

# Economic Evaluation of Female Hormone Replacement Therapy for Osteoporosis and Fractures in Elderly Women

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In this aging society, female hormone replacement therapy (HRT) has begun to attract close attention, not only for its efficacy in disease prevention and improvement of the quality of life of middle-aged and elderly women, but also from the aspect of health economics. In Western countries, HRT is administered to 20-30% of all postmenopausal women, and there has been discussion about its cost-effectiveness in helping to prevent fractures, angiopathy, etc. In Japan, this therapy is used less extensively (only about 1/10 as frequently) than in Western countries, and there has been little discussion on this therapy from a health economics standpoint in Japan. The present study aimed to evaluate HRT in Japan from the economic viewpoint, by calculating the cost of HRT itself and the economic impact through its effect of preventing bone fractures.

The present study focused on the relationship of HRT to osteoporosis and fractures, because its effectiveness in preventing other pathologic conditions has not yet been established. The medication cost of HRT was estimated at about 140 billion yen per year, if it were administered to all postmenopausal women with osteoporosis. The estimated cost of HRT was relatively small in comparison to that of other drug therapies for osteoporosis, even when side effects were taken into account.

When given to prevent osteoporosis and fractures, HRT was estimated, putting aside the cost of HRT itself, to reduce the direct cost of bone fracture care by 295.1 billion yen and the indirect cost by about 8.2 billion yen. Thus, a total reduction of about 303.3 billion yen by the administration of HRT was expected, suggesting that HRT could eliminate about 20% of the medical cost generally required for the treatment of osteoporosis and bone fractures. This analysis estimated the cost of the therapy itself and also the cost reduction due to the beneficial health effect of preventing osteoporosis, and suggested that HRT for postmenopausal women is comparable to or superior to other drug therapies conventionally used for osteoporosis. Considering also the clinical benefits of HRT of controlling conditions other than osteoporosis and fractures, HRT seems to be a promising therapy. It is desirable to analyze the factors hampering the acceptance of this therapy in Japan. In the future, clinical-epidemiological data should be collected and further economic analysis should be pursued, concerning this promising therapy and its related health conditions.

**[key words]** female hormone replacement therapy, osteoporosis, femoral neck fracture, vertebral fracture, economic evaluation

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## 1. Introduction

Now that the average life expectancy of females in Japan is about 84 years, more than one-third of a woman's life is post-menopause. This means that women live for about 35 years with estrogen deficiency. It has been revealed that estrogen not only plays an important role in reproduction but also exerts diverse functions related to the function of organs and the maintenance of life. As women's life-spans are prolonged, health management for women faces important problems, i.e., not only climacteric disorders (a problem recognized for many years), but also an increased risk of developing fractures due to osteoporosis and cardiovascular disorders due to arteriosclerosis. Under these circumstances, female hormone replacement therapy (HRT) was introduced to clinical practice to prevent and treat diseases specific to middle-aged or elderly women and to improve the quality of life (QOL) of these women<sup>1)-3)</sup>. This therapy has been attracting close attention from a medical economics viewpoint, on the grounds that the number of women receiving this therapy and the duration of therapy are expected to increase markedly in the aging society<sup>4),5)</sup>. In Western countries, 20-30% of postmenopausal women receive HRT, and the cost of this therapy has been debated in relation to its effects of preventing fractures, angiopathy, Alzheimer's disease, etc. In Japan, however, this therapy is given to only about one-tenth the numbers of those receiving it in Western countries. Discussion on this therapy from a medical

economics viewpoint has only recently begun in Japan<sup>6),7)</sup>. The present study was undertaken to review medical economics studies of HRT conducted in Western countries and to attempt to calculate the cost and benefits of this therapy if it were administered extensively in Japan, with the ultimate goal of providing perspectives on the desirability of using HRT in Japan.

As stated above, the effects on fractures and cardiovascular disorders have been highlighted as the positive results of HRT for elderly women. In recent years, there has been some controversy about the effects of this therapy regarding prevention of ischemic heart disease. In a large-scale secondary prophylaxis study entitled, "Heart and Estrogen/Progestin Replacement Study (HERS)"<sup>8)</sup>, HRT failed to prevent ischemic heart disease, and instead increased the incidence of venous thrombosis. A large-scale primary prophylaxis study "Women's Health Initiative (WHI)" is now under way, and the results will be reported in 2006. The predominant opinion in the United States now is that until the results of this study are confirmed, HRT should be confined to the treatment of climacteric disorders and osteoporosis, and that lipid-lowering agents of the statin family should be used as drugs of first choice for the treatment of hyperlipidemia<sup>9)</sup>. In view of this opinion, the purpose of this study was limited to the effects of HRT on osteoporosis and fractures, i.e., conditions for which HRT's effectiveness has been confirmed. No previous studies have examined the economic impact of HRT at the societal level in Japan, and we expect that such studies will contribute to spreading HRT and improving the QOL of

middle-aged and elderly women.

## 2. Subjects and Methods

### (1) Collection of papers and statistical data

Papers on HRT, osteoporosis and fractures published in Western countries were collected using Medline, and those published in Japan were collected primarily using *Japana Centra Revuo Medicina*, Reports from Japanese governmental organizations and nationwide statistics were also utilized as sources of statistics for Japan. In Japan, the percentage of elderly women receiving HRT is still very low, and there have been few epidemiological studies of the effects of this therapy on osteoporosis and fractures. For this reason, we referred primarily to Western papers when collecting information about the effects of HRT on osteoporosis and fractures.

### (2) Form of evaluation

This study calculated the cost of HRT itself if it were implemented in target populations on a national level, and estimated the economic impact of HRT through its effect in the prevention of bone fractures.

In the present study, reduced cost was only analyzed with regard to osteoporosis and fractures. HRT may potentially result in benefits not only in the control of osteoporosis and fractures, but also in the control of many other conditions, such as cardiovascular disease, atrophy of the urogenital organs and unidentified climacteric complaints. In recent years, it has also

been suggested that HRT is effective in preventing Alzheimer's disease. However, quantification and evaluation of HRT's effects against conditions other than osteoporosis and fractures would involve debatable issues, and for this reason the present study was limited to these two conditions.

### (3) Modeling

The target for HRT was set as women aged 50 years or older, considering the average age of menopause. **Figure 1** shows the clinical course of these women after menopause, which was followed by bone mass decrease, and then by osteoporosis. In the early stages of osteoporosis, patients have no subjective symptoms, and a considerable percentage of them remain untreated. Lower back pain is the most frequent symptom of the later stages of osteoporosis, and this symptom is controlled by drug therapy on an outpatient basis. Patients with osteoporosis are likely to develop fractures of the femoral neck, spine, distal end of the radius and proximal end of the humerus. Femoral neck fractures are the most problematic, as they tend to cause patients to become bedridden. Although other types of fractures may also cause a bedridden state and reduced QOL, their quantitative evaluation is difficult. For this reason, this study dealt with only those bedridden due to femoral neck fractures.

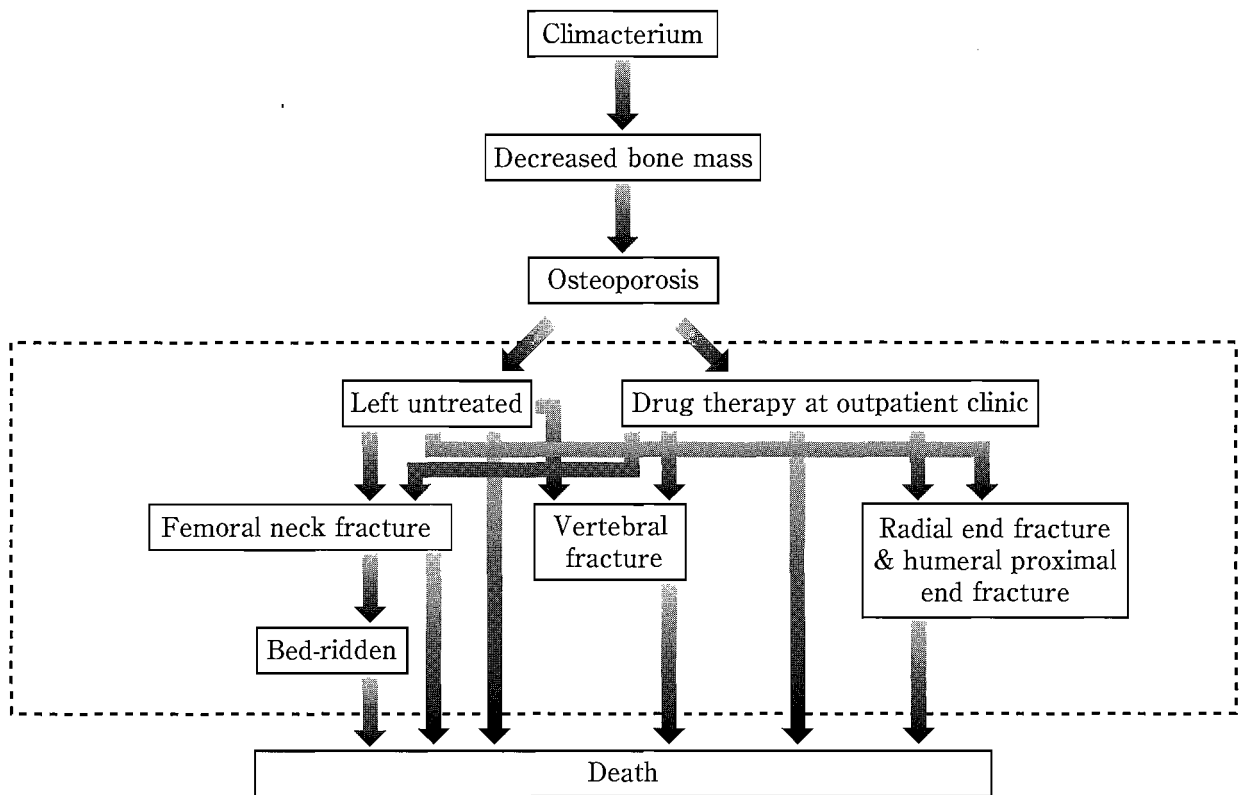
It is thought that some bedridden patients may receive care at home. The present study was based, however, on the assumption that all the patients would receive care at social welfare facilities for the aged. This assumption will not

cause significant bias in estimating the cost of caring for bedridden patients, because even patients cared for in their own home will require some financial support, and that total cost will not be significantly biased by using the cost of care at facilities to represent the cost for all patients in the described group. It was estimated, on the basis of published reports, that 3 months would be needed to treat fractures of the femoral neck and 42.6 days would be required for other fractures (see detailed accounts in Section 3 (2) -b) -ii), "Cost of treatment of bone fractures"). We believed that the remainder of the total period needed to care for fractures (9 months in the

case of femoral neck fractures) would be the period during which drug therapy is conducted at outpatient clinics.

The cost of HRT was based on a protocol that was considered to be one of the standards, and was estimated from the national fee schedule of the health insurance reimbursement for health care for the year 2000. The economic impact of HRT by controlling osteoporosis and fractures was evaluated with respect to both direct and indirect cost. For the direct cost, the amount saved was calculated for fractures and osteoporosis separately. The change (reduction) in the incidence of fractures due to HRT therapy

Figure 1 Course followed by middle-aged or elderly women with osteoporosis. The dotted line surrounds events that were included for estimation of cost in the present study.



was estimated from the published data of Western countries, because no such data were available in Japan. The cost reduction due to HRT by controlling osteoporosis was evaluated in patients currently receiving treatment, based on the assumption that this therapy can replace one of the following major drugs for osteoporosis, such as bisphosphonates, activated vitamin D<sub>3</sub>, ipriflavone, vitamin K<sub>2</sub> and elcatonin. It was not possible to obtain all the statistical data from the same year, and the latest data available were used. For the indirect cost, only the production loss during hospital stay for the treatment of bone fractures was calculated in the present study. Details of the method of calculation of production loss, which can be reduced by HRT, are shown in **Table 7**.

#### (4) Analysis viewpoints

Economic evaluation in medical fields is performed from various viewpoints, including those of clinicians, hospitals or provider institutions, patients or patient groups, private sector health care enterprises or insurance companies, payers and society as a whole. This study was based upon society's viewpoint with a nationwide scope.

### 3. Results

#### (1) Medical economics studies of HRT in Western countries

A literature search in 2001 through Medline (the National Library of Medicine, USA) using the key words "HRT or ESTROGEN REPLACEMENT THERAPY" AND "COST or

BENEFIT or EFFECTIVENESS or UTILITY or MINIMIZATION" AND "ECONOMICS" resulted in 76 hits (**Table 1**). Papers on cost-benefit analysis accounted for the highest percentage (48 papers, 63%) of the total, followed by those on cost-effectiveness analysis (13.17%). Out of them, 29 papers were on general topics, and "osteoporosis and fractures" (31.41%) was the most frequent specific subject.

#### (2) Estimation of economic impact of HRT in Japan

##### a) Expense of HRT itself

Several HRT regimens are available, and can be divided into the categories of estrogen alone and combined estrogen and progestogen therapy. There are several estrogen preparations used for HRT. Two methods, continuous administration and periodic administration, are used for combined estrogen and progestogen therapy. Female hormone preparations are inexpensive and similar in price. For example, Premarin 0.625 mg (a representative binding-type estrogen preparation) and Provera 2.5 mg are used for combined estrogen and progestogen therapy, and their price in the health insurance fee schedule is 12.5 yen and 33 yen, respectively. Therefore, the cost of this therapy is 45.5 yen/day. Estriol (1 mg), which is often used for the treatment of senile osteoporosis, is priced at 43 yen for two tablets (the daily dose), which is almost the same as the cost of the combined hormone regimen. We therefore used the cost of combined continuous administration of estrogen and progestogen, of 45.5 yen daily or 16,608 yen annually.

The mean age when women experience menopause is about 50 years. In 1999, the number of women aged 50 or older in Japan was estimated to be 25,784,000, and of women aged 65 or older was estimated at 12,369,000<sup>15)</sup>. The number of patients with osteoporosis was estimated at about 8,410,000 in 1994<sup>16)</sup>, and this number has probably been increasing annually. The number of patients with decreased bone mass is probably greater and there are at least 10,850,000 patients with this condition<sup>15), 16)</sup>. The above subpopulations could be potential targets for HRT medication, and the estimated medication expense for postmenopausal women with osteoporosis would be 139,669 million yen per year ( $= 8,410,000 \times 45.5 \text{ yen/day} \times 365 \text{ days}$ ).

In the next step, expenses related to pre-HRT care and post-HRT follow-up were considered. The results are summarized in **Table 2**, which shows the cost of the initial assessment before HRT and the annual cost based upon two-weekly follow-up primarily to prescribe and dispense the routine HRT medication and to check for potential adverse reactions. This calculation was based on the regimen of necessary tests and drugs proposed by Aono<sup>11)</sup>. The health insurance fee schedule for the year 2000 was used for this calculation<sup>12), 13)</sup>. The cost of care at the initiation of HRT was 38,970 yen, a little less than 40,000 yen per patient, and the annual cost of follow-up was about 111,000 yen per patient. The total expense thus calculated was about 40% higher than the cost previously estimated by Shiraki (at 79,482

Table 1 Search of papers on health economics of HRT by Medline in 2001

Key words	Number of papers found 1 <sup>(a)</sup> %	Number of papers found 2 <sup>(b)</sup>
# 1 : HRT or ESTROGEN REPLACEMENT THERAPY	6807	
# 2 : COST or BENEFIT or EFFECTIVENESS or UTILITY or MINIMIZATION	239643	
# 3 : ECONOMICS	116726	
#1 AND # 2 AND # 3	76 100%	
Cost-Benefit analysis	47 62%	
on general topics		27
on osteoporosis and fractures		17
on other conditions		3
Cost-Effectiveness analysis*	14 18%	
on general topics		0
on osteoporosis and fractures		10
on other conditions		4
Cost-of-illness analysis	7 9%	
on general topics		2
on osteoporosis and fractures		4
on other conditions		1
Others**	8 11%	

\* : Including some cost-utility analyses

\*\* : Papers not falling under any of the above-mentioned three categories of analysis

a) : Classification of the 76 papers containing all of the key words # 1, # 2 and # 3

b) : Subcategories

Table 2 Estimated cost of HRT per year (per patient)

Pre-treatment examinations and tests	N.H.I. Points	Amount (yen)		
Initial examination	270*	2,700		
Re-examination	74**	740		
LH, FSH, E2	640	6,400		
Biochemical tests	175	1,750		
Biochemical evaluation (I)	145	1,450		
Biochemical evaluation (II)	126	1,260		
Hematological tests	27	270		
Coagulation tests	94	940		
Hematological evaluation	126	1,260		
Bone metabolism markers	210	2,100		
Venous blood sampling	12	120		
ECG	150	1,500		
Chest X-ray	150	1,500		
Urinalysis	58	580		
Ultrasonography				
Pelvis	550	5,500		
Breasts	350	3,500		
Dual X-ray absorptiometry (DXA)	360	3,600		
Cytologic checks for uterine cancer	140	1,400		
Pathology	240	2,400		
Subtotal		38,970		
Tests and drug therapy at outpatient clinic	N.H.I. Points	Amount (yen)	Frequency (per year)	Annual cost (yen)
Re-examination	74	740	26	19,240
Outpatient management	52	520	26	13,520
Prescription	42	420	26	10,920
Dispensing	9	90	26	2,340
Basic technical charge for dispensing	8	80	26	2,080
Premarin (0.625 mg)		12.5	365	4,563
Provera (0.25 mg)		33	365	12,045
LH, FSH, E2	640	6,400	1	6,400
Biochemical tests	175	1,750	2	3,500
Biochemical evaluation (I)	145	1,450	2	2,900
Biochemical evaluation (II)	126	1,260	1	1,260
Hematological tests	27	270	1	270
Coagulation tests	94	940	1	940
Hematological evaluation	126	1,260	1	1,260
Bone metabolism markers	210	2,100	2	4,200
Venous blood sampling	12	120	2	240
ECG	150	1,500	1	1,500
Chest X-ray	150	1,500	1	1,500
Urinalysis	58	580	1	580
Ultrasonography				
Breasts	350	3,500	2	7,000
Dual X-ray absorptiometry (DXA)	360	3,600	2	7,200
Cytologic checks for uterine cancer	140	1,400	2	2,800
Pathological tests	240	2,400	2	4,800
Subtotal				111,058
Annual cost (per patient)	First year (yen)	150,028		
	Subsequent years (yen)	111,058		

\* : Points for GP. 250 points for hospitals. \*\* : Points for GP. 70 points for hospitals.  
N.H.I. points: national health insurance points

yen)<sup>14)</sup>. This difference is probably because the present calculation included all of the costs of various tests, re-examinations, checks for adverse reactions, etc. The adverse reactions to HRT reported to date include increased risk of cancer of the uterine body and breast. It has been reported that the risk of uterine body cancer can be suppressed almost completely by the combined estrogen and progestogen regimen. No consensus has yet been reached concerning countermeasures against the risk of breast cancer. In the present calculations, the cost of checking for adverse reactions was included, but that of treatment for such reactions was not included. The cost of other drug therapies for osteoporosis was also higher than previously reported<sup>14)</sup> when all related fees, such as those of test result assessment, re-examinations, checks for adverse reactions, etc., are taken into consideration. It is therefore considered that the cost of HRT is comparable to or lower than that of other osteoporosis drug therapies, as previously reported. We automatically calculated the cost on a national level when HRT was hypothetically administered to the several subpopulations described below (Table 3). For example, when all women aged 50 or older were given this therapy (although it is unrealistic),

the annual cost would be 2.9 trillion yen. If HRT with the above follow-up regimen were administered to patients with osteoporosis, it would cost 934 billion yen. This expense is not regarded as an additional burden to society, because many postmenopausal women with osteoporosis are under routine clinical care for osteoporosis, climacteric symptoms or other conditions.

#### b) Estimation of Cost Reduction Due to HRT

##### i) Epidemiology of bone fractures in elderly population

Incidence and prevalence are parameters used to describe the frequency of disease. Most statistics on fractures other than vertebral fractures show incidence only. Orimo et al. reported a nationwide survey of the incidence of femoral neck fractures for the year 1997<sup>17)</sup>, as shown in Table 4. According to their report, the number of women who developed this type of fracture during the year was 71,600. Its incidence per 10,000 population was 0.13 and 0.60 for women younger than 40 and for women between 40 and 49 years of age, respectively. Because there were about 30.3 million women younger than 40 and 8.6 million women between 40 and

Table 3 Estimation of total cost of HRT (in all postmenopausal women)

	Number of women	Annual cost (yen) /head	Total cost
All postmenopausal women (aged 50 or older)	25,784,000	111,058	2,863,519,472,000
Women aged 65 or older	12,369,000	111,058	1,373,676,402,000
Postmenopausal women with osteoporosis*	8,410,000	111,058	933,997,780,000
Postmenopausal women with decreased bone mass**	10,850,000	111,058	1,204,979,300,000

\* : <mean - 3 SD of T value of DXA (Ogawa et al.<sup>16)</sup>)

\*\* : <mean - 2.5SD of T value of DXA (Ogawa et al.<sup>16)</sup>)

The number of all postmenopausal women (aged 50 or older) and that of women aged over 65 were derived from the estimated population statistics for 1999<sup>15)</sup>.



Table 4 Estimated annual incidence of spinal fracture, radial end fracture and humeral proximal end fracture in Japanese women aged 50 or older

Age	Number of women* (in thousands)	Femoral neck fracture		Spinal fracture		Radial end fracture		Humeral proximal end fracture	
		Incidence per** 100,000	Subtotal (head)	Incidence per*** 100,000	Subtotal (head)	Incidence per **** 100,000	Subtotal (head)	Incidence per **** 100,000	Subtotal (head)
50	1,184	23.9	283	315	3,730	90	1,066	8	95
51	1,174	23.9	281	315	3,698	105	1,233	9	106
52	1,120	23.9	268	315	3,528	120	1,344	10	112
53	705	23.9	168	315	2,221	135	952	13	92
54	762	23.9	182	315	2,400	150	1,143	16	122
55	934	23.9	223	315	2,942	170	1,588	20	187
56	908	23.9	217	315	2,860	190	1,725	24	218
57	935	23.9	223	315	2,945	210	1,964	28	262
58	915	23.9	219	315	2,882	220	2,013	30	275
59	837	23.9	200	315	2,637	220	1,841	30	251
60	731	90.7	663	867	6,338	220	1,608	31	227
61	788	90.7	715	867	6,832	220	1,734	32	252
62	813	90.7	737	867	7,049	230	1,870	32	260
63	820	90.7	744	867	7,109	230	1,886	32	262
64	789	90.7	716	867	6,841	230	1,815	32	252
65	754	90.7	684	867	6,537	230	1,734	32	241
66	761	90.7	690	867	6,598	230	1,750	32	244
67	745	90.7	676	867	6,459	220	1,639	32	238
68	725	90.7	658	867	6,286	210	1,523	40	290
69	690	90.7	626	867	5,982	210	1,449	48	331
70	675	408	2,754	1,452	9,801	200	1,350	57	385
71	652	408	2,660	1,452	9,467	215	1,402	66	430
72	632	408	2,579	1,452	9,177	230	1,454	75	474
73	619	408	2,526	1,452	8,988	245	1,517	82	508
74	585	408	2,387	1,452	8,494	260	1,521	88	515
75	535	408	2,183	1,452	7,768	270	1,445	95	508
76	514	408	2,097	1,452	7,463	260	1,336	105	540
77	485	408	1,979	1,452	7,042	260	1,261	116	563
78	449	408	1,832	1,452	6,519	260	1,167	122	548
79	451	408	1,840	1,452	6,549	260	1,173	127	573
80	347	1478	5,129	1,647	5,715	260	902	132	458
81	346	1478	5,114	1,647	5,699	250	865	140	484
82	323	1478	4,774	1,647	5,320	240	775	148	478
83	308	1478	4,552	1,647	5,073	230	708	152	468
84	279	1478	4,124	1,647	4,595	220	614	156	435
85	261	1478	3,858	1,647	4,299	210	548	160	418
86	230	1478	3,399	1,647	3,788	210	483	160	368
87	205	1478	3,030	1,647	3,376	210	431	160	328
88	171	1478	2,527	1,647	2,816	210	359	160	274
89	146	1478	2,158	1,647	2,405	210	307	160	234
90 and over	481	2810	13,516	1,647	7,922	210	1,010	160	770
	25,784		83,905		228,150		52,502		14,073

\* : Estimated population by age groups in 1999<sup>15)</sup>

\*\* : Derived from incidences reported by Orimo et al.<sup>17)</sup>

\*\*\* : Derived from incidences in women in Hiroshima, born between 1900 and 1909, surveyed by Fujiwara et al.<sup>22)</sup>.  
Women over 90 years of age were assumed to be similar to those between 80 and 89 years of age.

\*\*\*\*: Estimated from graphic representation of incidences in Tottori Prefecture (1986-1988) by Ogino et al.<sup>24)</sup>

49 years of age in 1999, according to the statistics of the governmental bureau of statistics<sup>15)</sup>, the number of women aged 50 or older who develop this type of fracture during a year is estimated to be 70,700 (= 71,600 - 400 - 500). Femoral neck fractures can be subdivided into medial and lateral types. Since the lateral type is frequently associated with osteoporosis<sup>18)</sup>, only this type was examined in this study. Ogawa et al. also performed cost-of-illness analysis in such patients<sup>16)</sup>. It has been reported that lateral femoral neck fractures account for 59-66% of all femoral neck fractures<sup>18) -21)</sup>. If this percentage is regarded to be about 60%, it is estimated that the number of middle-aged or elderly women with femoral neck fractures associated with osteoporosis is 42,420 per year (Table 5).

No nationwide epidemiological survey has been reported concerning the incidence or prevalence of vertebral fractures. Fujiwara et al. calculated the incidence of fractures of the thoracic vertebrae on the basis of the long-term follow-up data of about 14,000 inhabitants of Hiroshima and Nagasaki<sup>22), 23)</sup>. Although available data are relatively old (data for 1958-1986) and do not contain data on lumbar vertebrae, their extrapolation to the entire country allows us to

estimate that the incidence of vertebral fractures among women aged 50 or older is about 228,200 per year (Tables 4 and 5).

No nationwide epidemiological survey has been conducted on the incidence of fracture of distal end of the radius or proximal end of the humerus, either. The major data available on the incidence of these types of fracture were collected by Ogino et al. in Tottori Prefecture for the period between 1986 and 1988<sup>24)</sup>. According to their report, the incidence of fracture of distal end of the radius among women aged between 60 and 79 was 270 to 330 per 100,000 population. If this figure is extrapolated to the entire country, the annual incidence of this type of fracture in women aged 50 or older is estimated at about 52,500 (Tables 4 and 5). The incidence of humeral proximal end fracture increased gradually as the age increased over 50, and its incidence in women rose linearly after age 70, reaching 160 per 100,000 population at ages over 85. If the data for Tottori Prefecture are extrapolated to the entire country, the incidence of humeral proximal end fracture in Japan is estimated at about 14,100 per year (Tables 4 and 5). When compared internationally, the incidence of fractures of distal end of the radius and proximal end of the humerus in Japan

Table 5 Estimated incidence of each type of fracture in women aged 50 or older in 1999\*

Fracture type	Incidence (women/year)
Femoral neck fracture	83,900
Lateral femoral neck fracture	50,300**
Spinal fracture	228,200
Radial end fracture	52,500
Humeral proximal end fracture	14,100

\* : See Table 4

\*\* : Estimated from total incidence of femoral neck fracture reported in references 18 through 21

was lower than that reported from Western countries<sup>24)</sup>.

ii) Cost of treatment of bone fractures

The treatment of fractures and osteoporosis involves direct and indirect costs as shown in **Table 6**. The direct costs of fracture treatment include the costs of surgical treatment and follow-up management. Treatment can vary depending on the type of fracture. Although the cost of treatment of femoral neck fracture varies greatly between femoral head prosthesis and osteosynthesis<sup>20) ,24)</sup>, Ida et al. reported that its treatment involving three months of hospitalization required 1.95 million yen on average<sup>25)</sup>. This figure was used in subsequent calculations. Concerning the cost of vertebral fracture treatment, Inoue reported that it costs 776,200 yen if the patient is hospitalized for 42.6 days<sup>21)</sup>. Although no exact cost of treating fracture of distal end of the radius or proximal end of the humerus has been reported,

Chrischilles et al. found that the cost of treating fractures of distal end of the radius is approximately equal to that of treating vertebral fractures<sup>26)</sup>. We therefore assumed in subsequent calculations that the cost of treating fracture of distal end of the radius or proximal end of the humerus is equal to that of treating vertebral fractures. The cost of follow-up of patients with fracture varies greatly depending on the type of fracture. In cases of femoral neck fracture, the follow-up cost will highly depend on whether the patient remains bedridden or can receive treatment at an outpatient clinic (**Table 6**). For the calculation of each cost, we used the methods described in “Modeling” of the “Subjects and Methods” section. Even in cases of fractures other than femoral neck fracture, the patient sometimes has to remain bedridden for some period of time, but many patients can receive treatment of their osteoporosis or pain at an outpatient clinic. For this reason, the follow-up

Table 6 Direct cost of treatment, care, etc. for fractures (per patient)

Category	Subcategory	Cost	Source
Cost of fracture treatment (yen/time)	Femoral neck fracture		
	Average	1,950,000	Reference 25
	Femoral head prosthesis	900,000-2,000,000	Reference 20
	Osteosynthesis	800,000-1,300,000	Reference 20
	Spinal fracture	776,200	Reference 20
	Radial end fracture	(776,200)	Reference 26
	Humeral proximal end fracture	(776,200)	(Assumption)
Cost of after-care (yen/month)	Bedridden patients		
	Social welfare home for the aged	325,000	Reference 25
	Care at patient's own home	195,000	Reference 25
	Short stay services	330,000	Reference 25
	Day services	156,000	Reference 25
	Lower back pain care (wet compress, vitamin D)	48,000	Reference 16

cost for fractures other than femoral neck fracture was deemed to be equal to that of femoral neck fracture (48,000 yen/month<sup>16)</sup>). Since the cost of receiving care during daily living after discharge (direct non-medical cost) is difficult to distinguish from the above-mentioned direct medical cost, it was excluded from the cost calculation in the present study.

Production loss was calculated as the main indirect cost according to the method reported by Ogawa et al.<sup>16)</sup>. Details of the method and results of calculation of production loss, which can be reduced by HRT, are shown in **Table 7**.

### iii) Health effects of HRT and their economic impact

No study on the effects of HRT on the risk of bone fracture has yet been published in Japan. We therefore referred to the data published in Western countries. The search results are shown in **Table 8**. For femoral neck fracture, 7 case-control studies<sup>27)-33)</sup>, 6 cohort studies<sup>34)-39)</sup> and 2 reviews of case control and cohort studies<sup>40), 41)</sup> were available. The percent decrease in the incidence of fracture following HRT varied greatly from report to report (range 0-80%). In more than half of all reports, the percent decrease was in the range of 40 to 60%, and their simple average was 44%. Using this average figure, it was assumed for the subsequent calculations that the incidence of femoral neck fracture would be decreased by 44% when HRT was administered to postmenopausal women with osteoporosis. The only paper found concerning vertebral fracture was a randomized controlled trial. This paper reported a 61% decrease in the incidence of vertebral fracture following HRT<sup>41)</sup>. Only cohort

studies were found on fractures of distal end of the radius and proximal end of the humerus, reporting an incidence of 54% and 34%, respectively<sup>39)</sup>. These two figures were adopted for calculations in this study, because they had been used for health economics studies carried out in Western countries<sup>26), 43)</sup>.

**Table 9** shows the estimated reduction in direct cost related to bone fracture, based on the figures in **Tables 6 and 8**. The hospitalization rate due to each type of fracture was estimated from the report by Chrischilles et al.<sup>26)</sup>. It was estimated at 100% for femoral neck fracture, 25% for vertebral fracture, 10% for fracture of distal end of the radius, and 10% for humeral proximal end fracture. The methods of the other calculations are shown in "Modeling" of the "Subjects and Methods" section. The reduced cost due to HRT in controlling bone fractures was estimated to be about 187.3 billion yen.

With regard to osteoporosis care, we focused on reduction in the cost of medication. At present, drug therapy for osteoporosis primarily uses bisphosphonates, activated vitamin D<sub>3</sub>, ipriflavone, vitamin K<sub>2</sub> and elcatonin in addition to HRT, and these drugs are used independently or in combination. Adequate calcium intake, exercise and lifestyle habits are also important in the control of osteoporosis. HRT and bisphosphonate are known to reduce the bone density decrease and fractures more powerfully than activated vitamin D<sub>3</sub>, ipriflavone and vitamin K<sub>2</sub><sup>14)</sup>. As shown in **Table 9**, Orimo et al. estimated the annual cost of these drugs to be between 31,000 and 91,000 yen<sup>48)</sup>. We assumed that HRT can make at least one of these drugs

Table 7 Estimated production loss by hospitalized women with fracture aged 50 or older (indirect cost that can be saved by HRT)

	A	B	No. of hospitalized patients				$A \times B \times [C \times 3 + (D+E+F) \times 1.4]$	G	H (=1,450x3x30)	$[C \times 3 + (D+E+F) \times 1.4] \times G \times H$
Age	Percentage of women with occupation (%)	Average monthly income (yen)	C Femoral neck fracture	D Spinal fracture	E Radial end	F Humeral proximal end fracture	Total income lost during hospital stay (yen)	Percentage of jobless housewives (%)	Cost of housework per month (yen/month)	Cost of housework during hospital stay (yen)
50-54	58.8% (1)	206,600 (4)	1,182	3,894	574	53	1,199,531,486	73% (6)	130,500	430,647,787
55-59	58.8% (2)	135,000 (2)	1,082	3,567	913	119	768,853,906	73% (6)	130,500	438,116,456
60-64	41.1% (2)	109,000 (2)	3,574	8,542	891	125	1,079,911,026	62% (3)	130,500	773,408,255
65-69	28.1% (2)	94,000 (2)	3,333	7,966	810	134	593,601,254	55% (3)	130,500	639,489,542
70-74	14.5% (3)	50,000 (5)	12,905	11,482	724	231	406,921,490	57% (3)	130,500	925,174,630
75-79	21.2% (3)	50,000 (5)	9,931	8,835	638	273	460,438,221	36% (3)	130,500	457,930,698
Total							4,509,257,382			3,664,767,368
Grand total										8,174,024,750 (8,174,020,000)

(1) Reproduced from reference 44 (data for 55-59 year age group) (2) From reference 44 (3) From reference 45  
(4) From reference 46 (5) Assumption (6) From reference 47

unnecessary, and calculated that HRT would allow about 60,000 yen to be saved on average. The cost cut due to such drugs no longer being necessary for osteoporosis care was estimated to be about 107.8 billion yen per year. Therefore, the total reduction in direct cost by HRT was estimated to be 295.1 billion yen.

Concerning indirect costs, only the production loss during hospital stay for the treatment of bone fracture was calculated in the present study. As shown in **Table 7**, this loss was estimated to be about 8.2 billion yen.

#### 4. Discussion

Forms of economic evaluation of HRT used to date include cost-benefit analysis, cost-effectiveness analysis, cost-of-illness analysis and cost-utility analysis, as shown in **Table 1**<sup>6),10)</sup>. Cost-effectiveness analysis of HRT from a nationwide perspective has been reported not

infrequently in Western countries, where HRT was compared with other drug therapies (bisphosphonate, vitamin D<sub>3</sub>, ipriflavone, vitamin K<sub>2</sub>, elcatonin, etc.) for the treatment of osteoporosis and fractures. In Japan, no detailed nationwide cost-effectiveness analysis has been reported, with only few studies with this form of analysis based on regions of Japan<sup>14)</sup>. On the other hand, cost-benefit analysis, either covering the entire nation or parts of the country, has not been published. The number of cost-of-illness studies on osteoporosis and fractures conducted in Japan is also very low. In our extensive literature search, the analysis reported by Ogawa et al. is the only detailed nationwide cost-of-illness analysis of osteoporosis<sup>16)</sup>. Several studies of this form but covering only parts of Japan have been reported, including those conducted by Inoue<sup>20)</sup>, Orimo<sup>49)</sup> and Ohta<sup>50)</sup>. The present study was not a cost-of-illness study with a focus on an illness, but calculated the cost of HRT itself and

Table 8 Decrease of fractures by HRT

Fracture type	Percent decrease	Reference	Type of study
Femoral neck fracture	80%	27	Case control study
	60%	28	Case control study
	30%	29	Case control study
	30%	30	Case control study
	60%	31	Case control study
	60%	32	Case control study
	40%	33	Case control study
	50%	34	Cohort study
	60%	35	Cohort study
	40%	36	Cohort study
	20%	37	Cohort study
	0%	38	Cohort study
	40%	39	Cohort study
(Simple mean)	44%		
Spinal fracture	61%	40	Randomized controlled trial
Radial end fracture	54%	37	Cohort study
Humeral proximal end fracture	34%	37	Cohort study

Table 9 Direct cost of treatment of fractures and osteoporosis that can be saved by HRT

Category of cost		Total no. of patients	Hospitalization rate** (%)	No. of hospitalized patients	No. of outpatients (head)	Cost (yen)	Percent decrease	No. of cases with reduced cost	Subtotal (yen)
Cost of fracture treatment (yen/time)	Lateral femoral neck fracture	50,300	100%	50,300		1,500,000	44%	22,132	33,198,000,000
	Vertebral fracture	228,200	25%	57,050		776,200	61%	34,801	27,012,148,100
			75%		171,150	61%	104,402	15,660,225,000	
	Radial end fracture	52,500	10%	5,250		776,200	54%	2,835	2,200,527,000
			90%		47,250	54%	25,515	3,827,250,000	
	Humeral proximal end fracture	14,100	10%	1,410		776,200	34%	479	372,110,280
90%			12,690		34%	4,315	647,190,000		
Cost of after-care (yen/month)	Bedridden patients (fracture of lateral femoral neck) *	12,590							
	Social welfare home for the aged	1,813				325,000	44%	798	1,555,554,000
	Care at patient's own home	10,777				195,000	44%	4,742	5,547,999,600
Care for osteoporosis and pain	Lateral femoral neck fracture	50,300				48,000	44%	22,132	9,561,024,000
	Vertebral fracture	228,200				48,000	61%	139,202	70,825,977,600
	Radial end fracture	52,500				48,000	54%	28,350	14,424,480,000
	Humeral proximal end fracture	14,100				48,000	34%	4,794	2,439,187,200
(Total cost of fracture treatment)									187,271,672,780
Cost of anti-osteoporosis drugs saved by HRT (yen/year) ***		1,800,000			1,800,000	59,900	-	-	107,820,000,000
Grand total									295,091,672,780 (295,091,670,000)

\* : Numbers of cases estimated from report of Ogawa et al.<sup>16)</sup>

\*\* : Estimated from report of Chrischilles et al.<sup>26)</sup>. Since no data were available on the incidence of humeral proximal end fracture, its incidence was assumed to be equal to that of radial end fracture.

\*\*\* : Based on the assumption that one out of bisphosphonates, vitamin D3, ipriflavone, vitamin K2 and elcatonin becomes unnecessary following the start of HRT, the annual costs of these drugs (Orimo et al.<sup>48)</sup> were averaged. The number of patients receiving drug therapy was estimated from the reports of Orimo et al.<sup>48)</sup> and Ogawa et al.<sup>16)</sup>.

estimated the economic impact of nationwide introduction of HRT.

The annual medication cost of HRT for the nation was estimated to be about 140 billion yen when administered to postmenopausal women with osteoporosis (**Table 2**). The cost of female hormone preparations for HRT was estimated as only 16,608 yen per year (15% of the total cost). On the other hand, the cost of checking for potential problems with HRT, such as uterine body cancer, breast cancer and impaired coagulation, was estimated to be as high as 16,800 yen. Thus, the total drug cost and the cost of checking for adverse reactions was 33,408 yen for HRT, which is much lower than, or at least comparable to, the cost of only medications for other osteoporosis treatment (**Table 10**). Because we adopted strict guidelines for follow-up, its cost could potentially be reduced substantially based upon future evidence regarding efficient methods to monitor side effects. In addition, HRT is more beneficial than other osteoporosis drugs in the control of cardiovascular disease, urogenital disease and climacteric complaints.

It is necessary to perform an updated nationwide epidemiological survey concerning

various types of fracture in our country. Only surveys in a local area or on particular types of fracture have been conducted. As mentioned above, no nationwide epidemiological survey has been reported concerning the incidence or prevalence of vertebral fracture, or the incidence of fracture of distal end of the radius or proximal end of the humerus. In view of the recent trend of Westernization of the diet in Japan and the possibility that the frequency of fracture may vary from district to district, it is desirable that a new nationwide survey is conducted using internationally accepted criteria diagnostic. Regarding the prevalence of vertebral fracture, Fujiwara et al. compared the prevalence in inhabitants of Hiroshima with that of foreign cities<sup>51)</sup>. Their comparison revealed that the prevalence of vertebral fracture was higher for Japanese than for Western people, but that it has been decreasing in recent years in Japan.

Due to the health effects of HRT in preventing bone fractures, the total cost reduction was estimated to be 303.3 billion yen, consisting of a direct cost reduction of about 295.1 billion yen (**Table 8**) and an indirect cost reduction of about 8.2 billion yen (**Table 7**), putting aside the cost of HRT itself. Ogawa et al. estimated in their cost-

Table 10 Annual cost of major drugs used to treat osteoporosis (estimated as of April 1998) (reproduced from Table 25 of reference 48 with modification)

Drug	Annual cost (yen/year)
Ethidronate (200 mg/day for 2 weeks)	31,158
Alpha-calcidol (1 $\mu$ g/day)	48,180
Ipriflavone (600 mg/day)	62,634
Vitamin K <sub>2</sub> (45 mg/day)	66,357
Elcatonin (20 units/ampoule/week)	91,194
(Average)	59,905



of-illness analysis that the medical cost needed for osteoporosis and fractures is 1.4974 trillion yen per year. We can therefore say that HRT can reduce the medical cost by about 20%. If these data are combined with the fact that HRT can powerfully suppress bone density decrease and fractures, HRT is expected to produce benefits not smaller than those of other drugs used for osteoporosis. In view of these features and the fact that the cost of treating osteoporosis and fractures accounts for about 6% of total medical costs in Japan<sup>16)</sup>, HRT is expected to be extremely useful.

We were obliged to use some assumed values because of the lack of data on many aspects, due to the current limited body of knowledge on HRT and related health conditions. To deal with the uncertainty of the cost of HRT, we used several scenarios. In the future, not only sensitive analyses from other perspectives, but also discounting future costs and benefits would be necessary<sup>43)</sup>. Clinical epidemiological data are quite insufficient in Japan, and it is desirable that such data, which can serve as a basis for more accurate and deeper health economics studies of HRT, will accumulate in the future.

This study was designed to explore the indications for HRT from the viewpoint of health economics. The analysis estimated the cost of the therapy itself and also the reduction in cost due to the beneficial health effects in preventing osteoporosis, and suggested that HRT for postmenopausal women is comparable to or superior to other drug therapies for osteoporosis. Considering also the clinical benefits of HRT in controlling conditions other than osteoporosis and fractures, HRT seems to be a promising therapy.

However, the use of HRT has not yet spread widely in Japan. It is urgently needed to analyze the factors hampering the spread of HRT, evaluate the usefulness of this therapy and improve its shortcomings, if any. The Japanese society is already extremely aged, and moreover, is aging rapidly. Further studies on this therapy will be indispensable not only from health and clinical viewpoints, but also from economics and social points of view.

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