

# Appendix D: Summary of Hip Fracture Prediction Methods | D

**T**his appendix describes the assumptions used in OTA's analysis of the impact of hormone replacement therapy (HRT) on hip fractures.<sup>1</sup>

OTA's model assumes that HRT affects fracture risk through its impact on bone mass as measured by bone mineral density (BMD). The rationale for this assumption is twofold. First, the causal relationship between HRT and bone loss is well-established and precisely estimated, at least in the short-run. In contrast, the evidence of a direct relationship between HRT and fracture rests on studies with relatively weak designs that do not lend themselves readily to precise estimates of effect size. (See appendices B and C.) Second, the relationship between BMD measured at each age and the risk of hip fracture has been quantified in some recently reported studies.

## REQUIREMENTS OF THE OTA HIP FRACTURE PREDICTION MODEL

OTA's model predicts the probability of hip fracture at every age between 50 and 90 as a function of an individual's BMD at age 50. The model is

based on earlier work by Black and colleagues on the relationship between bone mass at menopause and lifetime risk of hip fracture (3). In that model, as in the present one, BMD at any age is predicted from BMD at menopause. (OTA used age 50 as a reasonable proxy for the age at menopause.) The predicted BMD at each age is then used to estimate the risk of fracture at that age.

The parameters required for such a model fall into two general categories: 1) those related to the longitudinal distribution of BMD; and 2) those relating BMD to the short-term risk of fracture. Most of the data available to estimate these relationships are based on studies of white women, the group at highest risk of osteoporosis and the only ethnic-sex group for whom data are available for estimations of sufficient precision for modeling. Where data on racial or ethnic groups or sexes other than white women are available, however, their findings are described in this appendix.

## MEASURING BONE MASS

Different technologies are available for measuring bone mass at different sites in the body. How and

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<sup>1</sup>This appendix is based on a contract report prepared in 1992 for OTA by Dennis Black (1). The data in that report reflected information available in 1992. That report describes methods for predicting wrist, spine, and all fractures as well as hip fractures.

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where bone mass is measured can affect its predictive power for hip fracture.<sup>2</sup> OTA's model is based on bone mineral density measured at the proximal radius (the lower forearm above the wrist) using single photon absorptiometry as the measurement technology. The primary reason for this choice is that the proximal radius is the only site for which there are sufficient data from a number of sources to make reasonable estimates of all parameters of the model. In particular, the proximal radius is the only site for which the longitudinal pattern of bone mass measurement over time has been characterized.<sup>3</sup> Because OTA's model requires consistent data on both changes in bone mass and the relationship between bone mass and fracture, no other site is feasible for modeling at present.

There has been some discussion in the literature about whether bone mineral content (gm/cm) (BMC) or density (actually areal density, gm/cm<sup>2</sup>) is a better predictor of fracture risk. For predicting hip fracture, an analysis of data from the Study of Osteoporotic Fractures (SOF) showed that BMC was approximately the same as bone mineral density in predicting fracture (5). For predicting all fractures, other analyses performed on the SOF data have shown similar results. Although most studies have reported results in terms of BMD, some have reported BMC. This appendix treats these results as interchangeable, although the predictive model is measured in terms of BMD.

### PREDICTING BONE MASS OVER TIME

The OTA model assumes that bone mass at any age follows a normal distribution with an age-specific mean and standard deviation. The evidence to support this assumption is summarized in the next section. If BMD at any age is normally distributed over the cohort of individuals in the age category, then the joint probability distribution of BMD at any two ages can be assumed to be bivariate normal. This implies that a woman's BMD at a given age,  $t$ , is related to her BMD at the previous age,  $t-1$ , according to the following formulas:

$$CMBMD_t = \mu_t + \rho (BMD_{t-1} - \mu_{t-1})$$

$$CSDV_t = \sigma_t^2 (1 - \rho^2)^{1/2}$$

$$BMD_t = Z * CSDV_t + CMBMD_t$$

where:

$BMD_t$  = a woman's BMD at age  $t$ ;

$\mu_t$  = the mean BMD in the population of women at age  $t$ ;

$\sigma_t$  = the standard deviation of BMD in the population of women at age  $t$ ;

$\rho$  = the correlation between a woman's BMD at age  $t$  and her BMD at age  $t-1$ .

$CMBMD_t$  = the conditional mean of the probability distribution of BMD values at age  $t$  in women with BMD value at age  $t-1$  of  $BMD_{t-1}$ ;

$CSDV_t$  = conditional standard deviation at age  $t$ ;

<sup>2</sup> Although a paper from the Hawaii Osteoporosis Center (29) has suggested that bone mass measurements taken at the calcaneus (heel) predicted all fractures better than did measurements taken at the radius (a bone of the lower part of the arm) or in the spine, the Study of Osteoporotic Fractures (the only other study which has measured bone mass at the calcaneus) has shown a relationship of approximately equal magnitude between bone mass and fracture risk at all sites (radius, calcaneus, spine and hip) for all fractures and for wrist fractures (3). For hip fractures, the three appendicular sites (proximal radius, distal radius and calcaneus) have been shown to be approximately equal as predictors (5) although recent data have suggested that bone mass at the proximal femur (thighbone) is a better predictor of hip fracture risk than bone mass at the other sites (2,6). Unfortunately, no data on the longitudinal distribution of bone mass at the hip or the long-run predictive accuracy of any densitometry method are yet available.

<sup>3</sup> After the proximal radius, the bone mass site studied most frequently is the spine. At present, however, the information available to estimate the parameters of the model are insufficient for three reasons. First, most studies of bone mass at the spine are either small, have a very wide age range, or have been performed on samples of women who are unrepresentative of the general population of women. Second, bone mass at the spine is measured by several techniques, including quantitative computed tomography, dual photon absorptiometry, and dual x-ray absorptiometry, each of which might show a unique longitudinal pattern or relationship to fracture risk. Third, as women age and develop anatomical abnormalities (e.g., vertebral deformities, osteophytes, etc.) the spine presents special difficulties as a site for bone mass measurement.

TABLE D-1: Comparison of Observed to Predicted Percentile Values for Bone Mineral Density at the Proximal Radius (gm/cm<sup>2</sup>)

Percentile	Age 65-76		Age 75-79	
	Predicted <sup>a</sup>	Observed	Predicted <sup>a</sup>	Observed
1	0.415	0.412	0.372	0.396
5	0.484	0.484	0.438	0.441
10	0.521	0.522	0.473	0.476
25	0.582	0.584	0.532	0.529
50	0.651	0.650	0.598	0.596
75	0.719	0.719	0.663	0.659
90	0.781	0.780	0.722	0.722
Mean (gm/cm <sup>2</sup> )	0.6507		0.5978	
Standard deviation	0.1015		0.09705	

<sup>a</sup> Predicted values based on a normal distribution with the observed mean and standard deviation.

SOURCE: D. M. Black, "Cost Effectiveness of Screening for Osteoporosis: Review of Bone Mineral Density and Fracture Parameters Required for Model," University of California, San Francisco, CA, unpublished OTA contract report, Nov. 17, 1992

$Z$  = a random number drawn from the standard normal distribution.

Thus, knowledge of the mean and standard deviation of the BMD distribution at each age, and the coefficient of correlation between the two distributions, permits the generation of a BMD trajectory for an individual woman over her lifetime.

This section reviews the evidence on the following aspects of the BMD prediction formula given above:

- Age-specific distribution of BMDs
- Correlation between BMD values at successive ages

### ■ Age-Specific Distribution of BMDs

The age-specific distribution of BMDs is defined by the general shape of the distribution (i.e., whether it is a normal, or bell-shaped curve, or defined by some other general form) and, if it is a normal distribution, its mean and standard deviation.

#### *Shape of the BMD Distribution*

Three large studies of bone mass are available to assess the shape of the BMD distribution.

- Study of Osteoporotic Fractures (SOF): The unpublished analysis in table D-1 compares the

observed percentiles for bone mass at the proximal radius to the predicted percentiles based on a normal distribution. There is close agreement between the observed and predicted values, indicating that the normal distribution provides an excellent approximation to the observed, empirical distribution (1).

- University of Indiana: A study of bone mass in 583 women showed that the fit of bone mass data to a normal distribution was excellent (19). The investigators of this study have reported that they have found no evidence of significant skewing or other nonnormality in their cross-sectional data (15).
- University of Iowa: In a cross-sectional study of bone mass in 217 Caucasian women, bone mass variables were found to have a normal distribution (24).

These findings and the lack of any report suggesting that bone mass departs from a normal distribution, strongly suggest that at any age the distribution of bone mass across women is normal.

#### *Age-Specific Means*

Ideally, bone loss could be estimated directly from longitudinal data on cohorts of women followed for long periods of time. However, few such studies with sufficiently large numbers of subjects are

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available. In the absence of such longitudinal data, bone loss can be estimated from age-specific means derived from cross-sectional data. OTA used a combination of longitudinal and cross-sectional studies to estimate change in bone mass with age.

It is possible to establish age-specific means from cross-sectional studies of bone mass in population-based samples of individuals, but there are a number of potential problems in using cross-sectional data to estimate longitudinal changes in bone mass.<sup>4</sup> First, the sample may be biased. Second, the sample must be large enough in each age category to allow for sufficient precision. Third, cross-sectionally estimated changes in bone mass may differ from those estimated from longitudinal studies if there are cohort effects, such as nutritional factors or medication use patterns that vary with age.

Although many cross-sectional studies address the relationship of bone mass to age, most of these data are not very informative because they are from small studies without population-based samples. Two studies described in this section are exceptions.

Data from six separate studies of bone mass formed the basis for estimates of age-specific mean BMD. Each is described in detail below.

### University of Indiana

A total of 268 women were studied longitudinally and 583 were studied cross-sectionally. They were recruited as two distinct samples. The cross-sectional sample was younger (under age 65) and consisted primarily of gynecology clinic patients and employees of the Indiana University Medical Center. The longitudinal sample consisted of a group of older subjects (over age 55, mostly over age 65) who were residents of a retirement home. The older women had repeated bone mass measurements (between three and 45, with a mean of

20 measurements) over followup periods ranging from six weeks to seven years (mean = 4 years). The samples have been used for a number of different analyses. The exact participants and measurements used have differed in the various reports of the study depending on the research question being addressed.

One analysis of these data compared longitudinal with cross-sectional estimates of mean BMC in post-menopausal women (19). This analysis showed that the cross-sectional results agreed closely with longitudinal results. The results showed a quadratic relationship between BMC and age which was essentially linear in the age range 50 to 70. The average rate of bone loss decreased after about age 70, and there is a suggestion of an increase in bone mass after age 70. The actual rates of loss in the data are not useful for the purposes of the OTA study, because they were adjusted for body weight without reporting enough information to calculate overall population means.

A more recent analysis of the same data looked in detail at bone loss in the period zero to five years after menopause and five to 10 years after menopause (18). The large number of repeat measurements over time gives very precise estimates of bone loss. For the period zero to five years after menopause, a total of 89 women were available for analysis with an average of 11 measurements during the five-year period. These women showed an average loss of about 1.6 percent per year over the five years. For the period five to 10 years after menopause, a total of 47 women were used with an average of eight measurements each during the five years. These women showed an average loss of about 1.2 percent per year over the five years.

### University of Iowa

A sample of 217 Caucasian women from a rural community in Iowa between the ages of 22 and 80

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<sup>4</sup> Several studies have compared cross-sectional to longitudinal data sets for estimating bone loss with age (7,19). Only Davis and colleagues found the two approaches to lead to different results, although the methodology in their paper is difficult to interpret. Also, the data set which Davis used (a cohort of Japanese American women) may have cohort effects not present in other data sets.

**TABLE D-2: Bone Loss by Age in the University of Iowa Cohort**

Age at first measurement	Number of women	Percent loss per year
45-49	19	1.3%
50-54	36	2.0%
55-59	60	1.2%
60-64	55	1.2%
65-69	60	1.3%
70-74	43	1.2%
75-79	53	1.3%

SOURCE: M. Sowers, M. Clark, B. Hollis, et al., "Prospective Study of Radial Bone Mineral Density in a Geographically Defined Population of Postmenopausal Caucasian Women," *Calcified Tissue International* 48:232-239, 1991.

had bone mass measured at the radius in 1984, and 181 of them had repeat measurements made five years later in 1989 (24,25). The strength of these data is that they were collected longitudinally over a long period of time (five years). However, the precision of estimates based on the data is limited due to the small numbers of participants. The average annual bone loss for women who were postmenopausal at the time of followup is given in table D-2.

For ages 50 and over, the confidence intervals around the mean percent loss are approximately plus or minus 0.3 to 0.4 percent. The loss rates in this study are approximately the same as other studies. There is an approximate doubling of the rate of loss during the five years after menopause.

**University of Copenhagen**

121 women who were six months to three years post-menopausal and who were 45 to 54 in 1977 had BMD measured in the forearm. Their BMD measurements were repeated 12 years later in 1989 (14). The mean loss averaged 1.7 percent per year over the 12 years.

**Hawaii Osteoporosis Center**

A cohort of 1,098 Japanese-American women, all post-menopausal, was established in 1981. This cohort has been extensively followed with repeat

**TABLE D-3: Bone Mass by Age in Hawaii Osteoporosis Center Cross-Sectional Analysis**

Age	N	BMC at the proximal radius	
		Mean (gm/cm)	Percent loss per year
43-49	11	.849	—
50-54	38	.797	1.2%
55-59	196	.790	1.2%
60-64	411	.745	1.1%
65-69	306	.687	1.2%
70-74	108	.669	0.5%
75-79	24	.577	2.7%

KEY BMC = bone mineral content

SOURCE K Yano, R.D. Wasnich, J.M. Bogel, et al , "Bone Mineral Measurements Among Middle-Aged and Elderly Japanese Residents in Hawaii," *American Journal of Epidemiology* 119:751-764, 1984.

bone mass measurements. One analysis examined change in bone mass with age among post-menopausal women who did not use estrogen (7). These loss rates were adjusted for height, weight, and bone width. Longitudinal analyses (n = 636 women, mean length of followup = 3.2 years) in the same paper showed that the rate of loss was about 1.5 percent per year at age 55 and declined to about 0.8 percent at age 75. Cross-sectional analyses of bone density in 677 women showed a decrease in mean bone mass of approximately 1 percent for each year of age for women around the age of 55. The mean decrease by age increased to about 1.25 percent for each year of age for women around 75 years old.

The results of another cross-sectional analysis on the same sample, which *did not* exclude estrogen users, are shown in table D-3 (30). Through the early post-menopausal years, the results are essentially constant at about 1.2 percent per year. The results for age 70 to 74 are at odds with the remainder of the data and suggest either a typographic error (e.g., .699 should be .629) or imprecision due to small sample size.

An important caveat in interpreting analyses of these data is that the sample is drawn from a very special population (Japanese-American women

living in Hawaii) which may not reflect loss rates in a larger population. However, the general pattern of change in bone density with age is helpful in confirming the pattern found in other data sets.

### Study of Osteoporotic Fractures

The largest cross-sectional study (9,704 women over age 65) of bone mass, the SOF should be reasonably representative of healthy white women over age 65 years in the U.S. (5). Data are available for bone mass measured by SPA in the proximal radius, distal radius and calcaneus, but only in women over the age of 65.

Steiger and colleagues recently reported an analysis of cross-sectional bone loss in SOF (26). However, that paper does not exclude current estrogen users. The data shown in table D-4 are the same as those in the Steiger paper but exclude estrogen users.

### Framingham Osteoporosis Study

The investigators in the Framingham study performed cross-sectional analysis of bone mass at various sites, including the proximal radius in 708 women over age 68 years. At the time of preparation of this report, no data had yet been published. However, preliminary results have suggested a constant loss rate of about 0.9 percent per year from ages 68 to 90 (1,13).

### OTA's Estimate

Qualitatively, most studies have shown a slightly higher rate of bone loss at the appendicular sites just after menopause, which slows after about age 55 or 60. One interesting consistency among the data presented above is that the acceleration in bone loss just after menopause at these sites is only slight.

For the age range of 50 to 65, the various studies provide consistent results. The longitudinal data from Copenhagen suggest an average rate of loss of 1.7 percent per year for the 12 years after menopause. The Iowa data show a 1.6 percent loss for the five years after menopause with a 1.2 percent loss for the next five years. The estimated rates of loss from these three studies are quite con-

**TABLE D-4: Mean Bone Mass by Age for Non-Estrogen Users in the Study of Osteoporotic Fractures**

Age	N	Bone mass at the proximal radius	
		Mean (gm/cm <sup>2</sup> )	Percent loss per year
65-69	1,864	.650	—
70-74	1,507	.620	0.9%
75-79	907	.598	0.7%
80-85	537	.566	1.0%
85-89	140	.541	0.9%

SOURCE: S.R. Cummings, D.M. Black, M.C. Nevitt, et al., "Appendicular Bone Density and Age Predict Hip Fracture in Women," *Journal of the American Medical Association* 263:665-668, 1990

sistent given the inherent imprecision due to limited sample size. Some of the discrepancies among the studies may also be due to differences in the study population, methods of analysis, or differences in measurement technique.

The only longitudinal study in the age range of 65 and over is the study from Iowa which showed a mean loss of about 1.2 percent per year. Two large cross-sectional studies are available of women over age 65 years. SOF is much larger than any other study and shows a constant rate of loss after 65 of 0.8 percent per year. The results from the Framingham study are consistent with those from SOF showing an average loss of about 0.9 percent per year after age 65.

Based on the results of these studies, OTA developed a base-case set of assumptions about the rate of change in mean bone mass of a population of women as they age. These assumptions are shown in table D-5. Alternative assumptions reflecting reasonable upper and lower bounds on the bone loss rate are also shown in the table.

In addition to the percentage of bone loss in each year, the OTA model requires an estimate of mean BMD at each age. Although all the studies described above are consistent in their estimates of loss rates, recorded bone density levels vary with each densitometer. Consequently, it is not possible to pool mean values from various

**TABLE D-5: Assumptions About Bone Loss in OTA's Model**

Age interval	Annual rate of loss		
	Base case	Slow loss	Fast loss
50-54	1.8%	1.6%	2.0%
55-59	1.3%	1.2%	1.5%
60-64	1.0%	0.9%	1.2%
> 65	0.9%	0.8%	1.2%

SOURCE: Office of Technology Assessment, 1995.

sources. OTA used the estimated mean BMD value from SOF for ages 65 to 69 (0.650 gm/cm<sup>2</sup>) as an *anchor* value for the age-specific BMD levels. The means at the other ages were calculated from this value at age 67 using the loss rates given in table D-5. The derived age-specific means are shown in table D-6 for the base assumptions and two alternative assumptions. Under the base assumption, there is an overall loss of 35 percent between ages 50 and 90. For the slow loss assumption set, there is an overall loss of 32 percent and under the fast loss assumption set, the overall loss is 42 percent.

**Age Specific Standard Deviations**

The requirements for estimating the standard deviations of the distribution of BMDs are similar to estimating their means: a large, randomly chosen sample in which estrogen users have been excluded. Longitudinal data are not required, however. Again, the problem of scaling of bone density values taken from different densitometers makes comparisons across studies difficult, and the values of a given study must be used as an anchor. An important question in analyzing the data available on standard deviation is whether it varies with age.

Because of its size and relatively representative sample, the SOF study provides the best estimates of standard deviation for women overage 65. Unpublished data from that study for women who have never used estrogen are shown in table D-7.

Although these data suggest that, at least for women over 65 years of age, the standard deviation is fairly constant, other studies suggest some

**TABLE D-6: Age-Specific Mean BMD (gm/cm<sup>2</sup>) Under Various Assumptions About Bone Loss**

Age	Assumption set		
	Base	slow loss	Fast loss
50	0.814	0.796	0.844
51	0.799	0.783	0.827
52	0.785	0.770	0.811
53	0.771	0.758	0.794
54	0.757	0.746	0.778
55	0.743	0.734	0.763
56	0.733	0.725	0.751
57	0.724	0.717	0.740
58	0.714	0.708	0.729
59	0.705	0.699	0.718
60	0.696	0.691	0.707
61	0.689	0.685	0.699
62	0.682	0.679	0.690
63	0.675	0.673	0.682
64	0.669	0.667	0.674
65	0.662	0.661	0.666
66	0.656	0.655	0.658
67	0.650	0.650	0.650
68	0.644	0.645	0.642
69	0.638	0.640	0.634
70	0.633	0.635	0.627
71	0.627	0.629	0.619
72	0.621	0.624	0.612
73	0.616	0.619	0.605
74	0.610	0.614	0.597
75	0.605	0.610	0.590
76	0.599	0.605	0.583
77	0.594	0.600	0.576
78	0.588	0.595	0.569
79	0.583	0.590	0.562
80	0.578	0.586	0.556
81	0.573	0.581	0.549
82	0.568	0.576	0.542
83	0.562	0.572	0.536
84	0.557	0.567	0.529
85	0.552	0.563	0.523
86	0.547	0.558	0.517
87	0.542	0.554	0.511
88	0.538	0.549	0.504
89	0.533	0.545	0.498
90	0.528	0.540	0.492

SOURCE: Office of Technology Assessment, 1995; D.M. Black, "Cost Effectiveness of Screening for Osteoporosis: Review of Bone Mineral Density and Fracture Parameters Required for Model," University of California, San Francisco, CA, unpublished OTA contract report, Nov. 17, 1992.

variation with age. Data from the Indiana University sample of 268 post-menopausal women sug-

**TABLE D-7: Age-Specific Standard Deviations of BMD in SOF (excludes women who have ever used estrogen)**

Age	N	Standard deviation of bone mass (gm/cm <sup>2</sup> )
65-69	1,864	.102
70-74	1,507	.100
75-79	907	.097
80-84	537	.096
85+	140	.095

KEY: BMD = bone mineral density; SOF = Study of Osteoporotic Fractures,

SOURCE: D. M. Black, "Cost Effectiveness of Screening for Osteoporosis: Review of Bone Mineral Density and Fracture Parameters Required for Model," University of California, San Francisco, CA, unpublished OTA contract report, Nov. 17, 1992

gested that there is an *increase* in standard deviation with age, but no estimates of standard deviation were reported (19). Data from the University of Copenhagen study, on the other hand, showed a decrease in the standard deviation between the first measurement (age 45 to 54) and the second (age 57 to 66), by about 0.5 percent per year. The Framingham cross-sectional data also showed a decrease—about 0.6 percent per year—in women over age 68. The University of Iowa 1983 cross-sectional sample showed age-specific standard deviations of BMD that varied from a high of 0.119 gm/cm<sup>2</sup> (age 70 to 74) to a low of 0.081 gm/cm<sup>2</sup> (age 65 to 69). There was no clear trend with age, although the precision of the estimates is limited by the small numbers within each age group.

Estimates of standard deviations are less precise than estimates of means; it is therefore difficult to conclude from these data whether there is a real decrease in the variation of bone mass with age. In addition, the value of the standard deviation of bone mass depends on the technique used to measure bone mass as well as the population from which the sample was drawn. The data are most consistent with a slight decrease of standard deviation with age. However, the small decrease suggested would have a negligible effect on any results of the model. Therefore, OTA assumed that

the standard deviation of bone mass at the proximal radius is 0.10 gm/cm<sup>2</sup> and does not change with age in the age range 50 to 90 years.

### ■ Correlation Between Values of Bone Mass at Two Ages

The model requires an estimate of the correlation between bone mass at the age at which BMD screening takes place and at later ages. For example, if screening for bone mass occurs at age 50, the model requires the correlation between bone mass at age 50 and bone mass at ages 51, 52, etc. The correlation required is the correlation between the true values of bone mass in successive years, not the measured values, because it is the true values that predict fracture. For long-term studies (e.g., at least five to 10 years), the correlation between the true values will be about the same as that between the measured values. However, in studies of shorter duration, measurement error plays a larger role artificially deflating the correlation.

The accuracy of the estimate of this model parameter is important, because changes in the estimates would have large effects on the resulting fracture rates. Fortunately, sufficient data exist (see below) to restrict its possible values, and within this range its effect on outcomes is only moderate.

To estimate the long-term correlation, longitudinal data must be collected over as long a period of time as possible. For example, to estimate the correlation between bone mass at age 50 and age 65, 15 years of followup data are needed on a cohort who were age 50 at the initial measurements. For the correlation between BMD at age 50 and BMD at age 80, a 30-year followup period is necessary. The ideal data set would have bone mass measured on a large random sample of women from the age of 50 to 90. Clearly, such data do not (yet) exist.

Three studies have reported the correlation between bone mass measurement at widely separated intervals. The University of Indiana analysis of post-menopausal women estimated the correlation between bone mass measured within two



years of age 50 with bone mass measured about 10 years later based on the experience of 34 women (18). The data showed a correlation of about 0.81 between measurements taken at ages 50 and 60 and a correlation of about 0.7 between measurements made at ages 50 and 70.

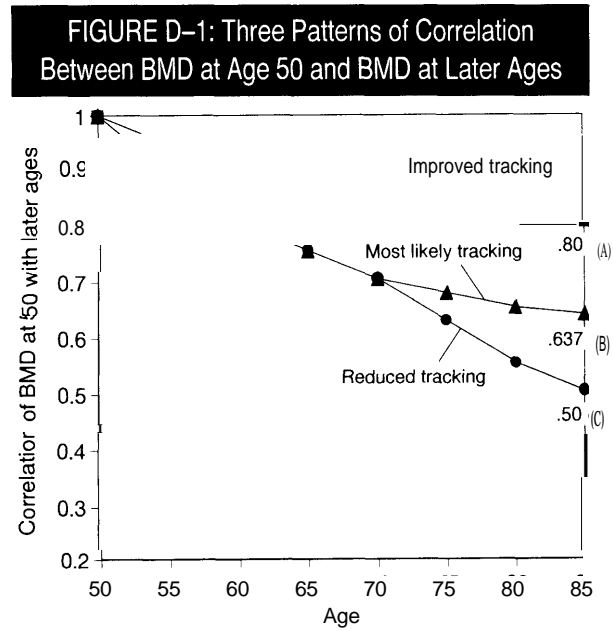
For women over age 55, the University of Iowa study found that the correlation between the two measurements taken five years apart was greater than 0.9 (24). However, the exact 5-year correlation was not given.

Finally, in the University of Copenhagen study of 121 post-menopausal women aged 45 to 54 at entry, the correlation between the first measurement and the second taken 12 years later was 0.8 (95 percent CI: 0.7 to 0.9) (14).

The two long-term data sets on early post-menopausal women agree closely in showing a 10-year correlation of about 0.8. OTA used this value as the base assumption about the longitudinal correlation from age 50 to age 60. For ages 50 to 70, we used the estimate of 0.7 from the University of Indiana. Beyond age 70, for the base assumption, a quadratic function was fit under the assumption that the degradation in correlation continues after age 70 in the same pattern as before age 70.

Alternative assumptions are possible. Figure D-1 shows three alternative correlation trajectories. Under the base-case assumptions, the extrapolation of correlation beyond age 70 (pattern B in figure D-1) continues to decrease along the same quadratic pattern as before age 70. As a woman ages and becomes less active and more ill, however, a second acceleration in bone loss may occur. Since this increased bone loss would be associated with factors that could not be predicted from bone mass at age 50, a decreased correlation between bone mass at age 50 and bone mass beyond age 65 would result. Pattern C represents the decreased correlation that might be associated with increased bone loss associated with severe immobility and/or illness or extreme old age.

Another correlation trajectory (pattern A in figure D-1) maps a correlation of bone mass at each age with bone mass at age 50 that is higher than the

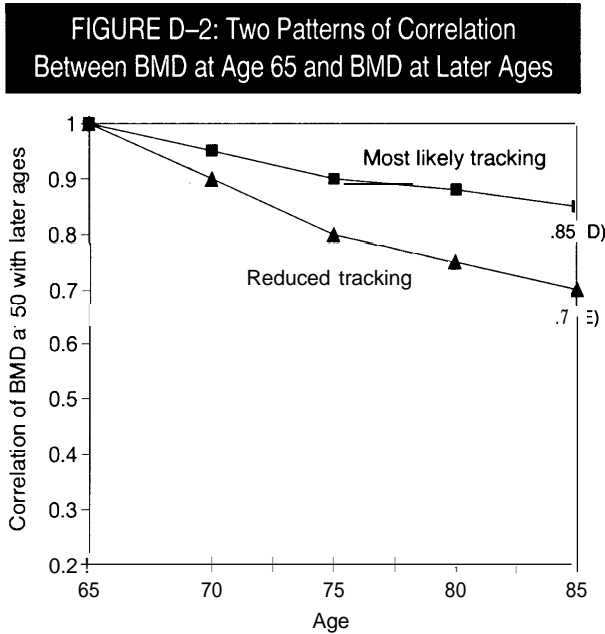


SOURCE D.M. Black, "Cost Effectiveness of Screening for Osteoporosis: Review of Bone Mineral Density and Fracture Parameters Required for Model," University of California, San Francisco, CA, unpublished OTA contract report, Nov 17, 1992

base-case pattern. This might occur if a more precise measurement of bone mass was made.

There is little published data specifically addressing the correlation between bone mass at age 65 and later ages. However, the correlation of bone mass between age 65 and subsequent ages will almost certainly be better than correlations with age 50, because a relatively high rate of perimenopausal bone loss after age 50 adds greater variability to predicting later values. Thus, the correlation between bone mass at age 65 and ages above 65 will almost certainly be higher than the correlation between bone mass at age 50 and later ages.

Because the OTA model uses year-to-year correlation estimates, the estimates projected in figure D-1 probably represent too steep a loss of correlation in later years. Consequently, we revised the correlation pattern after age 65 to account for the higher correlation pattern at older ages. Figure D-2 contains the results. Pattern D represents a correlation after age 65 that is slightly



SOURCE: D. M. Black, "Cost Effectiveness of Screening for Osteoporosis: Review of Bone Mineral Density and Fracture Parameters Required for Model," University of California, San Francisco, CA, unpublished OTA contract report, Nov. 17, 1992.

higher than that assumed after age 50 (pattern B in figure D-1). This pattern was used as the base-case assumption. Pattern E is analogous to the data from Hui for peri-menopausal women showing a correlation of 0.90 after five years (at age 70), a correlation of 0.80 after 10 years, etc. This pattern probably represents a lower limit on the correlation of bone mass after age 65 (18).

The OTA model requires correlations between bone mass at each age and bone mass at the next highest age. The patterns above include only the correlation between age 50, or age 65, and subsequent ages. However, the cost-effectiveness model requires the correlation between, for example, bone mass at ages 60 and 65 and between ages 80 and 85. We required a pattern of short-term correlations that approximates the long-term correlations shown in the figures above.

To approximate the long-term pattern in the base-case (pattern C in figure D-1) we assumed that the correlation between bone mass at any age and subsequent bone mass five years in the future is 0.90 for ages 50 to 60 and 0.95 for ages over 60. If the correlations follow an autoregressive model,

then the correlations between any two points can be found simply by multiplying the correlations in between. For example, the correlation between age 50 and 60 is  $0.9 \times 0.9$  or 0.81. Under the autoregressive model, the long-term pattern closely approximates pattern C. Similar sets of short-term correlations could be developed for the other long-term correlation patterns above.

### RELATIONSHIP OF BONE MASS TO HIP FRACTURE RISK

At any age, the OTA model must predict the probability of hip fracture as a function of the woman current BMD. Following work of Black and colleagues, OTA assumed a logistic relationship between BMD and hip fracture risk (4). A logistic is given by the following formula:

$$P = \frac{1}{1 + e^{-\alpha - \beta x}}$$

where:

- $P$  is the probability of hip fracture at a given age;
- $\alpha$  is a constant term that varies with age;
- $\beta$  is a term that varies with BMD, but not with age; and
- $x$  is the individual's BMD at the age in question.

When the risk of fracture is less than about 10 percent (as is the case for all hip fracture risks considered in this appendix), the logistic relationship between bone mass and risk is essentially linear. Therefore, data fitted to any other functional form that is similarly linear would yield essentially the same results as those obtained from fitting data to estimate the parameters ( $\alpha, \beta$ ) of the logistic model. However, if a nonlinear relationship (e.g., threshold model) were the true relational form between BMD and hip fracture, the logistic assumption would yield substantially erroneous results. It is therefore important to establish the validity of the logistic (or linear) relationship.

There is only one source of data (SOF) that has published data relating bone mass to risk of hip fracture (5). The results of that analysis suggest that the relationship of bone mass to hip fracture

TABLE D-8: Relationship of Proximal Radius Bone Mass to Non-Spine Fracture in SOF

Age group	N	Fractures	SD	RR <sup>a</sup>	95% CI
65-74	6,896	934	0.10	1.36	(1 .27,1 .45)
75+	2,441	470	0.10	1.33	(1 .21,1 .47)

<sup>a</sup>Relative hazard per standard deviation decrease in bone mass.

SOURCE: D. M. Black, "Cost Effectiveness of Screening for Osteoporosis' Review of Bone Mineral Density and Fracture Parameters Required for Model," University of California, San Francisco, CA, unpublished OTA contract report, Nov. 17, 1992

risk follows a linear pattern and that the logistic model is therefore a consistent description of the true relationship. A statistical test for the goodness of fit of the data to a logistic model did not reject the null hypothesis that the relationship is logistic.

The relationship between bone mass and fracture probability is usually estimated in terms of a standardized relative risk: the ratio of risk of a person whose bone mass is one standard deviation below the mean to the risk of a person whose bone mass is at the mean.

A critical assumption of the OTA model is that the relative risk of fracture is constant across age groups (or, alternatively, that  $\beta$  is constant across all age groups). For example, if the relative risk of fracture of a 70-year-old woman whose BMD lies 1 standard deviation below the mean BMD of 70-year-old women is 3, then the relative risk of a 50-year-old woman with BMD at 1 standard deviation below mean BMD of 50-year-old women is also 3. This assumption is equivalent to stating that there is no interaction between bone mass and age in predicting hip fractures. Virtually all published analyses in this field have included this assumption (e.g., 3,5,11,12,17,22,28).

Fortunately, data available to test the interaction between bone mass and age suggest that the assumption is valid. Table D-8 shows data provided by the SOF on the relationship of BMD (measured in the proximal radius) to hip fracture risk in ages 65 to 75 compared with ages 75 and over. There is a very slight suggestion of decreasing strength in the relationship of bone mass to hip fracture risk with increasing age. However, the large overlap in the two confidence intervals shows that the differences do not approach statisti-

cal significance. A recent analysis of SOF data of radial BMD prediction of hip fracture found no difference between women over 80 years of age and those under 80 years of age (23). Therefore, OTA assumed that the relative risk relating to bone mass and hip fracture risk is constant across all ages in the model.

### ■ Relative Risk of Bone Mass and Hip Fracture

Several sources of data are available on the short-run risk of hip fracture as a function of bone mass.

SOF published data using bone mass at three sites to predict hip fracture in the sample of 9,704 women (5). The average followup was 1.7 years. The standardized age-adjusted relative risk for BMD ( $\text{gm}/\text{cm}^2$ ) at the proximal radius was 1.4 (1.1 to 1.9). Analysis using BMC as the measure found slightly lower relative risks.

The University of Indiana reported on a total of 23 first hip fractures in 135 residents of a retirement home (17). Bone mass ( $\text{gm}/\text{cm}^2$ ) at the proximal radius was used as the predictor of hip fracture. The relative risk (95 percent CI) was 1.9 (1.3, 2.8) per 0.1  $\text{gm}/\text{cm}$  of BMC (approximately 1 SD). Age was not a significant predictor of hip fracture after adjustment for BMC.

An analysis of the data on 1,076 women in Malmö, Sweden, found that after adjusting for age, the relative risk was 1.8 (95 percent CI: 1.3 to 2.4) for BMC of the mid-radius. However, since these findings were not age-adjusted, they overestimate the age-specific relationship of bone mass to risk and therefore may not be of direct relevance to this study. (20,21). A recent analysis of a cohort of 304 women in Rochester, Minnesota, who were fol-

TABLE D-9: Annual Incidence of Hip Fracture in White Women, 1983

Age	Annual incidence of hip fracture (per 100.000)
50-54	69.5
55-59	135.4
60-64	169.6
65-69	314.3
70-74	493.5
75-79	1,033.2
80-84	1,669.3
85-89	2,552.5

SOURCE M.E. Farmer, L R., White, J. A., Brody, et al., "Race and Sex Differences in Hip Fracture Incidence," *American Journal of Public Health* 74:1374-1380, 1984.

lowed for an average of eight years, found a standardized relative risk of hip fracture of 2.7 (95-percent CI: 1.5 to 5.0) (21).

Black and colleagues performed a meta-analysis to calculate a pooled estimate and confidence interval for the relative risk of hip fracture for age-adjusted levels of bone mass in the radius, the only measurement site that was common to all three studies (4). Standard meta-analytic methods permit estimation of a pooled treatment effect and confidence intervals for data from numerous clinical trials (10). This pooled relative risk is calculated as the weighted mean of the individual standardized relative risks from each study, using the squares of the inverse of the standard error of the relative risk as the weights. The resulting combined relative risk was 1.65, with a 95 percent confidence interval of between 1.4 and 2.0. On the basis of this meta-analysis, OTA used a value of 1.65 as the base assumption for relative risk of hip fracture.

### ■ Calculation of the Constant Term for the Logistic Model

We have assumed that the relative risk relating bone mass to fracture is the same for all age groups. The absolute risk of fracture does increase with age, however. The constant term in the logistic model,  $a$ , must be estimated for each age to adjust the absolute risk for differences in age.

TABLE D-10: Logistic Parameters for Hip Fractures in OTA's Hip Fracture Model

Relative risk per standard deviation	1.65
Corresponding value of beta ( $\beta$ )	-5.0078
<b>Values of alpha (<math>a</math>)</b>	
<b>Bone loss = base case assumption</b>	
<b>Age</b>	<b>Value of <math>a</math></b>
50-54	-3.465
55-59	-3.10272
60-64	-3.0874
65-69	-2.62888
70-74	-2.32062
75-79	-1.70997
80-84	-1.35219
85-89	-1.04624
<b>Bone loss = slow</b>	
<b>Age</b>	
50-54	-0.2460
55-59	-0.2283
60-64	-0.2870
65-69	-0.2533
70-74	-0.3520
75-79	-0.3655
80-84	-0.1783
85-89	-0.3261
<b>Bone loss = fast</b>	
<b>Age</b>	
50-54	-3.3348
55-59	-3.0226
60-64	-3.0473
65-69	-2.6289
70-74	-2.3657
75-79	-1.8001
80-84	-1.4824
85-89	-1.2015

SOURCE: Off Ice of Technology Assessment, 1995, D M Black, "Cost Effectiveness of Screening for Osteoporosis Review of Bone Mineral Density and Fracture Parameters Required for Model," University of California, San Francisco, CA, unpublished OTA contract report, Nov. 17, 1992.

Under the assumption of an age-invariant relative risk, the constant term can be estimated using age-specific hip fracture incidence data (i.e., no age-specific data on the relationship of bone mass

to fracture is required). This method has been described elsewhere (4).

Briefly, the overall age-specific incidence of fracture ( $P(F_t)$ ) is the mean of the bone-mass-specific incidence ( $P(F_t|BM_t)$ ) weighted by the age-specific distribution of bone mass  $f(BM_t)$  or:

$$P(F_t) = \int P(F_t|BM_t) f(BM_t) dBM_t$$

If we have data on the age-specific incidence of fracture and on the age-specific distribution of bone mass (both of which are readily available from cross-sectional studies) and we know the relative risk parameter ( $\beta$ ) for the logistic model, the only unknown in the logistic function equation is the parameter  $\alpha$ .

OTA used data from the National Hospital Discharge Survey to estimate the age-specific incidence of hip fracture (8). Table D-9 shows those incidence estimates. Other population-based studies have yielded similar annual incidence rates of hip fracture among white women (9,27). Based on these data, the values of the parameters  $a$  and  $\beta$  in the logistic function are as given in table D-10.

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