netic protein-2 (rhBMP-2) to accelerate bone healing.[4–7] Most of these studies have showed successful results by using β-TCP itself as a BMP carrier.

Meanwhile, considerable efforts have been focused on finding ways to reduce the minimum dose of rhBMP-2 that is essential for adequate bone regeneration. One of the difficulties when using rhBMP-2 clinically is the significant amount of this protein required for complete bone healing in humans. Therefore, the development of a carrier system that controls the release of rhBMP-2 is very important to reduce the dosage of rhBMP-2. We have already developed a biodegradable delivery system for rhBMP-2 that has been shown to enhance bone formation.[8–12]

In this study, we attempted to make a new biodegradable bone-inducing material by adding osteoinductive capacity of rhBMP-2 to porous β-TCP granules using a newly developed delivery system for rhBMP-2. Our goal was to test whether this approach could enhance bone formation using lower doses of rhBMP-2. The efficacy of this new bone graft substitute was examined in terms of its bone-inducing capacity and degradability in an experimental mouse model as a first step to further study in the clinic.

MATERIALS AND METHODS

Materials

As a rhBMP-2 delivery system, a block copolymer composed of poly-D,L-lactic acid with random insertion of *p*-dioxanone and polyethylene glycol (PLA-DX-PEG) was synthesized and provided by Taki Chemical (Kakogawa, Japan). The details of physicochemical properties of this polymer have been reported previously elsewhere.[10] RhBMP-2 was produced at Genetics Institute (Cambridge, MA) and donated to us through Yamanouchi Pharmaceutical Company (Ibaraki, Japan). Porous β-TCP (OSferion®, coarse granule, approximately 3 mm in particle diameter and 5 mg in weigh, from 100 to 400 μm in pore size, porosity of 75%, 1050° sintering temperature) was manufactured by Olympus (Tokyo, Japan) and donated to us for the purpose of these studies.[3,13]

Preparation of porous β-TCP granules combined with BMP delivery system

To prepare implants, 600 mg of β-TCP together with 200 mg of PLA-DX-PEG and various amounts of rhBMP-2 (0, 1.25, 5, 20, or 100 μg in 200 μL of 0.01 N HCl) were mixed in 3 mL of distilled acetone in glass vials. The resultant mixtures were then placed in a vacuum for a few seconds to replace air in the pores of the β-TCP with solvent. Acetone was then removed from the β-TCP granules by evaporation with a centrifuge evaporator. The glass vials were shaken several times during evaporation so that rhBMP-2 delivery material thoroughly impregnated the β-TCP granules. The resultant dried β-TCP granules coated with rhBMP-2 delivery system were stocked in a freezer at −30°C until use. A total of eight experimental groups including controls were prepared (Table I). The surface of porous β-TCP granule was observed by scanning electron microscopy (SEM; Hitachi 4700SI) to examine a structural characteristic of the PLA-DX-PEG coating.

TABLE I
Contents of rhBMP-2/PLA-DX-PEG in 600 mg of β-TCP and Bone Formation at 3 and 6 Weeks

	rhBMP-2 (μg)	PLA-DX-PEG (mg)	Concentration of rhBMP-2 (wt %)	Bone Formation	
				3 Weeks	6 Weeks
1	100	200	0.0125	+	++
2	20	200	0.0025	−	+
3	5	200	0.000625	−	−
4	1.25	200	0.000156	−	−
5	0	200	0	−	−
6	100	0	0.0167	+	+
7	20	0	0.0033	−	+
8	0	0	0	−	−

Materials from each group were divided into 20 implants (five to six coarse granules), respectively, and implanted into the back muscle pouch. Bone formation was rated in three grades by the pattern of newly formed bone induced around the implant. (++; uniformly covered by new bone +; partially covered by new bone −; no bone formation, assessed in soft X-ray radiographs)

Experimental protocol

One hundred sixty male ddY mice at 5 weeks of age, weighing 25–30 g, were used (20 per group) for this experiment in strict accordance with the institutional guidelines for the care and use of laboratory animals. The implants were aseptically placed into the left dorsal muscle pouch of mouse under anesthesia with diethyl ether. Approximately 30 mg of β-TCP granules including PLA-DX-PEG and rhBMP-2 (5–6 granules per animal) were implanted. Five animals from each group were sacrificed at 1, 2, 3, and 6 weeks after surgery, and the implants were harvested together with surrounding soft tissues. Harvested specimens were fixed in 10% neutral-buffered formalin solution and processed for radiological and histological examinations.

Radiographic and histological examination

The samples were radiographed with a soft X-ray apparatus (SOFRON®, Tokyo, Japan). For histological examination, samples were decalcified in 10% formic acid, dehydrated in a gradient ethanol series, mounted in paraffin, sectioned in 4 μm thickness and stained with hematoxylin-eosin. To detect osteoclasts, tartrate resistant acid phosphatase (TRAP) was stained by use of a histochemical method.

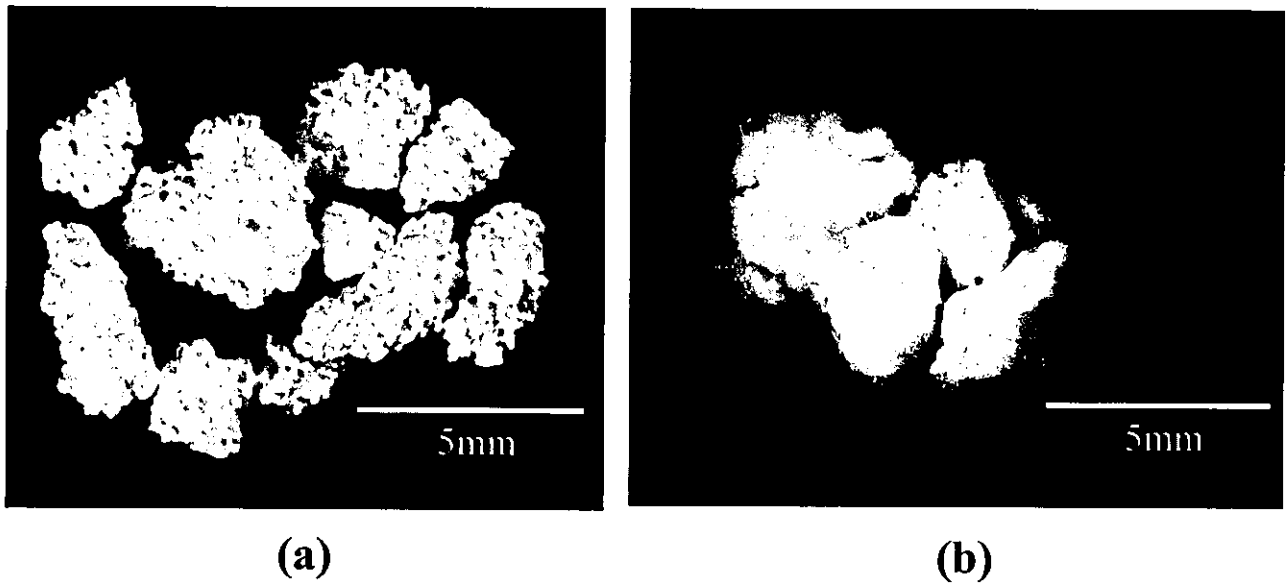

Figure 1. Macroscopic aspect of β-TCP coarse granules: (a) before coating, (b) after coating with PLA-DX-PEG. β-TCP granules exhibit adhesive-like properties at room temperature when coated with the polymer.

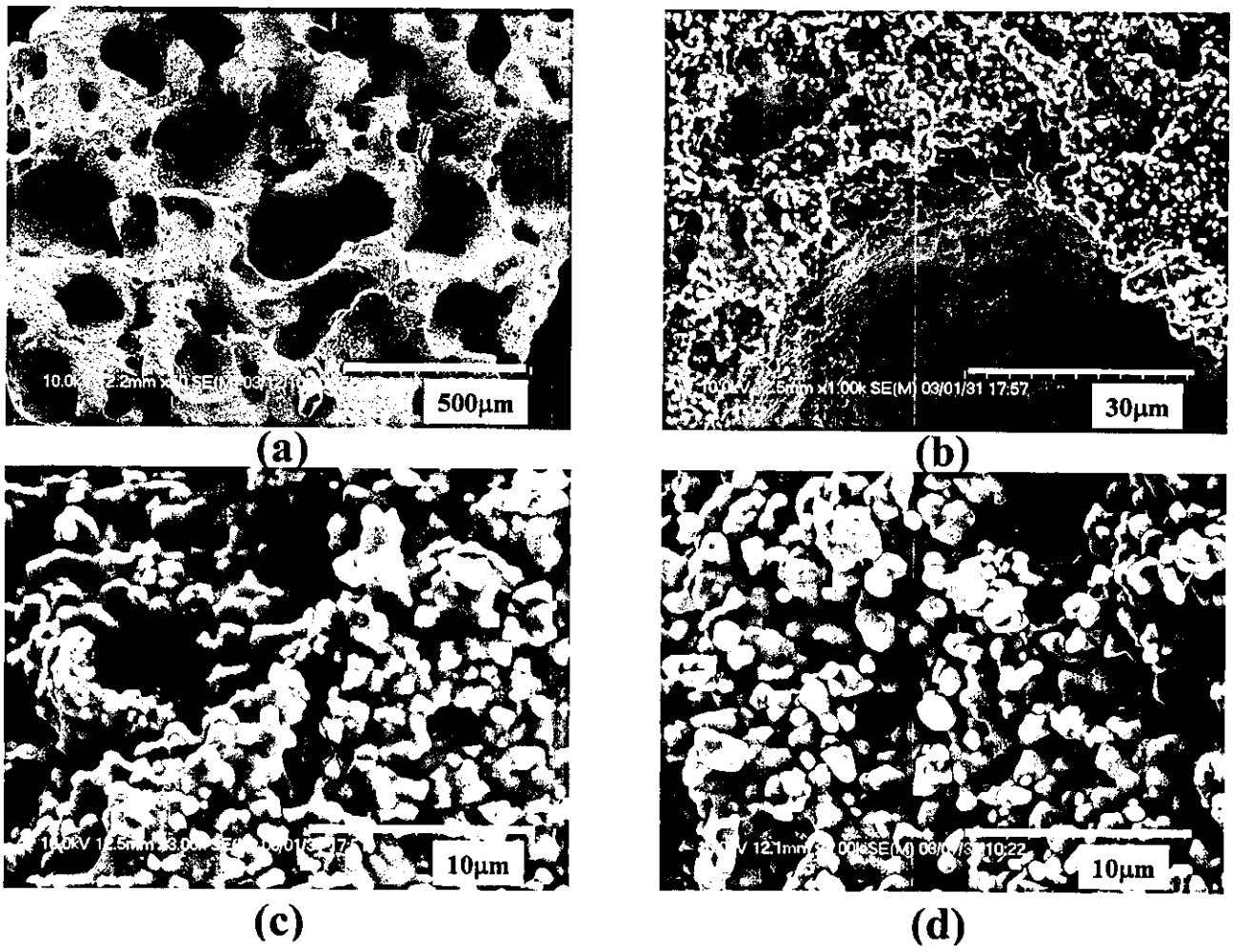

Figure 2. SEM micrographs of β-TCP granules coated with PLA-DX-PEG: (a) original magnification ×100, (b) original magnification ×1000, (c) original magnification ×3000 and noncoated β-TCP as a control; (d) ×3000. OSferion® is composed of 1 μm sintered β-TCP granules with 100~400 μm interconnected pores. The surface of β-TCP granules in the experimental group is uniformly covered by a thin polymer layer.

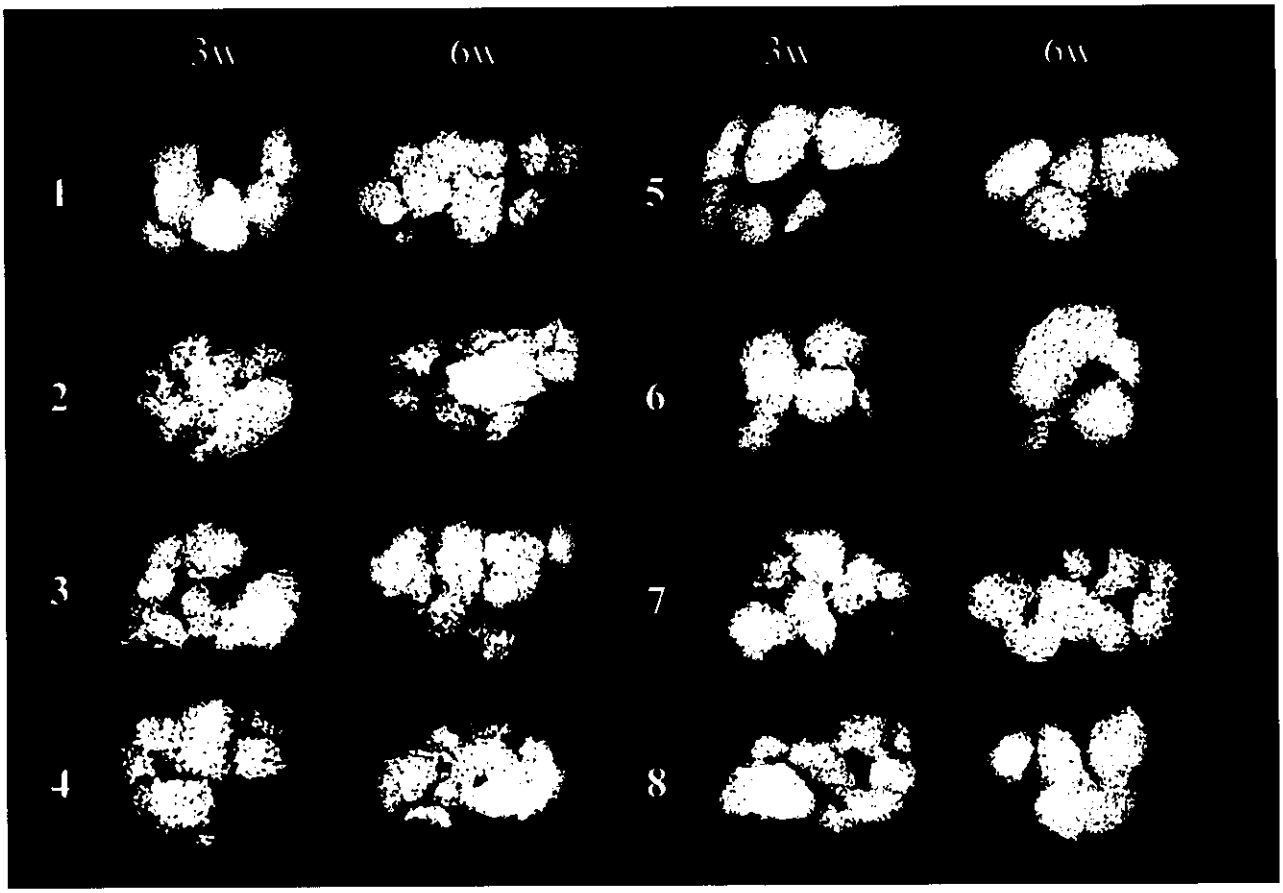

Figure 3. Typical soft X-ray photographs at 3 and 6 weeks after implantation are shown. The number on left side of each photograph indicates the number listed in Table I. Note that the new bone encasing the β-TCP granules is significant in group 1, 2, 6, and 7 compared to other experimental groups. The diminished density of β-TCP is recognized in the encased bone at 6 weeks in group 1.

Briefly, the deparaffinized sections were placed in the TRAP-staining solution consisting of acetate buffer (pH 5.0) 50 m*M* sodium tartrate, 25 mg/mL Naphthol-AS MX phosphate (Sigma Chemical Co., St. Louis, MO) and 0.5 mg/mL fast red violet salt (Sigma Chemical Co.). The specimens were incubated with the solution at 37°C for 120 min. After the solution was removed by washing, the specimens were counterstained with hematoxylin and observed under a light microscopy.

RESULTS

Surface structure of β-TCP granules

The porous granules of β-TCP are white in color and are easily crumbled by hand pressure. When combined with the polymer, the surface of the β-TCP granules became sticky to the touch at room temperature (Fig. 1). Scanning electron microscopy of the β-TCP granules revealed pores of 100–400 μm in diameter and the wall of the pores were comprised of tiny granules of approximately 1 μm in diameter. Electron micrographs (×3000) showed the uniform covering of each tiny β-TCP granule with the polymer (Fig. 2).

Ectopic bone formation on and in the implants

Soft X-ray examination

On soft X-ray radiographs, a shell-like radiopaque image encasing the β-TCP granules (indicating new bone formation) was noted in experimental groups 1 and 6 at 3 weeks after implantation. The same shell-like bone formation was recognized in groups 1, 2, 6, and 7 at 6 weeks after implantation. No bone formation on the X-ray radiographs was confirmed in other experimental groups at either 3 or 6 weeks after implantation. In the experimental group 1, the β-TCP granules had a more porous appearance and overall reduced density when compared with the original granules. At 6 weeks after implantation, the margins of the β-TCP granules became unclear as they were

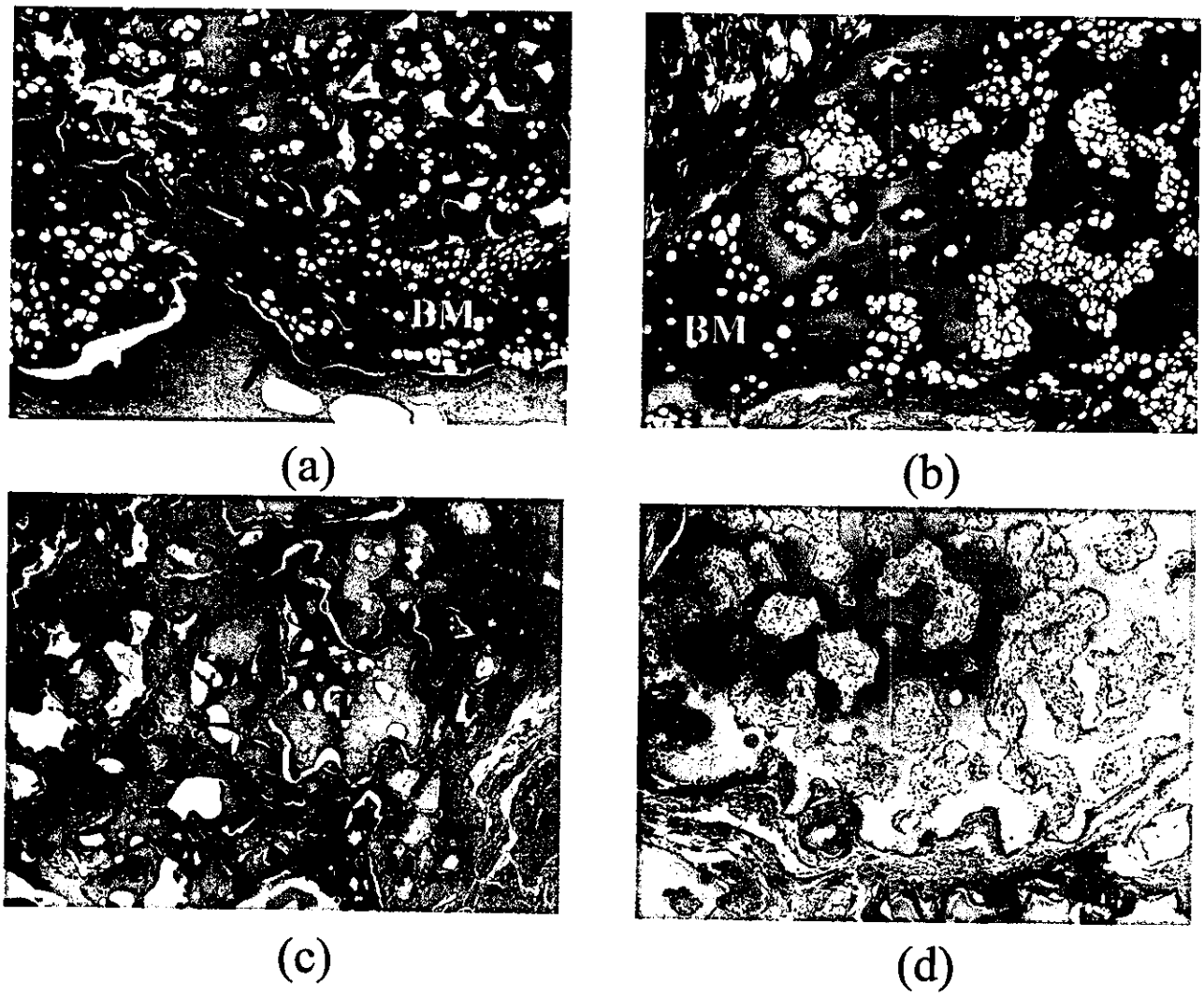

Figure 4. Typical histological sections at 6 weeks are shown: (a) group 1. (b) group 6, (c) group 5, and (d) group 8 (T, β-TCP; BM, bone marrow-like tissue; arrows, newly formed bone; Hematoxylin-eosin, decalcified sections; original magnification ×40).

progressively resorbed. The controls and composite implants from other groups did not show this appearance at the same interval after implantation (Table I and Fig. 3).

Histological examination

Histological examination of the composite implants revealed that both the outer and inner surface of the β-TCP was covered predominantly with new bone in the experimental groups 1, 2, 6, and 7 at 6 weeks. Hematopoietic and fatty marrows, like tissues, were also seen in the pore spaces. A significant difference in the amount of ectopically induced bone mass was noted between experimental groups 1 and 6. The implants used in these groups contained the same dose (5 μg per implant) of rhBMP-2 but used different amounts of carrier polymer (10 mg and 0 mg per implant, respectively). Harvested implants from group 1 were encased within the induced bone. However, in experimental group 6, a small amount of new bone mass unevenly covered the peripheral surface of the β-TCP granules. The implants lacking either rh-BMP-2 (group 5) or PLA-DX-PEG (group 8) failed to induce ectopic bone, and granulation tissues filled the β-TCP granules at 6 weeks (Fig. 4).

A typical pattern of ectopic bone formation induced by the material over time is shown. A large number of hypertrophic chondrocytes and mesenchymal cells were located between the β-TCP granules at 1 week. Trabecular bone encasing β-TCP granules and a few residual hypertrophic chondrocytes were seen at 2 weeks. The encasing bone had thickened and fatty marrow-like tissue occupied the space between the β-TCP granules at 3 weeks. At 6 weeks, prominent trabecular bone, and marrow-like tissue enveloped the

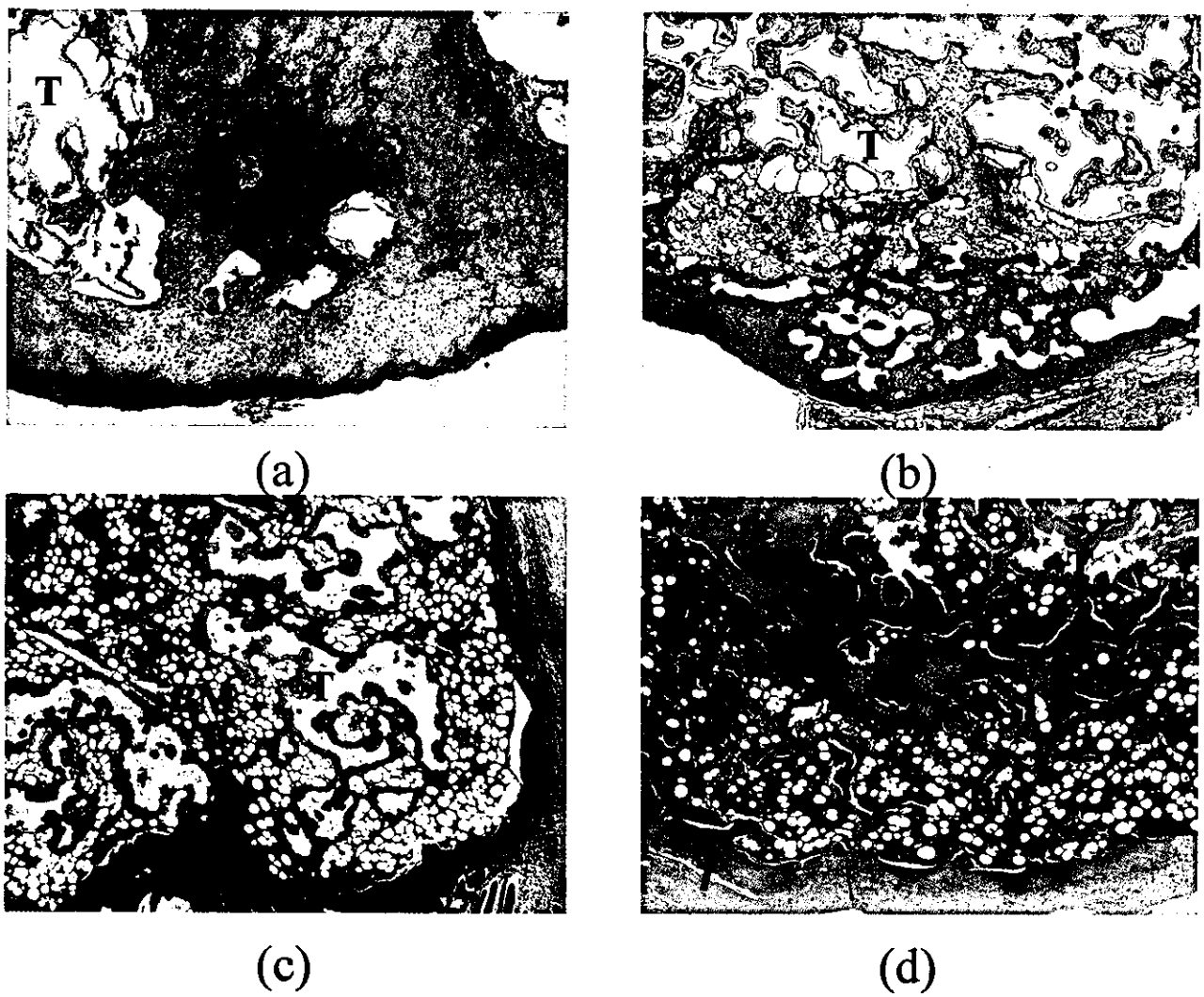

Figure 5. Time-dependent bone formation in group 1: (a) 1 week, (b) 2 weeks, (c) 3 weeks, and (d) 6 weeks after implantation (C, cartilage; T, β-TCP; BM, bone marrow-like tissue; arrows, newly formed bone; Hematoxylin-eosin, decalcified sections; original magnification ×40).

remnants of the β-TCP granules (Fig. 5). Dose-dependent ectopic bone formation was shown (Fig. 6). TRAP staining revealed that most of the surface of the BMP2/polymer-coated β-TCP granules was surrounded by numerous multinucleated TRAP positive osteoclasts. Few osteoclasts were seen on the surface of β-TCP in the group without polymer or rhBMP-2 for the duration of the experiment (Fig. 7).

DISCUSSION

To construct an artificial implant with bone-inducing capacity similar to that obtained with autogenous bone graft materials, porous β-TCP coarse granules were combined with a degradable polymer and rhBMP-2. The data from the present study indicates that this composite material retains bone-inductive and biodegradable properties. Because β-TCP itself is known to be osteoconductive, we examined the bone-inducing potential of the composite in tissues other than bone.[3,13] β-TCP granules with pore sizes of 100–400 μm in diameter were chosen in the present study to provide a sufficient local concentration of BMP2 via the polymer carrier material. The polymer carrier was critical for the induction of new bone in and on the β-TCP granules. In this study, we compared the ectopically induced bone among each implant at 3 and 6 weeks after implantation because the obvious bone formation was not detected by radiographs until 3 weeks. In control implants bearing rhBMP-2 in the absence of the carrier polymer, only a small amount of new bone was observed within the pores of the porous β-TCP. In a previous study, we had demonstrated that the carrier polymer enhanced new bone formation through its slow degradation and continuous release

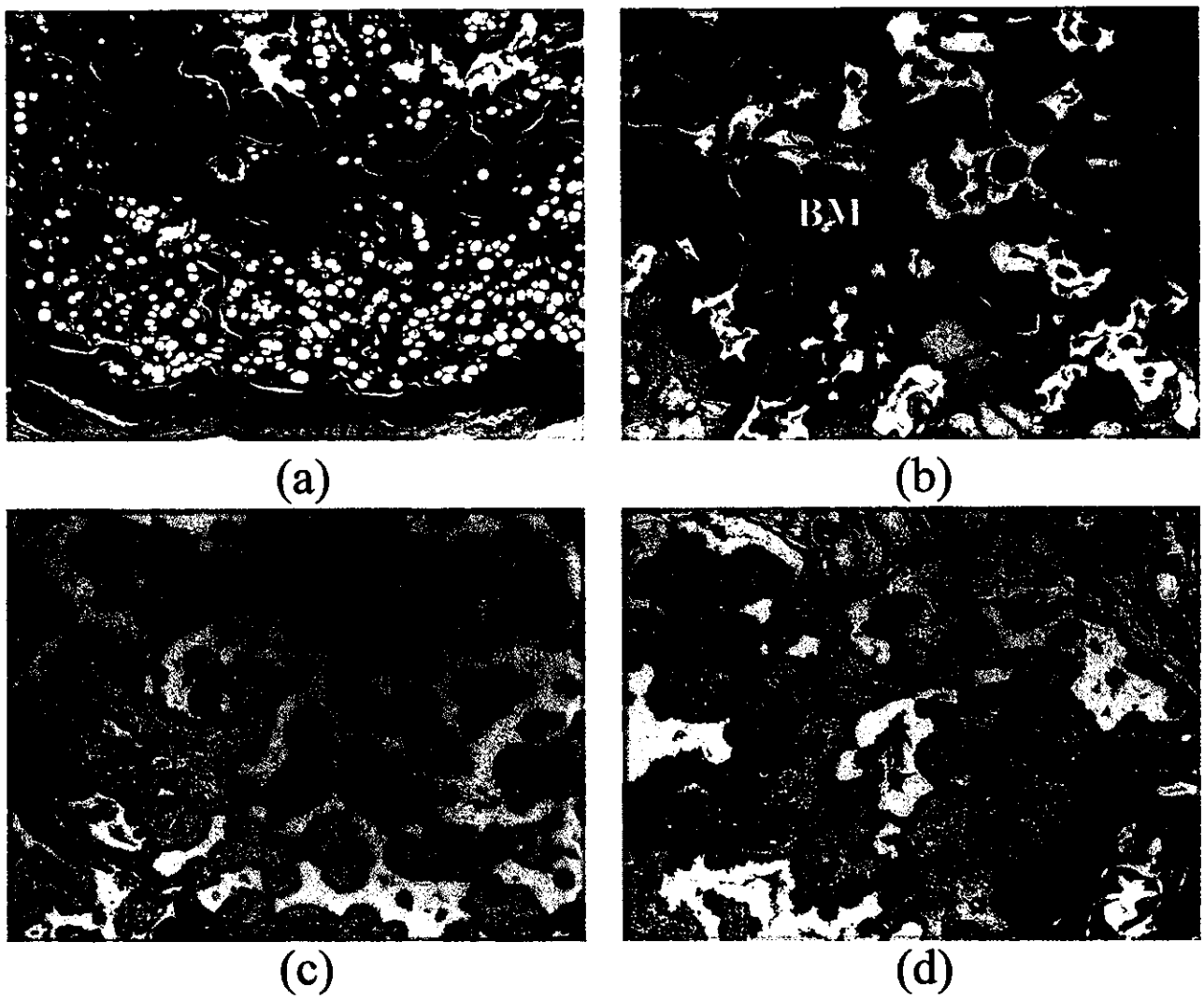

Figure 6. Dose-dependent bone formation at 6 weeks after implantation: (a) group 1 (b) group 6, (c) group 5, and (d) group 8 (T, β-TCP; BM, bone marrow-like tissue; arrows, newly formed bone; Hematoxylin-eosin, decalcified sections; original magnification ×40).

of rhBMP-2 *in vivo*. The dose of rhBMP-2 in β-TCP appeared to be the determinant of the bone mass in the present study.

The dose of rhBMP-2 required to elicit ectopic bone formation has been the focus of considerable experimental attention. It is known that the minimum dose of the rhBMP-2 required for bone formation is different depending on the animal species. The minimum dose required in primates or humans is approximately 1mg per 1 cm^3 carrier material (collagen sponge). This requirement makes this approach a very expensive clinical option. We have, therefore, pursued methods that would reduce the dose of rhBMP-2 required to repair injured bone in clinical practice. Another important consideration is the delivery system for rhBMP-2. Currently, collagen sponge, which has no mechanical strength, is used as the standard carrier material for the clinical use of rhBMP-2.[14–16] We postulated that one possible way to overcome these issues might be to coat the surface of biomaterials such as ceramics or metals with a thin layer of the rhBMP-2/polymer delivery material. The coating might enable a reduction in the efficacious dose ofrhBMP-2 required for bone induction. Additionally, the combination of the rhBMP-2 delivery system with the biomaterial would provide the implant with mechanical strength.[17]

In the present study, β-TCP granules with a porous structure and absorbable potential were used with expectation that they would enable bone formation by BMP and replacement by normal bone. This absorbable nature of β-TCP has been reported both in experimental animal models and in clinical cases.[3,13] In the murine model used in the present study, the β-TCP granules, as expected, appeared to be resorbed in the induced bone. Their reduced density and marginal line image became equivocal on radiography over the experimental period. The changes of the β-TCP im-

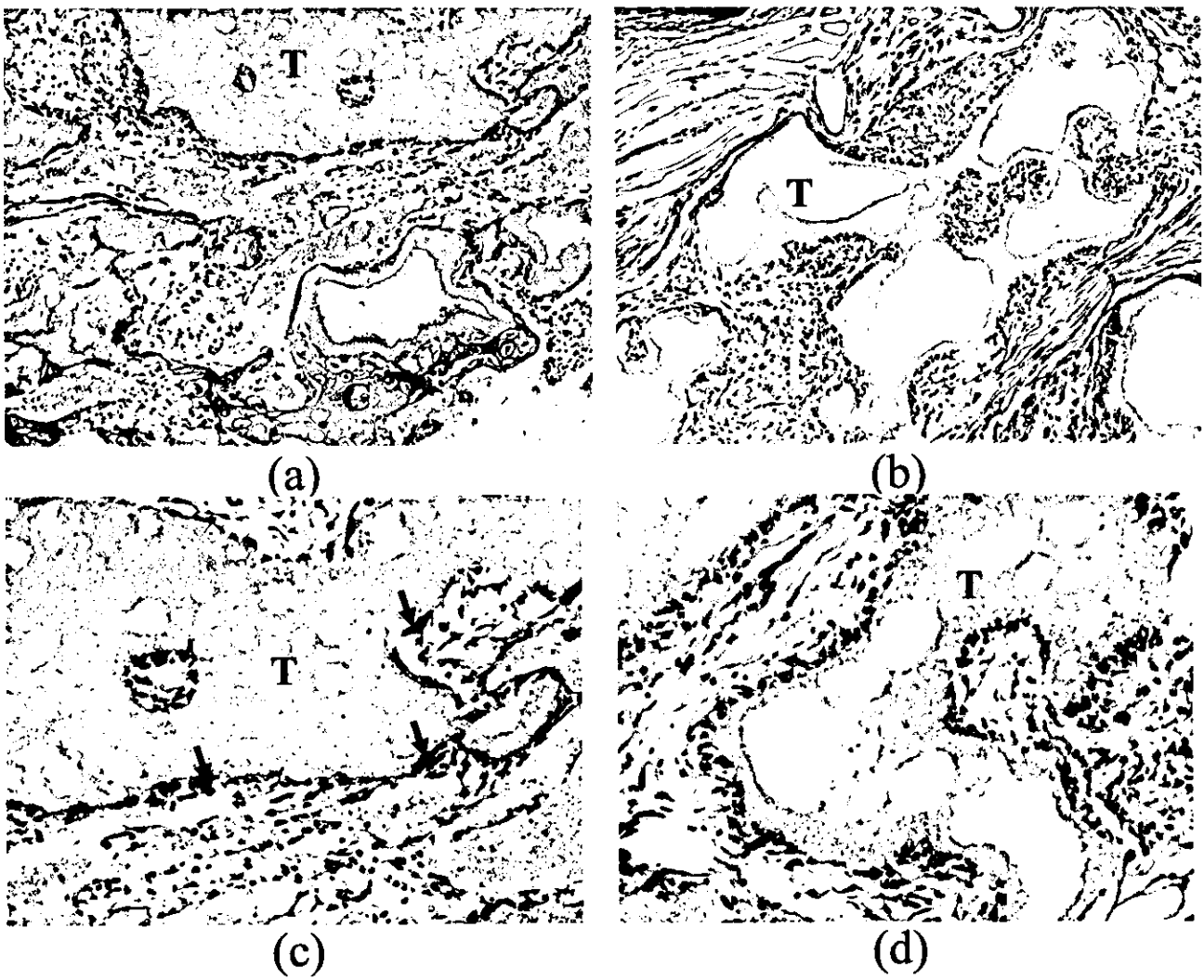

Figure 7. Tartrate resistant acid phosphatase (TRAP) stained histological sections of decalcified specimens harvested at 2 weeks: (a) original magnification ×40 and (c) original magnification ×200 from group 1, (b) original magnification ×40 and (d) original magnification ×200 from group 8. A wide range of β-TCP granules coated with PLA-DX-PEG and rhBMP-2 are surrounded by TRAP positive multinucleated osteoclasts (arrows, stained red). (T, β-TCP; OC, osteoclast; C, cartilage).

ages were seen consistently in samples with new bone and may have occurred through resorption of the β-TCP by osteoclasts within the bone. The reduction of β-TCP mass indicates enhanced degradation of β-TCP within bone because the densities of the β-TCP granules were not reduced in control samples in the absence of new bone formation over the experimental period. The time for complete disappearance of β-TCP granules in the ectopically induced bone was not determined due to the short length of the observation period.

In conclusion, an implant with properties similar to autogenous bone-graft material was constructed by combining porous β-TCP granules with a hydrogel polymer and rhBMP-2. The efficacy of the composite implants was determined by the degree of ectopic bone formation and mass reduction of β-TCP over a 6-week period. The composite implants retaining an adequate amount of the BMP delivery system consistently induced new bone on and in the porous β-TCP with a reduction in mass of β-TCP at 3 weeks after implantation. These findings suggest that it may be possible to develop a bone graft substitute through the combination of specific osteoinductive materials. This type of bone graft would obviate the need for autogenous bone and thereby eliminate the functional and cosmetic morbidities associated with surgical procurement of the bone grafts. However, further studies in large mammals or primates to check for safety and efficacy will be necessary before this material can be used in the clinic.

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A meta-analysis of previous fracture and subsequent fracture risk

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Abstract

Previous fracture is a well-documented risk factor for future fracture. The aim of this study was to quantify this risk on an international basis and to explore the relationship of this risk with age, sex, and bone mineral density (BMD). We studied 15259 men and 44902 women from 11 cohorts comprising EVOS/EPOS, OFELY, CaMos, Rochester, Sheffield, Rotterdam, Kuopio, DOES, Hiroshima, and two cohorts from Gothenburg. Cohorts were followed for a total of 250000 person-years. The effect of a prior history of fracture on the risk of any fracture, any osteoporotic fracture, and hip fracture alone was examined using a Poisson model for each sex from each cohort. Covariates examined were age, sex, and BMD. The results of the different studies were merged by using the weighted β-coefficients.

A previous fracture history was associated with a significantly increased risk of any fracture compared with individuals without a prior fracture (RR = 1.86; 95% CI = 1.75–1.98). The risk ratio was similar for the outcome of osteoporotic fracture or for hip fracture. There was no significant difference in risk ratio between men and women. Risk ratio (RR) was marginally downward adjusted when account was taken of BMD. Low BMD explained a minority of the risk for any fracture (8%) and for hip fracture (22%). The risk ratio was stable with age except in the case of hip fracture outcome where the risk ratio decreased significantly with age.

We conclude that previous history of fracture confers an increased risk of fracture of substantial importance beyond that explained by measurement of BMD. Its validation on an international basis permits the use of this risk factor in case finding strategies.

Keywords: Prior fracture; Meta-analysis; Hip fracture; Osteoporotic fracture

Introduction

It is well established from many cohort, case-control, and cross-sectional studies that a prior osteoporotic fracture increases the risk of future fractures [1–8]. A prior forearm fracture is associated with about a twofold increase in the subsequent risk of fracture [9–13]. More recently, significant increases in risk have been described for prior fractures at other sites characteristic of osteoporosis [6,7,14–21]. The risk of another vertebral fracture is particularly high after a spine fracture [7,22–24]. Similar observations are found in the setting of randomized clinical trials. In the placebo arm, the risk of vertebral deformities is approximately fivefold

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higher in patients with a prior vertebral deformity than in those without [4,25,26]. The interrelationships between the site of prior fracture and site of subsequent fracture have been summarized by meta-analysis [27] and a large case-control study, published more recently found broadly similar relationships [8].

Increased fracture risk may be in part due to the fact that patients with fracture have low bone mineral density (BMD). Studies that have adjusted for BMD suggest that the relative risk is only modestly downward adjusted [3,20,24,28–31].

The consistent association between a prior fracture and subsequent fracture risk has led to the inclusion of prior fracture as a risk factor to be used in assessment guidelines [32–35]. For example, in Europe, it is recommended that patients be identified on the basis of risk factors for subsequent assessment by BMD [33–35]. Patients are then considered for intervention on the finding of osteoporosis (i.e., a T score of ≤ -2.5 SD). This approach is conservative since it does not recognize the independent contribution of the risk factor from BMD. This has been recognized in some guidelines where the intervention threshold is less conservative in the presence of a risk factor such as a prior fragility fracture [32,36]. The consideration of several independent risk factors permits the more accurate categorization of risk [37], and attention has focussed recently on the assessment of fracture risk using multiple risk factors, rather than the use of BMD alone, to define intervention thresholds [38,39]. This demands knowledge of the interrelationships between these risk factors.

The aim of the present study was to quantify the risk associated with a history of prior fracture for future fracture in an international setting and to explore the dependence of this risk with age, sex, and BMD.

Methods

We studied 60 161 men and women of whom 26% had a prior fracture history taken from 11 prospectively studied cohorts. Brief details of the cohorts studied are given below and summarized in Table 1.

OFELY

The OFELY cohort comprises an age-stratified cohort of 1039 women aged 31–89 years randomly selected from the regional section of a large health insurance company (Mutuelle Generale d'Education Nationale, Lyon) [40]. Eighteen percent of women contacted participated in the study. Baseline characteristics were obtained using a standardized questionnaire, including the documentation of prior wrist, humeral, vertebral, and hip fracture that occurred after the age of 45 years. Only low trauma fractures (falls from a standing height or less) were recorded. BMD was measured at the lumbar spine, at the proximal femur, distal radius, and whole body by DXA using a Hologic QDR 2000. Women were reviewed annually and fractures registered. Peripheral fractures were confirmed by radiography. Vertebral fractures were identified from sequential X-rays of the thoracic and lumbar spine by morphometry in 80% of patients, but only clinical fractures were used for this analysis.

EVOS

The European Vertebral Osteoporosis Study (EVOS) comprised age- and sex-stratified random samples from 36 centers in 19 European countries [41–43]. Equal numbers of men and women were drawn in each center within six 5-year age bands (50–54 to 75–79 years). A baseline radiograph for vertebral fracture prevalence was undertaken in 15 570 men and women (response rate, 29%). BMD was measured in 3461 men and women from 13 centers by DXA at the femoral neck using pencil beam machines that were cross-calibrated using the European spine phantom. The sample provided the framework for the European Prospective Osteoporosis study (EPOS) where repeated assessment was undertaken in 29 of the centers. Information on clinical fractures were used for this report.

Table 1
Details of cohorts studied including individuals with information on follow-up time, prior fracture, and subsequent fracture

Cohort	Sample size	Person-years	Mean age (years)	Age range (years)	% Female	Fracture history (%)	Any fracture	Osteoporotic fracture	Hip fracture
EPOS	13366	40160	63.8	41–91	52	36	715	715	44
OFELY	426	2124	64.2	50–89	100	16	53	–	–
CaMos	9400	26653	62.1	25–103	69	44	586	316	42
Rochester	1001	6228	56.8	21–94	65	18	289	244	42
Sheffield	2147	6826	80.0	74–96	100	51	284	236	62
Rotterdam	7774	43606	70.3	55–106	61	14	992	768	284
Kuopio	11798	56602	52.3	47–57	100	17	1053	–	–
Gothenburg I	2375	16439	78.8	69–86	61	9	431	431	336
Gothenburg II	7098	29750	58.9	21–89	100	18	441	312	29
Dubbo	2163	16333	70.7	57–96	61	15	532	418	107
Hiroshima	2613	9861	65.1	47–95	70	26	187	90	32
Totals	60161	254582	62.9	21–106	75	26	5563	3530	978

CaMos

The Canadian Multicentre Osteoporosis Study (CaMos) is an ongoing prospective age-stratified cohort. The study is documenting the incidence of fractures and risk factors in a random sample of 9424 men and women aged 25 years or more selected by telephone listings. The sampling frame is from nine study centers in nine provinces [44]. Characterization of individuals was by interview. BMD was measured by DXA at the hip (Hologic QDR 1000) and lumbar spine, and an ultrasound scan taken at the heel in individuals aged 50 years or more.

Rochester

The Rochester cohort was recruited from two random population samples stratified by decade of age, one comprising women who were subsequently followed for up to 20 years [45] and another sample of women and men followed for 8 years [46]. The response rates were 49.8% in the women and 38.7% in the men. BMD of the right femoral neck was measured by dual photon absorptiometry in the first cohort (cross calibrated to DXA) and by DXA (Hologic QDR 2000) in the second group. Fractures were ascertained by periodic interview combined with review of the inpatient and outpatient medical records of all local care providers.

Sheffield

The Sheffield cohort comprised women aged 75 years or more selected randomly from the population of Sheffield, UK, and surrounding districts between 1993 and 1999. Approximately 35 000 women, identified from general practitioner listings, were contacted by letter and invited to attend for assessment of their skeletal status. Five thousand eight hundred and seventy-three women were willing to attend for the screening visit. Of these, 281 were excluded, and the remainder randomly allocated after informed consent to treatment with the bisphosphonate clodronate, or to an identical placebo. This study is still in progress, and the material used for the present paper comprised 2148 women allocated to treatment with placebo [47]. All women had baseline assessment of BMD undertaken at the femoral neck using the Hologic 4500. Outcomes were assessed by 6 monthly home visits.

Rotterdam

The Rotterdam study, begun in 1990, is a prospective cohort study that aimed to examine and follow-up all residents aged 55 years and older living in Ommoord, a district of Rotterdam [48]. By 1993, 7983 residents had been included (response rate, 78%). Bone mineral density was assessed at the femoral neck by DXA using a Lunar DPX-L [49]. Fracture follow-up was undertaken using an automated link with general practitioner computer systems and hospital admission data. Fracture data were collected and validated by two independent research physicians. For this analysis, validated fracture follow up was available for 7774 participants (3065 men) with an average follow up time of 6 years. Femoral neck BMD was measured in 5776 individuals (2432 men).

Kuopio

The Kuopio osteoporosis risk factor and prevention (OSTPRE) study in Finland comprised a postal inquiry sent to all 14220 women aged 47–56 who were residents of Kuopio province in 1989. Thirteen thousand and one hundred women responded to the inquiry, of whom 1214 were excluded for incomplete information. This left a study population of 11 886 women. A random stratified sample of 3222 women underwent bone mineral densitometry by DXA using the Lunar DPX [50].

Gothenburg I

This study comprised four birth cohorts of 2375 randomly sampled men and women aged 70 years or more followed for up to 20 years at Gothenburg [51,52] after a baseline BMD measurement. The participation rate was 73%. The participants were drawn randomly from the population register in Gothenburg by the date of birth to provide cohorts aged 70, 76, 79, and 85 years at the time of investigation. Bone mineral density was measured at the right heel using dual photon absorptiometry.

Gothenburg II

The Gothenburg study comprised a randomly drawn population cohort of women aged 21–89 years followed up to 7.9 years (mean 4.2 years) [53]. Seventy percent of those invited (approximately 7000 women) participated in the study that examined risk factors for osteoporosis by use of a standardized questionnaire. BMD was assessed at baseline at the distal forearm using the Osteometer DTX 200.

DOES

The Dubbo Osteoporosis Epidemiology Study (DOES) is a population-based study with multiple assessments of skeletal status in men and women aged 60 years or more from Dubbo, Australia [54]. Participation in the study was 56% of the population. Baseline measurements included BMD at the femoral neck assessed using DXA (GE-Lunar, DPX). Fractures are identified through radiologists reports from the two centers servicing the region.

Hiroshima

The Adult Health Study in Hiroshima (AHS) documents the late health effects of radiation exposure among atomic

Table 2
Details of the construct of the questionnaire on fracture history in the cohorts studied

Cohort	Question
EVOS/EPOS	Have you ever suffered a fracture?
CaMos	Have you ever fractured any bones?
Rochester	Prior fracture with moderate trauma
Rotterdam	History of any fracture in the past 5 years
Gothenburg I	Evidence of any fracture (in hospital records)
OFELY	History of a fragility fracture from low trauma since age of 30 years
Sheffield	History of any fracture
Kuopio	History of any fracture from the age of 15 years
Gothenburg II	History of fracture after the age of 25 years
Dubbo	Self-reported
Hiroshima	Self-reported

bomb survivors in Hiroshima and Nagasaki. The original AHS cohort consisted of about 15000 atomic bomb survivors and 5000 controls selected from residents in Hiroshima and Nagasaki using the 1950 national census supplementary schedules and the Atomic Bomb Survivors Survey. AHS subjects have been followed through biennial medical examinations since 1958 with a participation rate of approximately 80% throughout this period. BMD at the lumbar spine and proximal femur has been measured at each biennial health examination using DXA (Hologic QDR-2000) since December 1993. Trained nurses interviewed the subjects about baseline risk factors and measured height and weight at each biennial visit [55,56].

Baseline and outcome variables

The construct of the question to determine a prior fracture history differed between the cohorts studied (Table 2). Prospective fracture ascertainment was undertaken by self-report (Sheffield, Kuopio, EVOS/EPOS; Hiroshima) and/or verified from hospital central data bases (CaMos, Sheffield, EVOS/EPOS, Rochester, Rotterdam, Kuopio, Gothenburg I and II, CaMos, DOES). The EPOS and OFELY study also included sequential systematic radiography to define incident vertebral deformities, but were not used in this analysis. Information on all clinical fractures was used for this report. In addition, fractures considered to be due to osteoporosis were analyzed, and finally, hip fracture alone was considered separately. For Kuopio and OFELY, all fractures were recorded and no distinction made between fracture sites. In the case of the EPOS study and Gothenburg I, osteoporotic fractures only were recorded. In the other cohorts, an osteoporotic fracture was one considered to be due to osteoporosis either by the investigator or by the Coordinating Centre. For the EVOS study, osteoporotic fractures comprised hip, forearm, humeral, or limb fractures. For the CaMos study, they comprised fractures of the spine, pelvis, ribs, distal forearm, forearm, and hip. In the other cohorts (Sheffield, Rotterdam, Rochester, Gothenburg I, DOES, Hiroshima), fractures at sites considered to be characteristic for osteoporosis were [38] extracted from the data.

Statistical methods

The risk of fracture was estimated by Poisson regression applied to each cohort and each sex separately. Covariates included time since start of follow up, current age, prior history of fracture, and BMD. We additionally excluded BMD from the model. A further model included the interaction term prior fracture × time to determine whether the strength of the association of prior fracture and fracture risk waned with time. The beta value for each sex in each cohort is age-dependent, beta_{k+} $\text{beta}_{k+1}\cdot\text{age}$. The estimated value of beta_{k+} $\text{beta}_{k+1}\cdot\text{age}$ was determined for each age from 50 to 85 years, together with the variance. Results of each cohort and the two sexes were weighted according to the variance and merged to determine the weighted means and standard deviations. The risk ratio (RR) of those with a prior fracture history versus those without a prior fracture history was equal to e^{mean}.

The component of the risk ratio explained by BMD was computed from a meta-analysis of BMD and fracture risk [57]. The risk of any fracture was assumed to increase 1.6-fold for each SD decrease in BMD. For hip fracture, the gradient of risk was assumed to be 2.6 per SD. The proportion of risk attributed to a low BMD was computed as

$$\frac{[\log RR_a/\log GR] - [\log RR_b/\log GR]}{[\log RR_a/\log GR]}$$

where RR_a is the unadjusted risk ratio, RR_b is the risk ratio adjusted for BMD, and GR is the gradient of risk.

Results

Of 60161 men and women studied, 877 men and 4686 women were identified as having a subsequent fracture of any kind, of which 680 and 2850 were characterized as osteoporotic in men and women, respectively. Two hundred and eleven men and 767 women sustained a hip fracture. The total follow-up was 61938 person years in men and 192644 in women. BMD measurements were available in 62% of individuals.

Table 3
Prevalence of a prior fracture history in men and women by age

Age (years)	Probability of fracture history (%)		
	Men	Women	Combined
30	44	15	24
40	43	18	27
50	42	23	30
60	41	29	34
70	40	35	37
80	39	41	41
90	38	48	45

Table 4
Risk ratio (RR) and 95% confidence interval (CI) of fracture associated with a history of prior fracture in men and women, without and with adjustment for BMD

Outcome fracture	Men		Women		Combined	
	RR	95% CI	RR	95% CI	RR	95% CI
A. Without BMD						
Any	2.02	1.73–2.38	1.84	1.72–1.96	1.86	1.75–1.98
Osteoporotic	1.93	1.61–2.33	1.85	1.70–2.01	1.86	1.72–2.01
Hip	2.30	1.56–3.41	1.77	1.49–2.11	1.85	1.58–2.17
B. With BMD						
Any	2.04	1.67–2.48	1.73	1.59–1.88	1.77	1.64–1.91
Osteoporotic	1.91	1.50–2.43	1.74	1.57–1.92	1.76	1.60–1.93
Hip	1.97	1.12–3.48	1.56	1.23–1.98	1.62	1.30–2.01

Probability of fracture history rose almost linearly with age (Table 3). The probability of recording a history of a prior fracture was higher in men than in women (OR = 1.19; 95% CI = 1.14–1.25).

Risk of any fracture

Previous fracture was associated with a significantly increased risk of any subsequent fracture (Table 4). There was no difference in the risk ratio between men and women. In men and women combined, the risk ratio ranged from 1.83 to 2.03 depending upon age (Table 5). The risk ratio was marginally lower by approximately 10% when account was taken of BMD. If it is assumed that the risk of any fracture increases 1.60-fold for each SD deviation decrease in hip BMD, then the difference in risk between those with and without a prior fracture is equal to an expected difference in BMD of 1.32 SD [log(1.86)/log(1.60)]. In reality, the difference in BMD at all ages in men and women combined was approximately 0.11 SD ([log(1.86)/log(1.60)] − [log(1.77)/log(1.60)]). Thus, low BMD accounts for the minority (8%; 0.11/1.32) of the difference in risk between those with or without a prior fracture.

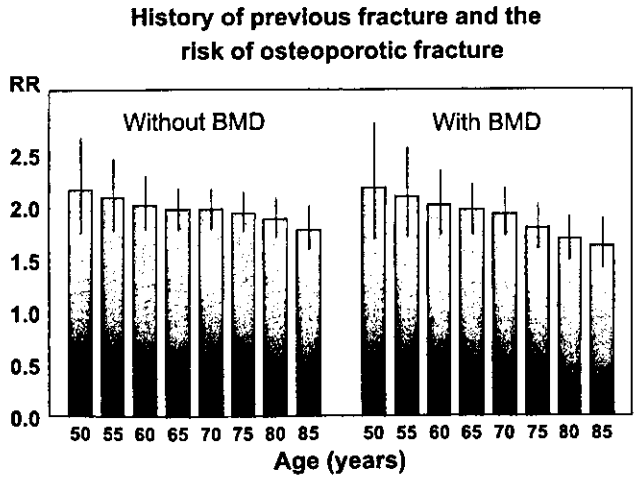

Fig. 1. Risk ratio for an osteoporotic fracture in men and women with a prior history of fracture with and without adjustment for BMD.

Risk of osteoporotic fracture

Previous fracture was also associated with a significantly increased risk of an osteoporotic fracture at all ages with and without adjustment for BMD (Table 4). The unadjusted risk ratios for an osteoporotic fracture were almost identical with the risks of a prior fracture for any fracture. For example, at the age of 80 years, the risk of any fracture was 1.88 (95% CI = 1.72–2.06) and for an osteoporotic fracture was 1.89 (95% CI = 1.72–2.09). There was no difference in risk ratio between men and women. Fracture risk decreased somewhat with age by about 10% per decade of age (Fig. 1), but the trend was short of conventional significance ($P = 0.089$).

Risk of hip fracture

A prior fracture history was a significant risk factor for hip fracture at all ages (Table 6). The risk ratio was highest at younger ages and decreased progressively with age ($P < 0.002$ for the interaction term). The risk decreased by 3%

Table 5
Risk ratio (RR) for any fracture and 95% confidence intervals (CI) comparing men and women with and without a previous fracture by age, with or without adjustment for BMI

Age (years)	RR without BMD[a]		RR with BMD[a]	
	Mean	95% CI	Mean	95% CI
50	1.92	1.63–2.20	1.91	1.59–2.29
55	1.90	1.73–2.09	1.83	1.60–2.10
60	1.98	1.80–2.18	1.94	1.73–2.17
65	2.02	1.86–2.20	1.99	1.81–2.20
70	2.03	1.87–2.21	1.98	1.79–2.18
75	1.96	1.80–2.13	1.82	1.65–2.02
80	1.88	1.72–2.06	1.72	1.54–1.91
85	1.83	1.65–2.04	1.72	1.51–1.96
All ages	1.86	1.75–1.98	1.77	1.64–1.91

[a] Prior fracture versus no fracture.

Table 6
Risk ratio (RR) for hip fracture and 95% confidence intervals (CI) comparing men and women with and without a prior fracture by age, with and without BMD

Age (years)	RR without BMD[a]		RR with BMD[a]	
	Mean	95% CI	Mean	95% CI
50	5.04	2.66–9.56	3.88	1.79–8.43
55	4.20	2.46–7.15	3.98	2.08–7.62
60	3.40	2.21–5.24	3.16	1.88–5.32
65	2.60	1.85–3.64	2.28	1.52–3.41
70	2.31	1.76–3.02	1.90	1.37–2.65
75	2.14	1.71–2.68	1.64	1.24–2.17
80	1.90	1.58–2.28	1.41	1.12–1.78
85	1.66	1.39–1.98	1.32	1.04–1.68
All ages	1.85	1.58–2.17	1.62	1.30–2.01

[a] Prior fracture versus no fracture.

(95% CI = 1–5%) for each year of age. The RR was significantly increased at all ages, but at ages less than 60 years, the confidence estimates were wide (very few hip fractures). There was no difference in RR between men and women. Adjustment for BMD had an effect on the risk estimate for hip fracture that was quantitatively greater than for all fractures. The RR adjusted for BMD fell by approximately 30%. As in the case of all fractures, differences in BMD explained a minority of the increased risk ratio for hip fracture. In men and women combined, low BMD explained 22% of the increase in risk ratio and was constant by age (assuming a gradient of risk for hip fracture of 2.6/SD decrease in BMD).

The exclusion of data from Gothenburg (where BMD was assessed at the forearm or heel) had no material effect on these results (data not shown). There was no significant interaction of fracture history with time since baseline assessment.

Discussion

The present study confirms that a history of prior fracture is a significant risk factor for future fractures. In addition, the effect is over and above that which can be explained by variations in BMD. The risk of subsequent fractures is not as great as that identified in some studies [8], but as expected, falls within the confidence estimates of most estimates [27]. Discrepancies may be related to the duration of follow-up since the risk of subsequent fracture may not be linear over time [4,5]. Other possible reasons may relate to differences in the populations studied and the questionnaire used to identify prior fractures. A particular strength of the present study is that the estimate of risk is made in an international setting from randomly selected population cohorts. Calculations were based on the primary data, decreasing the risk of publication biases. The consistency of the association between cohorts (data not shown) additionally indicates the international validity of the importance of this risk factor. The risk of any subsequent fracture was comparable to the risk of a new osteoporotic fracture or a hip fracture. The large sample size permitted the quantification of risk by age. For all fractures and for osteoporotic fractures, the risk ratios were relatively constant with age. In the case of hip fracture, risk ratios decreased with age.

The present study also quantifies the independent contributions of low BMD and prior fracture. At all ages, low BMD explained a minority of the total risk, a proportion that decreased with age. The mechanism for the BMD-independent increase in risk could not be determined from this study but is likely due, in part, to coexisting morbidity that might increase the risk of falls or impair the protective responses to injury [6,21,29,58]. In addition, changes in the microarchitecture of cancellous and cortical bone with rapid bone loss after fracture or immobilization [59–61] may weaken the resistance to mechanical force out of proportion to any effect on BMD.

Irrespective of the underlying mechanism, these data indicate that the risk of fractures is substantially greater in individuals with a prior fragility fracture than in individuals of the same age, sex, and BMD without such a fracture. This has important implications for intervention thresholds. Health economic analysis suggests that intervention is cost-effective when treatment is targeted to women without a prior fracture with a T score of -2.5 SD at the femoral neck [39]. Since a prior fracture confers a risk over and above that provided by BMD, intervention thresholds for BMD can be less stringent (say at a T score of -1.5 SD) for those with a prior fracture, and still yield the same cost effectiveness. This approach has been incorporated into health economic analyses [32,62]. However, a large number of additional independent risk factors for fracture have been identified. These include smoking, corticosteroid exposure, a family history of fracture, secondary osteoporosis [39], and possibly the biochemical indices of bone turnover [63]. The interrelationships of all these risk factors will need to be determined before they can be easily used for assessing fracture risk in the general population.

The majority of reports have provided risk ratios for fracture in those with a prior fracture history compared to those without. For practical use, it is appropriate to express risk relative to the general population since risks expressed in this way can be more readily adjusted with other risk factors, such as the risk provided by BMD measurements [64]. For this purpose, knowledge of the prevalence of the risk factor is required. The adjustment decreases the risk ratios by a factor proportional to the prevalence of the risk factor. The relative risk is computed as $RR/[p.RR + (1 - p)]$ where RR is the risk ratio and p the prevalence of the risk factor [64]. Since the prevalence of fracture history is high (26%), the quantitative effect of adjustment is substantial.

The present study has some limitations that should be mentioned. As with nearly all randomly drawn populations, nonresponse biases may have occurred, which we were unable to document for all cohorts. The effect is likely to exclude sicker members of society, and may underestimate the absolute risk of fracture. Thus, the probability of a prior fracture may be underestimated from a societal perspective (Table 3), but this is unlikely to affect risk ratios. The greatest problem is the construct of the question concerning prior fractures and the methods of documenting and characterizing subsequent fracture events. These differed substantially between cohorts. The effect of this heterogeneity is likely, however, to weaken rather than to strengthen the associations that we found, that is, the association in reality may be stronger.

We conclude that prior fracture confers a substantial risk for future fractures and that this risk is largely independent of BMD. The consistency of the association in an international setting provides the rationale for the use of this risk factor in case of finding strategies. Moreover, patients

identified can be targeted for treatment at a higher BMD than individuals of the same age without a fracture history.

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Noncancer Disease Incidence in Atomic Bomb Survivors, 1958–1998

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We examined the relationships between the incidence of noncancer diseases and atomic bomb radiation dose using the longitudinal data for about 10,000 Adult Health Study (AHS) participants during 1958–1998. The current report updates the analysis we presented in 1993 with 12 additional years of follow-up. In addition to the statistically significant positive linear dose–response relationships detected previously for the incidence of thyroid disease ($P < 0.0001$), chronic liver disease and cirrhosis ($P = 0.001$), and uterine myoma ($P < 0.00001$), we also found a significant positive dose response for cataract ($P = 0.026$), a negative linear dose–response relationship for glaucoma ($P = 0.025$), and significant quadratic dose–response relationships for hypertension ($P = 0.028$) and for myocardial infarction among survivors exposed at less than 40 years of age ($P = 0.049$). Significant radiation effects for calculus of the kidney and ureter were evident for men but not for women (test of heterogeneity by sex: $P = 0.007$). Accounting for smoking and drinking did not alter the results. Radiation effects for cataract, glaucoma, hypertension, and calculus of the kidney and ureter in men are new findings. These results attest to the need for continued follow-up of the aging A-bomb survivors to fully elucidate the effects of radiation exposure on the occurrence of noncancer diseases.

INTRODUCTION

The Adult Health Study (AHS) was begun in 1958 by the Atomic Bomb Casualty Commission (ABCC), succeeded in 1975 by the Radiation Effects Research Foundation (RERF), as biennial clinical examinations of a subset of the Life Span Study (LSS) cohort to examine the late effects of atomic bomb exposure. The 1993 report (*1*) showed for the first time that the incidence of uterine myoma, chronic liver disease and cirrhosis, and thyroid disease increased with radiation dose during 1958–1986, confirming some of the impressions from an earlier prevalence study (2). The current report, covering 40 years between 1958–1998, updates the first incidence study results with 12 additional years of follow-up and two more diseases. Cigarette smoking and alcohol consumption were also examined as potential confounders and as dose–response modifiers.

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MATERIALS AND METHODS

Study Population

The AHS was established in 1958 as a subset of the LSS cohort, comprising 19,961 Hiroshima and Nagasaki subjects. The AHS biennial health examinations presented clinical information complementary to the LSS death and tumor registries data. To enhance detection of radiation effects, the AHS included disproportionately more individuals exposed at higher doses than were present in the LSS: about half were within 2 km of the hypocenter (proximal exposure), a quarter were at distances over 3 km (distal exposure), and a quarter were not in city (NIC) at the time of bombing (ATB).

The study subjects attended at least two examinations between July 1, 1958 and June 30, 1998. This report uses data from 10,339 subjects (2.2×10^5 person-years of follow-up), which is the original cohort reduced by 5,000 NIC subjects, 2,064 who lacked Dosimetry System 86 (DS86) dose estimates (*3*), and 2,558 who attended fewer than two examinations. Compared to the 1993 report (*1*), an additional 698 subjects and 3×10^4 person-years (15.8%) are represented here. Since case identification relied on the biennial health examinations, the AHS data are qualitatively different from those of the LSS mortality and tumor registry program.

Sixty-three percent of the subjects were women and 73% were Hiroshima residents (Table 1). About 50% of the AHS subjects had died by July 1998. The proportion of participants who were under 20 years of age ATB increased from 1/3 in 1958–1960 to 60% in 1996–1998, reflecting age-related mortality. Conversely, those over 40 years ATB decreased from 29% in 1958–1960 to 2% in 1996–1998. A high participation rate (75 to 90%) was maintained throughout the examinations for study subjects living in Hiroshima and Nagasaki and their neighboring towns. More than half had attended 11 or more examinations.

A subject's follow-up began at the initial AHS visit and ended on the earlier of the date of the last disease-free visit or the date of the disease onset. The disease onset date was estimated as the midpoint between the first disease diagnosis date and the date of the previous disease-free examination. For each disease, cases present at the initial visit were excluded.

Clinical Procedures and Selection of Diseases for Study

The biennial health examinations, conducted with informed consent, consist of history-taking, physical examination, and laboratory tests. Details are available elsewhere (*1*, *2*). Incident cases were ascertained by scanning for the first occurrence of the three-digit International Classification of Diseases (ICD) (*4*) codes stored in the AHS database. The ICD codes of the 21 diseases examined are listed in the Appendix. At each examination, the first three digits of the ICD codes, up to six diagnoses

TABLE 1
Distribution of the 10,339 AHS Participants by DS86 Weighted Total Shielded Kerma Categories (Sv)

		DS86 categories (RBE = 10) in Sv							
	Total	0.0	0.001–0.49	0.5–0.99	1.0–1.49	1.5–1.99	2.0–2.49	2.5–2.99	3.0+
Hiroshima	7575	2750	2541	941	454	252	193	131	314
Men	2698	1004	823	335	174	102	77	48	136
Women	4877	1746	1718	606	280	150	116	83	178
Mean dose	0.57	0	0.21	0.72	1.23	1.75	2.24	2.75	4.14
Mean age ATB	30.6	30.4	31.2	31.3	30.7	31.2	29.0	29.2	27.2
Nagasaki	2764	1205	532	345	338	166	76	35	67
Men	1111	514	192	125	129	75	32	14	30
Women	1653	691	340	220	209	91	44	21	37
Mean dose	0.58	0	0.22	0.76	1.23	1.74	2.18	2.70	3.83
Mean age ATB	24.5	24.2	26.5	24.5	24.1	23.8	23.3	22.4	22.1
Total	10,339	3954	3073	1286	792	418	269	166	381

per person, were stored before June 1986; four-digit codes, up to 12 per person, were stored thereafter. Medical charts and death certificates were not reviewed for case validation.

Radiation Dosimetry

We used individual estimates of kerma and organ-specific dose in which survivor location and shielding by terrain and the body are taken into account based on the DS86. Kerma and organ doses, both expressed in sieverts, were calculated as weighted sums of their γ-ray and neutron components in grays, giving the neutron component a weight of 10. Before weighted sums were calculated, DS86 kerma estimates were truncated to 4 Gy, in consideration of the imprecision in dose assessment for proximal survivors (*5*). The estimated organ doses were adjusted for random dosimetry error, generally thought to be about 35%, to reduce bias in risk estimates (*5–7*). We used thyroid dose for the analysis of thyroid diseases, eye dose for eye diseases, liver dose for liver disease, uterine dose for gynecological diseases, bladder dose for prostate disease, and stomach dose for all others. Our 1993 report (*1*) used unweighted organ-specific doses for thyroid diseases, eye diseases, liver disease, gynecological diseases, prostate disease, and gastrointestinal diseases, and unweighted shielded kerma for residual diseases, with truncation to 6 Gy instead of 4 Gy and without adjustment for random dosimetry errors. As a result, the individual dose estimates used here were generally lower compared to those of the previous report.

Table 1 shows the distribution of the AHS participants by DS86 categories. Nearly 20% of the cohort had exposure doses of 1 Sv or more. The mean weighted shielded kerma was 0.57 Sv ± 0.94 [standard deviation of the mean (SD)]. The unexposed category (doses = 0) includes 38.2% of the study cohort. Among the exposed (doses > 0), the mean weighted shielded kerma was 0.92 Sv ± 1.06.

Cigarette Smoking and Alcohol Consumption

Cigarette smoking history was abstracted from four LSS mail surveys (administered to men in 1965, to women in 1969–1970, to both men and women in 1979–1980 and in 1991) and one survey administered during the AHS examinations of 1965–1966. All AHS participants were part of the pre-1991 surveys, but only about 15% were part of the 1991 survey. The response rate was over 95% for all surveys. Smoking and drinking statuses were considered as time-varying covariates. Follow-up time was classified as "never smoked", "smoke currently" or "smoked in the past" according to changes in smoking status. We also used composite classification of "never smoked" and "ever smoked" for descriptive purposes. Among men, 11% never smoked, 79% smoked at some time, and 10% had no smoking information. Among women, 72% never smoked, 18% smoked at some time, and 10% had no smoking information.

We obtained alcohol intake information from two LSS mail surveys in 1979–1980 and 1991 and from the AHS epidemiological survey of 1965–1966. The classification scheme used for smoking was applied to alcohol. Among men, 16% never drank, 70% drank at some time, and 14% had no data. Among women, 63% never drank, 26% had drunk at some time, and 11% had no data. Due to lack of timely information, nonsmoking and nondrinking groups most likely included actual smokers and drinkers.

There was no significant difference in dose among the smoking and drinking classes except for smoking in women: The mean dose was significantly higher by 15% for ever-smokers than for never-smokers ($P < 0.01$).

The background disease incidence rates were significantly higher for "ever smoked" than for "never smoked" subjects for cardiovascular disease, gastric ulcer, chronic liver disease, and cholelitiasis. However, the background risk of cataract was significantly lower among the "ever smoked". Alcohol-related increase in risk was found for chronic liver disease, and protective effects were observed for hyperplasia of the prostate and Parkinson's disease.

Statistical Methods

We applied Poisson regression methods for the longitudinal analysis of incidence data, using AMFIT of the EPICURE program package (*8*). We stratified disease incidence rates by city (Hiroshima, Nagasaki), sex (male, female), age ATB in years (upper bounds: 10, 20, 30, 40, 50, 60, 60+), age at examination (age ATE) in years (upper bounds: 20, 30, 40, 50, 60, 70, 80, 80+), calendar time (July 1, 1958–December 31, 1967; January 1, 1968–December 31, 1977; January 1, 1978–December 31, 1987; January 1, 1988–June 30, 1998), and DS86 total weighted organ dose in sieverts (upper bounds: 0, 0.5, 1.0, 1.5, 2.0, 3.0, 3.0+). For some analyses, cigarette smoking (never smoked, smoke currently, smoked in the past) and alcohol intake (never drank, drink currently, drank in the past) were also included as time-varying covariates in disease rate stratification. The number of disease cases in each stratum was assumed to be an independent Poisson variate with mean $PY_{ij}\gamma_{ij}$, where PY_{ij} is person-years and γ_{ij} is disease incidence rate in the jth dose category and the ith category defined by other cross-classifications. γ_{ij} may also be represented by $\gamma_{ij} = \gamma_{i0}\,RR_{ij}$, where γ_{i0} is the incidence rate in stratum i in the absence of radiation exposure and RR_{ij} is the relative risk due to radiation dose associated with the jth exposure level. We assumed an additive linear dose–response model: $RR_{ij} = 1 + \beta d_{ij} \exp[\alpha_k(Z_k)]$, where d_{ij} is the jth dose level in stratum i, β is the excess risk per sievert averaged over all strata, and z_k represents the effect modifiers. We used the mean dose in each ijth stratum for d_{ij}. For diseases with a significant linear dose effect (β), the presence of curvature was assessed by the significance of η in the linear-quadratic model, $RR_{ij} = 1 + \beta d_{ij} + \eta d_{ij}^2$. We also examined purely quadratic effects for all diseases by testing the significance of η in the model $RR_{ij} = 1 + \eta d_{ij}^2$. We used a two-sided type I error of 0.05.

TABLE 2
Number of Disease Cases and Observed Background Incidence

Disease	No. of cases		Background incidence per 10,000 PY				
			Crude rates			Standardized rates[a]	
	Male	Female	Total	Male	Female	Male	Female
Hypertension	1792	3243	286.44	304.33	276.92	178.2	185.2
Hypertensive heart disease	585	1301	80.73	80.13	81.06	38.0	42.3
Ischemic heart disease	600	946	63.40	76.10	56.67	31.5	27.3
Myocardial infarction	65	52	5.36	9.88	2.94	4.0	1.3
Occlusion, stenosis	232	208	17.69	27.46	12.47	9.9	5.5
Aortic aneurysm	74	110	6.78	9.88	5.12	3.8	2.4
Stroke I	272	259	20.79	30.76	15.47	11.3	6.9
Stroke II	356	373	27.98	41.01	21.04	15.7	9.6
Thyroid disease	182	782	36.99	19.82	46.66	12.9	48.5
Cataract	975	2509	154.25	123.01	171.98	53.8	97.9
Gastric ulcer	476	454	37.45	60.23	25.81	37.2	15.5
Duodenal ulcer	219	152	14.46	25.96	8.47	22.3	6.3
Chronic liver disease and cirrhosis	785	989	71.66	93.72	60.32	59.2	35.2
Cholelithiasis	271	688	40.64	35.59	43.38	16.3	22.6
Calculus of kidney and ureter	170	153	11.02	16.47	8.1	8.8	5.0
Uterine myoma	—	922	51.68	—	51.68	—	37.7
Cervical polyp	—	281	15.48	—	15.48	—	11.8
Hyperplasia of prostate	461	—	60.68	60.68	—	22.7	—
Dementia	79	237	11.32	6.36	13.99	2.3	6.7
Parkinson's disease	35	62	3.12	4.05	2.63	1.5	1.3
Glaucoma	52	159	10.16	6.67	12.03	2.9	5.4

[a] Directly standardized to the Japanese population of 1985.

The reference group consisted of 3954 persons with DS86 dose estimates of zero.

We evaluated the significance of the effect modifiers (city, sex, age ATB, age ATE, calendar time, smoking and drinking) for the diseases for which the main effects of radiation were significant or suggestive. Generally, covariates were treated as categorical except for age ATB and age ATE, for which we used the cell-specific means. We used the likelihood ratio method for significance testing and for computing the 95% confidence intervals.

RESULTS

The number of disease cases and the background incidence rates for the 21 diseases are shown in Table 2. We estimated the background rates using the unexposed subjects. We calculated the standardized rates using the Japanese population of 1985 (*9*), as in the previous report (*1*). The standardized rates increased for only dementia and Parkinson's disease, in spite of the aging of the population and implementation of more specific diagnostic procedures such as ultrasonography.

Table 3 shows the estimated relative risk at 1 Sv (RR_{1Sv}), the average excess disease per 10^4 PY Sv, and the attributable risk based on the linear model. Attributable risk is the percentage of the disease cases due to over 0.001 Sv of exposure. The last two columns also show the significance level and the RR_{1Sv} obtained by further stratifying the background rates by smoking and drinking. Between 1958–1998, a significant linear increase with radiation dose ($P < 0.05$) was detected for the incidence of thyroid diseases, chronic liver disease and cirrhosis, uterine myoma, and cataract and was suggested for calculus of the kidney and ureter ($P = 0.07$). A significant linear decrease was detected for the incidence of glaucoma. There was no indication of a curvilinear increase/decrease in risk at high doses for these diseases. The fitted linear models and the estimated relative risks are shown in Fig. 1. The relative risk estimate for uterine myoma at over 3 Sv was omitted, since only three women had that exposure level. A nonlinear dose–response relationship was evident for hypertension (Fig. 2A). Significant radiation effects were not detected for other cardiovascular diseases, including MI. However, in accord with our previous results (*1*), MI incidence during 1968–1998 for survivors under 40 years ATB ($MI^{<40}$, 78 cases) showed a significant curvilinear dose–response relationship (Fig. 2B). Adjustment for smoking and drinking only slightly affected the significance level of the linear dose response for hypertension and calculus of the kidney and ureter. The results of the examination of city, sex, age ATB, age ATE, and calendar time as modifiers of the dose–response relationship are shown in Table 4; significant or suggestive evidence of radiation effects is shown in the results for each disease.

Thyroid Disease

The relative risk at 1 Sv (RR_{1Sv}) for thyroid disease was 1.33 ($P < 0.0001$, 95% CI: 1.19–1.49). The average number of excess disease cases per 10^4 PY Sv was 12, and the attributable risk was 18%. These estimates are similar to

those obtained previously (*1*), which were based on 13.5% fewer cases.

Radiation risk was higher for subjects exposed at younger ages and for subjects examined at younger ages. With age ATB included as the most significant effect modifier, age ATE was not additionally significant ($P = 0.58$), indicating age ATB as the stronger factor. In fact, increased radiation risk was apparent for survivors exposed at less than 20 years of age ($P < 0.0001$, $RR_{1Sv} = 1.54$, 95% CI: 1.33–1.81) but not for those exposed at older ages ($P = 0.18$, $RR_{1Sv} = 1.11$, 95% CI: 0.96–1.30).

Chronic Liver Disease and Cirrhosis

RR_{1Sv} for liver disease was 1.15 ($P = 0.001$, 95% CI: 1.06–1.25). The average excess risk was 11 cases per 10^4 PY Sv and the attributable risk was 8%. Similar estimates were obtained in our previous report, with 42% fewer cases. The effect modifiers were not significant.

The ICD code for chronic liver disease (571) includes alcoholic liver disease (571.1–571.3), chronic hepatitis (571.4), cirrhosis without mention of alcohol (571.5), biliary cirrhosis (571.6), and other chronic nonalcoholic liver disease (571.8). The use of the four-digit ICD after June 1986 resulted in a large increase in cases after June 1986, due mainly to nonalcoholic fatty liver (571.8) detected by ultrasonography, comprising 69% of the incident cases. Ultrasonography began to be used in the Hiroshima laboratory in 1981 and in the Nagasaki laboratory in 1984. Participation in ultrasonography was voluntary before 1991, raising the possibility of dose-related bias. Ultrasonography has been performed routinely since 1991, resulting in a dramatic rise in fatty liver diagnoses, but diagnoses of other chronic liver diseases did not change noticeably.

We examined radiation effects for fatty liver alone and for all other chronic liver diseases occurring after 1986. For all liver diseases, there was significant linear dose response ($P = 0.054$, $RR_{1Sv} = 1.14$, 95% CI: 1.0–1.32). No significant heterogeneity in the risk estimates was observed before and after June 1986 ($P = 0.76$). For fatty liver alone (445 cases), a linear dose response was suggested ($P = 0.073$, $RR_{1Sv} = 1.16$, 95% CI: 0.99–1.37). For 199 cases of other chronic liver diseases, radiation effects were nonsignificant ($RR_{1Sv} = 1.06$, $P = 0.64$, 95% CI: 0.84–1.40).

Uterine Myoma

RR_{1Sv} for uterine myoma was 1.46 ($P < 0.00001$, 95% CI: 1.27–1.67). There were 25 excess cases per 10^4 PY Sv, and the attributable risk was 19%. Similar estimates were obtained previously (*1*), with 23% fewer cases. Much of the increase in cases could be attributed to the use of ultrasonography.

Radiation risk varied significantly by calendar time or, equivalently, time since exposure ($P = 0.015$) and by age ATB ($P = 0.042$). The risk decreased steadily in the first three decades of follow-up ($RR_{1Sv} = 2.0, 1.7, 1.1$), which was noted in our previous report (*1*), then increased slightly in the fourth decade ($RR_{1Sv} = 1.3$).

Years since exposure was the most significant effect modifier compared to age ATB and age ATE. Neither age ATB ($P = 0.75$) nor age ATE ($P = 0.75$) was additionally significant with years since exposure included as dose–effect modifier.

We also found that radiation risk was elevated for the exposed nondrinkers ($P < 0.0001$, $RR_{1Sv} = 1.62$, 95% CI: 1.36–1.94), but not for exposed drinkers ($P < 0.50$, $RR_{1Sv} = 1.09$, 95% CI: 0.86–1.40) (test of heterogeneity, $P = 0.011$).

Cataract

We detected a significant positive linear dose–response relationship ($P = 0.026$, $RR_{1Sv} = 1.06$, 95% CI: 1.01–1.11). The estimated number of excess cataract cases per 10^4 PY Sv was 8, and the attributable risk was 4%. Radiation risk varied significantly by age ATE ($P < 0.001$) and possibly by follow-up period ($P = 0.09$). A decreasing trend for the first three decades was observed here as well as in the previous report, although RR_{1Sv} increased to 1.08 in the most recent decade. Considered simultaneously with age ATE as effect modifier, follow-up period was also significant ($P = 0.012$), but their interaction was not ($P = 0.78$). Since lens opacities surge after age 60 years (*11*), we looked for heterogeneity in the dose response between age ATE ≤ 60 and >60 years. Radiation effects were significant for the younger group ($P = 0.009$, $RR_{1Sv} = 1.16$, 95% CI: 1.04–1.32) but not for the older group ($P = 0.24$, $RR_{1Sv} = 1.03$, 95% CI: 0.98–1.09) (test of heterogeneity: $P = 0.08$).

Glaucoma

Examined for the first time in this report, glaucoma showed a significant negative dose–response relationship ($P = 0.025$, $RR_{1Sv} = 0.82$, 95% CI: 0.80–0.97). The lower 95% confidence bound was the lowest value feasible before RR became negative. There was a deficit of -1.5 glaucoma cases per 10^4 PY Sv, and rates were reduced by 15% for subjects exposed to over 0.001 Sv. The dose–response relationship was not modified by the covariates considered.

Since rural/urban variation in baseline disease rates could bias radiation risk estimates (*12*), distal/proximal exposure indicator was used as a surrogate for adjustment. This resulted in a lack of dose response ($P = 0.14$), with RR_{1Sv} essentially unchanged.

Hypertension

Radiation effects were not evident under the linear dose–response model ($P = 0.15$), but they were significant under the purely quadratic model ($P = 0.028$, $RR_{1Sv} = 1.03$, 95% CI: 1.00–1.06) (Fig. 2A). Based on the quadratic model, there were seven excess hypertension cases per 10^4 PY Sv, and 2% were attributed to radiation exposure. Incident cases increased by 16% since the previous report. There was