A Large Case-Control Study Reveals a Positive Association Between Bisphosphonate Use and Delayed Dental Healing and Osteonecrosis of the Jaw†

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Abstract
This study sought to investigate, using a case-control study design, the association between bisphosphonate therapy and delayed dental healing and osteonecrosis of the jaw. Identification of potential cases of delayed dental healing was by consecutive screening of Specialist Oral and Maxillofacial and Special Needs Dentist clinic records for patients aged over 50 years, during a 6-month window, in Victoria, Australia. Cases were confirmed by a case adjudication panel blinded to bisphosphonate status. Cases associated with malignancy or local radiotherapy were excluded. Controls were matched for age, gender and source of dental referral (1:4, n=160 controls). Variables of interest were dental precipitants, dental clinic type, smoking history and medical comorbidities. 4212 of 22,358 patients met inclusion criteria, of which 69 were potential cases with 40 (0.95%) confirmed cases. The odds ratio for developing delayed dental healing when taking an oral bisphosphonate was 13.1 (95% CI 4.4 to 39.3; P<0.001). There were no cases associated with intravenous bisphosphonate use. There was some evidence of an interaction with age, gender and clinic type. When adjusted for smoking, the estimated odds ratio was 11.6 (95% CI 1.9 to 69.4; P=0.01). There was an association between having another illness and delayed dental healing (OR=2.3; 95% CI 1.0 to 5.2). A dental precipitant was present in 39 out of 40 (97.5%) delayed dental healing cases. An important association between bisphosphonate use and delayed dental healing in the setting of benign bone disease, predominately in individuals with a dental precipitant has been demonstrated.

Key Words: dental biology, osteoporosis, antiresorptives
Introduction

Osteonecrosis associated with bisphosphonate use is defined as exposed bone in the maxillofacial region of greater than 8 weeks duration following a dental intervention or occurring spontaneously and in the absence of other potential bone pathology such as is seen in metastatic bone disease or irradiation to the jaw.\textsuperscript{1-3} Delayed dental healing, a potential osteonecrosis precursor, is similar in clinical presentation where the failure to heal occurs within 6 weeks of initial recognition by a clinician.\textsuperscript{4}

Oral bisphosphonates have good efficacy and safety profiles in the management of osteoporosis.\textsuperscript{5} Similarly, intravenous bisphosphonates have well-established roles in the management of oncological and benign bone conditions.\textsuperscript{3,6} However, a concern about the use of bisphosphonates is their potential relationship with jaw osteonecrosis, a painful chronic condition recalcitrant to conventional dental treatment.\textsuperscript{2,7} The link between osteonecrosis and bisphosphonate use remains controversial, with uncertainty about causal association, level of risk and many potential risk factors such as type of bisphosphonate, length of exposure and cumulative dose, and potential comorbidities, such as smoking history and prednisolone or thalidomide use.\textsuperscript{8} Osteonecrosis risk may also be associated with dental comorbidities such as periodontal disease and dental interventions such as tooth extraction, implant placement or denture use.\textsuperscript{8,9}

Understanding the potential risk of jaw osteonecrosis and delayed dental healing associated with bisphosphonate use is crucial to patient care, particularly when considering initiation of bisphosphonate therapy and the risks associated with dental treatment. The prevalence of jaw osteonecrosis in users of oral bisphosphonates has been estimated\textsuperscript{7}, but these data were uncontrolled so did not demonstrate a significant association between the two. This issue is of increasing significance as bisphosphonate prescribing is likely to increase with population ageing. The main aim of this study was to investigate the association between bisphosphonate therapy for management of benign bone disease and delayed dental healing.

Materials and Methods

Study design

A case-control study design was used to investigate the association between delayed dental healing and the use of bisphosphonate therapy for management of postmenopausal osteoporosis and other non-cancer-related bone conditions. A detailed description of the methodology has been published\textsuperscript{4} and is summarised below.
Case definition

Delayed dental healing was defined as a breach in the oral mucosa and/or exposure of bone in the mandible or maxilla persistent for greater than 6 weeks that failed to heal, in an individual who has not had previous radiotherapy to the jaw or a history of malignancy.\textsuperscript{2,4} Although the definition of osteonecrosis of the jaw by the American Society for Bone and Mineral Research\textsuperscript{2} is given at 8 weeks, we chose to use the earlier time of 6 weeks for delayed dental healing to ensure we did not miss any cases of healing delay that may not have been associated with bisphosphonate use\textsuperscript{4}.

Recruitment

Recruitment was a 2-step process involving initial recruitment of the practices of Specialist Oral and Maxillofacial Surgeons (OMFS) and Special Needs Dentists (SNDs) followed by recruitment of individual cases and controls.

Specialist OMFS and SNDs who between March and September 2006, were registered with the Australian Health Practitioner Regulation Agency as specialists, and were working in public and/or private dental care settings in metropolitan and regional centres across Victoria, Australia, were invited to take part in the study.

Six metropolitan public hospitals (Dental Health Services Victoria, Royal Melbourne Hospital, St Vincent’s Hospital, The Alfred, Western Health and Monash Health) and 3 regional hospitals (Barwon Health including Geelong Hospital, and Southern Health Dandenong) were included. Trained data collectors independent of the clinic and patient treatment undertook screening of all eligible clinical records to identify potential delayed dental healing cases. They were provided with a glossary of key words to seek in files and instructed to assess each potential case for inclusion criteria.

Case inclusion criteria included age greater than 50 years, a dental wound that did not heal within 6 weeks of initially recorded diagnosis and a qualifying visit during a designated 6-month window period, March 1, 2006 – August 30, 2006. Exclusion criteria were a history of current malignancy or previous malignancy between 2001 and 2006 (excluding basal or squamous cell carcinoma of the skin), previous radiotherapy involving the jaws, other causal local pathology such as osteomyelitis, and bisphosphonate use for any indication other than post-menopausal osteoporosis or other benign bone disease.
A case adjudication panel, comprising medical and dental specialists blinded to patients’ medical history and bisphosphonate status, assessed potential cases that met the inclusion criteria. The composition and operation of the panel have been described previously. A case adjudication panel radiography sub-committee reviewed all available radiographs for pathology that would explain the clinical findings.

For each confirmed case, 4 controls were identified selected on the basis of age, gender and referral source from the referring community dental practice or specialist medical clinic for each case or, where consent was not obtained from this practitioner, from another dentist or medical practitioner working in the same geographical area, based on case residential postal code.

Data collection

Data collected included: demographic information (date of birth, gender, postal code), treatment setting (public clinic, private clinic), and information regarding delayed dental healing, comorbidities and medications. Ethics approval was obtained from all involved institutions.

Statistical analysis

The primary outcome measure was the presence or absence of delayed dental healing that occurred either spontaneously or following dental treatment precipitants. Potential explanatory variables, in addition to bisphosphonate use, included age (dichotomised to age greater than 70 years, age less than 70 years), medical co-morbidities (any medical condition, diabetes), medications (any bone-active medications other than bisphosphonate), and smoking history.

The relationship between delayed dental healing and the explanatory variables was assessed using conditional logistic regression, which automatically incorporated age, gender and clinic type due to the matched design of the study. Each explanatory variable was included singly and in combination with bisphosphonate use. The interaction of bisphosphonate use with each of the matching variables was tested. The estimated odds ratio (OR) was found for each explanatory variable, together with a 95% confidence interval and a p value for testing the null hypothesis that the true OR was 1. Cross tables of frequencies were examined to give further insight into the relationships.
Missing data occurred where patient files were unable to be located and where variables of interest were not recorded.

Descriptive statistics, cross tables of frequencies and statistical analysis were performed using the package SPSS version 20.

Ethics approval

Ethics approval was obtained from all the involved institutions.

Results

Recruitment and number of cases and controls

Fifteen out of a possible 51 (29%) OMFS and 2 of 2 (100%) SNDs, including all public facility specialist dental clinics, agreed to allow their records to be examined (Table 1).

A total of 4212 files were screened and met the eligibility criteria, of which, 2079 (64%) were located in private sector clinics (practice location number 1, Table 1). Of the 69 potential cases presented to the case adjudication panel, 40 (58%) met the definition of delayed dental healing (20 public patients, 20 private patients). Of these, 25 (62·5%) were referred from general dental practices, three (7.5%) from specialist medical practices, and 12 (30%) from OMFS practices (referred to the public sector clinics). The case adjudication panel did not confirm some potential cases (n=29) because they did not meet the criteria for case definition. All cases except one had delayed dental healing for between 10 weeks and 5 years, fulfilling the definition of jaw osteonecrosis. The other case had delayed dental healing for 7 weeks and 4 days and this case was not on a bisphosphonate.

Overall, 160 controls were recruited, 72 (45%) from the referring community dental practice [24 (33%) from specialist and 48 (67%) general dental practice], 12 (7·5%) from community non-dental practice, 72 (45%) from local private dental practice and 4 (2·5%) from specialist medical clinics.

Primary outcome measure

The odds ratio for developing delayed dental healing when taking a bisphosphonate was 13·1 (95% confidence interval [CI] 4·4 to 39·3; p<0·001) (Table 2). Among the cases, 21 (52·5%) were taking a
bisphosphonate, all of whom met the osteonecrosis definition; 19 (48%) had delayed dental healing not related to bisphosphonate use. One of the non-bisphosphonate-associated cases had non-healing documented at 7 weeks and 4 days; all others met the definition of osteonecrosis. Among cases, the longest time to healing was 5 years and this was due to implant failure; this case was not on a bisphosphonate nor had any recorded medical comorbidity. Twenty-three (14·4%) controls were taking a bisphosphonate with no delayed dental healing events recorded. Among the 21 cases taking a bisphosphonate, 20 were taking alendronate (95%) and 1 risedronate (5%). Among the 160 controls there were 23 bisphosphonate users [15 (65 %) alendronate; 8 (35 %) risedronate]. Intravenous bisphosphonate use was not documented in cases or controls.

The association between bisphosphonate use and delayed dental healing tended to be stronger in the public sector patients than in the private sector, but this difference was not significant (p=0·09).

**Gender and age**

There was a significantly greater proportion of females (n=30, 75%) than males (n=10, 25%) among delayed dental healing cases. It was not possible to analyse the interaction of gender with bisphosphonate use since there were too few male cases. Age was an essential criterion for control recruitment; the cohort was divided into two categories, younger than 70 (n = 112; 52·5% cases versus 56·9% controls) and older than 70 (n = 88; 47·5% cases versus 43·1% controls). In both categories, the age distribution for cases and controls was very similar, as follows (mean, SD): younger than 70: cases (57·9, 6·2), controls (58·2, 6·9); older than 70: cases (74·5, 3·2), controls (74·4, 3·3).

The interaction of age with bisphosphonate use was not significant (OR 21·6 for older subjects compared to OR 4·8 for younger subjects; p=0·20).

**Medical comorbidity**

The associations of delayed dental healing with other comorbidities are depicted in Table 2. Having another medical condition (“comorbidity”) was a significant risk (p=0·04). These were medical conditions not directly related to bisphosphonate use and included cardiovascular, respiratory, renal disease or diabetes.

When corrected for these comorbidities, the OR for delayed dental healing and bisphosphonate therapy was
12.9 (95% CI, 4.2 to 39.3, p<0.01). There was no association with a history of diabetes (p=0.24) or between non-bisphosphonate bone-active medication use and delayed dental healing (p=0.89), though the number on such medications was small (n=14).

Smoking status was recorded in 134 subjects (Table 2). The association of smoking with delayed dental healing was significant (p=0.02). The estimated OR for bisphosphonate therapy, after adjustment for smoking status, was 11.6 (95% CI, 1.9 to 69.5, p=0.01).

Evaluable imaging investigations were available in 30 potential cases. There were 7 cases with possible other pathology contributing to delayed dental healing. These lesions included peri-implantitis (n=1), sinusitis (n=2), retained tooth root (n=3), impacted tooth (n=1). These numbers were too small for statistical analysis.

Almost all cases had a recorded dental precipitant (n=38, 95%), mostly a prior dental extraction (n=34, 89.5%). Where a prior dental extraction was the precipitant, 17 (50%) were taking a bisphosphonate and this was exclusively alendronate. The other precipitants were implant placement (n=1) and implant failure (n=1); neither of these patients was taking a bisphosphonate. In two cases of delayed dental healing, both of whom were taking alendronate, there was no recorded precipitant. There were no cases of delayed dental healing associated with denture use.

**Discussion**

This comprehensive case control study sought to determine for the first time whether bisphosphonate use for the treatment of non-cancer-related bone disease was associated with delayed dental healing. Most cases (n=39, 97.5%) had healing delayed in excess of 10 weeks thereby also meeting the case definition of osteonecrosis. Notably, only one case with failed healing at 6 weeks (our definition of delayed dental healing) did not go on to fulfil the definition of jaw osteonecrosis, so delayed dental healing predicted osteonecrosis in at least 98% of patients.

The most significant finding of this study was the 13-fold increased odds of developing delayed dental healing in individuals on oral bisphosphonate therapy (11.6-fold after adjusting for smoking). This is the first time such a significant independent association has been reported in non-cancer patients with only one other
study showing oral bisphosphonate use to be a predictor for osteonecrosis.\textsuperscript{10} There was no recorded intravenous bisphosphonate use in either cases or controls.

The present study is unique in that it examined the potential link between delayed dental healing and bisphosphonate therapy by screening dental practices where it would be more likely to first present. Other studies have accessed electronic databases and physician records using limited terminology including “ONJ”, “osteonecrosis”, “necrosis”, “osteomyelitis”, or “bone lesion” or “aseptic necrosis of bone, jaw” as found in International Classification of Disease version 9 (ICD-9).\textsuperscript{10, 11} ICD-10 has included “idiopathic aseptic necrosis of bone, other site” which is potentially limiting when identifying osteonecrosis.\textsuperscript{11} Broader terms not part of the ICD-10 and used in the present study included exposed bone on view, pus, non-healing socket, exudate, swelling, draining sinus, dry socket, bone sloughing, sore sockets, OAC, healing not completed, pain, fistula, and infection.

A key strength in the present study was the rigorous case adjudication process. Previous reports have either had no blinded assessment of potential osteonecrosis, only study investigators assessing cases, potentially biasing disease interpretation or recall bias accounting for underestimation or overestimation of the link between bisphosphonate use and osteonecrosis.\textsuperscript{10,12}

Several case series reported osteonecrosis in patients prescribed oral bisphosphonates, finding a significant but sometimes low number of osteonecrosis cases.\textsuperscript{10,13-16} The number of osteonecrosis cases identified in the present study was comparable to previous research and case series.\textsuperscript{15,17} Within the confines of the present study, assuming that the percentage bisphosphonate use in the recruited control group (14.4\%) is representative of the whole cohort, then it can be estimated that, in patients over the age of 50 who are taking bisphosphonates and attending a dental specialist, there was a prevalence of 3.46\% (21/607 x 100) at a rate of 1 in 28.9. Nevertheless, the rarity of the condition, particularly in the benign bone disease setting, makes it difficult to address research questions such as causality, incidence, risk factors and disease outcome.\textsuperscript{7,12}

It was not surprising that more females had delayed dental healing as they are more likely to be taking bisphosphonates primarily in the management of post-menopausal osteoporosis.\textsuperscript{10,12} In the present study only 3 males cases (14\%) were taking alendronate compared to 7 (37\%) not prescribed such medications. Age can also be a potential confounder for osteonecrosis and this is more pertinent in the osteoporotic setting where the average age of patients is greater than 50 years.\textsuperscript{18}
There was no association of bisphosphonate exposure with osteonecrosis risk independently of a predisposing dental intervention, thereby highlighting the importance of a thorough dental assessment at the outset of bisphosphonate therapy. The observation that almost all cases of delayed dental healing involved a prior dental intervention may suggest a difference from oncology-related cases which warrants further investigation. It is noteworthy that almost half of all delayed dental healing cases occurred in patients without recorded bisphosphonate exposure, so delayed healing risk should be considered in all patients in whom invasive dental procedures are planned. Several other factors including smoking have been reported to be major risk factors for osteonecrosis in cancer patients and to a lesser extent in benign bone disease. Even taking into account contributory factors such as smoking, the bisphosphonate odds ratio remained high. Therefore, the effect of bisphosphonate therapy was significant whether an individual smoked or not. Others have reported smoking in individuals with osteonecrosis; however, results linking the two were inconclusive. Diabetes is another potential risk factor for jaw osteonecrosis with bisphosphonate use but we were unable to show an association possibly due to the relatively low number of patients with diabetes. The present study showed a link between having another medical condition such as diabetes, or cardiovascular, respiratory or renal disease and developing delayed dental healing and osteonecrosis of the jaw. Taken together with the effects of a potential dental precipitant, this link emphasises the cooperation required between the dental and medical professions in prevention of osteonecrosis.

There were some limitations in the current study. The most significant was the low response rate amongst oral and maxillofacial surgeons despite they being the most likely to be referred these patients. This was in part because some did not want researchers viewing patient files (our purpose was to eliminate recall bias by clinicians). Other reasons reported in the literature include apathy, a non-participation in research policy, or the belief in a lack of potential cases in their practices, which has been previously reported in conjunction with factors such as the clinicians’ gender and age.

Another possible limitation of the study may relate to recording of information in that clinicians may have sought a history of bisphosphonate exposure more rigorously in patients presenting with jaw osteonecrosis, or been more likely to refer patients for specialist care if they were bisphosphonate users. Ascertainment bias is a potential problem in case-control studies. In an effort to minimise this potential
problem we chose an observation window in 2006, before a high level of awareness of jaw osteonecrosis had arisen. Moreover, it is usual practice for community dentists to refer all patients with delayed healing for specialist management regardless of a history of bisphosphonate use. It is also possible that patients may have had a prior history of bisphosphonate exposure in the period before their available clinical record began, but we would expect such misclassification to affect cases and controls equally. As with any retrospective study, there were some incomplete data (for example, re smoking status where only 134 of 200 individuals had a known smoking history (40% of cases and 71% of controls) and as such the association of tobacco use with prevalence of ONJ could not be reliably assessed) but we have no evidence that these missing data biased the main study findings.

This study has shown for the first time that there is strong, significant association between oral bisphosphonate use and delayed dental healing and jaw osteonecrosis in patients attending specialist dental services across Victoria, Australia. The need for osteoporosis therapy is on the rise with population ageing and hence the potential for a significant impact on oral health cannot be ignored.\textsuperscript{29} However, some evidence has suggested an adverse impact on treatment rates for osteoporosis due to concerns re bisphosphonate side-effects including jaw osteonecrosis.\textsuperscript{30} Clearly, more research is needed into prevention and management of delayed dental healing and jaw osteonecrosis particularly in the non-oncology setting.

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Authors’ roles: Study design: GLB, CB, JGC, MM and JDW. Study conduct: GLB, CB, JGC, MM, LC and JDW. Data analysis: GLB, CB, JGC, MM, LC, GH and JDW. Data interpretation: GLB, CB, JGC, MM, LC, GH and JDW. Drafting manuscript: GLB, CB, JGC, MM, LC, GH and JDW. Revising manuscript content:
GLB, CB, JGC, MM, LC, GH and JDW. Approving final version of manuscript: GLB, CB, JGC, MM, LC, GH and JDW. GLB takes responsibility for the integrity of the data analysis.
References


Table 1. Distribution of number of patients in the age and visit window period, number of eligible patients, and potential and confirmed delayed dental healing cases according to practice sources.

<table>
<thead>
<tr>
<th>Practice location*</th>
<th>Total files in 6-month window</th>
<th>Total meeting study criteria</th>
<th>Total potential cases</th>
<th>Confirmed cases (case adjudication panel)</th>
<th>Records not available</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14725</td>
<td>2709 (18.9%)</td>
<td>29</td>
<td>20</td>
<td>816</td>
</tr>
<tr>
<td>2</td>
<td>3357</td>
<td>641 (19.1%)</td>
<td>19</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>122</td>
<td>30 (24.5%)</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>829</td>
<td>280 (33.8%)</td>
<td>5</td>
<td>2</td>
<td>19</td>
</tr>
<tr>
<td>5</td>
<td>150</td>
<td>18 (12.0%)</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>319</td>
<td>150 (47.0%)</td>
<td>3</td>
<td>3</td>
<td>18</td>
</tr>
<tr>
<td>7</td>
<td>287</td>
<td>83 (28.9%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>66</td>
<td>15 (22.7%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>494</td>
<td>290 (58.7%)</td>
<td>9</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>10</td>
<td>1727**</td>
<td>56 (3.2%)</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>11</td>
<td>282</td>
<td>80 (28.4%)</td>
<td>3</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>TOTAL</td>
<td>22,358</td>
<td>4212 (18.8%)</td>
<td>69 (1.6%)a</td>
<td>40 (58%)b</td>
<td>861 (3.8%)c</td>
</tr>
</tbody>
</table>

* Practice location 1 refers to private oral and maxillofacial and special needs dental clinics. Practice locations 2 to 11 refer to hospital outpatient clinics (dental and medical). **1727 consisted of inpatient (n=1623) and outpatient (n=104) files for Plastics, Hand surgery, Head and Neck and Oral and Maxillofacial Surgery (OMFS). From this group, 582 files (inpatient = 537; outpatient = 45) were from OMFS; 56 were dental only, meeting age and visit window criteria. Numbers in parenthesis as follows: a total meeting study criteria as a percentage of the total number of files in the visit window period; b Total number of potential cases expressed as a percentage of those meeting total study criteria; c total number of adjudicated cases expressed as a percentage of all potential cases; d records not available expressed as a percentage of all files in the visit window period.
Table 2. Medical profile of all cases and controls as determined by analysis of patient records.

<table>
<thead>
<tr>
<th>Profile investigated</th>
<th>Response</th>
<th>Cases</th>
<th>Controls</th>
<th>Odds Ratio (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisphosphonate therapy (medication risk)</td>
<td>Yes</td>
<td>21 (52·5%)</td>
<td>23 (14·4%)</td>
<td>13·1 (4·4 to 39·3)</td>
<td>&lt;0·001</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>19 (47·5%)</td>
<td>137 (85·6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of any other medical condition not directly related to bisphosphonate use*</td>
<td>Yes</td>
<td>20 (50%)</td>
<td>54 (33·8%)</td>
<td>2·3 (1·0 to 5·2)</td>
<td>0·04</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>20 (50%)</td>
<td>106 (66·3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of diabetes alone</td>
<td>Yes</td>
<td>7 (17·5%)</td>
<td>17 (10·6%)</td>
<td>1·8 (0·7 to 4·6)</td>
<td>0·24</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>33 (82·5%)</td>
<td>143 (89·4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-bisphosphonate bone-active medications **</td>
<td>Yes</td>
<td>3 (7·5%)</td>
<td>11 (6·9%)</td>
<td>1·1 (0·3 to 4·4)</td>
<td>0·89</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>37 (92·5%)</td>
<td>149 (93·1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking status***</td>
<td>Yes</td>
<td>6 (37·5%)</td>
<td>14 (11·9%)</td>
<td>5·5 (1·3 to 22·9)</td>
<td>0·02</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>10 (62·5%)</td>
<td>104 (88·1%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Medical conditions recorded in clinical notes included cardiovascular, respiratory, renal disease or diabetes; ** hormone replacement therapy, raloxifene, calcitriol or tibolone; *** 66 subjects did not have a smoking status recorded in the clinical records
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