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Increased risk of osteoporotic fracture in community-dwelling elderly men 20 or more years after gastrectomy: The Fujiwara-kyo Osteoporosis Risk in Men (FORMEN) Cohort Study

Masayuki Iki[a,*], Yuki Fujita[a], Katsuyasu Kouda[b], Akiko Yura[a], Takahiro Tachiki[a], Junko Tamaki[c], Yuho Sato[d], Jong-Seong Moon[e], Masami Hamada[f], Etsuko Kajita[f], Nozomi Okamoto[g], Norio Kurumatani[h]

[a] Department of Public Health, Kindai University Faculty of Medicine, 377-2 Oono-higashi, Osaka-Sayama, Osaka 589-8511, Japan
[b] Department of Hygiene and Public Health, Kansai Medical University, 2-5-1 Shin-machi, Hirakata, Osaka 573-1010, Japan
[c] Department of Hygiene and Public Health, Osaka Medical College, 2-7 Daigakumachi, Takatsuki, Osaka 569-8686, Japan
[d] Department of Human Life, Jin-ai University, 3-1-1 Ohdecho, Echizen, Fukui 915-8586, Japan
[e] Department of Nursing, Kio University, 4-2-2 Umami-naka, Koryo-cho, Nara 635-0832, Japan
[f] Chukyo Gakuin University Faculty of Nursing, 2216 Tokicho, Mizunami, Gifu 509-6192, Japan
[g] Graduate School of Education, Hyogo University of Teacher Education, 942-1 Shimokume, Kato-City, Hyogo 673-1494, Japan
[h] Nara Medical University School of Medicine, 840 Shijocho, Kashihara, Nara 634-8521, Japan

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ABSTRACT

Purpose: Many studies have reported that patients with a history of gastrectomy (gastrectomized patients) have lower areal bone mineral density (aBMD) and higher fracture risk than those without. However, population-based studies on this topic are scarce, and little is known regarding the bone metabolic status of gastrectomized patients in the long-term. This study aimed to clarify the association of gastrectomy with aBMD, bone metabolism markers, and fracture risk in community-dwelling elderly Japanese men.

Methods: A total of 1992 men aged ≥65 years completed baseline measurements including aBMD at the spine and hip, serum levels of intact parathyroid hormone (PTH), intact osteocalcin (OC), tartrate-resistant acid phosphatase isoenzyme 5b (TRACP5b), and undercarboxylated OC (ucOC), and an interview regarding past medical history including gastrectomy. Osteoporotic fractures (OPFs) that occurred during the 5-year follow-up period were determined through structured interviews.

Results: After excluding participants with type 1 diabetes mellitus and those with missing values, 1985 men, including 132 gastrectomized men, were analyzed. Gastrectomized men had significantly higher PTH, TRACP5b, and ucOC levels, and lower aBMD, than non-gastrectomized men. Gastrectomy was associated with a significantly higher risk of OPF after adjusting for confounding variables (hazard ratio (HR): 2.55, 95% confidence interval (CI): 1.17, 5.55), and the risk was no longer significant when further adjusted for PTH and aBMD. Even in this model, however, increase in OPF risk was significant in gastrectomized men who survived 20 years or more after the surgery (HR: 3.56, 95% CI: 1.33, 9.52).

Conclusions: History of gastrectomy was associated with elevated bone resorption, decreased aBMD, and increased fracture risk in community-dwelling elderly Japanese men. This increase in fracture risk was more prominent long after gastrectomy.

1. Introduction

Despite a reduction in the incidence of gastric cancer in recent years, it remains one of the most common cancers worldwide. It occurs in more than one million people a year and kills nearly 80 thousand annually [1,2]. Curative treatment for gastric cancer involves gastrectomy, although endoscopic mucosal resection has become popular for early stage gastric cancer. Nonetheless, gastrectomy is indicated for > 70% of patients with gastric cancer [3,4], and more than half of gastrectomized patients survive long-term [3]. Moreover, many elderly

* Corresponding author.
E-mail address: masa@med.kindai.ac.jp (M. Iki).

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individuals who previously underwent gastrectomy for peptic ulcer remain alive, despite the dramatic decrease in the number of gastrectomies performed for ulcers [5]. Thus, the gastrectomized population in society is considerable, and postgastrectomy syndrome remains an issue.

Postgastrectomy syndrome includes bone-related disorders. Many studies have reported an increased prevalence of osteoporosis and elevated risk of osteoporotic fractures in gastrectomized patients. However, most of these studies have been cross-sectional [6–12], and lacked a non-gastrectomized control group for comparison [7,9–16]. In addition, only a few population-based longitudinal studies have shown an increase in risk of osteoporotic fracture associated with gastrectomy [16–18]. For instance, Seo et al. [16] performed a nationwide medical insurance claim database study in South Korea in which 37,076 gastrectomized men and women with gastric cancer were examined for subsequent osteoporotic fracture risk. That study reported that older age, female gender, diabetes mellitus, total gastrectomy (compared with partial gastrectomy), and chemotherapy were associated with increased fracture risk. Although a population-based study targeting an Asian population, it did not report a risk estimate of fracture for gastrectomized people compared with non-gastrectomized people due to the lack of a non-gastrectomized control group. In another study, Nilsson et al. [17] reported a three-fold higher fragility fracture risk in patients with a history of gastrectomy for peptic ulcer than those without in a retrospective 20-year follow-up study of a cohort in Sweden. Increased risk of fracture was also observed in another population-based cohort in Rochester, Minnesota, with 2.2- to 4.7-fold higher risk at different skeletal sites in gastrectomized people during a mean follow-up period of 14.5 years compared to values expected from the general population [18]. While these studies clearly demonstrate a significantly increased fracture risk after gastrectomy, they did not assess bone metabolic status or areal bone mineral density (aBMD) of their study populations.

On the other hand, several clinic-based follow-up studies have reported increased levels of PTH [13] and bone turnover markers [14], decreased aBMD [13,14,19], and increased incidence rate of fractures [15] during relatively short follow-up periods ranging from one to six years, again without a non-gastrectomized control group for comparison. Thus, the effects of gastrectomy on bone metabolism, aBMD, and fracture risk remain unclear, especially in the long-term.

The present study aimed to clarify the association of gastrectomy conducted long before a baseline survey with bone metabolism markers and aBMD at baseline and subsequent five-year fracture risk in community-dwelling elderly Japanese men.

2. Materials and methods

2.1. Study setting

The Fujiwara-kyo Osteoporosis Risk in Men (FORMEN) study is an ancillary study of a larger prospective cohort study, “The Cohort Study for Functioning Capacity and Quality of Life in Elderly Japanese”. The study, also referred to as the Fujiwara-kyo study, aims to provide a scientific basis for comprehensive strategies to prevent frailty, increase the number of healthy life years, and enhance the functioning and quality of life of elderly men and women in Japan, enrolled volunteer men and women in four cities of Nara Prefecture, Japan, who were aged ≥65 years at enrollment, living at home, able to walk without assistance from another person, and able to provide self-reported information and written informed consent. The study included various measurements necessary for geriatric and gerontologic assessments and 250 item-questionnaire covering past history and present involvement of diseases, injuries and fractures, lifestyle factors, quality of life scales, and current health status and symptoms. The FORMEN study evaluates bone health in male participants of the Fujiwara-kyo study. Most of the non-skeletal measurements and interviews were conducted in the Fujiwara-kyo study, and these data form a comprehensive geriatric and gerontologic basis for the FORMEN study to evaluate risk factors of osteoporosis and osteoporotic fracture in elderly men. Details of the Fujiwara-kyo and FORMEN studies have been described elsewhere [20].

2.2. Study participants

Of the 4427 participants of the Fujiwara-kyo study, 2012 men completed the FORMEN baseline study, and were invited to follow-up surveys conducted five years later with the aim of identifying osteoporotic fractures as the outcome.

The study protocol of the Fujiwara-kyo study was approved by the Medical Ethics Committee of Nara Medical University. The protocol of the FORMEN study was approved by the Ethics Committee of Kindai University Faculty of Medicine.

2.3. Identification of outcome

Trained nurses determined the site of fracture, time of fracture event, situation in which the fracture occurred, and X-ray diagnosis of the fracture (yes/no) from interviews conducted during the follow-up surveys. The same information was obtained in supplemental postal and telephone surveys conducted just after the follow-up surveys for those who did not participate in the follow-up surveys. Osteoporotic fracture (OPF) was defined as a fracture at any skeletal site other than the head, finger, lower thigh, and foot that occurred after baseline without strong external force and was diagnosed by a medical doctor with radiographs. We excluded lower thigh and foot fractures from OPF since the risk of these fractures does not increase with age [21]. Major OPF (MOF) included an OPF at the spine, hip, proximal humerus, or distal radius. In cases of multiple fractures, the first fracture during the follow-up period was adopted as the outcome.

This method was validated using 21 incident fractures identified during the first two years of follow-up. Of these, 19 cases provided consent for us to contact the attending surgeon in order to confirm the occurrence, date, and skeletal site of the fracture. All surgeons responded to our inquiries and confirmed the occurrence of all self-reported fractures, that differences between the self-reported date and real date of fracture events were within six months, and that the self-reported fracture site did not differ from the correct site at the bone level. We concluded that the false positive rate for fracture detection using the present method was extremely low (0% in this study) and that the margin of error in fracture dates and skeletal sites would be acceptable [22,23].

2.4. Medical history

Trained nurses interviewed participants based on answers to a self-administered questionnaire consisting of 250 items that covered lifestyle factors including smoking (current, ex-, or non-smoker) and drinking habits (number of drinking days per week and number of drinks on drinking day), and medical history of fracture, gastrectomy, malignant diseases, hypertension, diabetes mellitus, coronary heart disease, dyslipidemia, asthma, kidney disease, prostate disease, and medications to treat these diseases. When a history of gastrectomy was reported, information regarding age or calendar year at the time of gastrectomy and the reason for gastrectomy were additionally requested. Participants were asked to bring current prescriptions of medications to the baseline visit, and interviewers recorded the names and doses of the medications.

2.5. Laboratory measurements

Blood was drawn from each participant after an overnight fast. Plasma and serum samples were obtained for the following biochemical

measurements: fasting plasma glucose (FPG), glycated hemoglobin A_{1c} (HbA1c), creatinine, triglycerides, cholesterol, and biochemical markers of bone metabolism including intact osteocalcin (OC), tartrate-resistant acid phosphatase isoenzyme 5b (TRACP5b), intact parathyroid hormone (PTH), and undercarboxylated osteocalcin (ucOC).

OC (ng/ml) was measured as a bone formation marker by a two-site immunoradiometric assay (BGP IRMA kit Mitsubishi, Mitsubishi Kagaku Iatron Inc., Tokyo, Japan) with a sensitivity of 1 ng/ml [24], 4.9% intra-assay coefficient of variation (CV), 3.7% inter-assay CV, and 6.1% overall CV. TRACP5b was measured as a bone resorption marker by a fragment-absorbed immunocapture enzyme assay (Osteolinks-TRAP-5b, Nitto Boseki, Kooriyama, Japan) with a sensitivity of 19.2 mU/dl [25], 4.9% intra-assay CV, 7.3% inter-assay CV, and 8.8% overall CV. Intact PTH (pg/ml) was measured by an electrochemiluminescence immunoassay (Elecsys PTH assay, Roche Diagnostics K. K., Tokyo, Japan) [26] with a sensitivity of 4 pg/ml, 2.6% intra-assay CV, 1.2% inter-assay CV, and 2.8% overall CV. ucOC (ng/ml) was measured as a marker for vitamin K sufficiency by an electrochemiluminescence immunoassay (Picolumi ucOC, Sanko Junyaku Co. Ltd., Tokyo, Japan) with a sensitivity of 0.39 ng/ml [27], 4.1% intra-assay CV, 3.5% inter-assay CV, and 5.4% overall CV.

To evaluate renal function, estimated glomerular filtration rate (eGFR) was calculated with the Modification of Diet in Renal Disease Study equation modified for the Japanese population by the Japanese Society of Nephrology, as follows: eGFR (ml/min/1.73 m^2) = 194 × serum creatinine$^{-1.094}$ × age$^{-0.287}$ [28].

2.6. Bone mass measurements

aBMD (g/cm^2) was measured at baseline and follow-up by dual-energy X-ray absorptiometry (DXA) at the lumbar spine and total hip in the posteroanterior projection (QDR4500A, Hologic Inc., Bedford, MA, USA). The region of interest at the spine was set as the second to fourth vertebrae, in accordance with Japanese guidelines for diagnosing osteoporosis at the time of the survey [29]. We excluded vertebrae with fractures or degenerative changes causing more than a 1 SD greater aBMD from the immediately adjacent vertebrae, in accordance with the International Society for Clinical Densitometry guidelines for individual vertebrae exclusion [30]. Consequently, 1897 participants at baseline and 1518 at follow-up had at least two assessable vertebrae. We scanned the right hip unless the right hip showed significant deformity or had been replaced with an artificial hip. Valid hip aBMD values were obtained from 1987 participants at baseline and 1634 at follow-up.

Imputations for missing aBMD values were conducted with values estimated from the multivariate regression equation incorporating age, height, weight, and hip aBMD for spine aBMD imputation or spine aBMD for hip aBMD imputation. We imputed aBMD values of 95 spines and 5 hips at baseline, and 118 spines and 2 hips at follow-up, with estimated BMD values. BMD values at the spine and hip were available in 1992 men at baseline and 1636 men at follow-up.

Short-term precision of aBMD measurements was 1.2% for both the spine and hip, as calculated from five measurements on different days from five male volunteers (age range, 21–41 years) [31]. Quality assurance was conducted using a spine phantom throughout the study period, and no significant drift in measurements was detected.

2.7. Body size measurements

We measured the height (cm) and weight (kg) of participants using an automatic scale and calculated BMI (kg/m^2).

2.8. Statistical analyses

All statistical analyses were performed with SAS software (Version 9.4, SAS Institute, Cary, NC, USA). Levels of conventional biochemical tests and biochemical markers for bone metabolism were all distributed log-normally; therefore, these values were logarithmically converted and then statistically analyzed. These data are expressed as geometric means and SDs. Participants were classified into two sets of three groups. The first set included participants without a history of gastrectomy (non-gastrectomized men), those who underwent gastrectomy for gastric cancer, and those who underwent gastrectomy for gastric or duodenal ulcer. The second set included non-gastrectomized men, those who underwent gastrectomy < 20 years before the baseline survey (years since gastrectomy, YSG < 20), and those with YSG ≥ 20. Fracture risk in these groups was evaluated with Cox proportional hazards models including potential confounding factors as covariates. We applied a stepwise selection of independent variables for the final model of fracture risk. Correlations between reasons for gastrectomy and YSG groups were evaluated with the Kendall rank correlation coefficient Tau-b.

3. Results

3.1. Baseline characteristics of gastrectomy groups

Of the 2012 men who completed the FORMEN baseline study, 1637 underwent the follow-up survey. We conducted supplemental mail and telephone surveys to obtain outcomes for 375 men who did not participate in the follow-up survey, and 373 men responded. Consequently, we obtained study outcome data for 2010 men in total. We excluded 4 men with type 1 diabetes mellitus and 21 with missing values for predictors or outcome. None of the men had hyperparathyroidism. From the remaining 1985 men, we identified 132 who underwent gastrectomy for gastric cancer or gastric or duodenal ulcer. Mean YSG was 18.8 years, and 9.7 years for men who underwent gastrectomy for cancer and 30.4 years for ulcer.

Table 1 shows participant characteristics by reason for gastrectomy or YSG. Gastrectomized men showed higher levels of bone metabolism markers and lower aBMD at baseline, and suffered greater decreases in aBMD during the follow-up period than non-gastrectomized men. Gastrectomized men were significantly older and lighter in weight, had lower hemoglobin, triglyceride, and LDL-cholesterol levels, and had higher HDL-cholesterol levels than non-gastrectomized men.

During the median follow-up of 4.5 years (8626 person-years (PY)), there were 44 OPFs (5.1/1000 PY) (spine, 18; distal forearm, 9; rib, 9; hip, 3; pelvis, 2; clavicle, 1; proximal humerus, 1; elbow, 1). MOFs occurred in 31 men (3.6/1000 PY). A significantly higher incidence rate of OPF was found in gastrectomized men (13.9/1000 PY) than in non-gastrectomized men (4.5/1000 PY). This difference in OPF incidence was more prominent in men who underwent gastrectomy for ulcer (16.5/1000 PY) and those with YSG ≥ 20 (24.2/1000 PY).

3.2. Gastrectomy and bone metabolism markers and aBMD

Table 2 shows age- and BMI-adjusted mean levels of bone metabolism markers and aBMD in gastrectomized and non-gastrectomized men. PTH, TRACP5b, and ucOC levels were elevated in men who underwent gastrectomy for cancer and men with YSG < 20, while aBMD was significantly lower in men who underwent gastrectomy for ulcer and men with YSG ≥ 20 compared to non-gastrectomized men. Gastrectomized men with YSG < 20 had suffered a significantly greater loss of hip aBMD during the follow-up period than non-gastrectomized men.

3.3. Age-adjusted HRs of baseline variables on the incidence of OPF

Table 3 shows age-adjusted HRs of baseline variables on incident osteoporotic fractures. Gastrectomized men had a higher risk of OPF and MOF, although this increase in risk did not reach statistical significance for MOF. Men who underwent gastrectomy for ulcer and those with YSG ≥ 20 both showed significantly increased fracture risk

Table 1
Baseline characteristics and change in aBMD and incidence rate of fracture during the 5-year follow-up period in participants of the FORMEN Cohort Study grouped by history of gastrectomy.

	Non-gastrectomized	Gastrectomized	*p* value	Reason for gastrectomy				Years since gastrectomy			
				Cancer	*p* value	Ulcer	*p* value	< 20	*p* value	≥20	*p* value
N (%)	1853 (93.4)	132 (6.6)		74 (56.1)		58 (43.9)		75 (56.8)		57 (43.2)	
Years since gastrectomy	–	18.8 ± 14.8		9.7 ± 8.3		30.4 ± 13.3		7.4 ± 4.5		33.9 ± 9.1	
PTH (pg/ml)[A]	20.2 $^{\times}/_{+}$ 1.6	22.7 $^{\times}/_{+}$ 1.6	$p = 0.004$	23.7 $^{\times}/_{+}$ 1.5	$p = 0.003$	21.5 $^{\times}/_{+}$ 1.8	$p = 0.401$	23.9 $^{\times}/_{+}$ 1.5	$p = 0.001$	21.3 $^{\times}/_{+}$ 1.8	$p = 0.510$
Osteocalcin (ng/ml)[B]	4.9 $^{\times}/_{+}$ 1.5	5.3 $^{\times}/_{+}$ 1.6	$p = 0.034$	5.5 $^{\times}/_{+}$ 1.7	$p = 0.058$	5.0 $^{\times}/_{+}$ 1.5	$p = 0.518$	5.4 $^{\times}/_{+}$ 1.6	$p = 0.075$	5.1 $^{\times}/_{+}$ 1.5	$p = 0.381$
TRACP5b (mU/dl)[B]	208.4 $^{\times}/_{+}$ 1.7	274.3 $^{\times}/_{+}$ 1.7	$p < 0.001$	298.3 $^{\times}/_{+}$ 1.8	$p < 0.001$	247.2 $^{\times}/_{+}$ 1.6	$p = 0.021$	287.7 $^{\times}/_{+}$ 1.8	$p < 0.001$	257.6 $^{\times}/_{+}$ 1.6	$p = 0.005$
ucOC (ng/ml)[B]	2.8 $^{\times}/_{+}$ 1.9	3.8 $^{\times}/_{+}$ 2.0	$p < 0.001$	4.1 $^{\times}/_{+}$ 2.2	$p < 0.001$	3.4 $^{\times}/_{+}$ 1.8	$p = 0.021$	4.0 $^{\times}/_{+}$ 2.1	$p < 0.001$	3.6 $^{\times}/_{+}$ 2.0	$p = 0.007$
LS-aBMD (g/cm^2)	1.016 ± 0.189	0.938 ± 0.176	$p < 0.001$	0.942 ± 0.186	$p = 0.001$	0.934 ± 0.164	$p = 0.001$	0.967 ± 0.158	$p = 0.012$	0.900 ± 0.193	$p < 0.001$
Hip-aBMD (g/cm^2)	0.884 ± 0.125	0.807 ± 0.126	$p < 0.001$	0.820 ± 0.138	$p < 0.001$	0.791 ± 0.109	$p < 0.001$	0.834 ± 0.119	$p < 0.001$	0.771 ± 0.128	$p < 0.001$
Age (years)	72.9 ± 5.2	74.6 ± 5.5	$p < 0.001$	74.2 ± 5.6	$p = 0.002$	75.1 ± 5.3	$p = 0.002$	74.1 ± 5.6	$p = 0.048$	75.2 ± 5.3	$p < 0.001$
Height (cm)	162.8 ± 5.7	163.0 ± 5.7	$p = 0.665$	162.0 ± 5.5	$p = 0.039$	164.4 ± 5.6	$p = 0.039$	162.3 ± 5.7	$p = 0.431$	164.0 ± 5.5	$p = 0.114$
Weight (kg)	61.3 ± 8.5	56.1 ± 8.4	$p < 0.001$	54.7 ± 8.1	$p = 0.004$	58.0 ± 8.4	$p = 0.004$	55.0 ± 7.8	$p < 0.001$	57.6 ± 8.9	$p = 0.001$
BMI (kg/m^2)	23.1 ± 2.7	21.1 ± 2.5	$p < 0.001$	20.8 ± 2.4	$p < 0.001$	21.4 ± 2.6	$p < 0.001$	20.8 ± 2.3	$p < 0.001$	21.4 ± 2.8	$p < 0.001$
Red blood cell count (/mm^3)	460 ± 45.0	429 ± 49	$p < 0.001$	422 ± 52	$p < 0.001$	439 ± 45	$p < 0.001$	126 ± 53	$p < 0.001$	434 ± 44	$p < 0.001$
Hemoglobin (g/dl)	14.7 ± 1.2	13.6 ± 1.6	$p < 0.001$	13.4 ± 1.7	$p < 0.001$	13.9 ± 1.5	$p < 0.001$	13.7 ± 1.5	$p < 0.001$	13.5 ± 1.8	$p < 0.001$
FpG (mg/dl)	101.3 $^{\times}/_{+}$ 1.2	99.9 $^{\times}/_{+}$ 1.3	$p = 0.401$	95.7 $^{\times}/_{+}$ 1.2	$p = 0.276$	105.5 $^{\times}/_{+}$ 1.3	$p = 0.276$	98.3 $^{\times}/_{+}$ 1.2	$p = 0.241$	102.0 $^{\times}/_{+}$ 1.3	$p = 0.801$
HbA1c (%)	5.3 $^{\times}/_{+}$ 1.1	5.4 $^{\times}/_{+}$ 1.1	$p = 0.024$	5.4 $^{\times}/_{+}$ 1.1	$p = 0.076$	5.5 $^{\times}/_{+}$ 1.2	$p = 0.122$	5.4 $^{\times}/_{+}$ 1.1	$p = 0.190$	5.5 $^{\times}/_{+}$ 1.2	$p = 0.047$
Triglycerides (mg/dl)	116.2 $^{\times}/_{+}$ 1.6	90.9 $^{\times}/_{+}$ 1.6	$p < 0.001$	81.9 $^{\times}/_{+}$ 1.6	$p < 0.001$	103.8 $^{\times}/_{+}$ 1.5	$p = 0.077$	85.4 $^{\times}/_{+}$ 1.5	$p < 0.001$	98.7 $^{\times}/_{+}$ 1.6	$p = 0.012$
HDL-cholesterol (mg/dl)	53.4 $^{\times}/_{+}$ 1.3	60.2 $^{\times}/_{+}$ 1.3	$p < 0.001$	62.7 $^{\times}/_{+}$ 1.3	$p < 0.001$	57.2 $^{\times}/_{+}$ 1.3	$p = 0.044$	63.5 $^{\times}/_{+}$ 1.3	$p < 0.001$	56.2 $^{\times}/_{+}$ 1.3	$p = 0.143$
LDL-cholesterol (mg/dl)	119.9 $^{\times}/_{+}$ 1.3	106.8 $^{\times}/_{+}$ 1.3	$p < 0.001$	104.0 $^{\times}/_{+}$ 1.4	$p < 0.001$	110.4 $^{\times}/_{+}$ 1.3	$p = 0.013$	106.5 $^{\times}/_{+}$ 1.3	$p = 0.001$	107.1 $^{\times}/_{+}$ 1.3	$p < 0.001$
eGFR (ml/min/1.73 m^2)	65.5 $^{\times}/_{+}$ 1.2	67.7 $^{\times}/_{+}$ 1.3	$p = 0.086$	67.0 $^{\times}/_{+}$ 1.3	$p = 0.482$	68.7 $^{\times}/_{+}$ 1.2	$p = 0.042$	66.9 $^{\times}/_{+}$ 1.3	$p = 0.504$	68.8 $^{\times}/_{+}$ 1.2	$p = 0.027$
History or comorbidity, n (%)											
Osteoporosis medication	19 (1.0)	4 (3.0)	$p = 0.062$	2 (2.7)	$p = 0.192$	3 (3.5)	$p = 0.132$	2 (2.7)	$p = 0.200$	2 (3.5)	$p = 0.128$
Type 2 diabetes mellitus	220 (11.9)	14 (10.6)	$p = 0.781$	5(6.8)	$p < 0.265$	9 (15.5)	$p = 0.409$	7 (9.3)	$p = 0.588$	7 (12.3)	$p = 0.837$
Prostate cancer with hormone therapy	28 (1.5)	3 (2.3)	$p = 0.457$	0(0)	$p = 0.624$	3 (5.2)	$p = 0.065$	0 (0)	$p = 0.624$	3(5.3)	$p = 0.063$
Glucocorticoid therapy	42 (2.3)	3 (2.3)	$p = 1.000$	3(4.1)	$p = 0.248$	0 (0)	$p = 0.637$	2 (2.7)	$p = 0.688$	1(1.8)	$p = 1.000$
Stroke	123 (6.6)	6 (4.6)	$p = 0.464$	1(1.4)	$p = 0.086$	5 (8.6)	$p = 0.588$	2 (2.7)	$p = 0.231$	4(7.0)	$p = 0.789$
eGFR < 60	538 (29.0)	31 (23.5)	$p = 0.195$	17(23.0)	$p = 0.296$	14 (24.1)	$p = 0.465$	19 (25.3)	$p = 0.603$	12(21.1)	$p = 0.235$
Osteoporotic fracture	54 (2.9)	5 (3.8)	$p = 0.590$	3(4.1)	$p = 0.479$	2 (3.5)	$p = 0.687$	3(4.0)	$p = 0.485$	2(3.5)	$p = 0.683$
Major osteoporotic fracture	21 (1.1)	2 (1.5)	$p = 0.663$	1(1.4)	$p = 0.580$	1 (1.7)	$p = 0.494$	1(1.3)	$p = 0.584$	1(1.8)	$p = 0.488$
Lifestyle factors, n (%)											
Current smokers	318 (17.2)	18 (13.6)	$p = 0.338$	9 (12.2)	$p = 0.342$	9 (15.5)	$p = 0.860$	10 (13.3)	$p = 0.437$	8 (14.0)	$p = 0.720$
Daily drinkers	443 (23.9)	38 (28.8)	$p = 0.208$	19 (25.7)	$p = 0.781$	19 (32.8)	$p = 0.122$	20 (26.7)	$p = 0.196$	18 (31.6)	$p = 0.208$
Change in aBMD (%/year)[C]											
LS-aBMD	0.03 ± 1.55	−0.36 ± 1.57	$p = 0.018$	−0.51 ± 1.64	$p = 0.011$	−0.15 ± 1.46	$p = 0.478$	−0.41 ± 1.63	$p = 0.034$	−0.27 ± 1.49	$p = 0.237$
Hip-BMD	−0.43 ± 0.82	−0.66 ± 0.94	$p = 0.009$	−0.75 ± 0.92	$p = 0.004$	−0.53 ± 0.97	$p = 0.471$	−0.79 ± 0.93	$p = 0.001$	−0.45 ± 0.93	$p = 0.931$
Incidence, N (rate/1000 PY)											
Osteoporotic fracture	36 (4.5)	8 (13.9)	$p = 0.007$	3(9.4)	$p = 0.187$	5 (16.5)	$p = 0.007$	2 (6.1)	$p = 0.658$	6 (24.2)	$p = 0.001$
Major osteoporotic	27 (3.4)	4 (7.0)	$p = 0.147$	2 (6.3)	$p = 0.307$	2 (7.8)	$p = 0.219$	1 (3.1)	$p = 1.000$	3 (12.1)	$p = 0.058$

(*continued on next page*)

Table 1 (*continued*)

	Non-gastrectomized	Gastrectomized	*p* value	Reason for gastrectomy				Years since gastrectomy			
				Cancer	*p* value	Ulcer	*p* value	< 20	*p* value	≥ 20	*p* value
Follow-up time (year)	4.3 ± 1.0	4.4 ± 1.1	$p = 0.875$	4.3 ± 1.1	$p = 0.769$	4.4 ± 1.1	$p = 0.565$	4.4 ± 1.0	$p = 0.845$	4.3 ± 1.2	$p = 0.984$

Data are expressed as mean ± SD, geometric mean ×/÷ SD, or number (proportion in %).
% for men who underwent gastrectomy for cancer or ulcer, and those for years since gastrectomy (YSG) < 20 or YSG ≥ 20 are presented as the proportion of 132 gastrectomized men.
YSG were calculated for 132 gastrectomized men.
p values were calculated for differences relative to non-gastrectomized men.
N: number of men.
BMI: body mass index.
LS: lumbar spine.
aBMD: areal bone mineral density.
FPG: fasting plasma glucose.
HDL: high-density lipoprotein.
LDL: low-density lipoprotein.
eGFR: estimated glomerular filtration rate.
TRACP5b: tartrate-resistant acid phosphatase 5b isoenzyme.
PTH: parathyroid hormone.
ucOC: undercarboxylated osteocalcin.
PY: person years.
[A] For 1785 men, reference range: 10–65 pg/ml.
[B] For 1941 men.
[C] For 1517 men.

compared to non-gastrectomized men. Since ex-smokers did not have a significant HR compared with non-smokers, they were included in the non-smoker category.

3.4. Adjusted HRs for gastrectomy on the incidence of OPF

To evaluate independent effects of gastrectomy on the incidence of OPF, we adjusted this association for baseline characteristics that showed significant or nearly significant ($p < 0.1$) age-adjusted HRs on incident OPF (Table 3), i.e., PTH, spine and hip aBMD, weight, hemoglobin, FPG, HbA1c, triglyceride, history of stroke and OPF, current smoker, and daily drinker. Among these, hip aBMD and HbA1c were not included in the analysis since they were highly correlated with LS-aBMD and FPG, respectively. PTH and aBMD were intermediate factors between gastrectomy and fracture, and analyzed separately from other confounding factors.

The results of this analysis are shown in Table 4. After adjusting for confounding factors, history of gastrectomy was associated with an increased risk of incident OPF (Model 1). When classified by reason for gastrectomy, those who underwent gastrectomy for ulcer showed a significantly increased risk of OPF, but those who underwent gastrectomy for cancer did not (Model 1b). When stratified by YSG, men with YSG ≥ 20 showed a significantly higher risk of OPF than non-gastrectomized men (Model 1c). Gastrectomy did not show a significantly increased risk in any model for MOF (data not shown).

To evaluate effects of PTH and aBMD on the association between gastrectomy and OPF risk, we additionally entered PTH and aBMD into the models. When PTH was entered into Model 1a, HR of OPF for gastrectomy decreased from 2.81 to 2.41, but the latter HR remained significant (Model 2). When aBMD was further entered, HR of OPF for gastrectomy was no longer significant (Model 3a). However, in the model incorporating gastrectomy stratified by reason for gastrectomy (Model 3b) or YSG (Model 3c), those who underwent gastrectomy for ulcer or those with YSG ≥ 20 showed a significantly higher risk of OPF.

Men who underwent gastrectomy for cancer had a shorter YSG and those who underwent gastrectomy for ulcer had a longer YSG (Table 1), with an extremely high correlation between reason for gastrectomy and YSG (Tau-b = 0.922, $p < 0.001$). To clarify which was associated with the increased risk of OPF (ulcer or long YSG), we calculated the incidence rate of OPF in gastrectomized men for cancer and ulcer in men with YSG < 20 or YSG ≥ 20. Incidence rates were 0 (/1000 PY) and 7.4 for ulcer and cancer, respectively, for men with YSG < 20, and 25.0 and 21.0, respectively, for men with YSG ≥ 20. There were no significant differences in fracture incidence rates between those who underwent gastrectomy for cancer and for ulcer in men with either YSG < 20 or YSG ≥ 20 (or both combined), while a significant difference in incidence rates was observed between YSG < 20 and YSG ≥ 20 when combining men who underwent gastrectomy for cancer and for ulcer by the Mantel-Haenszel method ($p = 0.0497$).

4. Discussion

In the present study, community-dwelling elderly gastrectomized Japanese men had significantly higher bone resorption, lower aBMD, and higher risk of osteoporotic fractures independently of confounding factors, compared to non-gastrectomized men. Increased OPF risk was more prominent in men who survived for > 20 years after gastrectomy.

Most, but not all [9], previous studies on this topic reported an association between gastrectomy and low aBMD or elevated risk of fracture, but only a few studies [17,18] have provided a quantitative risk estimate. These studies reported an approximately three-fold higher risk of fracture in gastrectomized people compared to non-gastrectomized people. The present study showed for the first time that Japanese elderly men have a similar level of risk to that previously reported for Caucasians.

We first demonstrated an association between gastrectomy and

Table 2
Age- and BMI-adjusted mean values of bone metabolism markers and bone mineral density according to history of gastrectomy in participants of the FORMEN Cohort Study.

	Non-gastrectomized (N = 1853)		Gastrectomized (N = 132)			Reason for gastrectomy		
						Cancer (N = 74)		
	Adjusted mean	95% CI	Adjusted mean	95% CI	p value	Adjusted mean	95% CI	p value
At baseline								
PTH (pg/ml)[A]	20.2	(19.8, 20.6)	22.2	(20.5, 24.0)	$p = 0.027$	22.9	(20.6, 25.4)	$p = 0.044$
Osteocalcin (ng/ml)[B]	4.9	(4.8, 5.0)	5.1	(4.8, 5.5)	$p = 0.203$	5.3	(4.8, 5.9)	$p = 0.181$
TRACP5b (mU/dl)[B]	209.6	(204.4, 214.9)	253.5	(230.4, 279.0)	$p < 0.001$	273.0	(240.3, 310.3)	$p < 0.001$
ucOC (ng/ml)[B]	2.8	(2.8, 2.9)	3.6	(3.3, 4.1)	$p < 0.001$	3.9	(3.4, 4.6)	$p < 0.001$
LS-aBMD (g/cm^2)	1.013	(1.005, 1.021)	0.976	(0.945, 1.007)	$p = 0.026$	0.962	(0.916, 1.008)	$p = 0.405$
Hip-aBMD (g/cm^2)	0.881	(0.876, 0.886)	0.846	(0.826, 0.865)	$p < 0.001$	0.863	(0.894, 0.853)	$p = 0.337$
Change during 5-year follow-up								
LS-aBMD (%/year)[C]	0.01	(−0.07, 0.09)	−0.16	(−0.46, 0.15)	$p = 0.297$	−0.30	(−0.71, 0.10)	$p = 0.242$
Hip-aBMD (%/year)[C]	−0.44	(−0.48, −0.40)	−0.56	(−0.72, −0.40)	$p = 0.159$	−0.66	(−0.87, −0.45)	$p = 0.085$

	Reason for gastrectomy			Years since gastrectomy					
	Ulcer (N = 58)			< 20 years (N = 75)			≥ 20 years (N = 57)		
	Adjusted mean	95% CI	p value	Adjusted mean	95% CI	p value	Adjusted mean	95% CI	p value
At baseline									
PTH (pg/ml)[A]	21.9	(18.8, 24.0)	$p = 0.653$	23.2	(20.9, 25.7)	$p = 0.023$	20.9	(18.5, 23.6)	$p = 0.826$
Osteocalcin (ng/ml)[B]	4.9	(4.4, 5.5)	$p = 0.994$	5.3	(4.8, 5.8)	$p = 0.266$	5.0	(4.4, 5.6)	$p = 0.943$
TRACP5b (mU/dl)[B]	231.5	(200.9, 266.6)	$p = 0.319$	264.6	(233.3, 300.1)	$p < 0.001$	239.7	(207.5, 276.9)	$p = 0.139$
ucOC (ng/ml)[B]	3.3	(2.8, 3.9)	$p = 0.164$	3.8	(3.3, 4.4)	$p < 0.001$	3.4	(2.9, 4.0)	$p = 0.071$
LS-aBMD (g/cm^2)	0.987	(0.946, 1.028)	$p = 0.072$	1.011	(0.970, 1.052)	$p = 0.997$	0.931	(0.884, 0.977)	$p = 0.001$
Hip-aBMD (g/cm^2)	0.824	(0.794, 0.853)	$p < 0.001$	0.876	(0.850, 0.902)	$p = 0.918$	0.806	(0.776, 0.832)	$p < 0.001$
Change during 5-year follow-up									
LS-aBMD (%/year)[C]	0.05	(−0.42, 0.52)	$p = 0.242$	−0.21	(−0.60, 0.18)	$p = 0.483$	−0.08	(−0.57, 0.41)	$p = 0.922$
Hip-aBMD (%/year)[C]	−0.42	(−0.67, −0.17)	$p = 0.984$	−0.71	(−0.92, −0.51)	$p = 0.023$	−0.32	(−0.58, −0.07)	$p = 0.616$

Mean values are adjusted for age and BMI.
p values were calculated for differences relative to non-gastrectomized men.
Data are expressed as mean ± SD, geometric mean ×/÷ SD, or number (proportion in %).
N: number of men.
CI: confidence interval.
LS: lumbar spine.
aBMD: areal bone mineral density.
TRACP5b: tartrate-resistant acid phosphatase 5b isoenzyme.
PTH: parathyroid hormone.
ucOC: undercarboxylated osteocalcin.
[A] For 1785 men.
[B] For 1941 men.
[C] For 1517 men.

Table 3
Age-adjusted hazard ratio for baseline characteristics on incident osteoporotic fractures during the 5-year follow-up period in participants of the FORMEN Cohort Study.

Variables for baseline characteristics	Unit/category	Outcome					
		Osteoporotic fracture			Major osteoporotic fracture		
		HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Gastrectomy	Overall (N = 132)/no gastrectomy	2.85	(1.31, 6.16)	0.008	1.96	(0.68, 5.63)	0.213
	For cancer (N = 74)/no gastrectomy	1.94	(0.60, 6.32)	0.272	1.76	(0.42, 7.42)	0.442
	For ulcer (N = 58)/no gastrectomy	3.96	(1.55, 10.2)	0.004	2.21	(0.52, 9.35)	0.282
	YSG < 20 y (N = 75)/no gastrectomy	1.26	(0.30, 5.23)	0.753	0.86	(0.12, 6.31)	0.879
	YSG ≥ 20 y (N = 57)/no gastrectomy	4.95	(2.07, 11.8)	< 0.001	3.45	(1.04, 11.5)	0.044
PTH[A]	1 SD increase	2.46	(1.19, 5.09)	0.016	2.73	(1.14, 6.50)	0.024
Osteocalcin[B]	1 SD increase	0.97	(0.72, 1.31)	0.852	0.70	(0.31, 1.57)	0.386
TRACP5b[B]	1 SD increase	0.94	(0.55, 1.61)	0.833	0.73	(0.40, 1.33)	0.300
ucOC[B]	1 SD increase	1.31	(0.81, 2.13)	0.267	1.46	(0.82, 2.60)	0.200
LS-aBMD	1 SD increase	0.40	(0.28, 0.56)	< 0.001	0.30	(0.19, 0.45)	< 0.001
Hip-aBMD	1 SD increase	0.49	(0.36, 0.67)	< 0.001	0.41	(0.29, 0.59)	< 0.001
Height	1 SD increase	0.97	(0.72, 1.32)	0.857	1.03	(0.72, 1.47)	0.882
Weight	1 SD increase	0.79	(0.58, 1.09)	0.147	0.97	(0.92, 1.01)	0.116
BMI	1 SD increase	0.82	(0.61, 1.11)	0.196	0.89	(0.78, 1.02)	0.095
Red blood cell count (/mm^3)	1 SD increase	0.82	(0.61, 1.12)	0.224	0.76	(0.53, 1.09)	0.133
Hemoglobin (g/dl)	1 SD increase	0.72	(0.55, 0.95)	0.018	0.68	(0.49, 0.93)	0.015
FPG	1 SD increase	1.37	(1.13, 1.67)	0.002	1.48	(1.20, 1.82)	< 0.001
HbA1c	1 SD increase	1.36	(1.08, 1.71)	0.009	1.48	(1.16, 1.91)	0.002
Triglycerides	1 SD increase	0.74	(0.54, 1.01)	0.060	0.80	(0.55, 1.15)	0.220
HDL-cholesterol	1 SD increase	1.28	(0.40, 4.04)	0.680	0.97	(0.68, 1.38)	0.862
LDL-cholesterol	1 SD increase	1.10	(0.81, 1.49)	0.356	2.00	(0.46, 8.67)	0.352
eGFR	1 SD decrease	0.82	(0.59, 1.14)	0.230	1.21	(0.82, 1.78)	0.340
History or comorbidity							
Osteoporosis medication	Present/absent	3.30	(0.78, 14.0)	0.105	2.52	(0.34, 18.9)	0.369
Type 2 diabetes mellitus	Present/absent	1.67	(0.78, 3.60)	0.188	2.20	(0.95, 5.10)	0.067
Prostate cancer with hormone therapy	Present/absent	2.70	(0.65, 11.3)	0.172	2.01	(0.27, 14.9)	0.493
Stroke	Present/absent	2.44	(1.08, 5.52)	0.033	2.00	(0.69, 5.78)	0.201
eGFR < 60	Present/absent	0.82	(0.42, 1.60)	0.553	0.78	(0.35, 1.78)	0.560
Osteoporotic fracture	Present/absent	4.36	(1.71, 11.1)	0.002	3.74	(1.13, 12.4)	0.031
Major osteoporotic fracture	Present/absent	1.86	(0.26, 13.5)	0.542	2.79	(0.38, 20.6)	0.314
Lifestyle factors, n (%)							
Current smokers	Yes/no	0.79	(0.58, 1.09)	0.063	0.36	(0.09, 1.53)	0.167
Daily drinkers	Yes/no	0.42	(0.17, 1.1)	0.071	0.34	(0.10, 1.1)	0.078

HR: hazard ratio.
95% CI: 95% confidence interval.
YSG: years since gastrectomy.
TRACP5b: tartrate-resistant acid phosphatase isoenzyme 5b.
PTH: parathyroid hormone.
ucOC: undercarboxylated osteocalcin.
LS: lumbar spine.
aBMD: areal bone mineral density.
BMI: body mass index.
FPG: fasting plasma glucose.
HbA1c: glycated hemoglobin A1c.
HDL: high-density lipoprotein.
LDL: low-density lipoprotein.
eGFR: estimated glomerular filtration rate.
No model incorporating glucocorticoid therapy was obtained since no fracture occurred in those undergoing glucocorticoid therapy.
[A] For 1785 men.
[B] For 1941 men.

bone metabolism status or aBMD in a population-based study. aBMD was lower in gastrectomized men, especially those with YSG ≥ 20, but levels of PTH and TRACP5b were significantly higher in those with YSG < 20 compared to non-gastrectomized men. Some clinic-based studies have reported increased levels of PTH and bone turnover markers soon after gastrectomy [14], but no study has reported bone metabolism status 20 years after gastrectomy. Our findings suggest that bone resorption increases, and aBMD decreases, during the first 20 years after gastrectomy, and that this elevated bone turnover subsides ≥20 years after gastrectomy while the decrease in aBMD remains, thereby leading to increased fracture risk.

The mechanism underlying the gastrectomy-related increase in fracture risk has been explained as follows: decreased absorption of calcium and vitamin D [32–34] due to resection of the stomach leads to reduced serum calcium levels, which in turn increases bone resorption by elevating PTH levels, leading to a decrease in aBMD. As shown in Table 4, the multi-adjusted HR of OPF for gastrectomy (2.81) was virtually unchanged from the age-adjusted HR (2.85). This suggests that the gastrectomy-related increase in fracture risk is independent of covariates in Model 1, including FPG, triglyceride, history of OPF and stroke, and drinking habits. However, this HR decreased from 2.81 to 2.41 when PTH was added to the model, and decreased to 2.13 by further addition of aBMD. These changes suggest that PTH and aBMD are intermediate factors among the causal chain between gastrectomy

Table 4
Adjusted hazard ratio for history of gastrectomy on incident osteoporotic fractures during the 5-year follow-up period in participants of the FORMEN Cohort Study (N = 1985).

Model	Predictors	Category/unit	Osteoporotic fracture	
			HR	95% CI
Model 1a	Gastrectomy	Overall (N = 132)/no gastrectomy	2.81	(1.28, 6.18)
	FPG	1 SD increase	1.45	(1.19, 1.77)
	Triglycerides	1 SD increase	0.72	(0.52, 1.00)
	History or comorbidity			
	Osteoporotic Fx	Present/absent	3.95	(1.55 10.1)
	Stroke	Present/absent	2.63	(1.16, 6.00)
	Daily drinker	Yes/no	0.38	(0.15 0.95)
Model 1b	Gastrectomy	For cancer (N = 74)/no gastrectomy	2.00	(0.59, 6.64)
		For ulcer (N = 58)/no gastrectomy	3.71	(1.43, 9.60)
Model 1c	Gastrectomy	YSG < 20 y (N = 75)/no gastrectomy	1.13	(0.27, 4.77)
		YSG ≥ 20 y (N = 57)/no gastrectomy	5.38	(2.24, 12.9)
Model 2	Gastrectomy	Overall (N = 132)/no gastrectomy	2.41	(1.04, 5.60)
	PTH	1 SD increase	3.44	(1.14, 10.3)
Model 3a	Gastrectomy	Overall (N = 132)/no gastrectomy	2.13	(0.92, 4.93)
	PTH	1 SD increase	2.87	(0.90, 9.17)
	LS-aBMD	1 SD increase	0.42	(0.29, 0.60)
Model 3b	Gastrectomy	For cancer (N = 74)/no gastrectomy	1.82	(0.54, 6.09)
		For ulcer (N = 58)/no gastrectomy	2.91	(1.02, 8.32)
Model 3c	Gastrectomy	YSG < 20 y (N = 75)/no gastrectomy	1.27	(0.30, 5.34)
		YSG ≥ 20 y (N = 57)/no gastrectomy	3.56	(1.33, 9.52)

N: number of men.
HR: hazard ratio.
95% CI: 95% confidence interval.
LS: lumbar spine.
aBMD: areal bone mineral density.
FPG: fasting plasma glucose.
Fx: fracture.
YSG: years since gastrectomy.
PTH: parathyroid hormone.
Stepwise selection of independent variables was applied from age, body mass index, hemoglobin, osteoporosis medication and current smoker in addition to variables incorporated in Model 1a.
All models incorporated the same covariates as Model 1a, and the covariates had similar estimates.

and fracture. However, PTH and aBMD may not explain all the effects of gastrectomy on the increase in fracture risk since gastrectomy had an insignificant but two-fold increase in fracture risk even in the fully adjusted model (Model 3a), and also showed a significant increase in men who underwent gastrectomy for ulcer or with YSG ≥ 20. This BMD-independent increase in HR could be explained by an increase in ucOC levels in gastrectomized men. ucOC is a marker for vitamin K sufficiency [35], and higher ucOC levels imply vitamin K insufficiency, which can lead to an increased risk of osteoporotic fractures [36,37]. Gastrectomized people exhibit a decreased ability to absorb lipids due to the shortening of passage time through the duodenum or due to bypassing the duodenum [38], resulting in reduced absorption of lipid-soluble vitamins including vitamin K. Thus, gastrectomy may have increased the fracture risk in our study population through a vitamin K-related pathway in addition to a decrease in bone mass.

Weight loss is a common symptom of postgastrectomy syndrome [39,40] and is related to changes in the levels of hormones, such as ghrelin, leptin, and adiponectin, following gastrectomy [41,42]. This could potentially lead to a decrease in aBMD. Weight loss may also be involved in the gastrectomy-related increase in fracture risk. Although we had data on baseline weight, which was significantly lower in gastrectomized men than in non-gastrectomized men, the weight was measured at a mean of 18.8 years after gastrectomy. Moreover, we did not have information on changes in weight following gastrectomy and serum concentrations of weight-related hormones. Further studies will be needed to elucidate the mechanism underlying the association between gastrectomy and fracture risk.

According to our results, surgeons should keep in mind the increased risk of osteoporotic fractures later in life (20 years later) in patients who undergo gastrectomy. In this regard, aBMD and vitamin D and vitamin K sufficiency should be monitored periodically over a long period, and patients should be treated as necessary when they present with low aBMD or vitamin D or K insufficiency. Long-term survivors are a target population for osteoporosis screening and for controlling osteoporotic fracture risk.

According to Seo et al., the median duration from gastrectomy to first fracture was 3.1 years in their nationwide 5-year longitudinal study [16], suggesting that an increased risk of fracture can present soon after gastrectomy. The mean duration since gastrectomy to outcome fracture in the present study was 31.6 years, which is much longer than that reported by Seo et al. [16]. This discrepancy is caused by the difference in study design, in which we registered fractures as an outcome at a mean of 18.8 years after gastrectomy, rather than soon after gastrectomy. We may therefore underestimate the risk of fracture soon after gastrectomy since gastrectomized men who suffered a fracture soon after gastrectomy may have less likely to participate in the present study.

The present study has several strengths. First, this is the first Japanese population-based study on this topic that touched on bone metabolism status and aBMD and that demonstrated increased ucOC levels in gastrectomized men. Second, the study had a relatively large sample size that likely reflects the health status of a community-dwelling elderly male population in Japan. Third, the study was conducted as part of an ongoing cohort study that anticipates 20 years of follow-up with several waves of clinical surveys at a university hospital, which allows for further follow-up studies with our present study population. Finally, as this is a single-center study, it lacks inter-center variation.

However, there are also several limitations worth noting. First, because our participants were volunteers, those who underwent gastrectomy for advanced cancer may have been less likely to participate. We identified only 44 men with incident osteoporotic fractures, which was approximately one-half of the expected number. This was not due to drop-outs from the cohort since the follow-up rate was extremely high. This also suggests that participating men were likely to be healthier than their counterparts in the general population. This could have led to healthy user bias, resulting in an underestimation of the association of interest and possibly leading to the lack of a significant association between gastrectomy and fracture risk in those with YSG < 20. Second, our sample size was not large enough to examine associations relating to MOF and skeletal site-specific fractures. Third, participants were restricted to elderly Japanese men; thus, caution should be exercised in applying the results to other racial/ethnic groups or women. Fourth, history of gastrectomy was based on self-report. Therefore, misclassification may have occurred, although this could have also underestimated the strength of the associations. Also, information regarding the type of resection (total or partial resection) and reconstruction methods of the stomach was not available from interview data. It was not possible, therefore, to examine differences in fracture risk by type of resection and reconstruction method. We also lacked data on whether men who underwent gastrectomy for cancer also underwent anti-cancer chemotherapy, which has been reported to increase fracture risk [16]. Thus, we could not evaluate the impact of chemotherapy on fracture risk after gastrectomy. Fifth, we did not measure serum calcium and 25-hydroxyvitamin D levels, and did not have information on the use of calcium or vitamin D supplements or multi-vitamins. We also did not have information on changes in body weight following gastrectomy. The lack of this information limited the ability to further consider the mechanism underlying the associations of interest. Finally, outcomes were based on self-reported data. This method of fracture detection has been repeatedly confirmed by medical charts or radiological chart reviews [43,44], but misclassification may still have occurred. In addition, two thirds of vertebral fractures are reportedly asymptomatic [45] and were therefore not examined for associations with fracture risk in the present study. Inclusion of asymptomatic vertebral fracture in the outcome may alter the association,

5. Conclusions

Gastrectomy was associated with elevated bone resorption, decreased aBMD, and elevated risk of OPF in community-dwelling elderly Japanese men. This increase in fracture risk was prominent in men who survived for 20 years or more after the surgery. Gastrectomized men should be observed long-term for the management of osteoporosis and OPF risk.

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Declaration of Competing Interest

The authors declare that they have no conflicts of interest.

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