SAHLGRENSKA UNIVERSITETSSJUKHUSET VGR

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Dental assessment for prevention of medication-related osteonecrosis of the jaw in adults with early breast cancer

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Dental assessment for prevention of medication-related osteonecrosis of the jaw in adults with early breast cancer

[Tandläkarbedömning för prevention av läkemedelsrelaterad käkbensnekros hos vuxna med tidig bröstcancer]

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The HTA report was approved by the regional board for quality assurance of activity-based HTA.

Ylva Carlsson
Head of HTA-centrum of Region Västra Götaland, Sweden, 2025-11-26

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1 Populärvetenskaplig sammanfattning – Plain language summary in Swedish

Frågeställning: Kan tandläkarbedömning före bisfosfonatbehandling minska risken för käkbensnekros och förbättra livskvaliteten hos patienter med tidig bröstcancer?

Bakgrund: Käkbensnekros innebär att delar av käkbenet dör. Det är en sällsynt men allvarlig komplikation efter tandbehandlingar, vid samtidig behandling med läkemedel av typen bisfosfonater. När behandlingsindikationen för bisfosfonater är cancer rekommenderas en tandläkarbedömning med förebyggande tandbehandling vid behov, såsom avlägsnande av tänder som är i dåligt skick, innan medicinering med bisfosfonater inleds. Detta görs i syfte att minska risken för större tandingrepp, som i värsta fall kan leda till käkbensnekros, efter att bisfosfonater satts in.

Metod: Med hjälp av etablerade metoder identifierades vetenskapliga artiklar som kunde bidra till att besvara den aktuella frågan. Studierna kvalitetsgranskades och resultaten och tilltron till det sammanlagda resultatet bedömdes enligt vedertagna metoder.

Resultat: Litteratursökningen identifierade en artikel som beskrev data från en randomiserad studie, i form av tre fallserier, som kunde inkluderas i denna rapport. Patienterna i studien hade genomgått en tandläkarbedömning inför behandling med bisfosfonater; antingen Klodronsyra (tabletter), Ibandronsyra (tabletter) eller Zoledronsyra (injektion). Av studiens 6,018 kvinnor med tidigt stadium av bröstcancer, utvecklade 48 (0,8%) käkbensnekros, under 7,5–8 års uppföljning. Drygt en tredjedel av käkbensnekroserna var tandbehandlingsrelaterade. I Sverige används endast Zoledronsyra och i en mindre dos än i studien.

Etiska aspekter: Käkbensnekros är en sällsynt men allvarlig och svårläkt biverkan som kan uppstå under eller efter bisfosfonatbehandling. Både tandläkare och patienter kan känna en oro för att käkbensnekros skall uppstå. Som en följd av att det inte finns evidensbaserade riktlinjer för huruvida man skall avlägsna tveksamma tänder i käkbensnekrosförebyggande syfte inför bisfosfonatbehandling, kan det leda till onödiga tandutdragningar. Detta kan medföra funktionell och estetisk nedsättning, och därmed försämrad munhälsorelaterad livskvalitet för patienten.

Slutsats: Det saknas vetenskapligt underlag för att kunna bedöma huruvida förebyggande tandläkarbedömning med tandingrepp vid behov, innan bisfosfonatbehandling påbörjas, påverkar risken för utveckling av läkemedelsrelaterad käkbensnekros, andra komplikationer och livskvalitet, hos vuxna med tidig bröstcancer. Baserat på mycket låg tillförlitlighet till det vetenskapliga underlaget var risken för käkbensnekros väldigt låg, och ungefär en tredjedel av samtliga käkbensnekroser uppkom efter en tandbehandling under pågående bisfosfonatbehandling.

2 Abstract

Background: Medication- related osteonecrosis of the jaw is a rare side effect of bisphosphonate medication, in this report used for treatment of early-stage breast cancer. Medication- related osteonecrosis leads to a progressive necrosis of the jawbone, which can be triggered by invasive dental procedures that traumatise the jawbone, such as tooth extraction. Evidence-based guidelines are absent, and to avoid invasive dental procedures during or after bisphosphonate treatment, prophylactic dental assessment with remedial dental procedures is often conducted prior to commencement of bisphosphonate treatment.

Question at issue: Does prophylactic dental assessment, with remedial dental procedures when necessary, prior to commencement of adjuvant bisphosphonate treatment, affect the risk of medication-related osteonecrosis of the jaw, other complications, and quality of life in adults with early-stage breast cancer?

Methods: Systematic literature searches were conducted in Medline, Embase, the Cochrane Library, and at websites of Scandinavian national and regional HTA organisations. The titles, abstracts, and subsequently full-text articles were independently screened by at least two authors. Final inclusion was decided in consensus. The included study was critically appraised using a checklist. The certainty of evidence was assessed according to GRADE. A protocol for this report was preregistered with PROSPERO (CRD420251047664).

Results: Only one publication fulfilled the inclusion criteria, reporting data from a randomised controlled trial, in form of three case series. The patients, with early-stage breast cancer, had undergone a dental assessment prior to treatment with different bisphosphonates; Clodronate (tablets), Ibandronate (tablets), or Zoledronic acid (intravenous) during 3-years. During the 7.5-8 years follow-up, 48 of the 6,018 patients, prevalence rate 0.80 (95% CI: 0.59 to 1.06)%, developed 57 medication-related osteonecrosis lesions. Twenty-two (dental extractions, n=20; other dental surgery, n=2, 39%) of the osteonecrosis lesions were related to dental treatments. In Sweden, only Zoledronate is used and in a lower dose than in the included study.

Ethical aspects: Although medication-related osteonecrosis of the jaw is a rare side effect during or after bisphosphonate medication, dentists and patients often have strong concerns about medication-related osteonecrosis of the jaw, which can lead to unnecessarily extensive tooth extractions, causing aesthetic and functional impairment, leading to reduced oral health-related quality of life for the patient.

Conclusion: There were no controlled studies assessing the effect of prophylactic dental assessment, with remedial dental procedures if deemed necessary, prior to commencement of adjuvant bisphosphonate treatment, on the risk of development of medication- related osteonecrosis of the jaw, other complications, or quality of life, in adults with early-stage breast cancer. Based on very low certainty of evidence (GRADE ⊕○○○), the risk of developing medication related osteonecrosis of the jaw was very low. About one third of the osteonecroses occurred after dental treatment during bisphosphonate medication.

The above summaries were written by representatives from HTA-centrum.

3 Summary of findings

Outcomes	Study design Number of studies	Absolute effect Number of cases (%)	Certainty of evidence (GRADE)
Medication related osteonecrosis of the jaw	3 case series (secondary analysis from one RCT)	Clodronate: 8/2,235 (0.36) Ibandronate: 12/1,552 (0.77) Zoledronic acid: * 28/2,231 (1.26)	Very low (⊕◯◯◯)[1]

*Currently used in Sweden; RCT: randomised controlled trial

[1] Case series starting at GRADE ⊕◯◯◯

4 Abbreviations

MRONJ	Medication-related osteonecrosis of the jaw
RCT	Randomised controlled trial
VGR	Region Västra Götaland

5 Background

Disease/disorder of interest and its degree of severity

Medication-related osteonecrosis of the jaw (MRONJ) is a rare but serious condition. The jawbone becomes exposed and fails to heal (>8 weeks) in patients receiving antiresorptive therapy, such as bisphosphonates or denosumab, without prior radiotherapy to the head and neck. To meet the criteria for a diagnosis of MRONJ, the patient should not previously have received radiotherapy. Both radiation therapy (osteoradionecrosis) and antiresorptive drugs (MRONJ or drug-related necrosis of the jaw) can cause jawbone necrosis. MRONJ can cause pain, infection, delayed healing, functional impairment, and may lead to a reduced oral health-related quality of life. The severity of MRONJ varies from asymptomatic exposed bone to severe infection with fistula formation and pathological fractures. While the overall risk for developing MRONJ is relatively low, the consequences for affected individuals can be significant, including the risk of permanent damage and functional impairment (Ruggiero et al., 2022; Khan et al., 2015).

Prevalence

Breast cancer is the most common malignancy among women in Sweden, with 9,898 new cases registered in 2024 (Nationellt kvalitetsregister för bröstcancer [NKBC], 2024). In early-stage breast cancer (non-M1; no metastasis), adjuvant bisphosphonate therapy (typically 4 mg zoledronic acid every six months at least two years) is used to reduce the risk of skeletal metastases and pathological fractures (Early Breast Cancer Trialists' Collaborative Group [EBCTCG], 2015).

The risk of MRONJ differs depending on the underlying disease and bisphosphonate dose (Ruggiero et al., 2022; Khan et al., 2015; Patel et al. 2018). Scientific evidence indicates that the total exposure to bisphosphonates—the cumulative dose—is a significant risk factor for the development of MRONJ (Patel et al., 2018, Ruggiero et al., 2022). In the general population, the risk of MRONJ is estimated at 0 to 0.02 percent. In patients receiving high-dose antiresorptive therapy for skeletal metastases or myeloma (intravenous 4 mg Zoledronic acid every month to every three months for at least two years), the risk is estimated at 1–5 percent (Ruggiero et al., 2022).

Present treatment and clinical pathway

Clinical practice varies considerably. Patients are often referred to specialist dental care for dental examination and elimination of infection sites, prior to initiation of the bisphosphonate treatment. However, there is no formal requirement for this indication to be referred to specialist dental care.

The risk of exacerbation of symptom free, chronic oral infections, that may be detected in x-ray images taken at the dental examination is relatively low. For example for a chronic apical periodontitis, the risk of exacerbation is estimated to be less than 5% per year (Eriksen, 2008).

The Region Västra Götaland (VGR) pays for the dental examination and elimination of infection sites, when the patient is eligible for bisphosphonate treatment where the indication can be attributed to cancer and there is a doctor's referral. This is subsidised through a specific regional dental care support as part of a healthcare treatment

coverage, and the patient cost is according to outpatient care fees in VGR, including high-cost coverage in outpatient care.

Current recommendations
Currently, there are no evidence-based national guidelines for dental management of patients receiving adjuvant bisphosphonate therapy for breast cancer. A regional medical guideline for VGR (Västra Götalandsregionen [VGR], 2024) suggests that patients receiving adjuvant bisphosphonate therapy should generally be managed in primary dental care, with a conservative treatment plan – as for the general population.

6 Health Technology at issue: Prophylactic dental assessment, with remedial dental procedure, prior to adjuvant bisphosphonate treatment

In early breast cancer, adjuvant treatment with bisphosphonates is given in order to prevent fractures and reduce the risk of skeletal metastases. In Sweden, Zoledronic acid 4 mg intravenous infusion is usually given every six months for three years. To minimise the risk of invasive dental procedures that traumatise the jawbone and could induce MRONJ, a prophylactic dental assessment—including necessary treatments—is recommended prior to initiating bisphosphonate therapy (e.g. dental examination with the aim of identifying potential foci of infection and other conditions that may cause complications or worsen the prognosis during or after ongoing medical treatment).

In VGR, the cost for a prophylactic dental assessment, including x-rays, is SEK 3,430-5,990 (additional costs may be added due to dental treatments deemed necessary).

At Sahlgrenska University Hospital in Gothenburg, approximately 60 patients per year are eligible for Zoledronic acid medication for breast cancer indication (node-positive and postmenopausal). These patients could thus also be subjected to referral for dental examination and elimination of infection sites, prior to initiation of the bisphosphonate treatment.

Although the overall risk of developing MRONJ appears to be low, concerns about its occurrence may lead to extensive tooth extractions, which may cause patient discomfort, surgical complications, surgical site infections, and delays in starting oncological treatment. Therefore, this HTA was initiated to evaluate the impact of prophylactic dental assessment and remedial procedures on the prevention of MRONJ in women with early breast cancer eligible for adjuvant bisphosphonate treatment.

7 Focused question

Does prophylactic dental assessment, with remedial dental procedures if necessary, prior to commencement of adjuvant bisphosphonate treatment affect the risk of Medication related Osteonecrosis of the Jaw MRONJ, other complications, and quality of life in adults with early breast cancer?

PICO	
P= patients	Adult patients with early breast cancer (non-M1; no metastasis) to receive adjuvant bisphosphonate treatment, with or without prior bisphosphonate therapy
I= intervention	Prophylactic dental assessment (with or without oral/dental procedures)* before bisphosphonate treatment
C=comparison	No prophylactic dental assessment before bisphosphonate treatment
O=outcome	Critical for decision making • Incidence of medication related osteonecrosis of the jaw (MRONJ) Important for decision making • Mortality • Oral health-related quality of life according to validated scales • Health-related quality of life according to validated scales • Complications • Oral health-related symptom scales, validated
Eligibility criteria	
Study design	Randomised controlled studies (RCT) non-RCTs Case series, only complications and ≥100 patients Systematic review (SR), only commented on
Publication year	2000-, SR: 2015-
Language	English, Swedish, Norwegian, Danish
Prespecified subgroup analyses for all interventions	• Comorbidity or other drug treatment • Extent of dental procedures • With or without previous bisphosphonate treatment • Different dosages • Sex • Age

* Can include everything from examining teeth to extracting teeth

8 Method

Systematic literature search (Appendix 1)

During April 2025, two of the authors, both medical librarians, performed systematic literature searches in Medline, Embase, and the Cochrane Library. Websites of Scandinavian national and regional HTA-organisations were searched as well. Reference lists of relevant reports were also scrutinised for additional references. Search strategies, eligibility criteria and a graphic presentation of the selection process are presented in Appendix 1. These authors conducted the literature searches, and independently of one another screened the obtained abstracts to decide eligibility for full-text retrieval. All abstracts were screened using the Rayyan tool (Ouzzani et al., 2016). Any disagreements were resolved in consensus. All full-text reports were read by at least two authors, independently of one another, and it was finally decided in a consensus meeting which reports should be included in the assessment.
PROSPERO registration 250523 CRD420251047664.

Critical appraisal and certainty of evidence

The included study was critically appraised independently by several authors, using a check list for case series, modified from Guo et al. (2013), with addition of the domains directness and precision by HTA-centrum (Checklist, no date). The assessments are summarised in Table 1.

Data was extracted by one author and checked by another author and summarised in Appendix 2. Data was not possible to pool in a meta-analysis, but MS Excel was used to create bar or pie charts of the results. The certainty of evidence was assessed according to the GRADE approach (Atkins et al., 2004). Summary of the results are presented in a Summary of Findings table (Chapter 3).

Ongoing research

The following search in Clinicaltrials.gov (2025-08-12) identified 39 trials: *(((breast OR breasts OR mammary OR mammaries OR mamma OR mammae OR ductal) AND (neoplasm OR neoplasms OR neoplasia OR neoplasias OR tumor OR tumors OR tumour OR tumours OR carcinoma OR carcinomas OR cancer OR cancers OR cancerous OR malignant OR malignancy OR malignancies OR sarcoma OR sarcomas OR angiosarcoma OR angiosarcomas OR adenocarcinoma OR adenocarcinomas)) AND(diphosphonate OR diphosphonates OR bisphosphonate OR bisphosphonates OR alendronate OR "alendronic acid" OR clodronate OR "clodronic acid" OR dichloromethanediphosphonate OR dichloromethanediphosphonates OR dichloromethylenebisphosphonate OR dichloromethylenebisphosphonates OR etidronate OR "etidronic acid" OR "phosphonic acid" OR ethanehydroxyphosphate OR ethanehydroxyphosphates OR ethanehydroxydiphosphone OR ethanehydroxydiphosphones OR hydroxyethanediphosphonate OR hydroxyethanediphosphonates OR hydroxyethylenediphosphonate OR hydroxyethylenediphosphonates OR ibandronate OR "ibandronic acid" OR propylidenebisphosphonate OR propylidenebisphosphonates OR pamidronate OR "pamidronic acid" OR aminopropanehydroxydiphosphonate OR aminopropanehydroxydiphosphonates OR amidronate OR risedronate OR "risedronic acid"*

OR hydroxyethylidenebisphosphonate OR hydroxyethylidenebisphosphonates OR methylenediphosphonate OR methylenediphosphonates OR zoledronate OR "zoledronic acid" OR "medicationrelated osteonecrosis" OR "medicationrelated osteonecroses" OR "medication-related osteonecrosis" OR "medication-related osteonecroses" OR MRONJ OR BRONJ)AND(dental OR dentist OR dentists OR odontology OR odontologic OR odontological OR tooth OR teeth OR jaw OR jaws OR maxilla OR maxillary OR maxillomandibular OR mandibular OR mandible OR temporomandibular OR stomatitis OR stomatitides OR oral OR intraoral OR periapex OR peri-apex OR periodontal OR periodontitis OR paradental OR parodontal OR alveolar OR alveolars OR cementum OR cementoblast OR cementoblasts OR gingivitis OR gingival OR gingiva OR gum OR gums OR papilla OR papillas OR interdental OR periapical OR peri-apical OR periapically OR peri-apically OR alveolodental OR endodontic OR endodontically OR root canal OR root canals OR caries OR carious OR exodontic exodontically OR exodentic OR exodentically OR periradicular OR orthopanthomogram OR orthopanthomography OR orthopanthomographic OR pantomogram OR pantomography OR pantomographic OR radiovisiogram OR radiovisiography OR radiovisiographic OR bitewing))

9 Results

Search results and study selection (Appendix 1)

The literature search identified 1,549 records after removal of duplicates. DedupEndNote (Lobbestael, 2023) was used for deduplication. After reading the abstracts 1,507 records were excluded. After reading full-text, 41 reports were excluded (Appendix 3), and one report was included in the assessment (Appendix 2).

Included studies

Three case series, from a pre-planned secondary analysis of an RCT (Gralow et al., 2020), were included (Kizub et al., 2021, n=6,018 women). In the RCT by Gralow et al. (2020), 6,097 women were randomised to either receive Zoledronic acid, Clodronate, or Ibandronate for three years (Table 1), 79 of which were either ineligible or withdrew. Women with planned oral surgery were discouraged from enrolment in the study. All the participants had been diagnosed with breast cancer stages I-III and had undergone surgery. Within 6 months prior to unset of bisphosphonates, the participants were required to have a dental examination performed by a dental health professional. They were monitored with a dental exam every 6-12 months for up to 5 years after completing their treatment with bisphosphonates.

Table 1 Treatment characteristics for the three case series

Bisphosphonate	Administration	Dosage	Follow-up, median
Zoledronic acid * (n=2231)	Intravenous	4 mg monthly for 6 months, then every 3 months for 3 years	7.5 years
Clodronate (n=2235)	Oral (tablets)	1,600 mg daily for 3 years	7.5 years
Ibandronate (n=1552)	Oral (tablets)	50 mg daily for 3 years	8 years

* In Sweden Zoledronic acid is the only bisphosphonate used for adjuvant treatment of breast cancer. Cumulative dosage Zoledronic acid: 72 mg, was used in Kizub et al. (2021). The currently used cumulative dosage Zoledronic acid used in Sweden: 24 mg over 3 years, for adjuvant treatment of breast cancer.

The case-series had some problems with directness (higher doses of Zoledronic acids compared to the doses used in Sweden, 18 vs. 6 doses), risk of bias (population not clearly described, not blinded), and imprecision (few events) (Table 2).

Table 2. Summary of critical appraisal

Author, year	Directness	Risk of bias	Precision
Kizub et al., 2021			

Green=no problems, yellow=some problems, red=major problems

Results per outcome

Only one outcome relevant for the PICO was reported in the included study (Kizub et al., 2021): incidence of MRONJ.

Outcomes critical for decision-making

Incidence of medication related osteonecrosis of the jaw (MRONJ) (Appendix 2)
Of 6,018 women with early-stage breast cancer, 48 (0.8%) developed MRONJ during the follow-up period (median 7.5-years for Clodronate and Zoledronic acid, and median 8-years for Ibandronate).

The 48 participants with MRONJ, developed a total of 57 osteonecrosis lesions. Twenty-two (39%) of the lesions were related to dental treatments (dental extractions, n=20; other dental surgery, n=2). Periodontal disease was considered as provoker in 25% (n=14) of the MRONJ lesions.

Of the 48 patients with MRONJ 28 were treated with Zoledronic acid, 12 with Ibandronate, and 8 with Clodronate.

Conclusion: There were no controlled studies assessing the effect of prophylactic dental assessment, with remedial dental procedures if deemed necessary, prior to commencement of adjuvant bisphosphonate treatment, on the risk of developing MRONJ, other complications, and on quality of life, in adults with early breast cancer. Based on very low certainty of evidence, the risk of developing medication related osteonecrosis of the jaw was very low (GRADE ⊕○○○).

Outcomes important for decision-making
The following outcomes were not reported: mortality; oral health-related quality of life according to validated scales; health-related quality of life according to validated scales; complications; oral health-related validated symptom scales.

10 Organisational aspects

Present use of the technology in Region Västra Götaland

At present there are no evidence-based national guidelines for dental management of patients receiving adjuvant bisphosphonate therapy for breast cancer. Clinical practice can therefore vary considerably. Patients are often referred to specialist dental care for dental examination and elimination of infection sites.

Consequences of the health technology for personnel

Dental assessment and elimination of infection sites before onset of adjuvant bisphosphonate therapy may lead to prophylactic extractions of teeth with questionable prognosis due to fear of MRONJ, even though the actual risk appears to be low. This may result in an increased burden on specialist dental services.

Consequences for other clinics or supporting functions at the hospital or in Region Västra Götaland

Prophylactic dental assessments and interventions prior to adjuvant bisphosphonate therapy may draw substantial resources from specialist dental care. This creates a risk of displacement effects, where other patient groups with greater or more urgent needs experience prolonged waiting times or reduced access to specialist services. Furthermore, in some cases oncological treatment may be delayed while awaiting dental clearance, which raises additional ethical concerns regarding timely cancer care.

11 Ethical aspects

The available evidence indicates that the absolute risk of MRONJ in patients receiving adjuvant bisphosphonate therapy for early breast cancer is low, especially when compared to high-dose regimens in metastatic disease. At the same time, prophylactic dental interventions, such as extractions of teeth with uncertain prognosis, may entail surgical risks, patient discomfort, delays in oncological treatment, and potential overtreatment.

In situations with limited evidence base and in absence of demonstrated patient benefits, the benefit–risk balance needs to be considered. The ethical principles of doing good and avoiding harm are generally applied with emphasis on the latter and therefore suggests a cautious and individualised approach, avoiding unnecessary invasive measures.

Breast cancer is a severe and potentially life-threatening condition, although patients with early-stage disease generally have a favourable prognosis. The risk of MRONJ is low but may cause chronic morbidity and reduced oral health-related quality of life. Given the severity of cancer and the potential long-term impact of MRONJ, there may be ethical justification to accept certain preventive measures, provided they are proportionate and based on the best available evidence. However, since the cumulative bisphosphonate dose in this context is comparable to osteoporosis treatment, where MRONJ risk is minimal, aggressive prophylactic strategies may not be ethically warranted.

Prophylactic referral to specialist dental care instead of public dental care, and especially routine extraction of teeth, entails costs both for the healthcare system and for patients in terms of morbidity and quality of life. Moreover, prioritising extensive prophylactic dental care for a patient group with low risk of MRONJ could lead to displacement of resources from other patients in greater need of dental care, where the patient benefit is more obvious. Thus, from an ethical standpoint, resource allocation should remain proportionate to demonstrated patient benefit.

13 Discussion

The present health technology assessment identified only one eligible study partly addressing the research question, namely three case series derived from an RCT (Kizub et al., 2021). A total of 6,018 women with early-stage breast cancer receiving adjuvant bisphosphonate therapy were included. The limited evidence base highlights a substantial knowledge gap regarding the role of prophylactic dental assessments and interventions in this patient group. Importantly, the included study reported only on the incidence of MRONJ and did not provide data on other outcomes, such as mortality, health-related quality of life, oral health-related quality of life, or treatment-related complications.

The overall incidence of MRONJ reported in the study was 0.8%, with a lower incidence observed for oral bisphosphonates (clodronate and ibandronate, 0.53%) compared to intravenous zoledronic acid (1.26%). These findings are consistent with previous reports and systematic reviews indicating that the risk of MRONJ varies by route of administration and dosage, with intravenous regimens associated with a higher risk compared to oral therapy (Ruggiero et al., 2022; Khan et al., 2015; Patel et al., 2018). The study further noted that MRONJ events were associated with dentoalveolar trauma, such as tooth extractions, or underlying periodontal disease, which aligns with the current understanding that local infection and trauma are key precipitating factors in the pathogenesis of MRONJ (Kizub et al., 2021).

Despite the large population size in the included study (Kizub et al., 2021), there were several limitations. First, there were only three case series and no control group, and the bisphosphonates used in two of the case series (clodronate and ibandronate) are currently not used for adjuvant breast cancer patients in Sweden. Second, the included study had issues with directness, as the cumulative bisphosphonate exposure was higher than in the current adjuvant breast cancer treatment in Sweden (18 versus 6 doses of zoledronic acid). This raises concerns regarding the generalisability of the results to adjuvant breast cancer patients in Sweden. Third, the risk of bias was judged to be moderate due to insufficient description of the study population, lack of blinding, and limited information on concomitant treatments or comorbidities. Fourth, the outcome reporting was narrow, focusing solely on MRONJ incidence without consideration of patient-reported outcomes, such as oral health-related quality of life, limiting the assessment of overall clinical relevance.

When comparing these findings with other studies, it is notable that the reported MRONJ incidence (0.8%) by Kizub et al. (2021) is somewhat higher than what has been reported in osteoporosis populations treated with low-dose bisphosphonates, where estimates range between 0.02% and 0.05% (Ruggiero et al., 2022; Khan et al., 2015). However, the incidence remains lower than that observed in patients treated with high-dose antiresorptive therapy for metastatic disease, where risk estimates range between 1% and 5% (Ruggiero et al., 2022). This intermediate level of risk suggests that adjuvant bisphosphonate therapy in early breast cancer, while not risk-free, is substantially safer than the high-dose regimens used in oncology settings such as multiple myeloma or advanced metastatic disease.

From a clinical perspective, the lack of robust evidence for the benefits of routine prophylactic dental care is concerning. Current practice often involves referral to

specialist dentistry, sometimes resulting in prophylactic extraction of teeth with questionable prognosis. Although such measures are intended to reduce the risk of MRONJ, the results of Kizub et al. (2021) suggest that the absolute risk is relatively low, and cases occur spontaneously at similar frequency as when associated with specific risk factors such as tooth extractions. This raises the possibility that extensive prophylactic interventions may constitute overtreatment, with associated surgical complications, patient discomfort, delays in cancer treatment and unnecessary strain on specialist services.

In conclusion, the current evidence is insufficient to establish whether prophylactic dental assessment and intervention prior to adjuvant bisphosphonate therapy in patients with early-stage breast cancer, reduces the incidence of MRONJ, improves quality of life, or prevents other complications. While the available data suggest that the overall risk of MRONJ in this patient population is low, further research is needed. Until such evidence becomes available, clinical decision-making should balance the relatively low risk of MRONJ against the potential harms and resource implications of extensive prophylactic dental procedures.

14 Future perspectives

Scientific knowledge gaps

Currently, the are no controlled studies assessing if prophylactic dental assessments and interventions prior to initiating adjuvant bisphosphonate therapy in patients with early-stage breast cancer effectively reduces the incidence of MRONJ, increase quality of life, or prevent other potential complications. Well-designed prospective studies that incorporate patient-reported outcomes are required to clarify the clinical and cost-effectiveness of prophylactic dental interventions.

Ongoing research

A search in Clinicaltrials.gov (12 Aug 2025) resulted in 39 records, none of which were relevant for the current PICO.

15 Participants in the project

The question was nominated by

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Declaration of interests

The authors declare no conflict of interest in relation to the current HTA.

Project time

The HTA was accomplished during the period of 2025-04-02 to 2025-11-25.
Literature searches were conducted 2025-04-25.

Components of this Health Technology Assessment

- ✓ Description of methods
- ✓ PICO
- ✓ Full literature search
- ✓ Flowchart
- ✓ Selection based on relevance
- ✓ Quality assessment
- ✓ Data tabulation
- ✓ Evidence synthesis
- ✓ Meta-analysis
- ✓ Certainty of evidence by GRADE
- ✓ Summary
- ✓ Economical aspects
- ✓ Organisational aspects
- ✓ Ethical aspects
- ✓ Ongoing studies
- ✓ Excluded articles
- ✓ Participation of experts
- ✓ External review
- ✓ Knowledge gaps identified
- ✓ Conflict of interest reported

Appendix 1: PICO, study selection, search strategies, and references

Question at issue: Does prophylactic dental assessment, with remedial dental procedures if necessary, prior to commencement of adjuvant bisphosphonate treatment affect the risk of Medication related Osteonecrosis of the Jaw MRONJ, other complications, and quality of life in adults with early breast cancer?

PICO: (*P=Patient I=Intervention C=Comparison O=Outcome*)

P= patients	Adult patients with early breast cancer (non-M1; no metastasis) to receive adjuvant bisphosphonate treatment, with or without prior bisphosphonate therapy
I= intervention	Prophylactic dental assessment (with or without oral/dental procedures)* before bisphosphonate treatment
C= comparison	No prophylactic dental assessment before bisphosphonate treatment
O= outcome	**Critical for decision making** Incidence of medication related osteonecrosis of the jaw (MRONJ) **Important for decision making** Mortality Oral health-related quality of life according to validated scales Health-related quality of life according to validated scales Complications Oral health-related symptom scales, validated
* Can include everything from examining teeth to extracting teeth	

<u>Eligibility criteria</u>

Study design:
Randomised controlled studies (RCT)
non-RCTs
Case series, only complications, ≥ 100 patients
Systematic review (SR), only comment on

Publication year:
2000-, Systematic reviews: 2015-

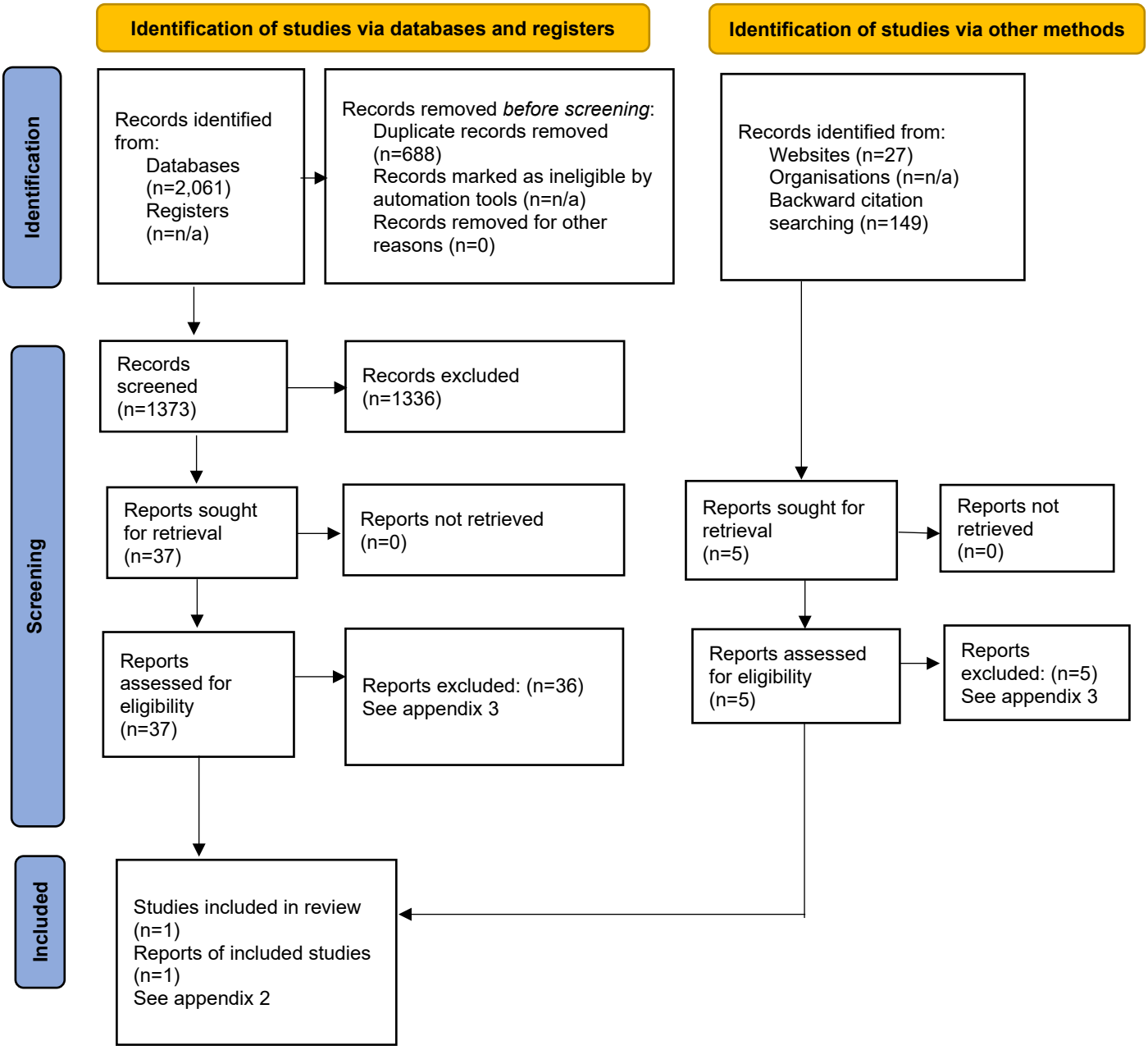
Language:
English, Swedish, Norwegian, Danish

Prespecified subgroup analyses for all interventions:

- Comorbidity or other drug treatment
- Extent of dental procedures
- With or without previous bisphosphonate treatment
- Different dosages
- Sex
- Age

Selection process – flow diagram

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources



From: Page et al., 2021

Search strategies

Database: Medline Ovid MEDLINE(R) ALL
Date: 25 Apr 2025
No. of results: 662

#	Searches	Results
1	exp Breast Neoplasms/	367771
2	((breast or breasts or mammary or mammaries or mamma or mammae or ductal) adj3 (neoplas* or tumor* or tumour* or carcinom* or cancer* or malign* or sarcoma* or angiosarcoma* or adenocarcinom*)).ab,kf,ti.	492496
3	1 or 2	554567
4	exp Diphosphonates/	29298
5	exp Bisphosphonate-Associated Osteonecrosis of the Jaw/	1911
6	(diphosphon* or bisphosphon* or alendronate* or Fosamax or MK-217 or MK217 or clodronic acid* or dichloromethanediphosphon* or dichloromethylenebisphosphon* or clodronate* or Bonefos or Cl2MDP or etidronic acid* or etidronate* or HEDSPA or phosphonic acid* or disodium salt* or ethanehydroxyphosphate* or ethanehydroxydiphosphon* or EHDP or hydroxyethanediphosphon* or hydroxyethylenediphosphon* or Didronel or Xidifon or Xidiphon or Xydiphone or ibandronic acid* or ibandronate* or propylidenebisphosphon* or Bonviva or Bondronat or Boniva or RPR-102289A or RPR102289A or "BM-21.0955" or "BM21.0955" or BM-210955 or BM210955 or pamidronate* or aminopropanehydroxydiphosphon* or amidronate* or AHPrBP or Aredia or pamidronic acid* or risedronic acid* or risedronate* or Actonel or Atelvia or hydroxyethylidenebisphosphon* or ((Tc-99 or Tc99 or Tc-99m or Tc99m or 99mTc) adj (medronate* or MDP)) or methylenediphosphon* or zoledronic acid* or CGP-42446A or CGP42446A or CGP-42446 or CGP42446 or "CGP-42'446" or "CGP42'446" or Zometa or zoledronate*).ab,kf,ti.	41429
7	((("medicationrelated osteonecros*" or "medication-related osteonecros*") adj3 jaw*) or MRONJ or BRONJ).ab,kf,ti.	2147
8	4 or 5 or 6 or 7	48692
9	exp Dentistry/	451538
10	(dent* or odontol* or tooth* or teeth* or jaw or jaws or maxill* or mandib* or temporomandib* or stomat* or oral or intraoral or periapex or peri-apex or periodont* or paradent* or parodont* or alveolar or alveolars or cementum* or cementoblast* or epitheli* or gingiv* or gum or gums or papilla or papillas or interdent* or periapical* or peri-apical* or alveolodent* or gomphos* or endodont* or root canal* or caries or carious or exodont* or exodent* or periradicular* or orthopanthomogra* or pantomogra* or radiovisiogra* or CBCT or ((radiogra* or radiolog* or xray* or x-ray* or imag* or tomogra*) adj1 (bitewing or panoram*))).ab,kf,ti.	2171530
11	9 or 10	2290050
12	3 and 8 and 11	817
13	animals/ not (animals/ and humans/)	5297610
14	12 not 13	803
15	child/ not (child/ and adult/)	1317396
16	14 not 15	802
17	(comment or editorial or letter).pt.	2321630
18	16 not 17	769
19	limit 18 to (danish or english or norwegian or swedish)	705
20	**limit 19 to yr="2000 -Current"**	**662**

Database: Embase 1974 to 2025 April 24 (OvidSP)
Date: 25 Apr 2025
No. of results: 1,211

#	Searches	Results
1	exp breast tumor/	728809
2	((breast or breasts or mammary or mammaries or mamma or mammae or ductal) adj3 (neoplas* or tumor* or tumour* or carcinom* or cancer* or malign* or sarcoma* or angiosarcoma* or adenocarcinom*)).ab,kf,ti.	699235
3	1 or 2	856578
4	exp bisphosphonic acid derivative/	84357
5	exp "bisphosphonate related osteonecrosis of the jaw"/	564
6	(diphosphon* or bisphosphon* or alendronate* or Fosamax or MK-217 or MK217 or clodronic acid* or dichloromethanediphosphon* or dichloromethylenebisphosphon* or clodronate* or Bonefos or Cl2MDP or etidronic acid* or etidronate* or HEDSPA or phosphonic acid* or disodium salt* or ethanehydroxyphosphate* or ethanehydroxydiphosphon* or EHDP or hydroxyethanediphosphon* or hydroxyethylenediphosphon* or Didronel or Xidifon or Xidiphon or Xydiphone or ibandronic acid* or ibandronate* or propylidenebisphosphon* or Bonviva or Bondronat or Boniva or RPR-102289A or RPR102289A or "BM-21.0955" or "BM21.0955" or BM-210955 or BM210955 or pamidronate* or aminopropanehydroxydiphosphon* or amidronate* or AHPrBP or Aredia or pamidronic acid* or risedronic acid* or risedronate* or Actonel or Atelvia or hydroxyethylidenebisphosphon* or ((Tc-99 or Tc99 or Tc-99m or Tc99m or 99mTc) adj (medronate* or MDP)) or methylenediphosphon* or zoledronic acid* or CGP-42446A or CGP42446A or CGP-42446 or CGP42446 or "CGP-42'446" or "CGP42'446" or Zometa or zoledronate*).ab,kf,ti.	62140
7	((("medicationrelated osteonecros*" or "medication-related osteonecros*") adj3 jaw*) or MRONJ or BRONJ).ab,kf,ti.	2462
8	4 or 5 or 6 or 7	98950
9	exp dentistry/	113353
10	exp dental examination/	12261
11	exp dental procedure/	254254
12	(dent* or odontol* or tooth* or teeth* or jaw or jaws or maxill* or mandib* or temporomandib* or stomat* or oral or intraoral or periapex or peri-apex or periodont* or paradent* or parodont* or alveolar or alveolars or cementum* or cementoblast* or epitheli* or gingiv* or gum or gums or papilla or papillas or interdent* or periapical* or peri-apical* or alveolodent* or gomphos* or endodont* or root canal* or caries or carious or exodont* or exodent* or periradicular* or orthopanthomogra* or pantomogra* or radiovisiogra* or CBCT or ((radiogra* or radiolog* or xray* or x-ray* or imag* or tomogra*) adj1 (bitewing or panoram*))).ab,kf,ti.	2614357
13	9 or 10 or 11 or 12	2686524
14	3 and 8 and 13	1932
15	animal/ not (animal/ and human/)	1244154
16	14 not 15	1931
17	child/ not (child/ and adult/)	1545470
18	16 not 17	1928
19	limit 18 to (embase or medline)	1444
20	limit 19 to (article or article in press or conference paper or note or "review")	1344
21	limit 20 to (danish or english or norwegian or swedish)	1261
22	**limit 21 to yr="2000 -Current"**	**1211**

Database: The Cochrane Library
Date: 25 Apr 2025
No of results: 188
Cochrane Reviews (3)
Other Reviews (0)

Trials (185)
Methods Studies (0)
Technology Assessments (0)
Economic Evaluations (0)
Cochrane Groups (0)

ID	Search	Hits
#1	MeSH descriptor: [Breast Neoplasms] explode all trees	20565
#2	((breast OR breasts OR mammary OR mammaries OR mamma OR mammae OR ductal) NEAR/2 (neoplas* OR tumor* OR tumour* OR carcinom* OR cancer* OR malign* OR sarcoma* OR angiosarcoma* OR adenocarcinom*)):ti,ab,kw (Word variations have been searched)	49476
#3	#1 OR #2	49497
#4	MeSH descriptor: [Diphosphonates] explode all trees	3275
#5	MeSH descriptor: [Bisphosphonate-Associated Osteonecrosis of the Jaw] explode all trees	44
#6	(diphosphon* OR bisphosphon* OR alendronate* OR Fosamax OR MK-217 OR MK217 OR (clodronic NEXT acid*) OR dichloromethanediphosphon* OR dichloromethylenebisphosphon* OR clodronate* OR Bonefos OR Cl2MDP OR (etidronic NEXT acid*) OR etidronate* OR HEDSPA OR (phosphonic NEXT acid*) OR (disodium NEXT salt*) OR ethanehydroxyphosphate* OR ethanehydroxydiphosphon* OR EHDP OR hydroxyethanediphosphon* OR hydroxyethylenediphosphon* OR Didronel OR Xidifon OR Xidiphon OR Xydiphone OR (ibandronic NEXT acid*) OR ibandronate* OR propylidenebisphosphon* OR Bonviva OR Bondronat OR Boniva OR "RPR-102289A" OR RPR102289A OR "BM-21.0955" OR "BM21.0955" OR "BM-210955" OR BM210955 OR pamidronate* OR aminopropanehydroxydiphosphon* OR amidronate* OR AHPrBP OR Aredia OR (pamidronic NEXT acid*) OR (risedronic NEXT acid*) OR risedronate* OR Actonel OR Atelvia OR hydroxyethylidenebisphosphon* OR (("Tc-99" OR Tc99 OR "Tc-99m" OR Tc99m OR 99mTc) adj (medronate* OR MDP)) OR methylenediphosphon* OR (zoledronic NEXT acid*) OR "CGP-42446A" OR CGP42446A OR "CGP-42446" OR CGP42446 OR "CGP-42'446" OR "CGP42'446" OR Zometa OR zoledronate* OR (medicationrelated NEXT osteonecros* NEAR/2 jaw*) OR (medication NEXT related NEXT osteonecros* NEAR/2 jaw*) OR MRONJ OR BRONJ):ti,ab,kw (Word variations have been searched)	6872
#7	#4 OR #5 OR #6	6907
#8	MeSH descriptor: [Dentistry] explode all trees	24647
#9	(dent* OR odontol* OR tooth* OR teeth* OR jaw OR jaws OR maxill* OR mandib* OR temporomandib* OR stomat* OR oral OR intraoral OR periapex OR "peri-apex" OR periodont* OR paradent* OR parodont* OR alveolar OR alveolars OR cementum* OR cementoblast* OR epitheli* OR gingiv* OR gum OR gums OR papilla OR papillas OR interdent* OR periapical* OR (peri NEXT apical*) OR alveolodent* OR gomphos* OR endodont* OR (root NEXT canal*) OR caries OR carious OR exodont* OR exodent* OR periradicular* OR orthopanthomogra* OR pantomogra* OR radiovisiogra* OR CBCT OR ((radiogra* OR radiolog* OR xray* OR (x NEXT ray*) OR imag* OR tomogra*) NEAR/1 (bitewing OR panoram*))):ti,ab,kw (Word variations have been searched)	316223
#10	#8 OR #9	316661
#11	#3 AND #7 AND #10	331
#12	(clinicaltrials OR trialsearch):so OR (conference proceeding):pt	815946
#13	#11 NOT #12	229
Limit search to publication year 2000-2025		**188**

The websites listed below were visited 25 Apr 2025.
Nothing relevant to the question at issue was found.

Source	Search terms / Browsing	No. of results	No. of relevant results
SBU www.sbu.se "Visa även träffar äldre än 5 år"	Bisfosfonat Bisfosfonater Bisfosfonatbehandling Bisfosfonatassocierad Bisfosfonatrelaterad Zoledronsyra	6 6 0 0 0 0 0	0 0 0 0 0 0 0

	Fokalutredning Fokalsanering Tandsanering Tandköttssanering Käkbensnekros Benvävsdöd	0 0 0 1 0	0 0 0 0 0
Folkehelseinstituttet (Norge) https://www.fhi.no/ku/metodevurdering/	Bisfosfonat Bisfosfonater Bisfosfonatbehandling Bisfosfonatassosiert Bisfosfonatrelatert Bisfosfonatindusert Zoledronsyre Fokal Fokale Fokalutredning Tann Tannsanering Tannkjøttsanering Kjeveosteonekrose	0 0 0 0 0 1 0 0 0 0 13 0 0 0	0 0 0 0 0 0 0 0 0 0 0 0 0 0
Behandlingsrådet (Danmark) https://behandlingsraadet.dk/	Browsat	0	0
Nationale Kliniske Anbefalinger og Retningslinjer (Danmark) https://www.sst.dk/da/Fagperson/Retningslinjer-og-procedurer/NKA-og-NKR/NKR-og-NKA-efter-omraade	Browsat "øvrige emner"	0	0
CAMTÖ https://www.regionorebrolan.se/sv/forskning/kontakt-och-organisation/hta-enheten-camto/	Browsat	0	0
HTA Region Stockholm https://www.chis.regionstockholm.se/hta/rapporter/	Browsat	0	0
Regional samverkansgrupp HTA (tidigare Metodrådet) i Sydöstra sjukvårdsregionen https://sydostrasjukvardsregionen.se/samverkansgrupper/hta/genomforda-bedomningar/	Browsat	0	0
HTA Syd https://vardgivare.skane.se/kompetens-utveckling/sakkunniggrupper/hta-skane/#110365	Browsat	0	0
Vetenskapliga rådet, Region Dalarna https://www.regiondalarna.se/plus/vard/utveckling-och-utbildning/kunskapsstyrning/vetenskapliga-radet/	Browsat	0	0

Reference lists

A backward citation search in Web of Science, 19 May 2025, resulted in 149 records after deduplication. Systematic reviews and guidelines assessed for eligibility in this report were used as seed references.

Articles used in backwards citation searching:

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Project: Medication-related osteonecrosis of the jaw
Appendix 2 Included studies
Outcome variable: Medication-related osteonecrosis of the jaw

* + No or minor problems
? Some problems
- Major problems

Author, year, country	Study design	Number of patients n=	Withdrawals - dropouts	Study group	Length of follow-up (median)	Age in years (median)	Events n (%)	Directness *	Study limitations *	Precision *
Kizub, 2021, USA	Case series (originally RCT)	2,235	33	Patients with stage I-III breast cancer on oral Clodronate treatment	7.5 years	52.7	8 (0.36%)	?	?	?
Kizub 2021, USA	Case series (originally RCT)	1,552	15	Patients with stage I-III breast cancer on oral Ibandronate treatment	8 years	52.7	12 (0.77%)	?	?	?
Kizub, 2021, USA	Case series (originally RCT)	2,231	31	Patients with stage I-III breast cancer on intravenous Zoledronic acid treatment	7.5 years	52.7	28 (1.26%)	?	?	?

RCT=randomised controlled trial

Project: Medication-related osteonecrosis of the jaw
Appendix 3 -Excluded articles

Author, year	Reason for exclusion
Alabdali, 2024	Wrong P (mixed breast cancer stadiums included metastasis and other cancer types), wrong I (dental procedure during bisphosphonate treatment)
Arya, 2024	Wrong P and I (already on bisphosphonate)
Avishai, 2022	Wrong P (no definition of breast cancer stadium), wrong I (no separate result for those with dental treatment before onset of bisphosphonate)
Barasch, 2011	Wrong P and I (already on bisphosphonates, no separate result for breast cancer)
Boonyapakorn, 2008	Wrong P (bone metastasis)
Borgioli, 2007	Wrong P (no definition of breast cancer stadium), unclear I (if dental treatment before onset of bisphosphonate)
Buchbender, 2022	Wrong P (no definition of breast cancer stadium), wrong I (already on bisphosphonate)
Carmagnola, 2008	Wrong P and I (already on bisphosphonates, no definition of breast cancer stadium)
Cuevas-Gonzalez, 2016	Wrong P (no definition of breast cancer stadium), wrong I (already on bisphosphonate)
Dhesy-Thind, 2017	Wrong publication type (Guidelines)
Eisen, 2022	Systematic review with wrong focus, update of a guideline
Falinda, 2022	Case series with too few participants (n=7), wrong P (no definition of breast cancer stadium)
Fehm, 2009	Wrong P (Several with bone metastasis, wrong I (already on bisphosphonate)
Francini, 2011	Wrong P (bone metastasis)
Fusco, 2013	Wrong P (bone metastasis), unclear I (if dental treatment before onset of bisphosphonate)
Hoff, 2008	Wrong P (mixed breast cancer stadiums included metastasis), wrong I
Jardim Caldas, 2021	Wrong P (mixed breast cancer stadiums), wrong I (already on bisphosphonate)
Kanno, 2023	Wrong P (no definition of breast cancer stadium)
Karaca, 2023	Wrong I (paused bisphosphonates before dental treatment)
Khayamzadeh, 2021	Systematic review with studies not suitable for our PICO
Kos, 2015	Wrong P (no definition of breast cancer stadium), wrong I (already on bisphosphonate)
Kyrgidis, 2008	Wrong P (metastasis), wrong I (already on bisphosphonate)
Kyrgidis, 2009	Wrong study design (review of another study)
Lorenzo-Pouso, 2020	Systematic review with studies not suitable for our PICO or no separate result for breast cancer or those with dental treatment before onset of bisphosphonate
Matsuo, 2016	Wrong P and I (already on bisphosphonate)
Nicolatou-Galitis, 2020	Wrong P (cancer with bone metastasis), wrong I (dental procedure after onset of bisphosphonate)
O`Connell, 2012	Wrong P and I (already on bisphosphonate)
Otto, 2015	Wrong P (no definition of breast cancer stadium, no separate results for breast cancer)
Raguladhithya, 2022	Systematic review with studies not suitable for our PICO
Rugani, 2014	Wrong P and I (already on bisphosphonate)
Sim, 2015	Wrong P (metastasis included and no separate result for breast cancer)
Skrepnek, 2010	Wrong P (mixed breast cancer stadium), wrong I (no prophylactic dental assessment)
Soares, 2020	Wrong P (metastasis), wrong I (already on bisphosphonates)
Thumbigere-Math, 2012	Wrong P (mixed breast cancer stadium), wrong I (already on bisphosphonates)

Project: Medication-related osteonecrosis of the jaw
Appendix 3 -Excluded articles

Author, year	Reason for exclusion
Thumbigere-Math, 2014	Wrong P (metastasis, no separate results for breast cancer)
Topaloglu, 2017	Wrong P (metastasis, no separate results for breast cancer)
Tsao, 2013	Wrong P (all had multiple myeloma, and one also had breast cancer, metastasis status unclear)
Ueda, 2021	Wrong P (mixed breast cancer stadium), wrong I (no prophylactic dental assessment)
Vahtsevanos, 2009	Wrong P (mixed breast cancer stadium), wrong I (no prophylactic dental assessment)
Vidal-real, 2015	Wrong P (mixed breast cancer stadium, no separate results for breast cancer), wrong I (already on bisphosphonates)
Yamazaki, 2012	Wrong P (no definition of breast cancer stadium)

PICO: P=Patients, I=Intervention, C=Comparison, O=Outcome.