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ORIGINAL ARTICLE

Bone fractures and feeling at risk for osteoporosis among women in Japan: patient characteristics and outcomes in the National Health and Wellness Survey

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Abstract
Summary Women aged 50 and older in Japan were compared according to perceived risk for osteoporosis and fracture history. Perceived risk was associated with family history of osteoporosis but few other risk factors. Few felt at risk, and perception was only loosely related to epidemiological risks, indicating a need for patient education.
Purpose Osteoporosis is prevalent but underdiagnosed and undertreated. This study was conducted to explore characteristics associated with history of fractures and feeling at risk for osteoporosis in women aged 50 and older in Japan.
Methods Data were provided by a large annual survey representative of Japanese aged 18 and older. Women 50 and older without diagnosed osteoporosis were categorized into four mutually exclusive groups based on fracture history since age 50 and feeling at risk for developing osteoporosis. Sociodemographic and health characteristics were compared across groups using bivariate statistics, and health outcomes were compared using generalized linear models.
Results A total of 16,801 women aged 50 and older were included in the analyses. Most (n=12,798; 76.2 %) had no fracture since age 50 and did not feel at risk for osteoporosis, 12.9 % (n=2170) felt at risk but had no fracture, 8.7 % (n=1455) did not feel at risk despite having a fracture, and 2.2 % (n=378) had a fracture and felt at risk for osteoporosis. Feeling at risk was slightly more common among those with than without a fracture since age 50 (20.6 vs. 14.5 %, p<0.001). Feeling at risk was most associated with family history of osteoporosis, though known risk factors for fracture did not significantly differ across the fracture/perceived-risk group.
Conclusions Approximately 15 % of women in Japan aged 50 and older felt at risk for developing osteoporosis in the future, far fewer than expected by epidemiologists. Risk perception was only loosely related to epidemiological risks for fracture, indicating a need for patient education.

Keywords Osteoporosis · Fractures · Risk perception · Quality of life · Japan

Introduction

Osteoporosis is a major public health issue in Japan, though not always recognized as such [1]. It is estimated up to a quarter of women of all ages in Japan have osteoporosis, with prevalence rising sharply after age 50 [2]. Despite the high prevalence, the condition is believed to be underdiagnosed and undertreated [3]. Fractures caused by osteoporosis contribute to back pain, reduce quality of life, and interfere with activities of daily living.

The consequences of osteoporosis also impose an economic burden on society, with costs of hip and vertebral fractures estimated at approximately 8.0 and 9.9 billion yen (US$78 and 97 million), respectively [4], with costs increasing with the age of the patient [5]. Recently the cost per hip fracture in Japan was identified as among the highest in the Asia-Pacific region, with average hospital cost reported as US$27,599 and involving an average of 38 hospital days [6]. While the incidence of hip fractures has stabilized in the West, the incidence of these fractures is increasing in Japan [7].

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A variety of treatments have demonstrated effectiveness in slowing or halting bone loss and reducing fracture risk in osteoporosis [8, 9]. Though multiple treatment options are available in Japan, only a low proportion of individuals suffering osteoporotic fractures in Japan are treated prior to fracture, suggesting many of those most at risk for fracture are not being identified and treated until after a fracture occurs [10, 11]. Indeed, osteoporosis has been called a silent disease because bone loss typically occurs without symptoms, becoming apparent only after the individual sustains a fragility fracture—that is, a fracture resulting from a trauma that would not break a healthy bone, such as a mild fall from standing height—or the individual has a bone densitometry test. Lack of awareness among those at risk and the asymptomatic nature of the disease are both barriers to effective fracture prevention.

Because osteoporosis is an underrecognized and underdiagnosed condition, it is important to understand the population that has not been diagnosed with osteoporosis, whether they understand the condition, take steps to prevent it, or feel at risk of developing it. Likewise, it is important to ascertain to what extent perceived risk of developing osteoporosis and actual risk for developing the condition coincide, with those at most risk also being the most likely to perceive being at risk. Previous research in the US has demonstrated that individuals' perception of their own risk for osteoporotic fractures is not closely related to established epidemiological risk factors [12], but this relationship has not been assessed among women in Japan.

Likewise, there is little information on women's perceptions of osteoporosis in Japan, how widely women who are actually at risk feel at risk, or what is driving perceived risk. In particular, prior fracture is the greatest predictor of future fracture [13, 14], but it is not clear how strongly women take their own fracture history into account when assessing their risk for osteoporosis. The Fracture Risk Assessment Tool (FRAX) calculator developed to estimate 10-year risk for major osteoporotic fracture includes a number of other risk factors, including age, smoking, alcohol consumption, and use of long-term glucocorticoid medication [15], and the extent to which an individual's perceived risk is sensitive to these epidemiological risk factors is also unknown. Bone mineral density (BMD) scanning is available as part of recommended osteoporosis screening in Japan, but it is not clear how widespread the practice is, and in 2005, fewer than 5 % of those eligible for screening participated [16].

The current study was conducted to better understand women in Japan age 50 years and older in terms of their perceived risk of osteoporosis and their experience with fractures and to assess the relationship between patient characteristics, perceived risk, and fracture history among women without diagnosed osteoporosis in this demographic group.

Methods

Data source

The current study used data from the 2008 (N=20,000), 2009 (N=20,573), 2010 (N=25,000), and 2011 (N=30,000) Japan National Health and Wellness Surveys (NHWS; Kantar Health, New York, NY), an annual, cross-sectional study of individuals aged 18 years or older in Japan. Response rates for these surveys were 40.0, 22.7, 24.9, and 15 % in 2008 through 2011, respectively. Because sampling for NHWS is without regard to previous participation, individuals can participate in multiple years of the survey, and approximately 10 % of the total responses (9206 of 95,573) was made by an individual who completed the survey in a subsequent year (e.g., completed the survey in 2008 and again in 2010). In these cases, only the most recent response made by the individual was included; older responses made by the same individual were excluded from analysis in order to avoid including the same respondent more than once. Only women aged 50 and older were included in the present study. The NHWS includes information related to diagnosis and treatment of a broad variety of conditions, health risk behaviors, and health-related outcome data. Potential respondents to the NHWS are recruited through an existing web-based consumer panel, which recruits its members through opt-in emails, co-registration with panel partners, e-newsletter campaigns, banner placements, and both internal and external affiliate networks. All panelists explicitly agreed to be a panel member, registered with the panel through a unique email address, and completed an in-depth demographic registration profile.

The sample for NHWS is selected from this panel using a stratified random sample framework with quotas based on gender and age. Previous research has found the demographic composition of the Japan NHWS to be comparable to that of the Japanese adult population on important parameters [17]. Though there were some minor changes and enlargements to the NHWS questionnaire during the years included in this study, the questions analyzed in the present study remained consistent, allowing for the combination of multiple years of survey data.

All respondents to NHWS provided informed consent, and the study was approved by Essex Institutional Review Board (Lebanon, NJ).

Measures

All measures were by self-report.

Sociodemographic characteristics Among the variables included in the NHWS, age, marital status, employment status, level of education, and household income were included in the present analyses.

General health characteristics Current use of cigarettes, daily use of alcohol, and whether an individual had exercised vigorously in the past month were included. Body mass index (BMI) was calculated from reported height and weight.

Comorbid health conditions The Charlson Comorbidity Index (CCI) [18] was used to summarize the overall comorbidity burden of the respondents. This index weights the presence of the following conditions and sums the result: HIV/AIDS, metastatic tumor, lymphoma, leukemia, any tumor, moderate/severe renal disease, hemiplegia, diabetes, mild liver disease, ulcer disease, connective tissue disease, chronic pulmonary disease, dementia, cerebrovascular disease, peripheral vascular disease, myocardial infarction, congestive heart failure, and diabetes with end organ damage. The greater the total index score, the greater the comorbid burden on the patient.

Perceived risk of developing osteoporosis Respondents were compared on the basis of their perceived risk of developing osteoporosis in the future and whether they had experienced a fracture since age 50. Perceived risk was assessed with an item asking the respondent to indicate which of a variety of age-related conditions the respondent felt at risk of developing in the future, of which osteoporosis was one. Respondents who selected osteoporosis were considered to feel at risk of osteoporosis.

Fractures since age 50 Respondents were asked to indicate the number of bone fractures they had experienced since age 50. Those who indicated one or more fractures were considered to have had a fracture.

Fracture risks and preventative steps Use of oral glucocorticoids was assessed by assessing the current medications the respondent reported in the survey; respondents also indicated whether they had completed menopause, if they had back pain, and if they had a family history of osteoporosis. Respondents were also asked if they were taking steps to prevent a variety of conditions, including osteoporosis and, if so, what specific steps they were taking. Respondents also indicated if they had ever had a bone mineral density scan.

Health status All respondents completed the revised Medical Outcomes Study 12-Item Short Form Survey Instrument (SF-12v2), a multipurpose, generic instrument comprising 12 questions [19]. This instrument can be used to summarize functional health by two summary scores: the physical component summary (PCS) and mental component summary (MCS). Each score has a mean of 50 and a standard deviation of 10 for the US population, with higher scores indicating better health. Several of the items from the SF-12v2 can be used to generate a health state utility score, the SF-6D. The SF-6D is a preference-based single-index measure for health using general population values [20]. The SF-6D index has interval scoring properties and yields summary scores on a theoretical 0–1 scale (with an empirical floor of 0.3). Higher scores indicate better quality of life.

Work productivity and activity impairment Impairment to work productivity was assessed using the Work Productivity and Activity Impairment (WPAI) questionnaire, a six-item validated instrument which consists of four metrics: absenteeism (the percentage of work time missed because of one's health in the past 7 days), presenteeism (the percentage of impairment experienced while at work in the past 7 days because of one's health), overall work productivity loss (an overall impairment estimate that is a combination of absenteeism and presenteeism), and activity impairment (the percentage of impairment in daily activities because of one's health in the past 7 days) [21]. Only respondents who reported being full-time or part-time employed provided data for absenteeism, presenteeism, and overall work impairment. All respondents provided data for activity impairment.

Healthcare use The number of physician visits (including visits to physicians, dentists, and nurses), the number of emergency room (ER) visits, and the number of times hospitalized in the past 6 months were used to define healthcare use.

Analysis

The sample was characterized with descriptive statistics, and Spearman's correlation was used to quantify the strength of the relationship between perceived risk and history of fracture. Women were categorized into four groups based on their perceived risk of osteoporosis and report of fractures since age 50: (1) not feeling at risk for osteoporosis, no fracture; (2) not feeling at risk for osteoporosis, with fracture; (3) feeling at risk for osteoporosis, no fracture; and (4) feeling at risk for osteoporosis, with fracture. These groups were first compared using one-way ANOVA for continuous variables and chi-square tests for categorical variables. The different perceived risk/fracture categories were compared using generalized linear models, with each outcome modeled separately. Models for MCS, PCS, and SF-6D incorporated a normal distribution and an identity link function and so were equivalent to linear regressions. For work productivity impairment, activity impairment, and healthcare use variables, models incorporated a negative binomial distribution with a log-link function to better accommodate the skewed nature of the data. All models were adjusted for age, university education (completed 4-year degree vs. less), smoking status (current vs. former vs. never), exercise (in the previous month vs. not), daily alcohol use (yes vs. no), household income (above median vs. below median

vs. decline to answer), BMI category (underweight vs. normal weight vs. overweight vs. obese vs. decline to answer), marital status (never married, divorced, or separated vs. widowed vs. married/living with partner), and the CCI. The main predictor of interest was the perceived risk and fracture group, which was a dummy-coded variable where the group not feeling at risk and without fractures served as the reference category against which each of the other three categories was tested. Regression-adjusted means and standard errors were also calculated for each group to assist in interpretation.

Factors typically considered health outcomes may also be driving perceived risk of osteoporosis; the cross-sectional design of the current study does not allow us to assess whether risk preceded poor outcomes or poor outcomes increase the perception of risk. Therefore, a binary logistic regression was used to test the association between feeling at risk for developing osteoporosis and the set of demographics and outcomes that may plausibly precede feeling at risk for osteoporosis. Because taking steps to prevent osteoporosis seems particularly unlikely to lead to (rather than result from) feeling at risk for the condition, taking such steps was excluded from the analysis.

Results

A total of 16,801 women without self-reported osteoporosis were included in the analysis. The respondents had a mean age of 60 years (range 50–93), 37 % were employed, and approximately 11 % indicated they were taking steps to prevent developing osteoporosis in the future. Forty-nine percent indicated they had never had a bone mineral density test. Approximately 11 % had fractured a bone since age 50, and approximately 15 % felt at risk for developing osteoporosis in the future.

Feeling at risk for developing osteoporosis in the future was more common among those who had experienced a fracture since age 50 than those who had not experienced a fracture in that time (20.6 vs. 14.5 %, $p<0.001$), though the magnitude of the correlation between perceived risk and history of fracture was small ($r_s=0.05$).

Most ($n=12,798$; 76.2 %) had no fracture since age 50 and did not feel at risk for osteoporosis, 12.9 % ($n=2170$) felt at risk but had no fracture, 8.7 % ($n=1455$) did not feel at risk despite having a fracture, and 2.2 % ($n=378$) had a fracture and felt at risk for osteoporosis. Respondent characteristics are compared among the four groups in Table 1. The size of the sample made the statistical tests sensitive to very small differences across the groups, and most variables were significantly different across the groups. The groups that had experienced fractures were several years older than the groups without fractures on average and so had more time to experience a fracture since age 50. The groups with fractures also had lower rates of employment and higher rates of menopause than the group with fractures.

Those who felt at risk for developing osteoporosis in the future were more likely to indicate that they were taking steps to prevent osteoporosis, with 33 % of those with a prior fracture and 26 % of those without a prior fracture taking preventative steps, compared to 12 and 7 % of those not feeling at risk with and without a fracture, respectively. The specific preventative steps taken were largely similar across risk groups and were most often the consumption of dairy products, reported by 80 to 85 % of those who reported taking preventative steps. BMD scanning was most common among those feeling at risk for osteoporosis and varied from 45 % among those not feeling at risk and without fracture to 66 % among those feeling at risk with a fracture. Those without a fracture who did not feel at risk were least likely to have visited a physician in the prior 6 months, followed by those who did not feel at risk but had a fracture since age 50. Having an emergency visit in the prior 6 months was approximately twice as likely among those who experienced a fracture since age 50 as those who did not have fractures since age 50, and a similar pattern was seen with having a hospital visit.

The relationships between previously identified risks for fracture and perceived risk of developing osteoporosis were generally weak, with some exceptions. Family history was rare among those not feeling at risk, at approximately 3 % for both groups, and approximately five times more common among those feeling at risk for developing osteoporosis at 16 and 17 % for those who felt at risk for developing the disease. Back pain was also associated with perceived risk, up to twice as common among those who felt at risk. In contrast, other predictors of risk included in FRAX were not strongly associated with perceived risk, including current smoking, daily alcohol use, and use of oral glucocorticoids.

Bivariate comparisons of health outcomes demonstrated that health status, work, and activity impairment were generally best among the group not feeling at risk and without fractures, though differences were relatively small (Table 2). Likewise, this group had the fewest physician visits and the lowest number of hospitalizations in the prior 6 months.

Generalized linear regression analysis of health outcomes revealed a generally consistent picture (Table 3). The group not feeling at risk and without fractures had significantly higher MCS and PCS scores than the three other groups, though none reached the 3-point threshold for minimally important difference. Only a few small differences in work productivity impairment were observed, with higher absenteeism among those not feeling at risk with a fracture relative to the reference group and higher presenteeism among those feeling at risk. Impairment to non-work activities (19 %) was significantly lower than those of the other three groups (24–25 %). The reference group also had fewer physician visits than all the other groups,

Table 1 Demographic and health characteristics among women in Japan age 50 and older by perceived risk of osteoporosis and fracture history

	Not feeling at risk, no fractures (*N*=12,798)		Not feeling at risk, fracture (*N*=1455)		Feeling at risk, no fractures (*N*=2170)		Feeling at risk, fractures (*N*=378)		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	*p* value[a]
Age of the respondent	59.43	7.61	64.52	7.52	59.04	7.34	63.90	7.25	<0.0001
BMI	21.92	3.27	22.15	4.02	21.29	2.91	21.46	2.79	<0.0001
CCI	0.12	0.40	0.19	0.52	0.16	0.49	0.17	0.51	<0.0001
	n	%	*n*	%	*n*	%	*n*	%	*p* value[b]
What is your marital status?									<0.0001
Married/living with partner	9918	77.5 %	1040	71.5 %	1636	75.4 %	267	70.6 %	
Widowed	958	7.5 %	175	12.0 %	155	7.1 %	46	12.2 %	
Never married/divorced/other	1922	15.0 %	240	16.5 %	379	17.5 %	65	17.2 %	
Employed	4834	37.8 %	398	27.4 %	819	37.7 %	110	29.1 %	<0.0001
Completed 4-year college	3251	25.4 %	309	21.2 %	627	28.9 %	96	25.4 %	<0.0001
Annual household income									<0.0001
¥5,000,000 or above	6257	48.9 %	572	39.9 %	1171	54.0 %	172	45.5 %	
Less than ¥5,000,000	4800	37.5 %	673	46.3 %	834	38.4 %	169	44.7 %	
Decline to answer	1741	13.6 %	210	14.4 %	165	7.6 %	37	9.8 %	
BMI categories									<0.0001
Underweight	1251	9.8 %	175	12.0 %	321	14.8 %	45	11.9 %	
Normal	9248	72.3 %	1017	69.9 %	1599	73.7 %	287	75.9 %	
Overweight	1520	11.9 %	189	13.0 %	180	8.3 %	39	10.3 %	
Obese	205	1.6 %	31	2.1 %	24	1.1 %	2	0.5 %	
Decline to answer	574	4.5 %	43	3.0 %	46	2.1 %	5	1.3 %	
Currently smokes	1809	14.1 %	172	11.8 %	351	16.2 %	50	13.2 %	0.0028
Currently drinks	7737	60.5 %	786	54.0 %	1385	63.8 %	228	60.3 %	<0.0001
Daily alcohol use	1421	11.1 %	170	11.7 %	240	11.1 %	41	10.8 %	0.9191
Currently exercises	6010	47.0 %	767	52.7 %	1042	48.0 %	195	51.6 %	0.0002
Back pain	568	4.4 %	82	5.6 %	171	7.9 %	38	10.1 %	<0.0001
On glucocorticoids	261	2.0 %	36	2.5 %	67	3.1 %	12	3.2 %	0.0100
Completed menopause	5794	45.3 %	891	61.2 %	1026	47.3 %	244	64.6 %	<0.0001
Visited physician (in the prior 6 months)	8469	66.2 %	1165	80.1 %	1662	76.6 %	329	87.0 %	<0.0001
Visited ER (in the prior 6 months)	370	2.9 %	87	6.0 %	67	3.1 %	22	5.8 %	<0.0001
Visited hospital (in the prior 6 months)	450	3.5 %	109	7.5 %	77	3.5 %	25	6.6 %	<0.0001
Have you ever had a bone mass density test/scan?									<0.0001
Yes	5767	45.1 %	884	60.8 %	1172	54.0 %	249	65.9 %	
No	6644	51.9 %	523	35.9 %	942	43.4 %	117	31.0 %	
Not sure	387	3.0 %	48	3.3 %	56	2.6 %	12	3.2 %	
Taking steps to prevent osteoporosis	919	7.2 %	176	12.1 %	561	25.9 %	124	32.8 %	<0.0001
Steps taken to prevent osteoporosis									
Take calcium	571	62.1 %	123	69.9 %	362	64.5 %	77	62.1 %	0.2418
Exercise regularly	479	52.1 %	110	62.5 %	298	53.1 %	65	52.4 %	0.0888
Drink or eat dairy products (e.g., milk, yogurt)	755	82.2 %	146	83.0 %	476	84.8 %	99	79.8 %	0.4428
Take a prescription medication	97	10.6 %	33	18.8 %	114	20.3 %	43	34.7 %	<0.0001
Take vitamin D	220	23.9 %	56	31.8 %	144	25.7 %	43	34.7 %	0.0185
Take steps but none of the above	6	0.7 %	1	0.6 %	0	0.0 %	1	0.8 %	0.2849
Family history of osteoporosis	371	2.9 %	49	3.4 %	338	15.6 %	65	17.2 %	<0.0001

BMI body mass index, *ER* emergency room, *CCI* Charlson Comorbidity Index

[a] *p* value according to one-way ANOVA

[b] *p* value according to Pearson's chi-square

Table 2 Unadjusted health outcomes among women in Japan age 50 and older by perceived risk of osteoporosis and fracture history

	Not feeling at risk, no fractures		Not feeling at risk, fracture		Feeling at risk, no fractures		Feeling at risk, fractures		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	*p* value
MCS	49.49	9.40	49.54	10.02	47.00	10.25	48.13	9.58	<0.0001
PCS	50.48	6.89	48.54	8.10	48.97	7.36	47.91	7.97	<0.0001
SF-6D	0.779	0.127	0.766	0.137	0.739	0.126	0.745	0.127	<0.0001
Absenteeism (%)	2.6 %	11.9 %	5.4 %	17.4 %	2.3 %	9.8 %	4.4 %	14.3 %	0.0001
Presenteeism (%)	12.3 %	19.0 %	13.0 %	20.6 %	15.0 %	19.9 %	17.1 %	23.3 %	0.0004
Overall work impairment (%)	14.0 %	21.6 %	16.3 %	25.4 %	16.2 %	21.7 %	18.1 %	25.8 %	0.0053
Activity impairment (%)	16.5 %	21.5 %	21.1 %	25.3 %	21.3 %	23.9 %	22.5 %	23.9 %	<0.0001
Physician visits	5.48	8.09	8.23	9.92	7.09	9.81	9.08	9.94	<0.0001
ER visits	0.09	1.18	0.16	1.03	0.07	0.73	0.09	0.58	0.0891
Hospitalizations	0.41	3.67	1.24	7.68	0.46	3.68	0.51	2.82	<0.0001

Higher scores on MCS and PCS indicate better health status. *p* values are from one-way ANOVA

MCS mental component summary, *PCS* physical component summary, *ER* emergency room

fewer ER visits than those not feeling at risk but with a fracture, and fewer hospitalizations than that group as well.

The results of the logistic regression of feeling at risk for developing osteoporosis in the future demonstrated that some variables usually considered outcomes were associated with feeling at risk for osteoporosis (Table 4). Lower MCS and PCS scores were associated with higher adjusted odds of feeling at risk for developing osteoporosis in the future, as was visiting a physician at least once in the past 6 months. Being hospitalized in the prior 6 months was associated with slightly lower adjusted odds of feeling at risk. Osteoporosis-related factors associated with feeling at risk included prior fracture since age 50, back pain, and having completed menopause. Having a BMD scan was associated with higher odds of feeling at risk than not having a BMD scan. Family history of osteoporosis was particularly closely associated with feeling at risk for developing osteoporosis, while use of glucocorticoids, alcohol use, and smoking were not associated with

Table 3 Regression-adjusted mean health outcomes by perceived risk of osteoporosis and fracture history

	Not feeling at risk, no fracture Mean (SE)	Not feeling at risk, fracture Mean (SE)	Feeling at risk, no fracture Mean (SE)	Feeling at risk, fracture Mean (SE)
Health-related quality of life				
MCS	48.1 (0.2)	47.2*** (0.3)	45.9*** (0.3)	45.9*** (0.5)
PCS	48.5 (0.1)	47.1*** (0.2)	47.0*** (0.2)	46.3*** (0.4)
SF-6D	0.75 (0.00)	0.73*** (0.00)	0.72*** (0.00)	0.71*** (0.01)
Work and activity impairment				
Absenteeism (%)	3.5 % (0.5)	6.7 %** (1.8)	2.9 % (0.6)	7.4 % (3.6)
Presenteeism (%)	13.7 % (0.7)	14.9 % (1.3)	15.7 %* (1.1)	20.7 %** (3.3)
Overall work impairment (%)	15.7 % (0.8)	18.3 % (1.6)	17.4 % (1.2)	22.2 %* (3.5)
Activity impairment (%)	19.0 % (0.5)	23.6 %*** (1.0)	24.0 %*** (0.9)	25.3 %*** (1.8)
Healthcare use (6 months)				
Physician visits	6.4 (0.2)	8.4*** (0.4)	8.2*** (0.3)	9.9*** (0.8)
ER visits	0.08 (0.02)	0.13* (0.04)	0.06 (0.02)	0.07 (0.04)
Hospitalizations	0.42 (0.07)	1.04*** (0.28)	0.44 (0.11)	0.51 (0.24)

All models adjusted for age, university education, smoking status, exercise, daily alcohol use, household income, BMI category, marital status, and the CCI. Mean and SE presented at the mean of the covariates. Higher scores on MCS and PCS indicate better health status

MCS mental component summary, *PCS* physical component summary, *ER* emergency room

Significance is relative to group not feeling at risk and without fractures; *$p<0.05$, **$p<0.01$, ***$p<0.001$

Table 4 Association between respondent characteristics and feeling at risk of developing osteoporosis

Factor	Odds ratio	95 % confidence limits		*p* value
		Lower	Upper	
Age (5-year interval)	0.95	0.91	0.99	0.008
CCI	1.04	0.94	1.14	0.4734
Fracture (since age 50)	1.39	1.22	1.58	<0.0001
PCS (5-point interval)	0.89	0.85	0.92	<0.0001
MCS (5-point interval)	0.90	0.88	0.93	<0.0001
Activity impairment (5 % interval)	0.99	0.98	1.01	0.3341
What is your marital status?				
Married/living with partner	Reference category			
Never married	1.08	0.95	1.22	0.2609
Widowed	1.00	0.84	1.19	0.9712
Employed	0.96	0.86	1.06	0.3681
Completed 4-year college	1.12	1.01	1.23	0.0354
Annual household income				
Below ¥5,000,000	Reference category			
¥5,000,000 or above	1.09	0.98	1.20	0.1154
Decline to answer	0.61	0.52	0.72	<0.0001
BMI category				
BMI: Underweight	1.32	1.15	1.50	<0.0001
Normal	Reference category			
Overweight	0.62	0.53	0.72	<0.0001
Obese	0.46	0.30	0.70	0.0003
Decline to answer	0.53	0.39	0.72	<0.0001
Currently smokes	1.11	0.97	1.26	0.1239
Currently exercises	1.05	0.96	1.15	0.3286
Daily alcohol use	0.92	0.80	1.06	0.2310
Back pain	1.33	1.11	1.58	0.0015
On glucocorticoids	1.09	0.84	1.43	0.5125
Completed menopause	1.25	1.12	1.39	<0.0001
Visited physician (in the prior 6 months)	1.41	1.27	1.58	<0.0001
Visited ER (in the prior 6 months)	0.85	0.66	1.09	0.1927
Visited hospital (in the prior 6 months)	0.79	0.63	1.00	0.0479
Have you ever had a bone mass density test/scan?				
Yes	1.32	1.20	1.44	<0.0001
No	Reference category			
Not sure	1.10	0.84	1.45	0.4780
Family history of osteoporosis	5.52	4.75	6.41	<0.0001

MCS mental component summary, *PCS* physical component summary, *ER* emergency room

feeling at risk. BMI category was also associated with feeling at risk for developing osteoporosis, with those underweight more likely to feel at risk than those of normal weight and those overweight or obese less likely to feel at risk. Finally, demographics were also related to feeling at risk, with younger age and declining to answer income associated with lower adjusted odds of feeling at risk, while college education was associated with higher odds of feeling at risk.

Discussion

Osteoporosis is often termed a silent disease because individuals do not realize they have developed the condition, and the disease progresses without symptoms until the individual experiences a clinical fracture. As osteoporotic spine fractures often go undetected, individuals may even suffer multiple osteoporotic fractures prior to diagnosis [22]. The current analysis demonstrated that women age 50 and older in Japan

generally do not feel at risk for developing osteoporosis in the future, though many will. Though individuals reporting a physician diagnosis of osteoporosis were excluded from the present study, it is possible that some of the respondents included in the present study in fact already have osteoporosis and are simply unaware of the weakened state of their bones. Indeed, while the majority of those who had experienced a fracture since age 50 indicated having a BMD scan, a substantial minority—approximately one in three—indicated they had never had a BMD scan, which is an integral part of the diagnostic procedure according to Japanese guidelines [16]. Thus, many of the respondents had not had the opportunity to be diagnosed with osteoporosis. Few indicated they were actively taking steps to prevent osteoporosis: slightly more than one in every four who felt at risk for developing it in the future and only about one in every ten among those who did not feel at risk. Feelings of risk themselves were most associated with family history of osteoporosis, though rates of BMD scanning and having visited a physician in the prior 6 months also differed across the groups and seemed to vary primarily in relation to perceived risk, suggesting that feeling at risk may be due to a mixture of family history and engagement with healthcare providers. The regression analysis directly assessing which factors were associated with perceived risk also indicated a strong relationship with family history and weaker relationships with recently seeing a physician, having a previous fracture since age 50, and lower mental and physical quality of life, among other factors.

Though previous fracture is widely understood to be an important predictor of future fracture [14], the relationship between fracture history and perceived risk of osteoporosis was quite small. Though there were differences across groups, no clear relationship emerged between perceived risk of osteoporosis and other predictors of fracture aside from family history. Smoking, alcohol use, and use of glucocorticoid medication were quite similar across the groups, indicating that women are either unaware of the relationship these have with risk of osteoporotic fractures or the knowledge does not have enough impact to affect their perceived risk for developing osteoporosis. The pattern of results was similar when using logistic regression, with none of those behavioral risk factors significantly associated with feeling at risk.

The pattern of results in regression analysis demonstrated that perceived risk and fracture history are related to outcomes, but these relationships are modest in size among those who do not have osteoporosis. Those with fractures among women age 50 and older in Japan have worse health outcomes than those who do not experience fractures, which seems to be clearest in the PCS and SF-6D scores, while lower PCS scores themselves are also associated with feeling at risk for developing osteoporosis. Analyses of work productivity impairment had limited power to detect differences, as only a minority of the sample was employed, and those who had not had a fracture were more likely to be working.

The current study has several limitations which should be considered. All information, including presence or absence of fractures, was assessed through self-report and could not be confirmed. The measure of perceived risk was a part of a checklist rather than a more sensitive measure, and the wording indicated the future in general rather than a designated time frame. This makes the comparability of the reported risk perception and epidemiological risk factors less clear. Use of the FRAX score to indicate risk of fracture rather than individual predictors would also have allowed for a stronger comparison. Likewise, it is worth noting that the perceived risk included in the NHWS was risk of developing osteoporosis, not perceived risk of a fracture. To the extent that these risks are perceived differently, the risk of fracture would be a more appropriate perception to compare with risk factors for fracture. An interesting direction for future research would be to incorporate a history of falls or risk factors for falls. Falling is often the cause of osteoporotic fractures, but this information regarding falls was not included in the NHWS [23]. The modest response rate of the survey may have resulted in some self-selection bias to the results, though the current survey indicated the prevalence of self-reported fracture in the current survey among menopausal women was similar to that previously reported in the literature (16 % [24]). The survey respondents were sourced through an opt-in Internet survey panel and therefore may differ in important ways relative to the population as a whole. By definition, all were Internet users, and though Japan has one of the highest rates of Internet use in the world (approximately three of every four individuals accessed the Internet in 2007, the year prior to the first survey included here), Internet use was less common among older adults [25]. Therefore, reliance on an Internet-based panel may have biased estimates, such as the mean age of the respondents and the proportion of women feeling at risk, having experienced a fracture, or who had received a bone mineral density scan, though it seems less likely that this would impact the relationships observed between variables. The accuracy of the lifetime rate of BMD scanning is particularly hard to assess, as we are not aware of any published population-based studies of lifetime prevalence of these scans among women aged 50 and older in Japan or elsewhere. This rate may be an overestimate, as the rate reported here is higher than reported rates of BMD scanning in other studies reporting BMD testing rates in large samples outside Japan, though the rates reported elsewhere are not lifetime rates [26–28]. The number may also reflect the availability of bone measurement at locations other than hospitals or medical offices in Japan, as calcaneal qualitative ultrasound (QUS) is sometimes made available in public places during health promotion events to raise awareness of osteoporosis and fracture risk. Some

women may have mistakenly indicated having had a BMD scan when in fact they have undergone QUS measurement. Finally, because of the cross-sectional and non-interventional nature of the study, the associations observed in the study should be considered correlational rather than indicating causal relationships.

In conclusion, the present study adds to the evidence that risk for osteoporosis is not well understood by the segment of the Japanese population most at risk for fractures, women age 50 and older. Those at risk for osteoporosis do not realize they are at risk, and few risk factors are strongly associated with perceived risk aside from family history. Furthermore, even some of those who do feel at risk are not necessarily taking steps to protect themselves against bone loss and future fractures. The lack of awareness and prevention is troubling considering the high personal, social, and economic cost of osteoporotic fractures, especially in the context of an increasingly aged populace such as Japan. These results suggest that in Japan, as elsewhere in Asia, continued efforts are needed to raise awareness of osteoporosis risk and available preventative measures.

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Conflicts of interest Masayo Sato and Jennifer A. Flynn are employees of Eli Lilly K.K. and stockholders in the company. Jeffrey Vietri is an employee of Kantar Health, who is a paid consultant to Eli Lilly K.K. Saeko Fujiwara has served on speakers' bureaus for Pfizer, Chugai, Daiichi Sankyo, and Ono Pharmaceutical Company.

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Clinical Interventions in Aging

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REVIEW

Systematic review of raloxifene in postmenopausal Japanese women with osteoporosis or low bone mass (osteopenia)

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Purpose: To systematically review the literature describing the efficacy, effectiveness, and safety of raloxifene for postmenopausal Japanese women with osteoporosis or low bone mass (osteopenia).

Materials and methods: Medline via PubMed and Embase was systematically searched using prespecified terms. Retrieved publications were screened and included if they described randomized controlled trials or observational studies of postmenopausal Japanese women with osteoporosis or osteopenia treated with raloxifene and reported one or more outcome measures (change in bone mineral density [BMD]; fracture incidence; change in bone-turnover markers, hip structural geometry, or blood–lipid profile; occurrence of adverse events; and change in quality of life or pain). Excluded publications were case studies, editorials, letters to the editor, narrative reviews, or publications from non-peer-reviewed journals; multidrug, multicountry, or multidisease studies with no drug-, country-, or disease-level analysis; or studies of participants on dialysis.

Results: Of the 292 publications retrieved, 15 publications (seven randomized controlled trials, eight observational studies) were included for review. Overall findings were statistically significant increases in BMD of the lumbar spine (nine publications), but not the hip region (eight publications), a low incidence of vertebral fracture (three publications), decreases in markers of bone turnover (eleven publications), improved hip structural geometry (two publications), improved blood–lipid profiles (five publications), a low incidence of hot flushes, leg cramps, venous thromboembolism, and stroke (12 publications), and improved quality of life and pain relief (one publication).

Conclusion: Findings support raloxifene for reducing vertebral fracture risk by improving BMD and reducing bone turnover in postmenopausal Japanese women with osteoporosis or osteopenia. Careful consideration of fracture risk and the risk–benefit profile of antiosteoporosis medications is required when managing patients with osteoporosis.

Keywords: bone density, fractures, osteoporotic, Japan, osteoporosis, raloxifene

Introduction

Osteoporosis is a major health problem worldwide that is "characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fractures".[1] In Japan, population-based estimates using 2005 data and no age cutoffs suggest that osteoporosis affects between 6.4 million and 11 million people, and that the incidence of osteoporosis increases with age and is significantly greater in women than men.[2] Given that Japanese people have the world's longest life expectancy from birth (currently at 83.7 years for 2010–2015)[3] and Japan's rapidly increasing aged population,[4] there is a clear need to reduce the burden of osteoporosis in the coming years.

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Fracture is the most serious consequence of osteoporosis. This is primarily because women with osteoporosis have marked deterioration in bone mineral density (BMD) and bone architecture, which results in deterioration in bone strength.[5] Of the types of osteoporotic fractures, vertebral fractures are of great concern, because of the risk of subsequent vertebral fractures and the resulting "vertebral fracture cascade",[6] the increased risk of nonvertebral fractures following vertebral fractures,[7,8] and the considerable effect vertebral fractures have on pain, health-related quality of life, and mortality rate.[9–14] The impact of vertebral fractures is particularly important for Japanese women, because findings in population-based or longitudinal studies that used similar morphometric methods to assess the incidence of vertebral fracture have shown a higher incidence of vertebral fractures in Japanese women than Caucasian women.[15–17] Hip fractures resulting from osteoporosis are also a significant burden. In Japan, hip-fracture incidence is expected to increase 68% from 2012 to 2040, with an average hospital cost of US$27,599 for surgical treatment.[18]

In Japan, therapeutic treatments recommended for osteoporosis include bisphosphonates (eg, risedronate, alendronate), selective estrogen-receptor modulators (eg, raloxifene, bazedoxifene), active vitamin D_3 derivatives (eg, alfacalcidol, eldecalcitol), and recombinant parathyroid hormone.[19] Bisphosphonates are the most familiar and well-studied of these treatments,[19,20] with proven efficacy for vertebral fracture reduction in Japanese patients.[21] Of the other treatments, raloxifene, a nonsteroidal benzothiophene derivative of the selective estrogen receptor-modulator class, has been used to treat postmenopausal osteoporosis in Japan since May 2004 (60 mg tablets).[19] Raloxifene is a suitable therapy for the treatment of postmenopausal osteoporosis, because the estrogen-like actions of raloxifene in bone averts the imbalance in bone turnover (excess resorption versus formation) caused by postmenopausal estrogen deficiency. In addition, the estrogen-like actions of raloxifene are tissue-specific, because raloxifene does not stimulate mammary or uterine endometrial tissue.[22] Compared with placebo, raloxifene has been shown to reduce the relative risk of vertebral fractures by up to 69% in postmenopausal Caucasian women with osteoporosis after 3 years of treatment.[23] Additional findings for raloxifene indicate increases in lumbar spine BMD[22] and in terms of bone quality, improvements in hip cortical geometry,[24,25] and collagen quality by reducing nonenzymatic collagen cross-links,[26] and the maintenance of heterogeneous mineralization in bone.[27] Although findings from a post hoc analysis of data from two independent studies indicated that postmenopausal Japanese and Chinese women treated with raloxifene had a lower incidence of vertebral fractures than those treated with placebo,[28] the available data describing the effect of raloxifene treatment in postmenopausal Japanese women have not been adequately synthesized. Synthesis and evaluation of these data may provide valuable information for Japanese physicians treating postmenopausal women with osteoporosis.

To evaluate the existing evidence for postmenopausal Japanese women with osteoporosis or low bone mass (osteopenia) treated with raloxifene, we performed a systematic review of the literature. The objective of this review was to examine the efficacy, effectiveness, and safety findings from clinical trials and observational studies of raloxifene and to provide clinical insight into the usefulness of raloxifene for preventing or reducing the risk of subsequent vertebral and nonvertebral fractures in Japan.

Materials and methods

Search strategy

A search for relevant publications was done on May 28, 2013 using the database Medline via PubMed and Embase. The search terms were Japan (Medical Subject Headings [MeSH], Emtree), raloxifene (MeSH, Emtree), Evista, osteoporosis (MeSH, Emtree), fracture (Emtree), fracture*, and bone density (MeSH, Emtree). Search terms were combined using the Boolean operators OR and AND to give the following strategy: Japan AND (raloxifene OR Evista) AND (osteoporosis OR [fracture OR fracture*] OR bone density). The search limits were human species only and publication date from January 1, 1980 onwards.

Study selection

Publications identified in Medline via PubMed and Embase were collated using Endnote X5 (Thomson Reuters, New York, NY, USA). Duplicate publications were discarded, and the remaining publications were screened using prespecified inclusion and exclusion criteria. The title and abstract of each publication were screened initially; the full text of a publication was screened only if screening of the title and abstract was inconclusive. Publications describing randomized controlled clinical trials and observational studies (prospective and retrospective) of postmenopausal women with osteoporosis or osteopenia receiving raloxifene treatment were included if they reported one or more outcome measures. Outcome measures were change in BMD of the lumbar spine, femoral neck, total hip, total neck, or other areas within the hip region; incidence of new vertebral fracture or nonvertebral fracture; change in biochemical markers

of bone turnover, hip structural geometry, or blood–lipid profile; occurrence of adverse events (AEs; type, incidence, and severity), in particular venous thromboembolism (VTE), cardiovascular events, stroke, vaginal bleeding, or hot flush; effect on coagulation parameters or breast, uterus, ovary, or reproductive tissues; and change in quality of life or pain.

Publications were excluded if they were case studies, editorials, letters to the editor, narrative reviews, or published in a non-peer-reviewed journal; were multidrug studies that did not include a subanalysis of raloxifene; were multicountry studies that did not include a subanalysis of Japanese participants; were multidisease studies that did not include a subanalysis of participants with osteoporosis or osteopenia; or if participants were on dialysis. The bibliographies of systematic reviews were screened for other potentially relevant publications.

Data extraction and analysis

Data extraction was conducted by one person, and the extracted data were reviewed by all authors. Data extracted were study and participant characteristics (study design, number and mean age of participants, therapy and dose, study duration [ie, number of weeks], disease definition, study objective), and findings for BMD of the lumbar spine, femoral neck, total hip, total neck, or other areas within the hip region (percentage change in BMD from baseline to 52 weeks or BMD at baseline and at 52 weeks), vertebral and nonvertebral fracture incidence, biochemical markers for bone turnover (percentage change in concentration from baseline to 52 weeks or concentration at baseline and at 52 weeks), hip structural geometry parameters (percentage change in parameters from baseline to 52 weeks), blood–lipid profile (percentage change in concentration from baseline to 52 weeks or concentration at baseline and at 52 weeks), AEs (type, incidence, and severity; incidence of VTE, cardiovascular events, stroke, vaginal bleeding, or hot flush) and quality of life and pain (mean change in scores from baseline to 24 weeks).

Results

Literature-search results

A total of 292 abstracts were retrieved from the search of PubMed and Embase (Figure 1). Duplicate publications were discarded (n=65), the remaining 227 abstracts screened, and 26 publications selected for full-text review. The main reasons for exclusion were no relevant outcomes reported, raloxifene not included, or study not conducted in humans (Figure 1). The remaining 15 publications were included for review.

Study and participant characteristics

Of the 15 publications included for review, there were seven randomized controlled trials[29–35] reporting evidence for efficacy and eight observational studies[24,36–42] reporting evidence of effectiveness (Table 1). Evidence of safety was reported in 12[29–33,35–38,40–42] of the 15 publications. The method of randomization and allocation (eg, randomly generated treatment codes, random self-drawing of prepared sealed envelopes) was described in four[29,32,33,35] of the seven randomized controlled trials. Only the double-blind placebo-controlled trial[35] and an open-label randomized controlled trial[30] described whether randomization and allocation were blinded. The number of participants enrolled varied from 39 in one randomized controlled trial[30] to 7,557 in two post-marketing surveillance observational studies.[40,41] The mean age of participants ranged from 63 to 80 years (Table 1). On average, most participants had undergone menopause at 50 years of age (data not shown). Most publications (14 of 15) assessed the effects of raloxifene for a minimum of 52 weeks (Table 1). A definition for osteoporosis and osteopenia was reported in 14 of the 15 publications, with most publications (n=11) defining osteoporosis and osteopenia according to the Japanese diagnostic criteria year 2000 revision[43] (Table 1).

BMD

Findings for BMD were reported in eleven of the 15 publications, and included BMD of the lumbar spine (nine publications),[29,31–33,35–38,40] of the femoral neck, total hip, or total neck (six publications),[29,32,33,36–38] or of other regions in the hip (five publications).[24,33,36,38,39] Findings were reported as the percentage change in BMD from baseline to 52 weeks or BMD at baseline and at 52 weeks in all publications. There were three longer-term studies reporting BMD at 104 weeks[24,32,40] and at 156 weeks.[40]

After 52 weeks of treatment with raloxifene 60 mg/day, lumbar spine BMD increased significantly from baseline in all nine publications reporting findings for lumbar spine BMD, including the randomized placebo-controlled trial[35] of raloxifene 60 or 120 mg/day (Table 2). In the randomized comparative trials, the increase in lumbar spine BMD for raloxifene was less than that for alendronate ($P<0.01$),[31] more than that for alfacalcidol,[29,32] and less than[32] or more than[29,33] that for combination treatment with raloxifene and alfacalcidol (Table 2).

Compared with lumbar spine BMD, the effect of raloxifene 60 mg/day on BMD in the femoral neck, total hip, or total neck (Table 2) or other regions of the hip (data not shown) was not consistent after 52 weeks of treatment.

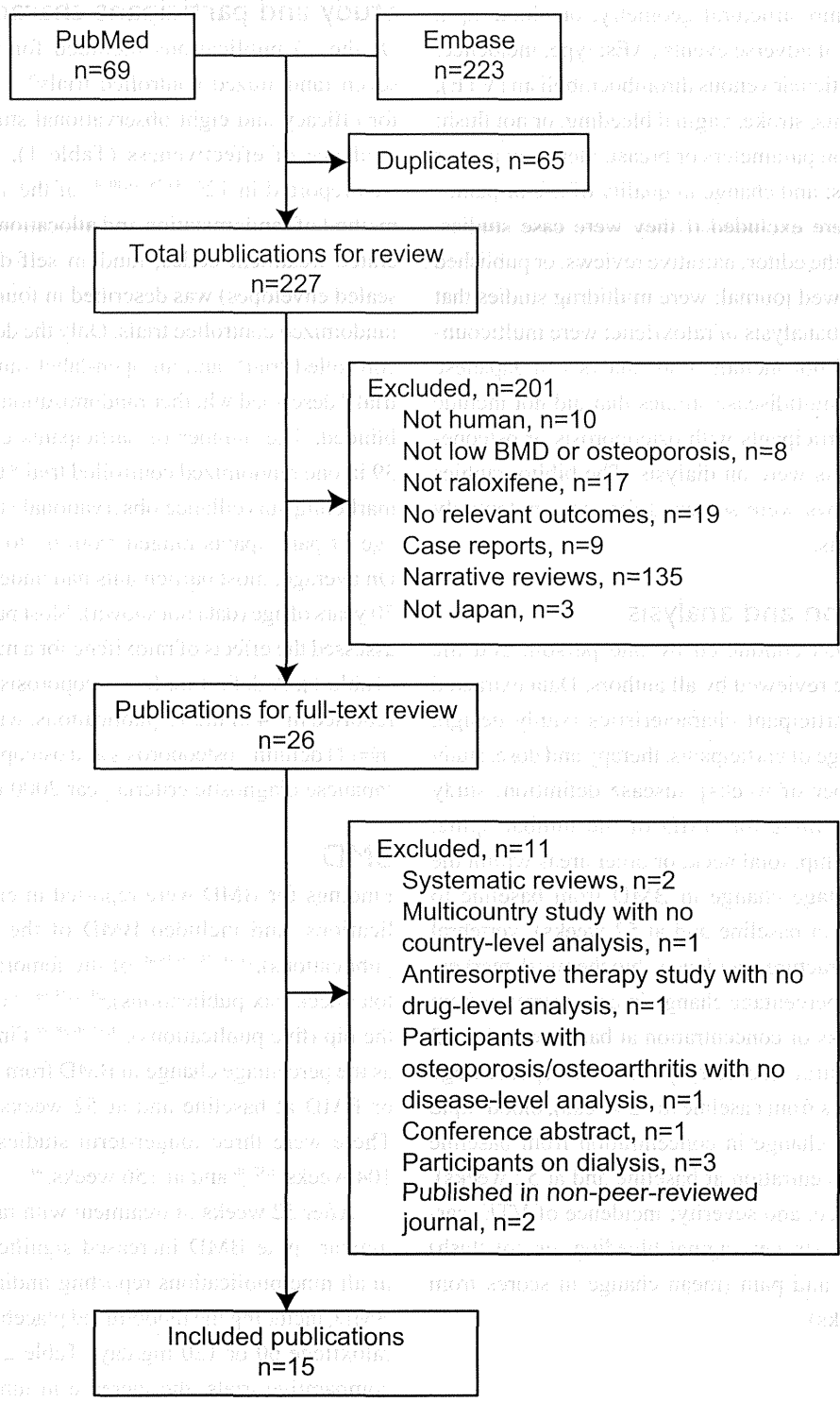

Figure 1 Flow diagram of literature-search results. Databases were Medline via PubMed and Embase. Searches were limited to human species and publications from 1980 onwards.
Abbreviation: BMD, bone mineral density.

In the eight publications[24,29,32,33,36–39] that reported findings for BMD in the femoral neck, total hip, total neck, or other regions of the hip, BMD increased, remained the same, or decreased; few of the increases in BMD were statistically significant.

Fracture incidence

Fracture incidence (vertebral or nonvertebral) was reported in three of the 15 publications, including publications from two randomized controlled trials[31,35] and one observational study.[40] However, only the observational study, which was a

Table 1 Study and participant characteristics

Authors	Enrolled, n	Therapy and dose, n	Mean (SD) age, years	Study period, weeks	Disease definition	Objective
Randomized controlled trials						
Morii et al[35]	302[a]	RLX 60 mg/day, 92[a] RLX 120 mg/day, 95[a] Placebo, 97[a]	65 (6)[b] 65 (6)[b] 64 (7)	52	L-BMD ≤2.5 SD of YAM and Japanese diagnostic criteria[c]	Assess safety and efficacy of RLX (double-blind, placebo-controlled)
Iwamoto et al[31]	122	RLX 60 mg/day, 61 ALN 5 mg/day, 61	69 (7) 70 (8)	52	Japanese diagnostic criteria[d]	Compare effects of RLX and ALN on L-BMD, bone turnover, and lipid metabolism
Majima et al[33]	60	RLX 60 mg/day, 32 RLX 60 mg + ALF 1 μg/day, 28	72 (9)[e] 70 (11)[e]	52	L-BMD ≤2.5 SD of YAM and Japanese diagnostic criteria[d]	Assess efficacy of RLX + ALF on BMD and bone turnover
Gorai et al[29]	137	RLX 60 mg/day, 45 ALF 1 μg/day, 44 RLX 60 mg + ALF 1 μg/day, 48	64 (7) 65 (7) 65 (8)	52	L-BMD ≤2.5 SD of YAM (osteoporosis) or 2.5 SD <L-BMD ≤2.0 SD of YAM (osteopenia)[d]	Assess adherence to RLX, ALF, and RLX + ALF
Hayashi et al[34]	46	RLX 60 mg/day, 16 HRT, 16 Control, 14[f]	71 (3) 72 (3) 73 (3)	52	L-BMD ≤2.0 SD of YAM	Compare atheroprotective and osteoprotective effects of RLX and HRT when switching from HRT to RLX (age-matched controls[f])
Gorai et al[32]	170	RLX 60 mg/day, 42[g] ALF 1 μg/day, 46[g] RLX 60 mg + ALF 1 μg/day, 45[g]	64 (7) 65 (7) 65 (7)	104	L-BMD ≤2.5 SD of YAM (osteoporosis) or 2.5 SD <L-BMD ≤2.0 SD of YAM (osteopenia)[d]	Assess efficacy of RLX + ALF on BMD and bone turnover and effect of RLX on serum PTH
Ando et al[30]	39	RLX 60 mg/day am, 20 RLX 60 mg/day pm, 19	77 (10)[h] 78 (7)[h]	52	Japanese Guidelines for the Prevention and Treatment of Osteoporosis[i]	Assess effects of RLX dosing time on coagulation, fibrinolysis, and bone turnover
Observational studies						
Majima et al[36]	50	RLX 60 mg/day, 50	72 (10)	52	L-BMD ≤2.5 SD of YAM and Japanese diagnostic criteria[d]	Assess effects of RLX on bone turnover, BMD, and lipid metabolism
Majima et al[37]	68	RLX 60 mg/day, 68	70 (9)[j]	52	L-BMD ≤2.5 SD of YAM and Japanese diagnostic criteria[d]	Assess associations between baseline bone turnover and BMD and their changes 52 weeks after treatment
Majima et al[38]	73	RLX 60 mg/day, 73	70 (9)[k]	52	L-BMD ≤2.5 SD of YAM and Japanese diagnostic criteria[d]	Assess associations between short-term reduction in bone turnover and BMD changes
Urushihara et al[41]	7,557	RLX 60 mg/day, 6,970[l]	70 (9)[m]	52[n]	NR	Compare risks of stroke and stroke death between RLX and general female population
Takada et al[24]	198	RLX 60 mg/day, 198	63 (8)	104	Japanese diagnostic criteria[d]	Clarify effects of RLX on proximal femoral geometry
Iikuni et al[40]	7,557	RLX 60 mg/day, 6,967 (safety)[l] RLX 60 mg/day, 2,784 (efficacy)[l]	70 (9) 70 (9)	156	Japanese diagnostic criteria[d]	Assess effectiveness and safety of long-term RLX use
Takada et al[39]	45	RLX 60 mg/day, 45	67 (5)	52	Japanese diagnostic criteria[d]	Assess correlations between bone turnover and proximal femur geometry
Yoh et al[42]	536	RLX 60 mg/day, 506[l]	71 (9)	24	Japanese diagnostic criteria[d]	Assess effect of RLX on QOL and pain

Notes: [a]A total of 302 participants were randomized, but only 284 participants were started on the study drug; [b]n=90 for the RLX60 group and n=93 for the RLX120 group; [c]as reported by Morii et al[35]; [d]Orimo et al[43]; [e]n=22 for the RLX group and n=20 for the RLX + ALF group; [f]control patients (age-matched) did not receive placebo medication, but did receive vitamin D (0.5 μg/day); [g]n values are for the modified intent-to-treat population; of the 170 participants who provided consent, 169 were randomized and 133 received treatment; the 36 participants who were randomized but did not receive treatment either withdrew their consent or dropped out of the study; [h]n=18 for the RLX am group and n=17 for the RLX pm group; [i]Committee of Japanese Guidelines for the Prevention and Treatment of Osteoporosis[19]; [j]n=58; [k]n=63; [l]participants eligible for analysis; [m]n=6,963; [n]median follow-up was 366 days.

Abbreviations: ALF, alfacalcidol; ALN, alendronate; BMD, bone mineral density; ELD, eldecalcitol; HRT, hormone-replacement therapy (estriol 1 mg/day and medroxyprogesterone 1.25 mg/day); L-BMD, lumbar spine BMD; NR, not reported; PTH, parathyroid hormone; QOL, quality of life; RLX, raloxifene; SD, standard deviation; YAM, young average mean.

Table 2 Studies reporting mean (SD) percentage change in bone mineral density or mean (SD) bone mineral density (g/cm²) of the lumbar spine, femoral neck, total hip, or total neck after 52 weeks of RLX treatment[a]

Authors	Therapy	Lumbar spine % or g/cm²	Femoral neck % or g/cm²	Total hip % or g/cm²	Total neck % or g/cm²
Randomized controlled trials					
Morii et al[35]	RLX	+2.9 (NR)***[b]	NM	NM	NM
Iwamoto et al[31]	RLX	+2.4 (NR)**	NM	NM	NM
	ALN	+8.0 (NR)**	NM	NM	NM
Majima et al[33]	RLX	+6.3 (5.8)**	+0.8 (6.3)	NM	+2.1 (5.3)
	RLX + ALF	+4.9 (7.7)**	+3.0 (17.4)	NM	+1.8 (7.9)
Gorai et al[29]	RLX	+3.0 (NR)*	NM	NR (NR)	NM
	ALF	+0.7 (NR)	NM	NR (NR)	NM
	RLX + ALF	+4.6 (NR)*	NM	+2.0 (NR)	NM
Gorai et al[32]	RLX	+2.9 (4.3)**	NM	+1.6 (3.5)*	NM
	ALF	−0.3 (4.4)	NM	−0.1 (3.8)	NM
	RLX + ALF	+4.1 (3.5)***	NM	+1.2 (4.1)	NM
Observational studies					
Majima et al[36]	RLX	0.67 (0.14), 0.72 (0.13)**	0.54 (0.10), 0.56 (0.10)	NM	0.60 (0.12), 0.61 (0.13)
Majima et al[37]	RLX	0.67 (0.12), 0.70 (0.12)**	0.55 (0.10), 0.55 (0.10)	NM	NM
Majima et al[38]	RLX	0.67 (0.12), 0.70 (0.12)**	0.55 (0.09), 0.55 (0.09)	NM	0.60 (0.11), 0.61 (0.12)
Iikuni et al[40]	RLX	+2.9 (NR)***	NM	NM	NM

Notes: *$P<0.05$, **$P<0.01$, and ***$P<0.001$ indicate significant differences from baseline; [a]data from two studies reporting bone mineral density (BMD) findings were not included in this table because BMD findings were of other regions in the hip;[24,39] [b]patients received either RLX 60 mg/day or RLX 120 mg/day, n=183.
Abbreviations: ALF, alfacalcidol; ALN, alendronate; NM, not measured; NR, not reported; RLX, raloxifene; SD, standard deviation.

postmarketing surveillance study, was sufficiently powered to detect the incidence of vertebral fractures.[40] Findings from this study suggested that after 36 months of treatment with raloxifene, the incidence of new clinical vertebral and nonvertebral fractures in postmenopausal women is low. Of the 6,967 participants, 36 (0.5%) reported new clinical vertebral fractures and 52 (0.7%) reported new clinical nonvertebral fractures.[40] Nearly half of these participants had prevalent fractures: 17 of the 36 participants (47%) with new clinical vertebral fractures and 19 of the 52 participants (37%) with new clinical nonvertebral fractures.

In a smaller randomized placebo-controlled study, few postmenopausal women taking raloxifene (60 mg/day or 120 mg/day) had a new vertebral fracture (0.05%, one of 183, versus placebo 2%, two of 97) or a new nonvertebral fracture (0.05%, one of 183, versus placebo 4%, four of 97) after 52 weeks of treatment.[35] In addition, findings from another randomized study suggested that the incidence of vertebral fractures was not significantly different between postmenopausal women taking raloxifene (13.1%, n=61) and alendronate (14.0%, n=61).[31]

Biochemical markers of bone turnover

Findings for biochemical markers of bone turnover were reported in eleven of the 15 publications: publications from six randomized controlled trials[29–33,35] and five observational studies.[36–40] The biochemical markers were alkaline phosphatase or bone-specific alkaline phosphatase (BAP; ten publications), type 1 collagen N-telopeptide (NTx; ten publications), type 1 collagen C-telopeptide (CTx; three publications), osteocalcin (one publication), tartrate-resistant acid phosphatase (one publication), and deoxypyridinoline (one publication) (Table 3). Findings were reported as the percentage change in concentration from baseline to 52 weeks or concentration at baseline and at 52 weeks.

Concentrations of all biochemical markers of bone turnover assessed decreased after 52 weeks of treatment with raloxifene (Table 3). The decreases in the biochemical marker concentrations from baseline were statistically significant when statistical significance was reported. When reported, the mean percentage decrease in concentrations after 52 weeks of treatment with raloxifene varied from 10%[31] to 38%[30] for BAP and 13.5%[39] to 35%[29,31] for NTx. In the randomized comparative trial of raloxifene and alendronate,[31] the mean percentage decreases in serum alkaline phosphatase concentrations after 52 weeks of treatment and urinary NTx concentrations after 12 weeks of treatment were less for raloxifene than alendronate (alkaline phosphatase not significant, NTx $P<0.05$, Table 3). In the randomized comparative trials of raloxifene and alfacalcidol, the effect of raloxifene on BAP, NTx, and CTx concentrations was more pronounced than that of alfacalcidol after 52 and 104 weeks of treatment,[32] and was less pronounced, similar to, or more pronounced than that combination treatment with raloxifene and alfacalcidol (Table 3).[29,32,33]

Table 3 Studies reporting mean (SD) percentage change in or mean (SD) concentrations for biochemical markers of bone turnover after 52 weeks of RLX treatment

Authors	Therapy	Serum BAP (% or U/L)	CTx (% or μg/L)	NTx (% or nmol BCE/L)
Randomized controlled trials				
Morii et al[35,a,b]	RLX	NR (NR)***	NR (NR)***,c	NR (NR)***,c
	RLX (120 mg/day)	NR (NR)***	NR (NR)***,c	NR (NR)***,c
Iwamoto et al[31]	ALN	−18 (NR)***,d	NM	−45 (NR)***,c,e
	RLX	−10 (NR)***,d	NM	−35 (NR)***,c,e
Majima et al[33]	RLX	−20 (37)*	NM	−29 (20)**,f
	RLX + ALF	−20 (29)**	NM	−25 (17)**,f
Gorai et al[29,g]	RLX	−22 (NR)	−37 (NR)c	NR (NR)c
	ALF	NR (NR)	NR (NR)c	NR (NR)c
	RLX + ALF	−37 (NR)	−42 (NR)c	−35 (NR)c
Gorai et al[32,a]	RLX	NR (NR)*	NR (NR)***,c	NR (NR)***,c
	ALF	NR (NR)	NR (NR)	NR (NR)
	RLX + ALF	NR (NR)***	NR (NR)***,c	NR (NR)***,c
Ando et al[30,g,h]	All	−32 (−43 to −22)i	NM	NM
	RLX am	−26 (−39 to −13)i	NM	NM
	RLX pm	−38 (−55 to −21)i	NM	NM
Observational studies				
Majima et al[36]	RLX	33 (16), 24 (9)**	NM	19 (6), 14 (3)**,f
Majima et al[37]	RLX	33 (17), 23 (9)**	NM	19 (5), 14 (3)**,f
Majima et al[38]	RLX	33 (16), 24 (9)**	NM	20 (5), 14 (3)**,f
Iikuni et al[40,a,j]	RLX	NR (NR)***	NM	NR (NR)***,c
Takada et al[39,g]	RLX	NM	NM	−13.5 (NR)f,k

Notes: *$P<0.05$, **$P<0.01$, and ***$P<0.001$ indicate significant differences from baseline; [a]study presented data of biochemical markers of bone turnover in figures, but did not report specific values in the figure or results text; [b]osteocalcin levels were also measured in this study; statistically significant ($P<0.001$) reductions from weeks 0 to 52 were reported; [c]urinary levels tested; [d]serum alkaline phosphatase levels were measured; [e]mean (SD) percentage change for NTx is from week 0 to week 12; [f]serum levels tested; [g]authors did not specify the value of statistical significance for bone biochemical marker reductions; [h]tartrate-resistant acid phosphatase levels were also measured in this study; the mean (95% CI) percentage change from week 0 to 52 was −27 (−33 to −21) mU/dL for all postmenopausal women, −31 (−40 to −22) mU/dL for the RLX am group, and −23 (−32 to −14) mU/dL for the RLX pm group; [i]values are means (95% CI); [j]urinary deoxypyridinoline levels were also measured in this study; statistically significant ($P<0.001$) reductions from week 0 to 52 were reported; [k]values are medians; median percentage change for NTx is from week 0 to week 26.

Abbreviations: ALF, alfacalcidol; ALN, alendronate; BAP, bone-specific alkaline phosphatase; BCE, bone collagen equivalents; CTx, type I collagen C-telopeptide; NM, not measured; NR, not reported; NTx, type I collagen N-telopeptide; RLX, raloxifene 60 mg/day; SD, standard deviation; CI, confidence interval.

Hip structural geometry

Findings for the hip structural geometry in the proximal femur were reported in two of the 15 publications, both of which were prospective observational studies.[24,39] The hip-structure analysis parameters were the cross-sectional area, mean cortical thickness, section modulus and buckling ratio of the narrow neck, intertrochanter, and shaft regions of the proximal femur; one publication reported the inner diameter,[39] and the other reported the outer diameter.[24] Findings were reported as the mean (95% confidence interval [CI]) percentage change in parameters from baseline to 52 weeks in both publications and from baseline to 104 weeks in one publication.[24]

Nearly all hip-structure analysis parameters for the intertrochanter and shaft regions of the proximal femur improved significantly after 52 weeks of treatment with raloxifene. For the intertrochanter and shaft regions, there were significant ($P<0.05$) increases in the cross-sectional area, mean cortical thickness, and section modulus after 52 weeks[24,39] and 104 weeks[24] of raloxifene treatment. In addition, there was a significant ($P<0.05$) decrease in the buckling ratio of the intertrochanter and shaft regions in one publication[39] and in the intertrochanter region in the other publication.[24] However, this difference for the intertrochanter region was not significant at 104 weeks.[24] In contrast, only a few hip-structure analysis parameters for the narrow neck regions for the proximal femur had improved significantly after 52 weeks of treatment with raloxifene.[24] These significant improvements ($P<0.05$) included increases in the cross-sectional area, section modulus, and outer diameter.[24]

Blood–lipid parameters

Findings for blood–lipid parameters were reported in five of the 15 publications, including publications from four randomized controlled trials[31,33–35] and one prospective observational study.[36] The blood–lipid parameters were total cholesterol (four publications), high-density lipoprotein cholesterol (five publications), low-density lipoprotein (LDL) cholesterol

Table 4 Studies reporting mean (SD) percentage change in blood–lipid parameters or mean (SD) blood–lipid parameters after 52 weeks of RLX treatment

Authors	Therapy	Total cholesterol % or mg/dL	Triglycerides % or mg/dL	HDL-cholesterol % or mg/dL	LDL-cholesterol % or mg/dL
Randomized controlled trials					
Morii et al[35]	RLX	NR (NR)*,a	NR (NR)	NR (NR)	NR (NR)*,a
	RLX (120 mg/day)	NR (NR)*,a	NR (NR)	NR (NR)	NR (NR)*,a
Iwamoto et al[31]	RLX	−3.9 (NR)**	+7.4 (NR)	+5.1 (NR)	−7.7 (NR)***
	ALN	−2.1 (NR)	−3.4 (NR)	−0.4 (NR)	+0.4 (NR)
Majima et al[33]	RLX	202 (39), 184 (30)**	133 (74), 125 (58)	57 (14), 53 (11)	119 (38), 106 (24)
	RLX + ALF	210 (29), 199 (28)*	144 (58), 124 (72)	57 (15), 56 (15)	125 (30), 118 (27)
Hayashi et al[34]	RLX	NR (NR), NR (NR)	95 (24), 86 (11)	56 (6), 64 (7)*	113 (14), 102 (15)
	HRT	NR (NR), NR (NR)	96 (25), 97 (18)	57 (5), 56 (8)	112 (11), 114 (13)
	Control	NR (NR), NR (NR)	97 (21), 95 (21)	57 (5), 56 (6)	119 (11), 125 (9)
Observational studies					
Majima et al[36]	RLX	204 (32), 192 (31)**	123 (66), 122 (63)	55 (13), 54 (11)	125 (33), 113 (27)*

Notes: *$P<0.05$, **$P<0.01$, and ***$P<0.001$ indicate significant differences from baseline; [a]statistical significance is for differences between placebo and RLX groups at week 52.

Abbreviations: ALF, alfacalcidol; ALN, alendronate; HDL, high-density lipoprotein; HRT, hormone-replacement therapy; LDL, low-density lipoprotein; NR, not reported; RLX, raloxifene 60 mg/day; SD, standard deviation.

(five publications), and triglycerides (five publications) (Table 4). Findings were reported as the percentage change in concentration from baseline to 52 weeks or concentration at baseline and at 52 weeks.

In general, the blood–lipid profile of participants had improved after 52 weeks of treatment with raloxifene (Table 4). Decreases in the concentrations of both total cholesterol and LDL cholesterol from baseline concentrations were reported in all publications reporting findings of these parameters. These decreases were statistically significant for total cholesterol concentrations in three publications[31,33,36] and LDL cholesterol concentrations in two publications.[31,36] The concentration of high-density lipoprotein cholesterol was significantly increased ($P<0.05$) in one publication,[34] but remained the same in the four other publications (Table 4). The concentration of triglycerides either decreased or remained the same (Table 4).

In the randomized controlled trial, decreases in total cholesterol concentrations and LDL cholesterol concentrations were significantly greater ($P<0.05$) for participants receiving raloxifene (60 mg/day and 120 mg/day) than those receiving placebo after 52 weeks of treatment.[35] In the randomized comparative trial of raloxifene and alendronate, decreases in LDL cholesterol concentrations were significantly greater ($P<0.05$) for participants receiving raloxifene than those receiving alendronate after 52 weeks of treatment.[31]

Safety

Findings for safety variables were reported in 12 of the 15 publications: publications from six randomized controlled trials[29–33,35] and six observational studies.[36–38,40–42] Safety variables were the type, incidence, and severity of AEs (four publications) (Table 5), study discontinuations resulting from AEs (nine publications) (Table 6), stroke risk (one publication),[41] and change in markers of coagulation and fibrinolysis (one publication).[30] Three publications from one randomized controlled trial[34] and two observational studies[24,39] did not report findings for any safety variables.

The type, incidence, and severity of AEs were reported in four publications from two randomized controlled trials[29,35] and two observational studies,[40,42] both of which were postmarketing surveillance studies (Table 5). The safety findings were consistent with those expected for raloxifene use in Japan.[44] In the randomized placebo-controlled trial,[35] almost half of the participants reported at least one AE, whereas about 10% of the participants in the long-term postmarketing surveillance study reported an AE.[40] Few postmenopausal women had hot flushes, leg cramps, breast pain, or vaginal bleeding (when reported) in the randomized trials (Table 5). Clinically relevant abnormal changes in breast tissue were reported in one woman taking raloxifene 120 mg/day (inspection and palpation) and in one woman taking placebo (ultrasound examination) in the randomized placebo-controlled trial.[35] In addition, clinically relevant abnormal changes in endometrial thickness were reported in two women taking raloxifene 60 mg/day and one woman taking raloxifene 120 mg/day.[35] Common AEs reported in the postmarketing surveillance studies were peripheral edema and abdominal discomfort (Table 5).

Table 5 Adverse events (AEs)

Authors	Therapy (n)	AEs n	Serious AEs n	Death n	Other
Randomized controlled trials					
Morii et al[35]	RLX (92)	32	5	0	No significant increases in incidence of hot flushes, leg cramps, breast pain or vaginal bleeding between RLX and placebo groups; no VTE events reported
	RLX (120 mg/day) (95)	40	3	1[b]	
	Placebo (97)	33	7[a]	0	
Gorai et al[29,c]	RLX (45)	17	NR	NR	Hot flush 1, leg cramp 2, limb cramp 2
	ALF (44)	11	NR	NR	Hot flush 1
	RLX + ALF (48)	13	NR	NR	Leg cramp 2
Observational studies					
Iikuni et al[40]	RLX (6,967)	776[d]	76[d]	3	Stroke 12 (8 serious), VTE 11 (3 serious) Most frequent AEs: peripheral edema 45, abdominal discomfort 39, abdominal pain 33
Yoh et al[42]	RLX (506)	34[e]	1	0	Most frequent AEs: abdominal discomfort 6, peripheral edema 3

Notes: [a]Seven participants reported nine serious AEs; [b]death caused by anaplastic thyroid cancer; not related to RLX; [c]adverse events were self-reported or observed; [d]961 AEs were reported in 775 participants, and 87 serious AEs were reported in 76 participants; [e]40 AEs were reported in 34 participants.
Abbreviations: ALF, alfacalcidol; NR, not reported; RLX, raloxifene 60 mg/day; VTE, venous thromboembolism.

In a postmarketing surveillance study of 6,970 postmenopausal women, the risk of stroke was not significantly increased after 52 weeks of treatment with raloxifene.[41] In this study, 23 treatment-emergent stroke cases were reported (crude stroke risk =0.33%). Of these 23 cases, four had a previous history of stroke, nine had risk factors for stroke (eg, hypertension), and ten had no risk factors for stroke. Four women died as a result of stroke.[41] In another postmarketing surveillance study of 6,967 postmenopausal women, there were 12 cases of stroke, eight of which were serious, after 156 weeks of treatment with raloxifene.[40]

Although no VTE events were reported in the randomized placebo-controlled trial, there were eleven cases of VTE, three of which were serious, in the 3-year postmarketing surveillance study (Table 5). In another publication, the concentration of plasminogen-activator inhibitor, a marker for the increased risk of VTE, was increased after 52 weeks of treatment with raloxifene.[30] This increase in

Table 6 Study discontinuations

Authors	Therapy (n)	Overall n	Because of AEs n	AE type n
Randomized controlled trials				
Morii et al[35]	RLX (92)	13	7	NR
	RLX (120 mg/day) (95)	14	8	NR
	Placebo (97)	10	3	NR
Iwamoto et al[31]	RLX (61)	9	6	Epigastric pain 4, liver dysfunction 1, urticaria 1
	ALN (61)	11	8	Epigastric pain 3, gastric ulcer 1, heartburn 1, liver dysfunction 1, diarrhea 1, constipation 1
Majima et al[33]	RLX (32)	10	2	Muscle pain entire body 1, leg cramps 1[a]
	RLX + ALF (28)	8	2	Increased BP 1, leg cramps 1[a]
Gorai et al[29]	RLX (45)	NR	7	Itching paresthesia 2, limb cramp 2, leg cramp 2, alopecia areata 1
	ALF (44)	NR	5	Hypercalciuria 4, hot flash 1
	RLX + ALF (48)	NR	6	Digestive symptoms 3, leg cramp 2, angina attack 1
Gorai et al[32]	RLX (42)	NR	7	Itching paresthesia 2, limb cramp 2, leg cramp 2, alopecia areata 1
	ALF (46)	NR	5	Hypercalciuria 4, hot flash 1
	RLX + ALF (45)	NR	6	Digestive symptoms 3, leg cramp 2, angina attack 1
Ando et al[30]	RLX am (20)	4	3	Muscle pain 1, headache 1, loss of fingernails 1
	RLX pm (19)	1	1	Hot flush 1
Observational studies				
Majima et al[36]	RLX (50)	16	4	Leg cramps 2, muscle pain entire body 1, increased BP 1[a]
Majima et al[37]	RLX (68)	10	2	Leg cramps 1, muscle pain entire body 1[a]
Majima et al[38]	RLX (73)	10	2	Leg cramps 1, muscle pain entire body 1[a]

Note: [a]AEs resolved spontaneously with cessation of RLX.
Abbreviations: AEs, adverse events; ALF, alfacalcidol; ALN, alendronate; BP, blood pressure; NR, not reported; RLX, raloxifene 60 mg/day.

plasminogen activator-inhibitor concentration was noted for participants taking raloxifene in the morning, but not those taking raloxifene in the evening, suggesting that dosing time may have influenced the safety of raloxifene in this study population.

Study discontinuations resulting from AEs were reported in nine publications from six randomized controlled trials[29–33,35] and three observational studies (Table 6).[36–38] Few participants discontinued treatment because of AEs; leg and limb cramps, and muscle pain were the most common reasons for participants discontinuing raloxifene treatment (Table 6).

Quality of life and pain

Findings for quality of life and pain were reported in one publication from a postmarketing surveillance study.[42] In this publication, quality of life was assessed using the Short Form (SF)-8 Health Survey, the European Quality of Life Instrument, and the Japanese Osteoporosis Quality of Life Questionnaire, whereas pain was assessed using a visual analog scale and a pain-frequency survey. Findings were reported as the mean (standard deviation) change in scores from baseline to 24 weeks.

Improvement in quality of life and relief from pain was reported after 24 weeks of treatment with raloxifene.[42] All scores for the SF-8 domains (general health, physical functioning, role physical, bodily pain, vitality, social functioning, mental health, and role – emotional) improved significantly ($P<0.001$) from baseline, as did the European Quality of Life Instrument score. Significant improvements ($P<0.05$) in the total score and the scores of individual domains, except for the recreation/social activities domain, for the Japanese Osteoporosis Quality of Life Questionnaire were also reported. Relief from pain was indicated by a significant decrease ($P<0.001$) in pain severity (decreased visual analog scale scores) and decreases in the frequency of pain (fewer participants reporting permanent frequent pain).

Discussion

This is the first systematic review describing the efficacy, effectiveness, and safety outcomes of postmenopausal Japanese women with osteoporosis or osteopenia treated with raloxifene. Overall, a broad range of outcomes were reported for raloxifene (eg, BMD, bone turnover, lipid metabolism, AEs) in randomized controlled studies and observational studies, which included postmarketing surveillance studies. Despite the variation in study designs and methods reported, the body of evidence in this systematic review supports the effectiveness of raloxifene in increasing lumbar spine BMD and reducing the incidence of subsequent fracture, is associated with improvements in other health-outcome measures, and is well tolerated in postmenopausal Japanese women. When reported, lumbar spine BMD increased significantly,[29,31–33,35–38,40] and biochemical markers of bone turnover decreased after 52 weeks of treatment with raloxifene.[29–33,35–40] However, limited data were available to confirm whether these improvements in bone quality were associated with a reduction in the incidence of vertebral or nonvertebral fracture in postmenopausal Japanese women. The AEs reported in the studies included in this review were consistent with the safety profile of raloxifene use in Japan.[44]

In bone cells, where postmenopausal estrogen deficiency has caused an imbalance in bone turnover (excess resorption versus formation), raloxifene binds to estrogen receptors and induces conformational changes that are distinct from the binding of estrogen.[45] Raloxifene then acts as an agonist to decrease bone resorption and normalize bone turnover, thereby preserving BMD. In the MORE (Multiple Outcomes of Raloxifene Evaluation) study (a pivotal multicenter, international, blinded, randomized, placebo-controlled trial of 7,705 postmenopausal women with osteoporosis from Europe, the Americas, and Oceania),[46] raloxifene was shown to increase BMD, improve bone strength, and prevent vertebral fractures, but not to reduce the risk of nonvertebral fractures as a primary outcome.[47,48] In our systematic review, the increase in lumbar spine BMD and decrease in biochemical markers of bone turnover in postmenopausal Japanese women support the findings from the pivotal studies of raloxifene conducted in Caucasian populations.[47,48] In another publication excluded from our review (because it was published in a non-peer-reviewed journal), the increase in lumbar spine BMD reported for raloxifene was 7.1% at 26 weeks.[49] In this study, raloxifene was coadministered with eldecalcitol, an active vitamin D_3 analog, which has been shown to enhance the mechanical properties of trabecular and cortical bone by suppressing bone turnover and increasing BMD more than either monotherapy in ovariectomized rats.[50] Although in our review there were few head-to-head studies of raloxifene compared with other osteoporosis medications, the data available suggest that the effect of raloxifene on BMD and biochemical markers of bone turnover was not as pronounced as that of alendronate.[31] However, it is not clear how these findings translate to any potential

differences in the effect of raloxifene on new vertebral fractures, because of the limited length of follow-up (52 weeks) and because this study was not sufficiently powered to assess incidence of vertebral fracture.[31]

We identified only one publication sufficiently powered to detect vertebral fracture incidence. In this postmarketing surveillance study[40] of Japanese women with osteoporosis treated with raloxifene, the low incidence of vertebral fractures was consistent with findings from the MORE study[47,48] and a post hoc analysis of combined study data from postmenopausal Japanese[35] and Chinese women with osteoporosis.[28] Interestingly, the incidence of new clinical nonvertebral fractures (0.7%) was slightly higher than new clinical vertebral fractures (0.5%) in the postmarketing surveillance study.[40] This finding may have been due to the criteria used to define new clinical fractures (reported signs or symptoms suggestive of fracture subsequently corroborated by radiographs) that excluded vertebral morphometry, which may have identified more patients with a vertebral fracture. In the post hoc analysis, which was not included in this systematic review because the analysis combined data from both Japanese and Chinese populations, the incidence of new clinical vertebral fractures was significantly lower for postmenopausal Japanese and Chinese women taking raloxifene (60 mg/day or 120 mg/day) than those taking placebo (0 of 289 versus seven of 199 [3.5%], P=0.002).[28]

Treatments that help improve lumbar spine BMD and bone quality and consequently reduce the incidence of vertebral fracture (which includes preventing or reducing the risk of subsequent vertebral and/or nonvertebral fractures) are important in Japanese populations. This is because the incidence of vertebral fractures in Japanese women appears to be higher than in Caucasian women. In studies using similar morphometric methods, the incidence of vertebral fracture in the Japanese study was about 40 per 1,000 person-years for women in their 70s,[15] whereas the incidence in studies of Caucasian women of a similar age are about twofold lower.[16,17,51] In another study, the prevalence of vertebral fracture in 70- to- 74-year-old women was greater in Japanese women (248 cases per 1,000) than women of Japanese descent (148 cases per 1,000) or Caucasian women (150 cases per 1,000).[52] The higher incidence of vertebral fractures for Japanese women is also apparent compared with women from other Asian countries. The prevalence of vertebral fractures was significantly greater in women aged 65–74 years from Japan than those from Hong Kong, Indonesia, and Thailand.[53] Factors specific to the Japanese lifestyle, culture, and ethnicity may influence the risk of fracture in Japanese women.[54] For example, BMD is lower in Japanese women than Caucasian women of the same age.[43,55] Other factors shown to be possibly associated with vertebral fractures in Japan include weight, age, menstrual history,[56] genetic factors,[57] bone and calcium metabolism,[58] calcium intake,[59] and vitamin D levels.[60] All of these factors contribute to BMD levels, and thus may indirectly influence the prevalence of vertebral fractures. However, although these other factors may contribute indirectly, future fracture risk in women from Japan can be accurately predicted using age, BMD, and prior vertebral fracture status.[61]

Findings from this review showed that although proximal femur structural geometry improved with raloxifene treatment,[24,39] the effect of raloxifene on the BMD of the femoral neck, total hip, total neck, or other regions of the hip in postmenopausal Japanese women was variable.[24,29,32,33,36–39] This variable effect on BMD in the hip region may be explained, at least in part, by participants having different BMD values for the hip region at baseline, because specific BMD values for the hip region were not an inclusion criterion in studies reporting these findings.[24,29,32,33,36–39] Hip-structure analysis is a valuable measure of proximal femur geometry and strength[62] that has been used to show age-, ethnic-, and sex-related differences in proximal femur geometry and strength,[63–67] as well as the effects of osteoporotic treatments.[25,68–71] The findings from the studies that assessed hip structure[24,39] suggest that raloxifene may have a beneficial effect on hip-bone quality. However, although this effect may translate to a reduction in the likelihood of hip fracture, there is no published evidence available to show that treatment with raloxifene reduces the incidence of hip fracture in postmenopausal women with osteoporosis.

The safety and tolerability findings in the publications included in this review suggested that raloxifene was well tolerated in most postmenopausal women in Japan. Few postmenopausal women discontinued because of AEs, and few postmenopausal women experienced AEs commonly associated with raloxifene use, such as leg cramps, hot flushes, and peripheral edema.[22] The main safety concern of treatment with raloxifene is an increased risk of VTE.[22] Although the incidence of VTE in clinical studies of raloxifene is low, findings from the pivotal MORE study, which excluded women with a history of thromboembolic events in the past 10 years, showed that the relative risk of VTE was