 2.5
Body-mass index at time of radiography†	25.4 $\pm$ 3.5	25.4 $\pm$ 4.3
Age at menopause (yr)	48.7 $\pm$ 4.5	48.1 $\pm$ 4.9
Age at first pregnancy (yr)	27.5 $\pm$ 5.1	25.9 $\pm$ 5.8
	% of women	
Education		
<12 yr	28.4	35.9
12 yr	42.1	33.1
>12 yr	29.6	31.0
Parity		
0	27.5	22.6
1	9.9	12.2
$\geq 2$	62.6	65.2
Years of estrogen use after radiography		
None	84.6	82.1
<5	12.1	10.8
$\geq 5$	3.3	7.1
Average alcohol consumption before radiography		
None	41.8	42.1
<2 oz (60 ml)/wk	30.8	31.5
$\geq 2$ oz (60 ml)/wk	27.5	26.4
Average no. of cigarettes smoked before radiography		
None	55.2	55.4
<10/day	14.9	15.5
$\geq 10$ /day	29.9	29.2
Physical-activity level before radiography‡		
26-29	35.1	30.7
30-32	32.5	42.2
$\geq 33$	32.5	27.1

\*To convert values to meters, multiply by 0.0254.

†Body-mass index was defined as the weight in kilograms divided by the square of the height in meters.

‡The level of physical activity was determined according to the Framingham Physical Activity Index<sup>20</sup>; each of the three categories represents a third of the index.

with higher bone mass, we adjusted for age by using the age-specific relative metacarpal cortical area. Specifically, we stratified all women into two-year age groups and then assigned each woman to one of four quartiles of bone mass according to the distribution of the relative metacarpal cortical area for her age group.

Using an analysis of variance for continuous variables and a chi-square test for categorical variables, we compared the characteristics of the participants according to the presence or absence of breast cancer and the quartile of bone mass. Person-years of follow-up for each woman were computed as the amount of time from the date the radiograph was obtained to the date of the first of the following events: a diagnosis of breast cancer; the last date of contact, for those lost to follow-up; death; or December 31, 1993, when the study was closed. Incidence rates of breast cancer

**TABLE 2.** CHARACTERISTICS OF STUDY PARTICIPANTS ACCORDING TO THE AGE-SPECIFIC QUARTILE OF RELATIVE METACARPAL CORTICAL AREA.

CHARACTERISTIC	QUARTILE OF METACARPAL CORTICAL AREA*			
	1	2	3	4
	mean $\pm$ SD			
Age at time of radiography (yr)	61.5 $\pm$ 8.0	61.5 $\pm$ 8.0	61.4 $\pm$ 8.2	61.4 $\pm$ 8.0
Height at time of radiography (in.) <sup>†</sup>	62.3 $\pm$ 2.5	62.2 $\pm$ 2.5	62.6 $\pm$ 2.5	62.3 $\pm$ 2.4
Body-mass index at time of radiography	24.7 $\pm$ 4.0	25.0 $\pm$ 4.0	25.6 $\pm$ 4.2	26.1 $\pm$ 4.6
Age at menopause (yr)	47.2 $\pm$ 5.5	47.6 $\pm$ 4.7	48.8 $\pm$ 4.5	49.0 $\pm$ 4.7
Age at first pregnancy (yr)	25.7 $\pm$ 5.3	26.4 $\pm$ 5.1	25.9 $\pm$ 4.8	26.3 $\pm$ 5.1
	% of women			
Education				
<12 yr	41.0	37.4	30.3	33.1
12 yr	35.7	31.2	35.0	33.1
>12 yr	23.3	31.5	34.7	33.7
Parity				
0	21.0	25.8	21.6	23.4
1	11.1	13.8	8.3	14.9
$\geq 2$	68.0	60.5	70.1	61.7
Years of estrogen use after radiography				
None	84.4	83.1	81.9	79.8
<5	10.8	11.8	11.5	9.4
$\geq 5$	4.8	5.1	6.6	10.8
Average alcohol consumption before radiography				
None	42.6	42.3	39.4	44.1
<2 oz (60 ml)/wk	33.2	31.6	34.1	26.8
$\geq 2$ oz (60 ml)/wk	24.2	26.1	26.5	29.1
Average no. of cigarettes smoked before radiography				
None	53.0	53.4	56.0	59.0
<10/day	12.8	15.9	17.4	15.5
$\geq 10$ /day	34.2	30.8	26.6	25.5
Physical-activity level before radiography <sup>‡</sup>				
26–29	29.3	31.6	29.0	34.1
30–32	42.4	42.2	43.0	38.6
$\geq 33$	28.3	26.2	28.0	27.3

\*Quartiles are numbered from the lowest (1) to the highest (4).

<sup>†</sup>To convert values to meters, multiply by 0.0254.

<sup>‡</sup>The level of physical activity was determined according to the Framingham Physical Activity Index<sup>20</sup>; each of the three categories represents a third of the index.

for each age-specific quartile of bone mass were calculated by dividing the number of cases of cancer by the number of person-years of follow-up. We plotted Kaplan–Meier survival curves to determine the cumulative incidence rate for each quartile of bone mass.<sup>21</sup>

We fitted a Cox proportional-hazards model to determine the relation of the age-specific quartile of metacarpal bone mass to the risk of breast cancer.<sup>21</sup> In the multivariate Cox proportional-hazards model, we adjusted for education, height, body-mass index, age at first pregnancy, parity, age at menopause, average alcohol consumption, average number of cigarettes smoked, level of physical activity, and use or nonuse of postmenopausal estrogen. The significance of the trend in the risk of breast cancer was determined by including a single variable for the age-specific quartile of metacarpal bone mass in the multivariate model.

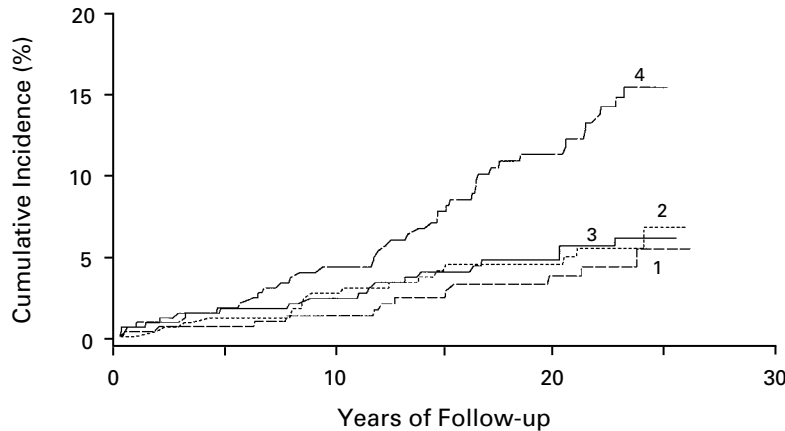
To determine whether the association between bone mass and breast cancer was modified by other risk factors, we examined the effect of the quartile of metacarpal bone mass within strata of other risk factors. We tested for a modification of the effect by including an interaction term (between the quartile of metacarpal

bone mass and a particular risk factor) in the multivariate regression model.

## RESULTS

Of the 1394 women who underwent hand radiography between 1967 and 1970, 21 had a history of breast cancer and were excluded from the analysis. During the follow-up period, postmenopausal breast cancer developed in 91 women. The median age at the time of the diagnosis was 74 years (range, 54 to 92), and the median follow-up after hand radiography was 22.1 years (range, 0.1 to 25.9).

Table 1 shows the characteristics of the women with breast cancer and those without breast cancer. The women with breast cancer were significantly older at the time of their first pregnancy ( $P = 0.02$ ). However, there were no statistically significant dif-



**Figure 1.** Cumulative Incidence of Breast Cancer among 1373 Postmenopausal Women in the Framingham Study, According to the Age-Specific Quartile of Metacarpal Bone Mass. The numbers on the curves indicate the quartiles.

**TABLE 3.** RELATION OF AGE-SPECIFIC QUARTILE OF RELATIVE METACARPAL CORTICAL AREA TO THE RISK OF BREAST CANCER.

QUARTILE*	NO. OF WOMEN WITH BREAST CANCER	INCIDENCE RATE (CASES/1000 PERSON-YEARS)	AGE-ADJUSTED RATE RATIO	MULTIVARIATE ADJUSTED RATE RATIO (95% CI)†
1	12	2.02	1.0	1.0
2	17	2.63	1.3	1.3 (0.6–2.8)
3	18	2.69	1.3	1.3 (0.6–2.7)
4	44	7.03	3.5	3.5 (1.8–6.8)

\*Quartiles are numbered from the lowest (1) to the highest (4).

†Adjustments were made for height, body-mass index, education, parity, age at first pregnancy, age at menopause, average number of cigarettes smoked, presence or absence of alcohol consumption, level of physical activity, and use or nonuse of postmenopausal estrogen. CI denotes confidence interval.

ferences between the two groups of women in terms of age at the time of radiography, height, body-mass index, age at menopause, education, parity, years of postmenopausal estrogen use, alcohol consumption, cigarette smoking, or level of physical activity.

Table 2 shows the distribution of potential risk factors for breast cancer according to the age-specific quartile of bone mass. As compared with the women in the lower quartiles of bone mass, those in the higher quartiles had a higher body-mass index ( $P < 0.001$ ), were older at menopause ( $P < 0.001$ ), had more years of education ( $P = 0.018$ ), and had used postmenopausal estrogen-replacement therapy for a longer period ( $P = 0.036$ ). Bone mass also varied according to parity ( $P = 0.037$ ).

The cumulative incidence of breast cancer in-

creased most rapidly among the women in the highest age-specific quartile of metacarpal bone mass (Fig. 1). As compared with the risk of breast cancer among the women in the lowest quartile, the rate ratios for the women in the second, third, and highest quartiles were 1.3 (95 percent confidence interval, 0.6 to 2.8), 1.3 (95 percent confidence interval, 0.6 to 2.7), and 3.5 (95 percent confidence interval, 1.8 to 6.8), respectively ( $P$  for trend,  $< 0.001$ ) (Table 3). Adjusting for additional potential confounding variables did not affect the association.

Women in the highest age-specific quartile of bone mass had an increased risk of breast cancer across almost all strata of other factors (Table 4). The relative effects of greater bone mass on the risk of breast cancer were stronger among taller women ( $P = 0.01$  for the interaction term). None of the other interaction terms were statistically significant.

## DISCUSSION

With the exception of age, race or ethnic group, and family history of breast cancer, most of the known risk factors for breast cancer carry a relative risk of 2.0 or less.<sup>22</sup> The effects of some of these risk factors, such as age at menarche, age at birth of first child, and age at menopause, may be limited because of relatively small variations in their distribution in the United States and most other industrialized countries. The results of our study indicate that metacarpal bone mass in middle-aged and elderly women is a strong predictor of postmenopausal breast cancer.

Estrogen may be the link between bone mass and the risk of breast cancer. Because of its influence on the mitotic activity of breast cells, estrogen may play a critical part in the development of breast cancer.

**TABLE 4.** RATE RATIOS FOR THE RISK OF BREAST CANCER ACCORDING TO THE AGE-SPECIFIC QUARTILE OF RELATIVE METACARPAL CORTICAL AREA AND OTHER RISK FACTORS.\*

RISK FACTOR	NO. OF WOMEN WITH BREAST CANCER	QUARTILE OF METACARPAL CORTICAL AREA				P VALUE FOR INTERACTION
		1	2	3	4	
Age at time of radiography						0.12
<60 yr	41	1.0	2.3	1.4	3.5	
60–65 yr	23	1.0	0.9	0.7	3.0	
>65 yr	27	1.0	0.5	2.2	7.9	
College education†						0.81
No	62	1.0	1.0	1.3	3.2	
Yes	26	1.0	2.0	1.2	4.6	
Height						0.01
≤62.5 in. (1.59 m)	52	1.0	1.4	1.2	2.1	
>62.5 in. (1.59 m)	39	1.0	0.9	1.6	7.8	
Body-mass index						0.59
<25.0	48	1.0	1.2	1.2	3.4	
≥25.0	43	1.0	2.1	1.8	4.7	
Parity						0.24
0	25	1.0	1.1	1.1	2.2	
≥1	66	1.0	1.3	1.3	4.3	
Age at first pregnancy						0.18
≤25 yr	25	1.0	0.8	1.0	2.3	
>25 yr	41	1.0	1.6	1.3	5.7	
Age at menopause						0.61
<50 yr	41	1.0	1.1	1.5	3.2	
≥50 yr	50	1.0	1.3	1.0	3.9	
Estrogen use						0.98
No	77	1.0	0.9	1.1	2.9	
Yes	14	1.0	1.0	1.5	4.3	
Smoker						0.29
No	48	1.0	1.2	0.8	2.4	
Yes	43	1.0	1.4	2.1	5.7	
Alcohol consumption						0.13
No	38	1.0	0.8	0.9	1.8	
Yes	53	1.0	1.9	2.1	6.1	
Physical-activity level‡						0.25
≤31	34	1.0	1.4	1.6	2.6	
>31	43	1.0	2.2	1.9	6.1	

\*For each variable, the rate ratios have been adjusted for all the other variables listed in the second footnote to Table 3.

†Data were missing for some women.

‡The level of physical activity was determined according to the Framingham Physical Activity Index.<sup>20</sup> Data were missing for some women.

Seven cohort studies have assessed the relation of a woman's serum estrogen level at a single point in time to her risk of breast cancer.<sup>23-29</sup> Three of these studies reported an increased risk among women with higher levels of serum estradiol<sup>27-29</sup> and higher percentages of estradiol in the bioavailable fractions.<sup>27</sup> In four of six meta-analyses of estrogen-replacement therapy and the risk of breast cancer,<sup>30-35</sup> long-term estrogen users had an increased risk of breast cancer.<sup>32-35</sup> Colditz et al. recently reported that women in the Nurses' Health Study who were currently using estrogen and had done so for five or more years had a 46 percent increase in the risk of breast cancer, and the effect was greater among older women.<sup>36</sup> The most convincing epidemiologic evidence of an association between estro-

gen and breast cancer would require studies in which estrogen levels in each woman were assessed repeatedly over a long period of time. Because of methodologic and logistical difficulties, such studies have not been performed.

Several investigators have hypothesized that bone mass or bone mineral density may indicate the effect of cumulative exposure to estrogen.<sup>10-14</sup> There is a strong positive association between serum or urinary estrogen levels and bone mineral density in premenopausal and postmenopausal women, and the skeletal effects of low levels of estrogens are clearly seen after menopause or removal of the ovaries.<sup>37-46</sup> In addition, women who have been receiving estrogen-replacement therapy, especially long-term estrogen users, have significantly higher bone mineral

density and a lower risk of osteoporotic fractures than women who have never used estrogens.<sup>47-51</sup>

The relation between bone mass and breast cancer may also involve endogenous androgens, which are determinants of bone mass<sup>52,53</sup> and are also associated with a risk of breast cancer.<sup>2</sup>

Two studies have examined the association between fractures and the risk of breast cancer or death from breast cancer.<sup>12,13</sup> The risk was 16 percent lower in women with hip fractures (standardized incidence ratio, 0.84; 95 percent confidence interval, 0.74 to 0.95)<sup>13</sup> and 58 percent lower in women with forearm fractures (standardized mortality ratio, 0.42)<sup>12</sup> than in those without fractures. However, factors other than bone density contribute to the risk of fractures. Cauley et al.<sup>14</sup> recently reported that, over four years of follow-up, women with bone mineral density above the lowest quartile had a risk of breast cancer that was two to two and a half times higher than the risk in those with bone mineral density in the lowest quartile. With more than 20 years of follow-up, we were able to examine the long-term relation of bone mass to the risk of breast cancer.

Measurements of relative metacarpal cortical area can be used to draw inferences about the relation of bone mass to the risk of breast cancer. Dual-energy x-ray absorptiometry is the standard method for measuring bone mass, but radiogrametry of the second metacarpal cortical area is precise<sup>54,55</sup> and accurate.<sup>56,57</sup> Relative metacarpal cortical area is highly correlated with the metacarpal-ash mineral content ( $r=0.85$ ),<sup>56</sup> and the mineral content of the metacarpals correlates well with that at other bone sites ( $r$  ranges from 0.75 to 0.95).<sup>57</sup> In the present study, both interobserver and intraobserver correlations of radiographic readings were above 0.9.

All cases of breast cancer in this study were confirmed by histologic reports. We believe that virtually all clinically detected incident cases of breast cancer were ascertained, since the incidence of cancer in the Framingham Study is similar to that in the Surveillance, Epidemiology, and End Results Program.<sup>18</sup>

Adjustment for risk factors other than age had little, if any, effect on the relation of bone mass to the risk of breast cancer. Information on a family history of breast cancer and age at menarche was not collected in the Framingham Study. Although the risk of breast cancer is two to three times higher for women with a family history of breast cancer than for those without such a history,<sup>22</sup> less than 10 percent of women in the general population have a family history of breast cancer.<sup>58</sup> Age at menarche is a significant predictor of breast cancer, but the magnitude of its association with the risk of breast cancer is unlikely to account for the present findings.

In conclusion, the results of our study suggest

that bone mass in middle-aged and elderly women is a strong predictor of the risk of postmenopausal breast cancer. Although the biologic mechanisms linking bone mass to the risk of breast cancer are not fully understood, cumulative exposure to estrogen may have a role.

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