

Vertebral Fracture Prevalence in Women in Hiroshima Compared to Caucasians or Japanese in the US

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Background. Although vertebral fractures are very common among elderly Caucasian women, no studies have compared the prevalence to that among Asian populations. Any observed differences in prevalence might lead to the identification of important environmental and/or genetic factors. We therefore compared the prevalence of vertebral fractures among US Caucasians to native Japanese and Japanese immigrants in Hawaii using a standardized approach.

Methods. Spinal radiographs of women aged ≥ 50 years were obtained from native Japanese in Hiroshima, Japanese-Americans in Hawaii, and North American Caucasians in Minnesota between 1982 and 1991. Fractures were defined as vertebral heights >3 standard deviations (SD) below the vertebra-specific mean.

Results. Compared to Japanese-Americans, odds ratios (OR) and 95% confidence intervals (CI) for prevalent vertebral fractures were 1.8 (95% CI : 1.3–2.5) for native Japanese women and 1.5 (95% CI : 1.1–2.1) for Minnesota Caucasians. The OR tended to be higher when comparing the prevalence of two or more fractures per person: OR = 3.2 (95% CI : 2.0–5.3) for native Japanese and OR = 1.9 (95% CI : 1.2–3.2) for Minnesota Caucasians. Similar results were observed for native Japanese using a fracture definition of ≥ 4 SD below the mean, but the OR for Caucasians was reduced to 1.2 (95% CI : 0.6–2.3).

Conclusion. The observation that, among these three populations, hip fracture incidence is lowest but spine fracture prevalence is greatest among native Japanese suggests that different risk factors may be responsible.

Keywords: cross-cultural comparisons, epidemiology, fracture prevalence, migrant studies, osteoporosis, vertebral fractures

Most studies of osteoporosis and its related fractures have been made among high-risk Caucasian women in North America and Europe. The homogeneity of these populations has precluded an assessment of pertinent environmental risk factors (e.g. diet, exercise, and reproductive patterns) over the full range seen in various populations around the globe. Moreover, evaluation of the interaction of these factors with differing genetic predispositions has not been possible. Cross-cultural studies have been helpful in distinguishing genetic from environmental determinants of other diseases, and we are pursuing this approach to identify modifiable factors that might be exploited in osteoporosis prophylaxis.

For example, hip fracture incidence rates have previously been shown to vary enormously in various populations,¹ and the incidence of hip and other non-spine fractures among native Japanese and Japanese-Americans is only about one-third to one-half that of US Caucasians.^{2,3} The prevalences of vertebral fractures in these populations have not been compared to our knowledge, though such a comparison could provide additional insight into possible aetiologic factors. We therefore examined the prevalence of spine fractures among native Japanese, second-generation Japanese-Americans in Hawaii, and Caucasians in Minnesota. Because many people are unaware that they have a vertebral fracture, we attempted to obtain radiographs for representative samples of each population.

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MATERIALS AND METHODS

Subjects

Details concerning recruitment and examination of participants in the Hawaii Osteoporosis Study (HOS), a

longitudinal study of bone loss and fractures, have been reported previously.^{4,5} Using Selective Service records, researchers in the Honolulu Heart Program (HHP) identified 11 136 men of Japanese ancestry residing on the island of Oahu, Hawaii. A total of 8006 men participated in the first HHP examination cycle, which commenced in 1965.⁵ Beginning in February 1981, a 30% random subsample of men who had participated in the HHP, and their wives, was invited to participate in the HOS. All subjects were of Japanese ancestry, but only data on the wives are presented here. These non-institutionalized women ($n = 1105$; participation rate = 72%) ranged in age from 43 to 80 years (mean = 63.3), and 99% were postmenopausal at the time of the first examination. An earlier analysis⁵ suggests that non-response bias probably does not exert a major influence on associations with osteoporosis for this cohort, on the basis of comparisons of more than 40 variables for a subset of the target population including both HOS participants and women who did not participate in the HOS. Additional HOS examinations were initiated in November 1981, August 1982, August 1983, October 1984, August 1986, February 1987, and August 1989. For the current analyses, only the most recent radiograph for each subject from examinations between 1986 and 1990 was used because radiographs obtained at earlier examinations did not include the entire spine. Women who were born in Japan and later moved to Hawaii (5% of the original HOS population) were excluded from analyses reported here because such women have lower bone density than American-born Japanese.⁶ Women <50 years old were also excluded from these analyses to ensure overlap of ages with the Japan and Minnesota groups. The 839 women in these analyses represent 80% of the original US-born cohort enrolled in the HOS. This study was approved by the local Investigational Review Board, and all subjects gave written informed consent before each examination.

Hiroshima participants were selected from the Adult Health Study (AHS) at the Radiation Effects Research Foundation. The original Hiroshima AHS members consist of 13 718 atomic bomb survivors and controls chosen from the 1950 national census supplementary schedules and the Atomic Bomb Survivors Survey. The original AHS sample was based on 6949 people who were within 2000 m of the hypocentre at the time of bombing, plus age- and sex-matched controls, stratified by distance from the hypocentre. Biennial medical examinations have been conducted on this cohort since 1958. The participation rate has been around 70 to 80%. The proportion of cumulative deaths reached one-third of the original population in 1987. Hip fracture incidence data are not available for the AHS sample.

However, the reported ratio of hip fractures in Hiroshima Prefecture compared to the national average was 1.02.⁷ Thus, it appears that hip fracture rates among women in Hiroshima are essentially identical to the national survey reported previously.²

For the current study, non-institutionalized subjects were selected for a special study on osteoporosis. Eligible subjects were identified from approximately 4000 participants in Hiroshima who underwent medical examination during the 1987–1989 examination cycle excluding subjects without estimated radiation dose and those who were not in the city at the time of bombing. To obtain an appropriate balance with respect to age, sex, and radiation dose, individuals were selected randomly within the categories stratified by gender (640 men and 960 women), age (ages 45–49, 50–59, 60–69, and 70–79 years at the time of examinations in 1987–1989), and radiation dose (0, 0.001–0.49, 0.5–0.99, and ≥ 1.0 Gy). The atomic bomb radiation dose estimates were based on the DS86 dosimetry system.⁸ When there was a shortage of subjects in a category, all subjects were selected; when there were sufficient subjects in a category group, about 40 men and 60 women were selected at random. A total of 883 women received spine radiographs during the 1989–1991 examination cycle. The analyses reported here were limited to the 803 women who were ≥ 50 years.

Potential participants in Rochester, Minnesota, were identified using the medical records linkage system of the Rochester Epidemiology Project.⁹ More than half of the Rochester population have annual contact with clinics and offices in this system, and most residents have contact in any 3-year period, including both free-living and institutionalized individuals. Initially, a total of 541 non-institutionalized residents, selected at random (from among those women with records in this system between 1979 and 1981) and stratified by age were contacted, and 304 (60%) agreed to participate and provided useful data.¹⁰ At the time of the 1980 census, 98% of the Rochester population was Caucasian. Only subjects aged ≥ 50 years ($n = 201$) had spine radiographs and are included in these analyses. A second sample using the same approach (from among women seen by the system between 1982 and 1984) identified 1020 eligible women aged >50 , of whom 561 (55%) agreed to participate and had spine radiographs.⁹ The women from these two studies were combined for the analyses reported here and represent approximately 9% of Rochester women in this age group. The overall non-response rate was 39%. The issue of non-response was formally assessed in an earlier report;¹¹ while there was some evidence that non-responders were less healthy, the differences were not great.

Spine Radiographs

In Honolulu, lateral radiographs were made with the subject lying on her side with knees bent, using an x-ray source-to-film distance of 105 cm.¹² Thoracolumbar spine radiographs (generally including all vertebrae below the level of T8) were centred approximately at the level of L2. Thoracic films (T3 through T12) were centred approximately at the level of T8. In Japan, lateral lumbar radiographs were made with the subject lying on her side with knees bent, using a source-to-film distance of 100 cm, centred approximately at the level of L3. Thoracic films were exposed with the subject standing, using a source-to-film distance of 180 cm, centred approximately at the level of T8. In Minnesota, radiographs were made at a source-to-film distance of 122 cm, with the thoracic film centred over T7 and the lumbar film centred over L2. At each research centre, the anterior (A), medial (M), and posterior (P) heights of each vertebral centrum were measured with the aid of a microcomputer-linked digitizing pad. In Hawaii, points indicating the border of the vertebral centrum were placed using a procedure similar to that described by Spencer *et al.*¹³ A similar method was used in Minnesota, but the middle height was based upon the average of the right and left middle heights instead of upon a single estimate of the height at the centre of the vertebra.⁹ The vertebral dimensions of the Hiroshima cohort were measured at the same locations on the vertebral border as described for the Hawaii study, on the basis of a pencilled outline of the vertebra instead of points. Interobserver variation was approximately 2.3% in Minnesota, 3.1% in Japan, and 3.5% in Hawaii. A sample of films from both Hawaii and Japan was exchanged to compare measurements; among 209 measurements, the mean difference was 0.10 mm greater for Hawaii (95% CI: -0.08, 0.28), suggesting little or no bias in measurement technique. Limited resources precluded a similar comparison with Minnesota.

Because vertebral size and shape vary with location in the spine, prevalent fractures were defined as vertebrae with dimensions >3 standard deviations (SD) below the vertebra-specific mean of each population.¹² A recent study suggests that approximately 80% of true fractures are identified using the 3 SD definition.¹² Because no universal definition of a prevalent fracture exists, we also examined a cutoff based on 4 SD. Fractures in the 4 SD category represent more severe vertebral deformities. Alternative definitions based on vertebral height ratios^{9,14} were also examined; however, the results are not shown here because they were generally similar to the results using unmodified vertebral heights.

In some analyses, fractures were further categorized by type (wedge, endplate, or crush). Vertebrae with posterior heights below the cutoff (either 3 or 4 SD below the mean) were classified as crush fractures. Among the remaining vertebrae, those with anterior heights below the cutoff were classified as wedge fractures, and vertebrae with only medial heights below the cutoff were classified as endplate fractures. Thus, each vertebra could be classified as one fracture type only, identified in the order of crush, wedge, and then endplate.

Statistical Methods

Logistic regression analysis was used to explore associations of vertebral fracture prevalence with predictor variables (population and age, plus radiation exposure for native Japanese). Each woman contributed only one observation per analysis. Binary indicator variables were used to represent the Japan and Minnesota populations, with Hawaii as the reference group (or Japan and Hawaii, with Minnesota as the reference group). Odds ratios (OR) were calculated as the antilogarithm of the coefficient from the logistic regression. The OR approximates the relative risk when prevalence of the outcome is rare in the population (<5–10%).¹⁵ For outcomes of higher prevalence, the OR may be substantially greater than the true relative risk.

RESULTS

Spine fracture prevalence increased dramatically with age in all three study populations. For example, the prevalence in Hawaii rose from zero below age 60 to 263 per 1000 women at age 80–84 using the 3 SD definition (Table 1). The prevalence was substantially greater among native Japanese at most ages, compared to Hawaii (3 SD and 4 SD) and Minnesota (4 SD only). The prevalence among the Minnesota population was greater than for Hawaii at most ages using the 3 SD definition, but there was no consistent difference using the 4 SD cutoff. The prevalence of both single and multiple fractures increased with age (Figure 1). The prevalence of women with single vertebral fractures appeared to be similar for all three populations, although the values fluctuated by age group due to the small number of cases in some age categories (Figure 1). By contrast, the prevalence of multiple (two or more) fractures was greater among the Japan and Minnesota groups, especially for the older age categories, compared to Hawaii. The prevalences of wedge, endplate, and crush fractures are shown by location within the spine in Figure 2. Wedge fractures were the most common fracture type in all three populations.

TABLE 1 Fracture prevalence (cases per 1000 women) by diagnostic criterion, age, and population

Age	Sample size			3 SD Fracture definition			4 SD Fracture definition		
	Hawaii	Japan	MN ^a	Hawaii	Japan	MN ^a	Hawaii	Japan	MN ^a
50–54	1	56	106	0	54	47	0	18	0
55–59	15	147	137	0	41	58	0	27	22
60–64	102	224	111	10	49	63	10	22	27
65–69	313	159	106	61	82	132	48	38	75
70–74	290	109	80	148	248	150	100	193	75
75–79	96	76	99	250	368	222	188	276	121
80–84	19	28	59	263	429	508	211	321	339
85+	4	4	61	0	250	508	0	250	361

^a Minnesota.

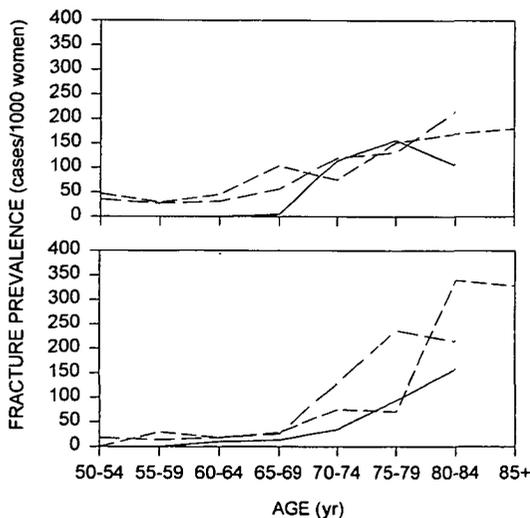


FIGURE 1 Prevalence of women with single vertebral fractures (upper graph) and women with two or more vertebral fractures (lower graph), stratified into 5-year age groups. The fracture definition was based on a cutoff of three standard deviations below the mean. Data for ages ≥ 85 are not shown for Hawaii and Japan because there were too few women in this age group. Solid line = Hawaii; long dashed line = Japan; short dashed line = Minnesota

Age-adjusted OR were calculated by logistic regression analysis, with either Hawaii or Minnesota as the reference group (Table 2). Atomic bomb radiation dose was not statistically significant in logistic regression models (OR = 1.01; 95% CI: 0.98–1.03 per 0.1 Gy radiation dose). Therefore radiation dose was omitted from the models reported here. Compared to Hawaii, the prevalence of one or more vertebral fractures among native Japanese women was significantly greater. The OR for two or more fractures were 2.2 to 2.5 times larger than

for single fractures, and the OR for single fractures failed to reach statistical significance. Similar findings were observed for both the 3 and 4 SD cutoffs. The OR comparing Minnesota Caucasians to Japanese-Americans were also greater for multiple fractures than single fractures, but OR were only significantly greater than 1.0 for the 3 SD definition. Consequently, it appears that Caucasian women may have a greater prevalence of multiple mild (>3 SD below the mean) vertebral fractures, compared to Japanese-Americans. The logistic regression models were repeated using Minnesota as the reference group (Table 2). The OR comparing Japan to Minnesota were greater for the 4 SD definition (compared to the 3 SD definition), and the OR were 1.4–1.7 times greater for multiple fractures, compared to single fractures.

DISCUSSION

Our findings indicate that the prevalence of vertebral fractures at ages 80–84 years is quite high—approximately 250–500 per 1000 women, on the basis of the 3 SD definition. The true prevalence may be even higher because the dimensions of some fractures overlap the normal range, thus eluding diagnosis.¹² About half of the women classified as having vertebral fractures had two or more. Because women who are currently 50 years old will live an average of 30 more years (and many will live much longer than that), vertebral fractures may represent a serious public health problem, especially if they are associated with chronic symptoms. Recent studies indicate that women with vertebral fractures have greater incidence and prevalence of back pain and back-related disability, which appears to be greatest among those with the most severe vertebral deformities (>4 SD below the mean), and increases with

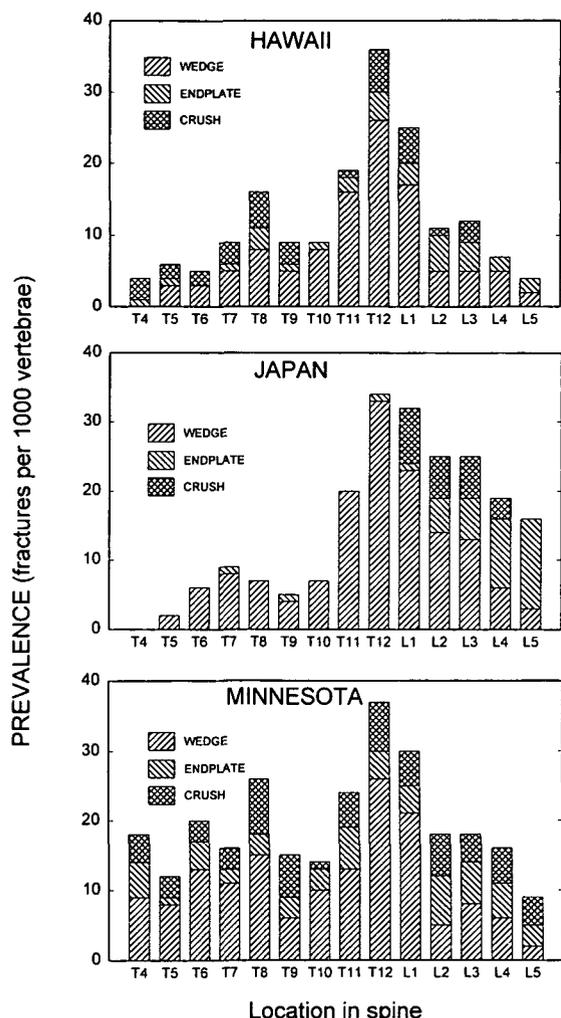


FIGURE 2 Stacked bar chart showing prevalence of the three types of vertebral fractures (wedge, endplate, and crush) by location in the spine for each population. The length of each bar segment indicates the prevalence of the corresponding fracture type. The fracture definition was based on a cutoff of three standard deviations below the mean

the number of fractures.¹⁶⁻¹⁹ By inference, back pain and related disability may be more common among women in Japan because they have a greater prevalence of multiple, severe fractures compared to Japanese-Americans in Hawaii and Caucasians in Minnesota.

The prevalence among women in Minnesota based on the 3 SD cutoff was 97 per 1000 participants aged 60-69, which is essentially identical to the value of 90 per 1000 reported for Caucasians in Great Britain based on a more restrictive definition using vertebral height ratios.²⁰ In our study, the highest prevalence

occurred in the thoracolumbar region (T11-L1) in all three populations. Anterior wedge fractures in the mid-thoracic region were also quite common. The bimodal distribution of fractures, with peaks around T12 and T8, has also been reported by other investigators and may be related in part to the shape and load distribution of the spine.²¹ Vertebrae tend to move together in groups, rather than individually, and certain regions of the spine are more flexible than others. These factors may increase the likelihood that specific regions will fracture more often than others and may also result in multiple fractures when mechanical forces act on groups of vertebrae.²¹

In an earlier study based on a larger sample of the Hiroshima cohort, Fujiwara *et al.*²² reported no effect of atomic bomb radiation on the incidence of thoracic vertebral fracture, which had been diagnosed by clinical reading of lateral chest radiographs during the period 1958-1986. The current study confirms that exposure to atomic bomb radiation has no significant effect on the prevalence of vertebral fractures, diagnosed here using vertebral dimensions.

Previous studies have found that the hip fracture incidence among both native Japanese and Japanese-Americans is similar, and is only about one-third to one-half the incidence among Caucasians.^{2,3} The different pattern for vertebral fractures reported here suggests that the profiles of risk factors between these three populations may differ. Low bone density is a known risk factor for both vertebral fractures and hip fractures, and bone density has been reported to be lower among native Japanese or Japan-born Japanese-Americans, compared with US-born Japanese-Americans or Caucasians.^{6,23,24} Thus, the greater vertebral fracture prevalence among native Japanese may be related to their lower bone density. The lower hip fracture incidence among Japanese suggests that their anticipated high risk is attenuated by other factors, such as a lower frequency of falls, or differences in hip geometry.^{25,26} A lower incidence of falls could be due to greater muscle strength, better balance, or other factors currently under investigation.

The lower bone density among Japanese, compared with Caucasians, may be related in part to differences in oestrogen exposure, or other factors. Oestrogen levels are reportedly lower among native Japanese women compared with American Caucasians.²⁷ Compared with American Caucasians, serum levels of several sex hormones were also lower in a small sample of Asian immigrants (of various ethnicities) in Hawaii, which may be related in part to diet.²⁸ These issues deserve further investigation.

TABLE 2 Age-adjusted odds ratios comparing vertebral fracture prevalence between populations

Outcome definition	Minnesota versus Hawaii ^a		Japan versus Hawaii ^a		Japan versus Minnesota ^b	
	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI
One or more fractures						
3 SD	1.5	1.1–2.1	1.8	1.3–2.5	1.2	0.9–1.6
4 SD	0.9	0.6–1.3	1.7	1.1–2.4	1.8	1.2–2.7
One fracture only						
3 SD	1.3	0.9–1.8	1.3	0.8–1.8	1.0	0.6–1.5
4 SD	0.8	0.5–1.3	1.3	0.8–2.0	1.6	1.0–2.6
Two or more fractures						
3 SD	1.9	1.2–3.2	3.2	2.0–5.3	1.7	1.0–2.6
4 SD	1.2	0.6–2.3	2.8	1.4–5.0	2.3	1.2–4.2

^a Reference group = Hawaii.

^b Reference group = Minnesota.

This study contains several potential sources of error. Differences in vertebral fracture prevalences in the populations might be related, in part, to technical differences in the measurement of vertebral dimensions. We attempted to avoid this source of error by using a diagnosis cutoff based on the mean and SD for each population separately. Thus, if anterior heights tended to be underestimated at one research centre, this would be reflected in the population mean for that centre and would not bias the prevalence estimates. However, there may be undetected differences in technique for which this method may not adequately adjust, particularly for comparisons involving the Minnesota population because the comparability to the other centres could not be determined.

Selection bias is another potential source of error. The prevalence of vertebral fractures among women who refused to participate could not be determined. If the prevalence is higher among non-participants, the current study may underestimate the prevalence in one or more of the three populations. Non-participation was generally greater among the oldest age groups. Therefore, the potential for bias may also be greatest among the oldest age groups. The issue of non-response was formally assessed both in the Minnesota and Hawaii samples.^{5,11} While there was some evidence that non-responders were less healthy in both populations, the differences were not great. However, as the population grows older, selection bias due to age-related health effects may become more pronounced. It is also uncertain to what extent the women in Hiroshima are representative of all women in Japan. Although nutrition and other health factors were poor in many areas of Japan during and after World War II, conditions may have been worse in Hiroshima as a

result of the atomic bomb blast. These issues deserve further study.

Cohort effects may exist within one or more of the populations used in this study, due to differences between birth cohorts in diet, physical activity, use of oestrogenic medications, and/or other factors. An earlier study found evidence of a cohort effect on the incidence of vertebral fractures in the Hiroshima population.²² The incidence decreased by a factor of 0.6 with each successive 10-year later calendar year of birth. However, it is uncertain to what extent the observed cohort effect might have been due to drift in the radiologist's readings during the 28 years of observation. Also, the earlier study only examined the thoracic spine, and may have missed many lumbar vertebral fractures. Unfortunately, it is not possible to investigate these issues, because the older films have deteriorated. In the current study, we tested for differences between populations in the magnitude of association with age by including interaction terms (the product of age and the population indicator variable) in the logistic models, but did not find any evidence of such differences. Therefore, the patterns with age (which may include cohort effects as well as age-related trends) appear to be similar in the US and Japan, or else the sample size was too small to detect a difference (fractures are rare in the younger birth cohorts).

In summary, vertebral fracture prevalence appears to be greater among women in Japan, compared with Caucasians in Minnesota and Japanese-Americans in Hawaii. This contrasts with the lower risk of hip fracture for both native Japanese and Japanese-Americans, compared with Caucasians. Additional studies may identify the risk factors responsible for the different patterns of hip and vertebral fracture occurrence.

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