

RESEARCH ARTICLE

Influence of alcohol sensitivity on bone metastases and skeletal-related events in primary operable breast cancer: A retrospective cohort study

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Abstract

Background

Bone metastases in breast cancer patients are a common concern for medical doctors and dentists. Bone-modifying agents, which are necessary to prevent skeletal-related events (SREs), are associated with osteonecrosis of the jaw as an adverse side effect. Hypersensitivity to alcohol is an unfavorable response caused by deficiency of aldehyde dehydrogenase-2 (ALDH2) activity. Inactive ALDH2 is associated with osteoporosis, but its influence on bone metastases is unclear. The aim of our study was to evaluate the effects of alcohol sensitivity on bone metastases and SREs in primary operable breast cancer patients.

Methods

We retrospectively analyzed patients who were administered docetaxel, an anti-tumor agent, for histologically diagnosed breast cancer between April 2004 and September 2015. Alcohol sensitivity was assessed based on medical records of hypersensitivity to alcohol. The primary endpoint was time to bone metastases and the secondary endpoint was time to first SRE from the initial docetaxel administration. Data were stratified by alcohol sensitivity and tumor stages, and differences were estimated by the Kaplan-Meier method. Prognostic risk factors were analyzed by the multivariate Cox proportional hazards model.

Results

The median follow-up period of patients with high sensitivity to alcohol ($n = 45$) was 54 months and that for those with low sensitivity ($n = 287$) was 64 months. Stratification by alcohol sensitivity revealed that tumor stage exhibited significant correlations with the cumulative incidence of bone metastases in low-sensitivity patients; however, no differences were

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found in high-sensitivity patients. In multivariate analysis, alcohol sensitivity was a significant prognostic risk factor for bone metastases (HR 2.721, 95% CI 1.268–5.841, $P = 0.010$).

Conclusion

Alcohol sensitivity may be a prognostic risk factor for bone metastases. More detailed genetic investigations and metabolic analyses are needed.

Introduction

Breast cancer is the most commonly diagnosed cancer among females and the leading cause of cancer death [1]. Bone is the most frequent metastatic site of breast cancer, and metastases cause a poor quality of life due to bone pain, pathological fracture, hypercalcemia, and spinal cord compression [2, 3]. Bone-modifying agents, such as bisphosphonates and denosumab, are clinically effective in delaying the onset of skeletal-related events (SREs) and reduce their incidence; however, both drugs are associated with medication-related osteonecrosis of the jaw (MRONJ) [2, 4, 5]. MRONJ is defined as exposed bone or bone that can be probed through an intraoral or extra oral fistula(e) in the maxillofacial region that does not heal within 8 weeks developing in a patient who received a bone-modifying agent or an angiogenic inhibitor agent with no history of head and neck radiation [6, 7]. Although MRONJ causes pain, malodor, and difficulty eating, and reduces the quality of life, it can be challenging to treat [8]. Preventive oral care methods, including comprehensive dental assessments and avoidance of modifiable risk factors, combined with effective oral health practices are recommended [6, 9]. MRONJ has become a common concern for dentists and medical doctors who are involved in the management of patients with a high risk of bone metastasis, and requires a multi-professional approach [6, 8, 10, 11].

Breast cancer cells in the bone microenvironment release soluble factors that engage osteoclasts and/or osteoblasts, resulting in bone breakdown. The breakdown of the bone matrix promotes the proliferation of cancer cells, creating a vicious cycle [12]. Breast cancer with bone metastasis is predominantly osteolytic. The outcome mainly depends on the impact of cancer cells on osteoblasts regardless of the role of osteoclasts in this process. Metastatic breast cancer cells or their conditioned media increase osteoblast apoptosis, and suppress osteoblast differentiation and expression of proteins required for new bone matrix formation [13]. Several studies suggested that aldehyde stress resulting from aldehyde dehydrogenase 2 (ALDH2) polymorphism leads to impaired osteoblastogenesis due to the lack of enzyme protection against aldehyde toxicity for osteoblasts and their progenitor cells [14–17].

Alcohol sensitivity has been studied as one of possible predictors of inactive ALDH2, as ALDH2 dysfunction contributes to various human diseases including esophageal and upper aerodigestive track cancers [17, 18]. Those with the dominant-negative form of ALDH2 protein (ALDH2*2) have high sensitivity to alcohol, which is associated with unpleasant responses, such as facial flushing, nausea, palpitations, and tachycardia, mainly in East Asian populations [18–21]. Yokoyama *et al.* assumed that individuals with current or former flushing had inactive ALDH2, and found that their responses to a simple flushing questionnaire yielded a sensitivity and specificity of approximately 90% for identifying ALDH2-deficient individuals among the Japanese general population of men and women aged 40 years or older [22–24]. Recently alcohol sensitivity has been reported to be a factor in the side effects of anticancer drugs such as paclitaxel or docetaxel containing alcohol as a solvent [25, 26]. The safety of

paclitaxel for alcohol intolerance has been studied and patients suspected of alcohol intolerance by a screening question were found to carry inactive genotypes of *ALDH2* GA (heterozygous *ALDH2* *1/*2) or *ALDH2* AA (homozygous *ALDH2* *2/*2) [26]. Such chemotherapeutic agents are essential for breast cancer treatment; thus, it is necessary to clarify alcohol sensitivity to protect patients from adverse reactions.

Aldehyde dehydrogenase-2 deficiency, which causes high sensitivity to alcohol, is associated with osteoporosis [27]; however, its influence on bone metastases is unclear. We hypothesized that high sensitivity to alcohol is a prognostic factor for bone metastases, and evaluated the effects of alcohol sensitivity on bone metastases and SREs in primary operable breast cancer patients.

Materials and methods

All procedures were approved by the Institutional Review Board at Tohoku University Graduate School of Dentistry (No. 2018-3-20). Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent. The patients were given the opportunity to opt out of the study at any time, which was announced on the website of Tohoku University Graduate School of Dentistry (http://www.dent.tohoku.ac.jp/general/open/info_02/files/2018-20.pdf).

Patients

Female patients administered docetaxel, an anti-cancer agent, for pathologically confirmed breast cancer between April 2004 and September 2015 at Tohoku University Hospital were included in this study. The data cutoff point was August 31, 2018. The medical records of each patient were retrospectively reviewed. Patients were regarded as eligible if they were aged 20 years or older, and had no recurrence or distant metastases (stage I, II, or III based on the UICC TNM classification) at the first administration of docetaxel. Docetaxel was prepared by dissolving the formulation in a solvent containing 13% ethanol. Alcohol-hypersensitive patients required ethanol-free preparations [25]. Patients with skin flushing or other uncomfortable reactions by alcohol according to their medical records and who required “alcohol-free” orders for docetaxel were assessed as having high sensitivity to alcohol. Alcohol-free orders that were requested because the patient was driving were excluded from the definition. Four hundred forty-six female patients with breast cancer who were administered docetaxel for cancer were extracted from medical records. Stage IV ($n = 95$) and recurrence ($n = 19$) were excluded from the study. Data from 332 patients were used for analysis. Forty-five patients had high sensitivity to alcohol, whereas 287 patients had low sensitivity to alcohol.

Outcome

Collected data included alcohol sensitivity (high, low), age (50 and older, younger than 50 years), clinical stage at primary diagnosis (stage I, stages II and III), local immunohistochemistry evaluation for estrogen and progesterone receptor status (ER-negative, ER-positive, PgR-negative, PgR-positive), human epidermal growth factor receptor 2 (HER2) expression (HER2-negative, HER2-positive), bone metastasis, and SREs. Types of SREs, administration of bisphosphonates or denosumab and incidence of MRONJ, were also collected from records of patients who developed bone metastasis. Bone metastasis was diagnosed using imaging studies, physical examination, or symptoms. SREs were defined as pathological fractures, need for radiation or surgical interventions to bone, spinal cord compression, bone pain, and hypercalcemia [28]. The primary endpoint of the study was time to bone metastasis, defined as the

interval from docetaxel administration to bone metastasis. The secondary endpoint was time to SREs, defined as the interval from docetaxel administration to the first SRE. The incidences of bone metastasis, pathological fractures, and development of MRONJ were also compared between patients with low sensitivity to alcohol and those with high sensitivity to alcohol.

Statistical analyses

Categorical data were compared between groups using chi-square test or Fisher's two-sided exact test as appropriate. Continuous data are presented as the median (interquartile range) and were compared by Mann-Whitney U test. Kaplan-Meier method with a log-rank test was used to estimate and compare the cumulative incidence of bone metastases and SREs. Data were stratified by alcohol sensitivity and tumor stages and a log-rank test was conducted in each stratum. Univariate analysis and multivariate analysis were performed using the Cox proportional hazards model to investigate associations between prognostic variables and time to bone metastasis or time to SREs.

Variables with $P < 0.05$ in univariate analysis were evaluated as potential covariates in multivariate analysis. A P -value less than 0.05 was considered significant. IBM SPSS Statistics for Macintosh (Version 25.0, IBM Corp., Armonk, NY) was used for statistical analysis.

Results

Baseline characteristics

Four hundred forty-six female patients with breast cancer were extracted from electric medical records for use of the anti-cancer agent docetaxel. Stage IV ($n = 95$) and recurrence ($n = 19$) were excluded from the study. Data from 332 patients were available for analysis. Forty-five patients had high sensitivity to alcohol, whereas the others had low sensitivity to alcohol (Fig 1).

Clinicopathological characteristics by sensitivity to alcohol are shown in Table 1. The clinical characteristics of age, staging, ER, PgR, and HER2 were similar between the two groups. The median follow-up period was 54 months (interquartile range 37–77 months) in patients

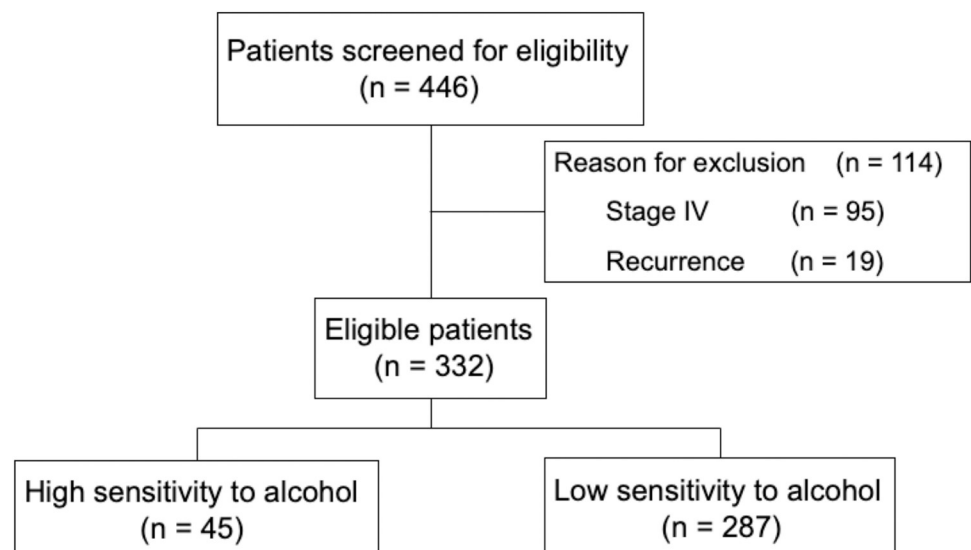


Fig 1. Flow diagram of the patients included in the analysis.

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Table 1. Clinicopathological characteristics by sensitivity to alcohol.

	Low sensitivity (n = 287)	High sensitivity (n = 45)	P-value
Age (years)			0.100
< 50	107 (37.3%)	23 (51.1%)	
≥ 50	180 (62.7%)	22 (48.9%)	
Primary staging			0.558
I	59 (20.6%)	11 (24.4%)	
II and III	228 (79.4%)	34 (75.6%)	
ER status			0.857
negative	78 (27.2%)	11 (24.4%)	
positive	209 (72.8%)	34 (75.6%)	
PgR status			0.870
negative	110 (38.2%)	18 (40.0%)	
positive	177 (61.7%)	27 (60.0%)	
HER2 status			0.086
negative	226 (78.7%)	30 (66.7%)	
positive	61 (21.3%)	15 (33.3%)	
Time (months)			
to bone metastasis	63 (41–92)	50 (34–72)	0.016
to SREs	73 (43–92.5)	50 (36–72)	0.017
Follow-up period (months)	64 (43–93)	54 (37–77)	0.037

Data are n (%) or median (interquartile range, IQR). Differences in distributions of categorical and continuous variables between groups were examined using Fisher's two-sided exact test and Mann-Whitney U test, respectively. SREs, skeletal-related events; ER, estrogen receptor; PgR, progesterone receptor; HER2, human epidermal growth factor receptor 2

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with high sensitivity to alcohol and 64 months (interquartile range 43–93 months) in patients with low sensitivity. The period was significantly shorter in patients with high sensitivity ($P = 0.037$). The median time to bone metastasis and time to first SRE were also significantly shorter in patients with high sensitivity to alcohol.

Incidence of bone metastases and SREs stratified by alcohol sensitivity and tumor stages

Bone metastasis developed in 9 of 45 patients with high sensitivity to alcohol (20%) and in 26 of 287 patients with low sensitivity to alcohol (9.1%). SREs were observed in 4 of 45 patients with high sensitivity to alcohol (8.9%) and in 10 of 287 patients with low sensitivity to alcohol (3.5%). The incidence of bone metastases and SREs were stratified by alcohol sensitivity and tumor stages and compared between stages or sensitivities in each stratum (Tables 2–5).

Risk factors

There were significant differences in the incidence of bone metastases between high and low sensitivities ($P = 0.008$) (Fig 2A) and between clinical stages (stage I vs. stages II and III) ($P = 0.026$) (Fig 2B). The high-sensitivity group had a significantly higher incidence of SREs ($P = 0.041$) (Fig 3A), whereas there was no significant difference in clinical stage (Fig 3B).

In univariate analysis, high clinical stage (stages II and III) and high sensitivity to alcohol were significant factors for bone metastases. In multivariate analysis, the hazard ratio (HR) of high clinical stage (stages II and III) for bone metastases was 4.449 (95% CI 1.066–18.564,

Table 2. Incidence of bone metastases stratified by alcohol sensitivity and tumor stages.

Strata			Number (%)	
			BM +	BM -
Alcohol sensitivity	low	stage I	1 (1.7)	58 (98.3)
		stage II	8 (6.2)	121 (93.8)
		stage III	17 (17.2)	82 (82.8)
	high	stage I	1 (9.1)	10 (90.9)
		stage II	4 (18.2)	18 (81.8)
		stage III	4 (33.3)	8 (66.7)
Tumor stage	stage I	low sensitivity	1 (1.7)	58 (98.3)
		high sensitivity	1 (9.1)	10 (90.9)
	stage II	low sensitivity	8 (6.2)	121 (93.8)
		high sensitivity	4 (18.2)	18 (81.8)
	stage III	low sensitivity	17 (17.2)	82 (82.8)
		high sensitivity	4 (33.3)	8 (66.7)

BM, bone metastases.

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$P = 0.041$). The HR of high sensitivity to alcohol for bone metastases was 2.721 (95% CI 1.268–5.841, $P = 0.010$). Both were significant prognostic factors for bone metastases (Table 6). There were no significant variables for SREs based on the Cox proportional hazards model in univariate analysis (Table 7).

SREs and MRONJ

No significant differences in the types of SREs were found by sensitivity. Pathological fracture was observed in one patient (primary staging: stage II) with high sensitivity to alcohol (Table 8). Bone-modifying agents, zoledronic acid or denosumab, were administered to 10 patients who developed bone metastases. MRONJ developed in one patient (primary staging: stage III) of the two (50%) patients with high sensitivity to alcohol, whereas no MRONJ was

Table 3. Differences of bone metastases between stages in patients stratified by alcohol sensitivity and between sensitivities in patients stratified by tumor stages.

Strata			P-value
Alcohol sensitivity	low	stage I vs. II	0.241
		stage I vs. III	0.003
		stage II vs. III	0.005
	high	stage I vs. II	0.55
		stage I vs. III	0.157
		stage II vs. III	0.249
Tumor stage	stage I	low vs. high	0.101
	stage II	low vs. high	0.017
	stage III	low vs. high	0.125

The cumulative incidence of bone metastases was significantly higher in high-sensitivity patients with tumor stage II. There were no significant differences between sensitivities in stage I and in stage III. The cumulative incidence of bone metastases was significantly higher in stage III compared to stage I or stage II in low-sensitivity patients; however, there were no significant differences between stages in high-sensitivity patients (see S1 Fig).

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Table 4. Incidence of SREs stratified by alcohol sensitivity and tumor stages.

Strata			Number (%)	
			SRE +	SRE -
Alcohol sensitivity	low	stage I	0 (0)	59 (100)
		stage II	5 (3.9)	124 (96.1)
		stage III	5(5.1)	94 (94.9)
	high	stage I	1 (9.1)	10 (90.9)
		stage II	1 (4.5)	21 (95.5)
		stage III	2 (16.7)	10 (83.3)
Tumor stage	stage I	low sensitivity	0 (0)	59 (100)
		high sensitivity	1 (9.1)	10 (90.9)
	stage II	low sensitivity	5 (3.9)	124 (96.1)
		high sensitivity	1 (4.5)	21 (95.5)
	stage III	low sensitivity	5(5.1)	94 (94.9)
		high sensitivity	2 (16.7)	10 (83.3)

SREs, skeletal-related events.

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observed in eight patients with low sensitivity to alcohol. Fisher's exact test demonstrated no significant differences between the two groups ($P = 0.20$) (Fig 4).

Discussion

Prognostic risk factors for bone metastases are a concern in breast cancer treatment worldwide [29–32]. Population-based studies in Denmark, the United Kingdom, and the United States revealed a greater incidence of bone metastases among patients with advanced stages at diagnosis of breast cancer [29, 31, 32]. A multicenter retrospective observational study in Japan reported that a large number of lymph node metastases and advanced disease stages or certain subtypes, such as luminal-HER2, HER2, and triple negative, are risk factors for bone metastases [30]. In the present study, advanced stage (stage I vs. stages II and III) was a significant prognostic factor for bone metastases, which is consistent with previous studies. In addition to stage, our multivariate analysis demonstrated that hypersensitivity to alcohol (low sensitivity vs. high sensitivity) was a significant prognostic factor for bone metastases in primary operable

Table 5. Differences of SREs between stages in patients stratified by alcohol sensitivity and between sensitivities in patients stratified by tumor stages.

Strata			P-value
Alcohol sensitivity	low	stage I vs. II	0.141
		stage I vs. III	0.076
		stage II vs. III	0.579
	high	stage I vs. II	0.617
		stage I vs. III	0.637
		stage II vs. III	0.323
Tumor stage	stage I	low vs. high	0.013
	stage II	low vs. high	0.682
	stage III	low vs. high	0.079

The cumulative incidence of SREs was significantly higher in high-sensitivity patients in tumor stage I; however, there were no significant differences between sensitivities in other stages and between stages (see S2 Fig).

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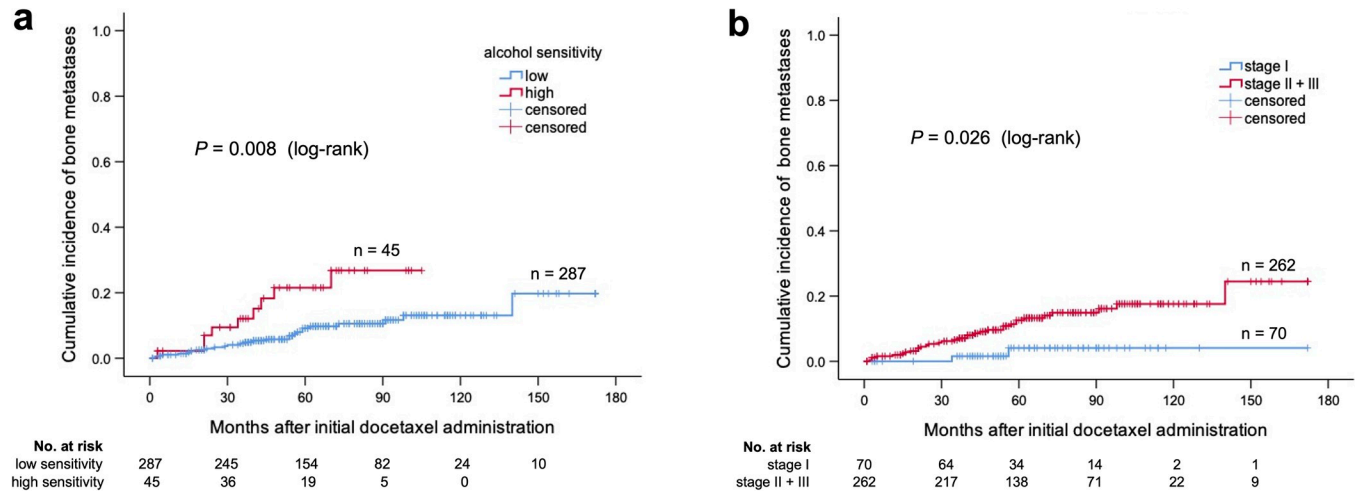


Fig 2. Cumulative incidence of bone metastases by alcohol sensitivity and clinical stages. (a) Cumulative incidence of bone metastases by alcohol sensitivity. (b) Cumulative incidence of bone metastases by clinical stage (stage I vs. stages II and III). The number below each figure is the number of patients at risk.

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breast cancer patients (Table 6). Kaplan-Meier estimates stratified by alcohol sensitivity support the hypothesis that the potential influence of tumor stages on bone metastases is relatively weaker in high-sensitivity patients (Tables 2 and 3 and S1A and S1B Fig). Knowledge about sensitivity to alcohol may be useful for reducing the risk of MRONJ because earlier dental consultation and treatment are recommended for cancer patients even before developing bone metastases [8]. In the present study, no significant variables remained in the univariate analysis for SREs (Table 7). We compared types of SREs and development of MRONJ by sensitivity to alcohol. Pathological fracture and MRONJ were observed in patients with high sensitivity to alcohol, whereas no significant differences were found between the two groups (Table 8) (Fig 4). However, the numbers of patients with SREs or MRONJ were insufficient to obtain significant results because those with stage IV and recurrence were excluded from this study.

In Japan, the consumption of alcohol among women is less prevalent than among men [33, 34]. Patients with high sensitivity to alcohol may drink fewer alcoholic beverages because of

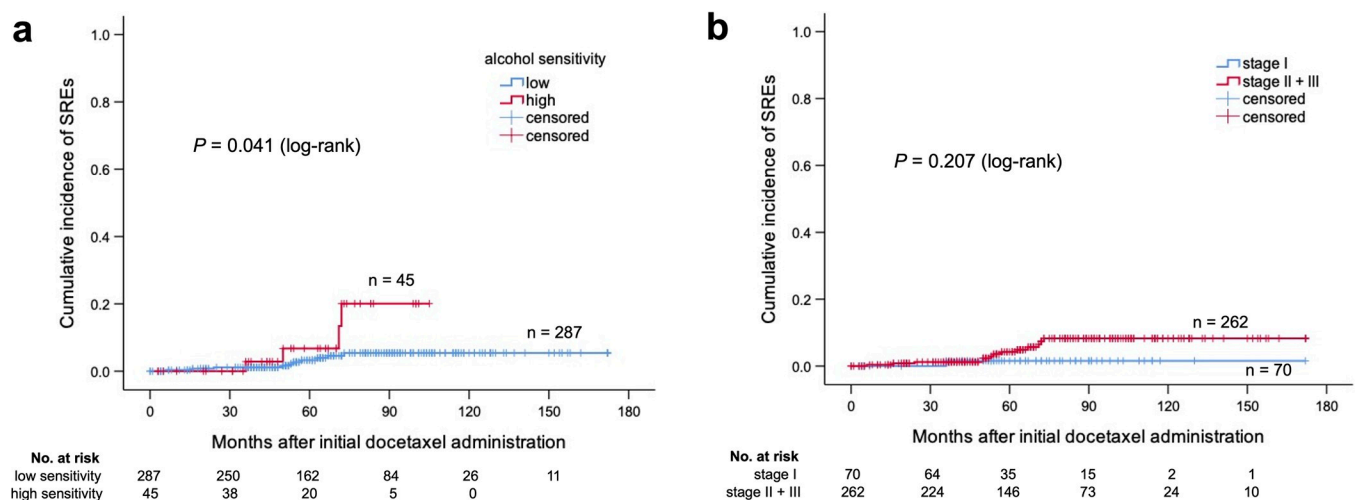


Fig 3. Cumulative incidence of SREs by alcohol sensitivity and clinical stage. (a) Cumulative incidence of SREs by alcohol sensitivity. (b) Cumulative incidence of SREs by clinical stage (stage I vs. stages II and III). The number below each figure is the number of patients at risk. SREs, skeletal-related events.

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Table 6. Univariate and multivariate analyses of risk factors for bone metastases.

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P-value*	HR	95% CI	P-value*
Age (< 50 vs. ≥ 50)	0.820	0.420–1.602	0.562			
cTNM stage (I vs. II and III)	4.409	1.057–18.393	0.042	4.449	1.066–18.564	0.041
ER (ER- vs. ER+)	1.429	0.624–3.271	0.399			
PgR (PgR- vs. PgR+)	0.996	0.502–1.977	0.991			
HER2 (HER2- vs. HER2+)	1.231	0.574–2.640	0.594			
Alcohol sensitivity (low vs. high)	2.698	1.256–5.793	0.011	2.721	1.268–5.841	0.010

ER, estrogen receptor; PgR, progesterone receptor; HER2, human epidermal growth factor receptor 2

*P-values were calculated using the Cox proportional hazards model.

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the flush reaction. In addition to alcoholic beverages, diet can be a local source of acetaldehyde as some dairy products, fruits, vegetables, and alcohol-free beverages include acetaldehyde due to the production process or as a flavor compound [35, 36]. Furthermore, mouthwashes used as oral hygiene products often contain alcohol. A large meta-analysis reported that the frequent use of mouthwash was related to oral cancer (OR = 1.11) and oropharyngeal cancer (OR = 1.28), likely through the carcinogenic activity of acetaldehyde [37]. These routes for acetaldehyde exposure may affect patients with impaired ALDH2. Host metabolism and oral microbial metabolism also function in acetaldehyde production [35, 38]. As for acetaldehyde originating from oral microbiota, a previous study reported that professional oral care reduced the level of acetaldehyde in perioperative patients with esophageal cancer [39]. A recent population-based study indicated that rs671 polymorphism of *ALDH2* increased breast cancer risk independently even after adjusting for alcohol consumption [40]. Earlier dental consultation and treatment may be useful for patients with breast cancer. Furthermore, endogenous or environmental aldehydes were suggested to play a role in genome instability by inducing haploinsufficiency of *BRCA2*, a breast cancer susceptibility gene [41]. It was reported that those deficient in ALDH2 activity accumulate endogenous formaldehyde because mitochondrial ALDH2 is essential for the metabolic clearance of formaldehyde together with cytoplasmic alcohol dehydrogenase 5 in human hematopoiesis [42]. High sensitivity to alcohol may reflect more complex metabolic cascades related to impaired ALDH2 with genetic polymorphisms or specific environmental exposure.

The present study has several limitations. The assessment of hypersensitivity to alcohol was based on medical records of alcohol sensitivity rather than genotyping of the rs671

Table 7. Univariate analyses of risk factors for SREs.

Variables	Univariate analysis		
	HR	95% CI	P-value*
Age (< 50 vs. ≥ 50)	0.462	0.160–1.332	0.153
cTNM stage (I vs. II and III)	3.423	0.448–26.174	0.236
ER (ER- vs. ER+)	2.014	0.451–9.004	0.359
PgR (PgR- vs. PgR+)	0.759	0.263–2.188	0.61
HER2 (HER2- vs. HER2+)	2.294	0.766–6.869	0.138
Alcohol sensitivity (low vs. high)	3.143	0.984–10.043	0.053

SREs, skeletal-related events; ER, estrogen receptor; PgR, progesterone receptor

HER2, human epidermal growth factor receptor 2

*P-values were calculated using the Cox proportional hazards model.

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Table 8. Types of SREs and sensitivity to alcohol.

SREs	Low sensitivity (n = 26)	High sensitivity (n = 9)	P-value*
Pathological fracture	0 (0%)	1 (11.1%)	0.226
Pain or radiation	10 (38.5%)	3 (33.3%)	
None	16 (61.5%)	5 (55.6%)	

SREs, skeletal-related events

*P-value was calculated using the chi-square test.

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polymorphism of *ALDH2*, even though a flushing questionnaire had a sensitivity and specificity of approximately 90% for identifying *ALDH2*-deficient individuals among Japanese women [23, 24]. In the present study, the rate of patients with high sensitivity to alcohol was 14% (45/332). There are two possible explanations for our results: (a) patients with high sensitivity to alcohol had the inactive form of *ALDH2* encoded by the rs671 polymorphism of *ALDH2*, and the other patients had the active form of *ALDH2*; or (b) patients with high sensitivity to alcohol had the inactive form of *ALDH2*, whereas a small number of *ALDH2*-deficient individuals were included among patients with low sensitivity to alcohol. Flushing after light drinking may disappear after a long history of drinking alcohol [18, 22]. Those with a long history of drinking may not have noticed their past flushing and received docetaxel with ethanol solution even though they have the inactive form of *ALDH2*. Thus, a lack of information about patients' lifestyle, such as alcohol consumption, diet, and oral hygiene, is a limitation of this study. Another limitation is that mild cases of MRONJ may be underestimated. Although the risk of osteonecrosis of the jaw should be evaluated before starting bone-modifying agents

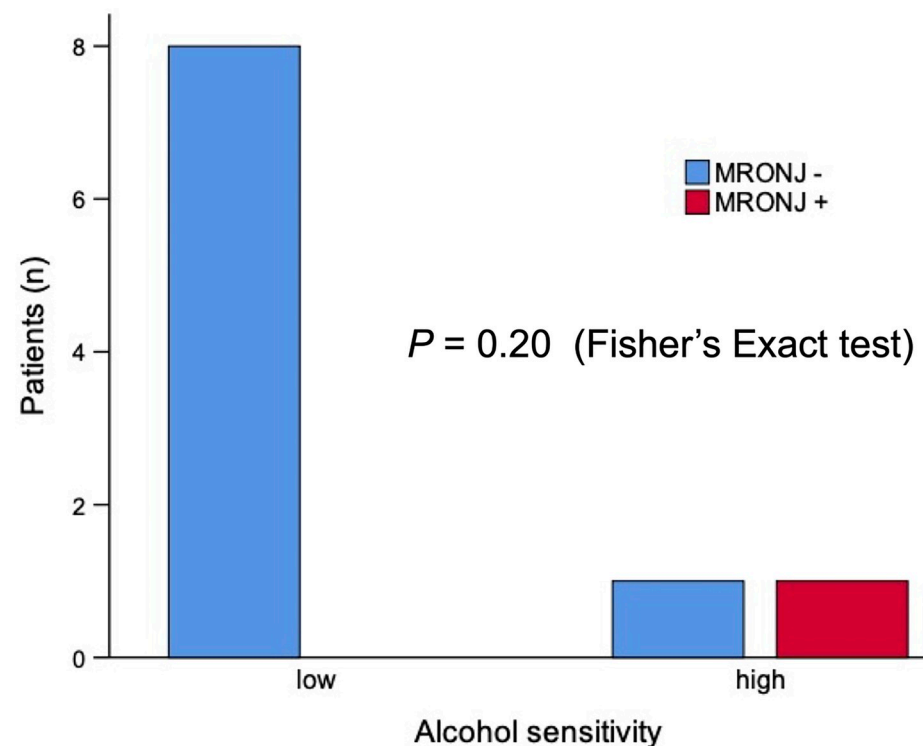


Fig 4. Alcohol-sensitivity and MRONJ in patients administered bone-modifying agents. MRONJ, medication-related osteonecrosis of the jaw.

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and patients should receive regular oral care during this treatment [43], medical doctors may have consulted dentists only after being requested to do so by patients that developed oral problems. Finally, the number of patients was small because the study was conducted at a single hospital.

In conclusion, this study suggested that sensitivity to alcohol and clinical stages are significant prognostic factors for bone metastases of primary operable breast cancer. Further genetic investigations and metabolic analyses are necessary to clarify causality.

Supporting information

S1 Fig. Kaplan-Meier estimates of cumulative incidence of bone metastases after initial docetaxel administration, stratified by alcohol sensitivity (a, b) and by tumor stages (c, d, e). (a) low sensitivity: stage I vs. III (log-rank test, $P = 0.003$), stage II vs. III ($P = 0.005$), (b) high sensitivity: no significant differences between stages, (c) stage I ($P = 0.101$), (d) stage II ($P = 0.017$), (e) stage III ($P = 0.125$).
(PDF)

S2 Fig. Kaplan-Meier estimates of cumulative incidence of SREs after initial docetaxel administration, stratified by alcohol sensitivity (a, b) and by tumor stages (c, d, e). (a) Low sensitivity: no significant differences between stages, (b) high sensitivity: no significant differences between stages, (c) stage I ($P = 0.013$), (d) stage II ($P = 0.682$), (e) stage III ($P = 0.079$).
(PDF)

S1 Dataset.
(XLSX)

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