Bone 124 (2019) 69–74

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Full Length Article

Use of oral bisphosphonates and risk of hospital admission with osteonecrosis of the jaw: Large prospective cohort study in UK women

Clare J. Wotton[a,*], Jane Green[a], Anna Brown[a], Miranda E.G. Armstrong[b], Sarah Floud[a], Valerie Beral[a], Gillian K. Reeves[a], for the Million Women Study collaborators[1]

[a] Cancer Epidemiology Unit, University of Oxford, Richard Doll Building, Old Road Campus, Oxford OX3 7LF, UK
[b] School of Policy Studies, University of Bristol, 8 Priory Road, Bristol BS8 1TZ, UK

ARTICLE INFO

Keywords:
Women
Oral bisphosphonate
Osteoporosis
Osteonecrosis of the jaw
MRONJ

ABSTRACT

About 1 in 10 postmenopausal UK women are currently prescribed oral bisphosphonates, but there are concerns about their adverse effects. Osteonecrosis of the jaw is a recognised uncommon but important side effect of intravenous bisphosphonates, but epidemiological evidence on risk of osteonecrosis of the jaw associated with oral bisphosphonate use is less conclusive.

The incidence of hospital admission with osteonecrosis of the jaw was examined among 521,695 Million Women Study participants, aged 64.7 years at baseline. Cox proportional hazards regression was used to estimate adjusted relative risks (RRs) and 95% confidence intervals (CIs) associated with use of oral bisphosphonates in postmenopausal women followed-up by record-linkage to National Health Service hospital admission databases.

During mean follow-up of 8.2 years per woman, 100 women were admitted to hospital with first recorded osteonecrosis of the jaw, at mean age 72.4 years. Almost a third (29/100) of the cases had ever-used oral bisphosphonates. Ever-users had a six-fold increased risk of hospital admission for osteonecrosis of the jaw, when compared with never-users (adjusted RR = 6.09, 95% CI 3.83–9.66; $p < 0.0001$). The relative risk for osteonecrosis of the jaw in never-users of oral bisphosphonates was increased in women with prior cancer (RR = 3.40, 2.22–5.22, $p < 0.0001$). The estimated absolute risk of hospital admission for osteonecrosis of the jaw over a 5-year period from age 70 to 74 in women without prior cancer was 0.09 per 1000 in never-users and 0.69 per 1000 in ever-users of oral bisphosphonates.

In this UK population of postmenopausal women, use of oral bisphosphonates was associated with a 6-fold increased risk of hospital admission with osteonecrosis of the jaw, accounting for around one-third of cases, with an excess risk of about 0.6/1000 users over 5 years.

1. Introduction

Since 2003, oral bisphosphonates have been recommended in the UK as first-line treatment for osteoporosis, following publications of the adverse effects of menopausal hormone therapy. Prescriptions for oral bisphosphonates have increased greatly since then, with some decline since about 2010 (Fig. 1) [1], such that about 1 in 10 postmenopausal women in the UK [2,3] and in other high-income countries [4,5] are prescribed them.

Oral bisphosphonates are effective at reducing the risk of osteoporotic fracture, [6,7] but there has been concern about their side effects, including increased risks of osteonecrosis of the jaw, atypical femoral fracture and atrial fibrillation [8].

Reliable population-based estimates of incidence of osteonecrosis of the jaw are lacking [9–11]. It is well-established that people given intravenous bisphosphonates as part of treatment for cancers such as breast cancer and multiple myeloma are at an increased risk of osteonecrosis of the jaw [12–16]; estimated prevalence is around 7–12% (depending on cancer and bisphosphonate types), with one study finding that the cumulative hazard of osteonecrosis of the jaw increases with duration of exposure to intravenous bisphosphonates by around 1% risk with 12 months treatment with intravenous bisphosphonates, around 3% with 24 months treatment, 6% with 36 months treatment, and around 13% with 48 months treatment [16], and other studies

* Corresponding author at: Nuffield Department of Population Health, University of Oxford, Richard Doll Building, Old Road Campus, Oxford OX3 7LF, UK.
E-mail address: clare.wotton@ndph.ox.ac.uk (C.J. Wotton).
[1] Listed at end of paper.

https://doi.org/10.1016/j.bone.2019.04.003
Received 14 November 2018; Received in revised form 19 March 2019; Accepted 4 April 2019
Available online 05 April 2019

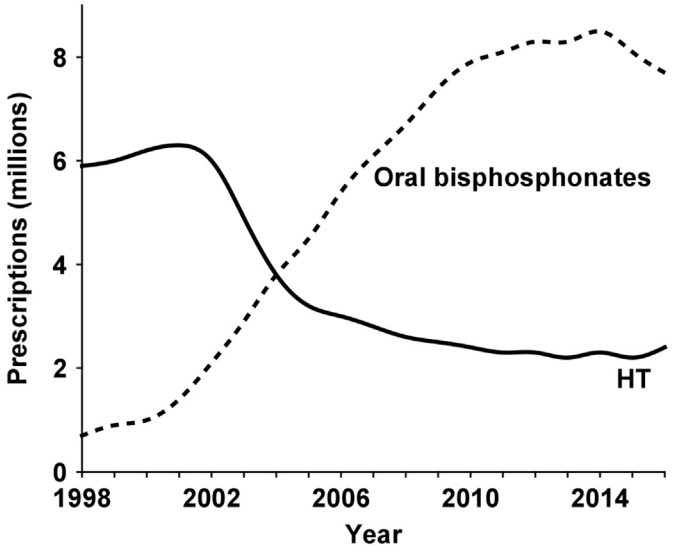

Fig. 1. Prescriptions for oral bisphosphonates and for menopausal hormone therapy (HT) dispensed in England, 1998–2017 [1].

showing similar increases in incidence with increasing duration of treatment [12,14]. In people taking oral bisphosphonates, however, there is uncertainty about the magnitude of any excess risk; recent epidemiological evidence has been limited by the lack of large scale medium-term to long-term prospective studies for this rare condition. Estimates of osteonecrosis of the jaw incidence in people taking oral bisphosphonates for osteoporosis or Paget's disease have ranged between 1 in 10,000 and < 1 in 100,000 patient-treatment years [9,17]; cumulative incidence of osteonecrosis of the jaw has been reported to rise with duration of oral bisphosphonate use in osteoporotic patients [18].

Using data from a large UK prospective cohort with virtually complete follow-up through routinely-collected national health databases, we report on the risk of hospital admission with osteonecrosis of the jaw in postmenopausal women by their use of oral bisphosphonates, history of cancer and other factors.

2. Materials and methods

2.1. Study design, data collection and follow-up

The Million Women Study is a prospective cohort study of 1.3 million women, recruited in England and Scotland from 1996 to 2001 through UK National Health Service (NHS) Breast Screening Programme mammography centres. At recruitment, women completed a questionnaire on socio-demographic, reproductive, medical and lifestyle factors, including medication use. The cohort is re-surveyed approximately every three to five years. The study design and methods are described in detail elsewhere [19]; study questionnaires, as well as information on data and access policies, can be viewed online at http://www.millionwomenstudy.org.

Electronic record linkage, using unique NHS identification numbers and date of birth as identifiers, links study participants to NHS records for follow-up of deaths, cancer registrations, emigration and hospital admissions. Linked data for England are provided by NHS Digital, and for Scotland by NHS National Services Scotland, with diagnoses and procedures coded using, respectively, the World Health Organization's International Classification of Diseases, 10th revision (ICD-10) and the NHS OPCS-4 Classification of Interventions and Procedures. The hospital admissions databases (Hospital Episode Statistics (HES) in England and Scottish Morbidity Records in Scotland) include information on inpatient stays (i.e. overnight) and day-case admissions; data are provided on hospital admission and discharge dates, and on diagnoses and procedures relating to the admission. All participants gave written consent to follow-up, at recruitment. Ethical approval was granted by the Oxford and Anglia Multi-Centre Research Ethics Committee (MREC 97/001).

2.2. Exposure variables

2.2.1. Oral bisphosphonate use

Specific questions about use of oral bisphosphonates were asked for the first time 8 years after recruitment (in 2006–2007), which is the baseline for the analyses reported here. Women were asked if they had ever taken alendronate (Fosamax), risedronate (Actonel), or etidronate (Didronel) and could answer 'never', 'previously', or 'currently' via a tick box. For analysis, women were classed as never or ever users of any of the named oral bisphosphonates.

To assess the reliability of self-reported data, study participants were linked to data on prescriptions in primary care in the Clinical Practice Research Datalink (CPRD) in England, which covers about an 8% sample of the UK population [20], and in Scotland to data from the Prescribing Information System (PIS) [21]. Among 28,762 women in England with a CPRD record, 93.6% of the 2761 study participants who in 2010–11 reported ever-use of oral bisphosphonate also had a prescription for the drug, and 97.0% of the 25,217 who reported never using bisphosphonate had no prescription for it. Among 38,095 women in Scotland, 90.5% of the 3489 study participants who in 2010–11 reported ever-use of oral bisphosphonate also had a prescription for the drug, and 98.1% of the 33,951 who reported never using bisphosphonate had no prescription for it.

2.3. Outcomes

During the follow-up period, there was no specific ICD-10 code in the UK for osteonecrosis of the jaw. ICD-10 codes K10.2 and M87.1 have been considered appropriate for identifying osteonecrosis of the jaw in disease register validation studies in Sweden and Denmark [22,23]. We included in the outcome: women with a first hospital admission with ICD-10 code K10.2 (inflammatory conditions of jaw), as primary or other diagnosis; or women with a first admission with ICD-10 code M87.1 (osteonecrosis due to drugs), except where code M87.1 was accompanied by an operation code for hip replacement, and no mention of a condition of the jaw: we considered that such women were likely to have steroid-induced osteonecrosis of the hip. We refer throughout to the outcome defined for these analyses as osteonecrosis of the jaw. Osteonecrosis of the jaw related to bisphosphonate use is sometimes known as bisphosphonate-related osteonecrosis of the jaw (BRONJ), or, to include osteonecrosis of the jaw related to use of other medications, such as Denosumab, as medication-related osteonecrosis of the jaw (MRONJ).

2.4. Statistical analysis

For the main analyses, women contributed person-years from the date they completed the 8-year follow-up questionnaire which asked for the first time about oral bisphosphonate use, up to the date of hospital admission for osteonecrosis of the jaw, the date of death, or last date of follow-up (31 March 2017), whichever was soonest. About 1% of participants have been lost to follow-up [19] (largely through emigration or leaving the National Health Service) and are censored at the date when they were lost, contributing person-years until then.

Women were classed as having or not having prior cancer, based on registration of any cancer (ICD10 C00 to D48, excluding C44) prior to their report on bisphosphonate use. A record of prior head and neck cancer (radiotherapy treatment for which is a known risk factor for jaw osteonecrosis) was an exclusion criterion for all analyses of bisphosphonate use, and for some analyses women with a history of any other

cancer were also excluded.

Cox regression models using attained age as the underlying time variable were used to estimate relative risks (RRs) and 95% confidence intervals (CIs) for osteonecrosis of the jaw. Floated confidence intervals were used when there were more than two categories for a risk factor; this allows valid comparisons to be made between any two groups [24]. Conventional confidence intervals were used for dichotomous risk factors, and are accordingly reported in the text. Analyses were stratified by single year at completion of the baseline questionnaire (8-year re-survey) and by single year of birth, and adjusted for the following variables: recruitment region (10 regions), deprivation (deprivation score in quintiles, using the area-based Townsend Index [25]), body mass index (BMI; < 20, 20.0–22.4, 22.5–24.9, 25.0–27.4, 27.5–29.9, ≥30 kg/m^2), strenuous activity (activity that causes sweating or heavier breathing - never, 1–2, 3–5, 6–10, ≥11 h per week), other physical activity (e.g. walking, gardening, leisure activities - never, 1–2, 3–5, 6–10, ≥11 h per week), smoking status (not current, current), alcohol consumption (< 3, 3–6, 7–14, ≥15 drinks per week), highest educational attainment (tertiary, secondary, technical, none - left at or after school leaving age, none - left before school leaving age or no schooling), menopausal hormone therapy use, (ever, never) and diabetes (yes, no). Missing data (generally < 2% for each variable) for the adjustment variables were included as a separate category. Analyses were performed using Stata, version 13 [26].

2.5. Other exposures

In the analyses, information on the exposures of interest and on smoking, alcohol, weight, physical activity, use of menopausal hormone therapy (HT) and diabetes were those recorded at baseline (the Million Women Study 8-year re-survey). For some variables, generally those which would not be expected to change during follow-up, we used information provided at recruitment: deprivation, education, recruitment region, year of birth, year of recruitment, height (to calculate body mass index, BMI), and use of oral contraceptives.

Among never users of oral bisphosphonates without prior cancer, number of cases and person-years of follow-up were used to calculate the rate of hospital admission with osteonecrosis of the jaw for women aged 70 over a 5-year period. Rates among women in other exposure categories (use of oral bisphosphonates, prior cancer, or both) were estimated by multiplying the rate among never users without prior cancer by the appropriate point estimate of relative risk.

3. Results

The 521,695 postmenopausal women included in these analyses were aged 64.7 (SD 4.9) years, on average at baseline. Overall 12% (60,440) reported ever use of oral bisphosphonates. Table 1 shows the baseline characteristics of women in the analysis by reported oral bisphosphonate status. Ever-users of oral bisphosphonates were slightly older and less likely to smoke than never-users, and had slightly lower BMIs. Ever-users were somewhat more likely to have had a history of cancer (18.5%, vs 15.5%).

During a mean follow-up of 8.2 years per woman (4.3 million person-years in total), 100 women had a first hospital admission with osteonecrosis of the jaw, at mean age 72.4 (89 with code K10.2, and 11 with code M87.1). No women with osteonecrosis of the jaw had a history of head or neck cancer. Of the 100 women identified with osteonecrosis of the jaw, 29 had used oral bisphosphonates (5 with, and 24 without, a history of cancer), and 71 had never used them (25 with a history of cancer and 46 without). In women who had never used oral bisphosphonates, the mean age at first hospital admission for osteonecrosis of the jaw was 71.0 (SD 5.0) years in those without prior cancer, and 73.6 (SD 5.8) years in those with prior cancer. In women who had used oral bisphosphonates, the mean age at first admission for osteonecrosis of the jaw was 73.6 (SD 6.2) years in those without prior cancer and 73.2 (SD 3.0) years in those who had prior cancer.

Fig. 2 shows adjusted relative risks for hospital admission with osteonecrosis of the jaw by oral bisphosphonate use, prior cancer and 6 other selected factors. Relative risks were greatest for ever use of oral bisphosphonates (RR = 6.09; 95% CI 3.83–9.66, $p < 0.0001$), and for a history of cancer (RR = 2.80; 95% CI 1.88–4.17, $p < 0.0001$); none of the remaining factors, smoking, body mass index, height, deprivation or use of menopausal hormone therapy or oral contraceptives showed a statistically significant association.

Fig. 3 shows relative risks taking never-users of oral bisphosphonates with no history of cancer as the baseline; never-users of bisphosphonates with a history of cancer were 3-times more likely to be admitted to hospital with osteonecrosis of the jaw (RR 3.40; 95% CI 2.22–5.22, $p < 0.0001$; Fig. 3); and ever-users of oral bisphosphonates with a history of cancer had a 10-fold risk of hospital admission with osteonecrosis of the jaw of 10.6 (95% CI 4.40–25.7, $p < 0.0001$). Among women with no prior cancer, ever users of oral bisphosphonates were over 7-times more likely to have a hospital admission with osteonecrosis of the jaw than never users (adjusted RR 7.88; 95% CI 5.21–11.9, $p < 0.0001$; Fig. 3). Of the 5 ever-users of oral bisphosphonates with prior cancer who developed osteonecrosis of the jaw, some, but not all, had a history of breast cancer, and none had a history of myeloma; of the 25 never users with prior cancer and osteonecrosis of the jaw, 6 had a history of breast cancer and 15 of myeloma.

In women who never used oral bisphosphonates and had no history of cancer, the hospital admission rate for the 5-year period from age 70 to 74 for osteonecrosis of the jaw was 0.09 per 1000. Corresponding rates were 0.69 per 1000 ever-users of oral bisphosphonates with no history of cancer, 0.30 per 1000 never users of oral bisphosphonates with prior cancer, and 0.93 per 1000 women aged 70 over 5 years in ever-users with prior cancer.

4. Discussion

In this UK population-based prospective cohort study of 521,695 postmenopausal women aged about 65 years followed up for an average of 8.2 years, ever users of oral bisphosphonates had a 6-fold increased risk of hospital admission with osteonecrosis of the jaw compared with never users. In women who had ever used oral bisphosphonates and had never had cancer, the risk of hospital admission with osteonecrosis of the jaw was increased nearly 8-fold compared with never users of oral bisphosphonates. The absolute risk of hospital admission with osteonecrosis of the jaw for women without prior cancer over the 5-year period from age 70 to 74 years was 0.09 per 1000 in never users of oral bisphosphonates, and 0.69 per 1000 in oral bisphosphonate users. The risk of hospital admission with osteonecrosis of the jaw was increased about 3-fold in never users of bisphosphonates with a history of cancer and about 10-fold in ever-users of bisphosphonates with a history of cancer.

Intravenous bisphosphonates given mainly for treatment of cancer have consistently been associated with an increased risk of osteonecrosis of the jaw, with around 7–12% of those treated reported to be affected [12–16], and some evidence for risk increasing with increasing duration of treatment [12,14,16]. Risk of osteonecrosis of the jaw has also been linked to use of oncology doses of another anti-resorptive therapy, Denosumab [17].

Epidemiological evidence is less consistent with respect to risk of osteonecrosis of the jaw in users of oral bisphosphonates typically taken for prevention of osteoporotic fracture. Some studies have reported no increase in risk associated with oral bisphosphonate use [27,28] though most, including recent large-scale registry-based studies and a meta-analysis [29–33], have reported increased risks in users of oral bisphosphonates, generally lower (2–5 fold relative risk) and possibly with a longer time to onset [34] than for intravenous bisphosphonate use. After adjustment for potential confounding factors, the relative risk of hospital admission for osteonecrosis of the jaw in ever-users of oral

Table 1
Baseline characteristics and follow-up for incident osteonecrosis of the jaw by oral bisphosphonate use at baseline in postmenopausal women in the Million Women Study.[a]

	Never used oral bisphosphonates	Ever used oral bisphosphonates
Characteristics at study baseline	*n* = 461,255	*n* = 60,440
Mean age, years (SD)	64.4 (4.8)	66.8 (5.2)
Deprivation: lowest fifth (%)[b]	15.7	17.5
Mean height, cm (SD)[b]	162.6 (6.5)	161.7 (6.8)
Mean weight, kg (SD)	69.4 (12.7)	64.9 (12.6)
Mean BMI, kg/m^2 (SD)	26.3 (4.7)	24.8 (4.7)
Mean alcohol, g/d (SD)	4.9 (6.5)	3.8 (6.0)
Current smoker (%)	8.7	7.6
Mean no. of children (SD)[b]	2.1 (1.2)	2.1 (1.3)
Ever users of menopausal hormones (%)	53.6	54.6
Ever users of oral contraceptives (%)[b]	62.1	52.1
History of any cancer (%)	15.5	18.5
Fracture in last 5 years (%)	9.0	31.4
Follow-up for osteonecrosis of the jaw incidence		
Person-years follow-up (in millions)	4.0	0.3
Number of cases of osteonecrosis of the jaw		
Total	71	29
Women without prior cancer	46	24
Women with prior cancer	25	5

[a] Women with missing values were excluded from calculations of means or percentages for that given variable.
[b] Characteristics at recruitment.

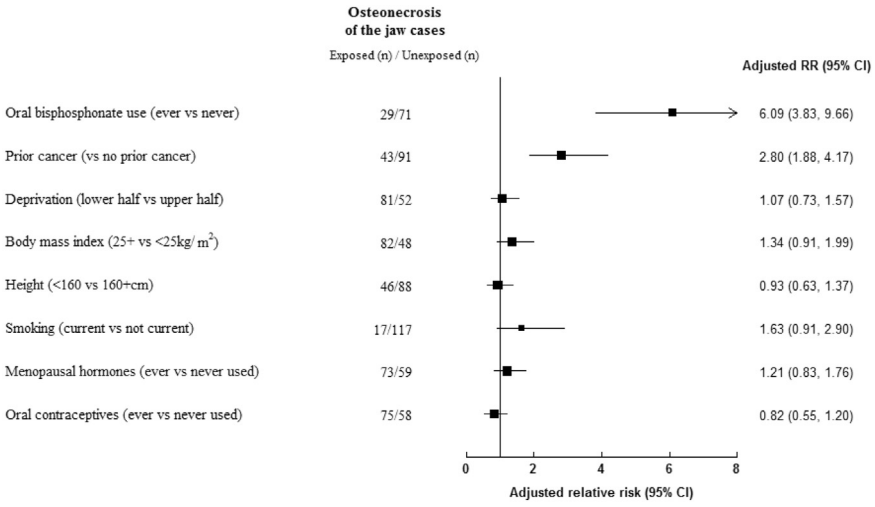

Fig. 2. Relative risk of osteonecrosis of the jaw in postmenopausal women, by selected risk factors.
Relative risks stratified by year of birth and year of recruitment, adjusted for region, educational attainment, physical activity, smoking status, alcohol consumption, diabetes, and deprivation, BMI, height, prior cancer, oral bisphosphonate, oral contraceptive and menopausal hormone use, where they are not the exposure of interest.
The size of the data markers is inversely proportional to the variance of the log RR, which indicates the amount of statistical information available for each estimate.

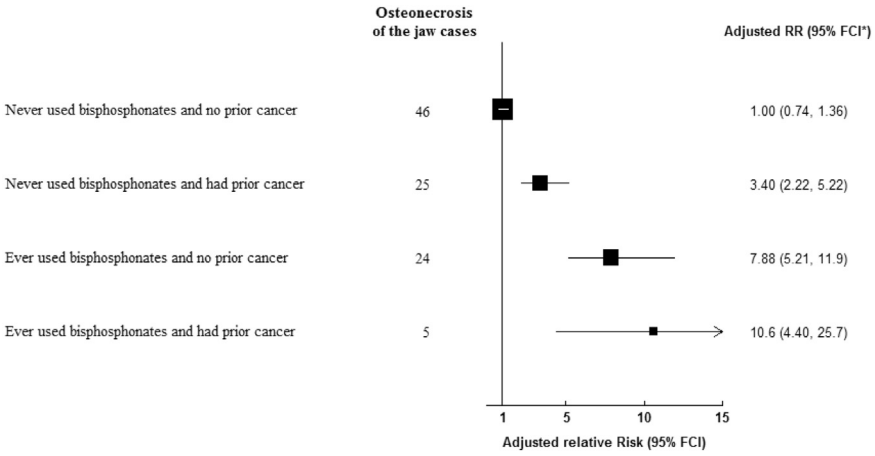

Fig. 3. Relative risk of osteonecrosis of the jaw in postmenopausal women, in relation to use of oral bisphosphonates and prior cancer.
Relative risks stratified by year of birth and year of recruitment, adjusted for region, deprivation, educational attainment, BMI, physical activity, smoking status, alcohol consumption and diabetes.
The size of the data markers is inversely proportional to the variance of the log RR, which indicates the amount of statistical information available for each estimate.
*Floated confidence interval.

bisphosphonates in this cohort was 6-fold overall and almost 8-fold in women with no history of cancer, with lower 95% confidence intervals of 4–5.

Reports from UK clinical surveys [11,35], several large register-based studies [30–32,36], and review articles [9,17] have estimated incidence rates of osteonecrosis of the jaw of between 0.0001 and 0.04% per year (i.e. between 0.005 and 2.0 per 1000 over 5 years) in those treated with oral bisphosphonates for osteoporosis or Paget's disease. In this cohort, hospital admission rates were 0.69 per 1000 users over 5 years, but we have no data on incidence rates that include women not admitted to hospital. A survey of UK dental and oral clinicians estimated some 700 cases of bisphosphonate-related osteonecrosis of the jaw annually in the UK [11]; and with some 7–8 million prescriptions annually (Fig. 1) [1], this suggests an incidence rate of about 0.25 per 1000 over 5 years (assuming an average of about 2 prescriptions annually per woman).

In this study almost a third (29/100) of the hospital admissions for osteonecrosis of the jaw were associated with use of oral bisphosphonates, consistent with other estimates that between 10% and 50% of all cases of osteonecrosis of the jaw may be related to use of oral bisphosphonates [11,17].

The main strengths of this study are the large study population, with validated prospective recording of exposure to oral bisphosphonates and long-term, virtually complete follow-up through reliable nationwide health service registers. While use of intravenous bisphosphonates was not recorded on the analysis baseline (8-year re-survey) questionnaire, in this study the great majority (over 99%) of women reporting use of bisphosphonates for osteoporosis on later questionnaires were using oral preparations; and our analyses in women without prior cancer exclude the possibility of unrecorded use of intravenous bisphosphonates at oncology doses. Many cases of osteonecrosis of the jaw arise in the context of invasive dental treatment; the hospital admissions registers used include specialist dental hospitals. To our knowledge, this is the first population-based cohort (non-register) study, in the UK or elsewhere, to provide estimated incidence rates and relative risks for osteonecrosis of the jaw in relation to use of oral bisphosphonates, taking into account a wide range of potential demographic and lifestyle confounders. A limitation of the study is identification of osteonecrosis of the jaw using the available hospital record ICD-10 codes, which were not designed to capture this specific outcome. It is also possible that in recent years recognition of a potential link between bisphosphonate use and osteonecrosis of the jaw may have led to changes in the diagnosis and/or recording of osteonecrosis of the jaw in hospital data. The codes on which our outcome definition was based, for inflammatory conditions of the jaw (K10.2) and for osteonecrosis due to drugs (M87.1), have been used previously [30], and validation against clinical records in Sweden and in Denmark [22,23] suggested that these codes are acceptable for use in large epidemiological studies, although positive predictive values were relatively low. The advantage of using all available data to specify the outcome has been noted previously [31]. A strength of the present study is the exclusion of about 10% of those with one of the above codes, whose detailed records suggested that code M87.1 was likely to reflect steroid-induced necrosis of the hip. We also had information on prior cancer by site, and were able to confirm that no women in the analysis were identified with osteonecrosis of the jaw following head and neck cancer, with possible radiotherapy to the jaw. All cases of osteonecrosis of the jaw diagnosed through surgery in hospital should be included, as hospital data include day-case admissions; nevertheless they are likely to represent the more severe cases (and may not include more recently-recognised variants without bone exposure). Hospital outpatient data in the UK do not contain full diagnostic coding and cannot be used to ascertain disease outcomes; and we do not have information on dental treatment in primary dental practice. Overall incidence of osteonecrosis of the jaw in this population is likely to be underestimated.

Even in this large cohort with 8 years' follow-up, there were relatively few incident cases of osteonecrosis of the jaw. Since most bisphosphonate use was recent, our analyses were limited to a comparison between ever and never users of bisphosphonates. We therefore have little reliable data about whether the excess risks observed here persist many years after bisphosphonate use ceases or about the effects of different duration of use of oral bisphosphonates.

The widespread use of oral bisphosphonates for prevention of osteoporotic fracture means that adverse effects, even if uncommon, may be of population health concern. Based on current guidelines for treatment of osteoporosis, it has been estimated that half of all postmenopausal women fulfil the criteria for pharmacological intervention [37,38]. Prevalence of use of oral bisphosphonates among postmenopausal women in many high-income countries, including the UK, is estimated to be above 10%. To limit the possibility of serious side effects, recent guidelines in the UK suggest that long-term bisphosphonate therapy in postmenopausal women should be reviewed after about 3–5 years and that a drug holiday should be considered in women without a fracture with a score below the National Osteoporosis Guideline Group intervention threshold [37].

In conclusion, in this large UK prospective cohort of postmenopausal women, ever-users of oral bisphosphonates had a 6–8 times higher risk than never users of a hospital admission with diagnostic codes indicative of osteonecrosis of the jaw. The absolute excess incidence of hospital admission for osteonecrosis of the jaw over a 5-year period from age 70 to 74 was 0.6 per 1000 ever users of oral bisphosphonates without prior cancer.

Acknowledgements

The authors thank the women who have participated in the Million Women Study as well as the staff from the participating NHS breast screening centres.

This study is based in part on data from the Clinical Practice Research Datalink obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. However, the interpretation and conclusions contained in this study are those of the authors alone.

This study is based in part on data provided by the Office for National Statistics, NHS Digital, and ISD Scotland. Those who carried out the original collection and analysis of the data bear no responsibility for their further analysis or interpretation.

We thank Adrian Goodill for production of Fig. 1.

The Million Women Study collaborators

Million Women Study Co-ordinating Centre staff: Hayley Abbiss, Simon Abbott, Rupert Alison, Miranda Armstrong, Krys Baker, Angela Balkwill, Isobel Barnes, Valerie Beral, Judith Black, Roger Blanks, Kathryn Bradbury, Anna Brown, Benjamin Cairns, Dexter Canoy, Andrew Chadwick, Dave Ewart, Sarah Ewart, Lee Fletcher, Sarah Floud, Toral Gathani, Laura Gerrard, Adrian Goodill, Jane Green, Lynden Guiver, Alicia Heath, Carol Hermon, Darren Hogg, Michal Hozak, Isobel Lingard, Sau Wan Kan, Nicky Langston, Kath Moser, Kirstin Pirie, Alison Price, Gillian Reeves, Keith Shaw, Emma Sherman, Rachel Simpson, Helena Strange, Sian Sweetland, Sarah Tipper, Ruth Travis, Lyndsey Trickett, Anthony Webster, Clare Wotton, Lucy Wright, Owen Yang, Heather Young.

Million Women Study Advisory Committee: Emily Banks, Valerie Beral, Lucy Carpenter, Carol Dezateux (Chair), Jane Green, Julietta Patnick, Richard Peto, Cathie Sudlow.

The NHS Breast Screening Centres which took part in the recruitment of participants were: Avon, Aylesbury, Barnsley, Basingstoke, Bedfordshire and Hertfordshire, Cambridge and Huntingdon, Chelmsford and Colchester, Chester, Cornwall, Crewe, Cumbria, Doncaster, Dorset, East Berkshire, East Cheshire, East Devon, East of Scotland, East Suffolk, East Sussex, Gateshead, Gloucestershire, Great Yarmouth, Hereford and Worcester, Kent, Kings Lynn,

Leicestershire, Liverpool, Manchester, Milton Keynes, Newcastle, North Birmingham, North East Scotland, North Lancashire, North Middlesex, North Nottingham, North of Scotland, North Tees, North Yorkshire, Nottingham, Oxford, Portsmouth, Rotherham, Sheffield, Shropshire, Somerset, South Birmingham, South East Scotland, South East Staffordshire, South Derbyshire, South Essex, South Lancashire, South West Scotland, Surrey, Warrington Halton St Helens and Knowsley, Warwickshire Solihull and Coventry, West Berkshire, West Devon, West London, West Suffolk, West Sussex, Wiltshire, Winchester, Wirral, Wycombe.

Funding

This work was supported by Cancer Research UK (grant number C570/A16491), and Medical Research Council (grant number MR/K02700X/1).

Authors' roles

Study design and data collection: VB, GKR, JG, SF. Co-principal investigators of the Million Women Study: VB, JG, GKR, SF. Patient enrolment: VB and GKR. Data analysis: CW and AB. First draft of manuscript: CW. Contributed to writing of manuscript: CW, JG, AB, MA, SF, VB, and GKR. Approved final version of manuscript: all authors. CW takes responsibility for data integrity and analysis accuracy.

References

[1] NHS Digital, Prescription cost analysis England, https://digital.nhs.uk/catalogue/PUB23631, (2016) , Accessed date: November 2017.
[2] J. Watson, L. Wise, J. Green, Prescribing of hormone therapy for menopause, tibolone, and bisphosphonates in women in the UK between 1991 and 2005, Eur. J. Clin. Pharmacol. 63 (9) (2007) 843–849.
[3] R.Y. van der Velde, C.E. Wyers, E. Teesselink, P.P. Geusens, J.P. van den Bergh, F. de Vries, C. Cooper, N.C. Harvey, T.P. van Staa, Trends in oral anti-osteoporosis drug prescription in the United Kingdom between 1990 and 2012: variation by age, sex, geographic location and ethnicity, Bone 94 (2017) 50–55.
[4] H.M. Devold, G.M. Doung, A. Tverdal, K. Furu, H.E. Meyer, J.A. Falch, A.J. Sogaard, Prescription of anti-osteoporosis drugs during 2004–2007-a nationwide register study in Norway, Eur. J. Clin. Pharmacol. 66 (3) (2010) 299–306.
[5] R.L. Drieling, A.Z. LaCroix, S.A.A. Beresford, D.M. Boudreau, C. Kooperberg, R.T. Chlebowski, M.G. Ko, S.R. Heckbert, Long-term Oral bisphosphonate therapy and fractures in older women: the Women's Health Initiative, J. Am. Geriatr. Soc. 65 (9) (2017) 1924–1931.
[6] R.A. Adler, G. El-Hajj Fuleihan, D.C. Bauer, P.M. Camacho, B.L. Clarke, G.A. Clines, J.E. Compston, M.T. Drake, B.J. Edwards, M.J. Favus, S.L. Greenspan, R. McKinney, R.J. Pignolo, D.E. Sellmeyer, Managing osteoporosis in patients on long-term bisphosphonate treatment: report of a task force of the American Society for Bone and Mineral Research, J. Bone Miner. Res. 31 (10) (2016) 1910.
[7] G.A. Wells, A. Cranney, J. Peterson, M. Boucher, B. Shea, V. Robinson, D. Coyle, P. Tugwell, Alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women, Cochrane Database Syst. Rev. 1 (2008) CD001155.
[8] C. Reyes, M. Hitz, D. Prieto-Alhambra, B. Abrahamsen, Risks and benefits of bisphosphonate therapies, J. Cell. Biochem. 117 (1) (2016) 20–28.
[9] S. Khosla, D. Burr, J. Cauley, D.W. Dempster, P.R. Ebeling, D. Felsenberg, R.F. Gagel, V. Gilsanz, T. Guise, S. Koka, L.K. McCauley, J. McGowan, M.D. McKee, S. Mohla, D.G. Pendrys, L.G. Raisz, S.L. Ruggiero, D.M. Shafer, L. Shum, S.L. Silverman, C.H. Van Poznak, N. Watts, S.B. Woo, E. Shane, A.S.f.B.a.M. Research, Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research, J. Bone Miner. Res. 22 (10) (2007) 1479–1491.
[10] S. Khosla, L.C. Hofbauer, Osteoporosis treatment: recent developments and ongoing challenges, Lancet Diabetes Endocrinol. 5 (11) (2017) 898–907.
[11] S.N. Rogers, N.O. Palmer, D. Lowe, C. Randall, United Kingdom nationwide study of avascular necrosis of the jaws including bisphosphonate-related necrosis, Br. J. Oral Maxillofac. Surg. 53 (2) (2015) 176–182.
[12] A. Bamias, E. Kastritis, C. Bamia, L.A. Moulopoulos, I. Melakopoulos, G. Bozas, V. Koutsoukou, D. Gika, A. Anagnostopoulos, C. Papadimitriou, E. Terpos, M.A. Dimopoulos, Osteonecrosis of the jaw in cancer after treatment with bisphosphonates: incidence and risk factors, J. Clin. Oncol. 23 (34) (2005) 8580–8587.
[13] A. Badros, D. Weikel, A. Salama, O. Goloubeva, A. Schneider, A. Rapoport, R. Fenton, N. Gahres, E. Sausville, R. Ord, T. Meiller, Osteonecrosis of the jaw in multiple myeloma patients: clinical features and risk factors, J. Clin. Oncol. 24 (6) (2006) 945–952.
[14] B.G. Durie, M. Katz, J. Crowley, Osteonecrosis of the jaw and bisphosphonates, N. Engl. J. Med. 353 (1) (2005) 99–102 (discussion 99–102).
[15] K. Zervas, E. Verrou, Z. Teleioudis, K. Vahtsevanos, A. Banti, D. Mihou, D. Krikelis, E. Terpos, Incidence, risk factors and management of osteonecrosis of the jaw in patients with multiple myeloma: a single-centre experience in 303 patients, Br. J. Haematol. 134 (6) (2006) 620–623.
[16] M.A. Dimopoulos, E. Kastritis, A. Anagnostopoulos, I. Melakopoulos, D. Gika, L.A. Moulopoulos, C. Bamia, E. Terpos, K. Tsionos, A. Bamias, Osteonecrosis of the jaw in patients with multiple myeloma treated with bisphosphonates: evidence of increased risk after treatment with zoledronic acid, Haematologica 91 (7) (2006) 968–971.
[17] A.A. Khan, A. Morrison, D.A. Hanley, D. Felsenberg, L.K. McCauley, F. O'Ryan, I.R. Reid, S.L. Ruggiero, A. Taguchi, S. Tetradis, N.B. Watts, M.L. Brandi, E. Peters, T. Guise, R. Eastell, A.M. Cheung, S.N. Morin, B. Masri, C. Cooper, S.L. Morgan, B. Obermayer-Pietsch, B.L. Langdahl, R. Al Dabagh, K.S. Davison, D.L. Kendler, G.K. Sandor, R.G. Josse, M. Bhandari, M. El Rabbany, D.D. Pierroz, R. Sulimani, D.P. Saunders, J.P. Brown, J. Compston, Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus, J. Bone Miner. Res. 30 (1) (2015) 3–23.
[18] W.Y. Chiu, J.Y. Chien, W.S. Yang, J.M. Juang, J.J. Lee, K.S. Tsai, The risk of osteonecrosis of the jaws in Taiwanese osteoporotic patients treated with oral alendronate or raloxifene, J. Clin. Endocrinol. Metab. 99 (8) (2014) 2729–2735.
[19] J. Green, G.K. Reeves, S. Floud, I. Barnes, B.J. Cairns, T. Gathani, K. Pirie, S. Sweetland, T.O. Yang, V. Beral, M.W.S. Collaborators, Cohort profile: the million women study, Int. J. Epidemiol. 48 (1) (2019) 28–29e.
[20] CPRD, Clinical practice research datalink, https://www.cprd.com, (2017) , Accessed date: November 2017.
[21] S. Alvarez-Madrazo, S. McTaggart, C. Nangle, E. Nicholson, M. Bennie, Data resource profile: the Scottish National Prescribing Information System (PIS), Int. J. Epidemiol. 45 (3) (2016) 714–715f.
[22] J. Bergdahl, F. Jarnbring, V. Ehrenstein, H. Gammelager, F. Granath, H. Kieler, M. Svensson, G.S. Tell, Y.T. Lagerros, Evaluation of an algorithm ascertaining cases of osteonecrosis of the jaw in the Swedish National Patient Register, Clin. Epidemiol. 5 (2013) 1–7.
[23] H. Gammelager, C. Sværke, S.E. Noerholt, B. Neumann-Jensen, F. Xue, C. Critchlow, J. Bergdahl, Y.T. Lagerros, H. Kieler, G.S. Tell, V. Ehrenstein, Validity of an algorithm to identify osteonecrosis of the jaw in women with postmenopausal osteoporosis in the Danish National Registry of Patients, Clin. Epidemiol. 5 (2013) 263–267.
[24] M. Plummer, Improved estimates of floating absolute risk, Stat. Med. 23 (1) (2004) 93–104.
[25] P.P. Townsend P, A. Beattie, Health and Deprivation. Inequality and the North, Croom Helm Ltd, London, 1987.
[26] StataCorp, Stata Statistical Software: Release 13, StataCorp LP, College Station, TX, 2013.
[27] M. Pazianas, C. Cooper, F.H. Ebetino, R.G. Russell, Long-term treatment with bisphosphonates and their safety in postmenopausal osteoporosis, Ther. Clin. Risk Manag. 6 (2010) 325–343.
[28] P. Tennis, K.J. Rothman, R.L. Bohn, H. Tan, A. Zavras, C. Laskarides, B. Calingaert, M.S. Anthony, Incidence of osteonecrosis of the jaw among users of bisphosphonates with selected cancers or osteoporosis, Pharmacoepidemiol. Drug Saf. 21 (8) (2012) 810–817.
[29] P. Vestergaard, K. Schwartz, L. Rejnmark, L. Mosekilde, E.M. Pinholt, Oral bisphosphonate use increases the risk for inflammatory jaw disease: a cohort study, J. Oral Maxillofac. Surg. 70 (4) (2012) 821–829.
[30] F. Lapi, F. Cipriani, A.P. Caputi, G. Corrao, A. Vaccheri, M.C. Sturkenboom, M. Di Bari, D. Gregori, F. Carle, T. Staniscia, A. Vestri, M. Brandi, V. Fusco, G. Campisi, G. Mazzaglia, B.E.-S.T.B.s. group, Assessing the risk of osteonecrosis of the jaw due to bisphosphonate therapy in the secondary prevention of osteoporotic fractures, Osteoporos. Int. 24 (2) (2013) 697–705.
[31] J.W. Kwon, E.J. Park, S.Y. Jung, H.S. Sohn, H. Ryu, H.S. Suh, A large national cohort study of the association between bisphosphonates and osteonecrosis of the jaw in patients with osteoporosis: a nested case-control study, J. Dent. Res. 94 (9 Suppl) (2015) 212s–219s.
[32] P.A. Eiken, D. Prieto-Alhambra, R. Eastell, B. Abrahamsen, Surgically treated osteonecrosis and osteomyelitis of the jaw and oral cavity in patients highly adherent to alendronate treatment: a nationwide user-only cohort study including over 60,000 alendronate users, Osteoporos. Int. 28 (10) (2017) 2921–2928.
[33] S.H. Lee, S.S. Chang, M. Lee, R.C. Chan, C.C. Lee, Risk of osteonecrosis in patients taking bisphosphonates for prevention of osteoporosis: a systematic review and meta-analysis, Osteoporos. Int. 25 (3) (2014) 1131–1139.
[34] P. Fung, G. Bedogni, A. Bedogni, A. Petrie, S. Porter, G. Campisi, J. Bagan, V. Fusco, G. Saia, S. Acham, P. Musto, M.T. Petrucci, P. Diz, G. Colella, M.D. Mignogna, M. Pentenero, P. Arduino, G. Lodi, C. Maiorana, M. Manfredi, P. Hallberg, M. Wadelius, K. Takaoka, Y.Y. Leung, R. Bonacina, M. Schiodt, P. Lakatos, T. Taylor, G. Riu, G. Favini, S.N. Rogers, M. Pirmohamed, P. Nicoletti, GENVABO Consortium, S. Fedele, Time to onset of bisphosphonate-related osteonecrosis of the jaws: a multicentre retrospective cohort study, Oral Dis. 23 (4) (2017) 477–483.
[35] S. Sammut, N. Malden, V. Lopes, S. Ralston, Epidemiological study of alendronate-related osteonecrosis of the jaw in the southeast of Scotland, Br. J. Oral Maxillofac. Surg. 54 (5) (2016) 501–505.
[36] T. Yamazaki, M. Yamori, K. Yamamoto, K. Saito, K. Asai, E. Sumi, K. Goto, K. Takahashi, T. Nakayama, K. Bessho, Risk of osteomyelitis of the jaw induced by oral bisphosphonates in patients taking medications for osteoporosis: a hospital-based cohort study in Japan, Bone 51 (5) (2012) 882–887.
[37] J. Compston, A. Cooper, C. Cooper, N. Gittoes, C. Gregson, N. Harvey, S. Hope, J.A. Kanis, E.V. McCloskey, K.E.S. Poole, D.M. Reid, P. Selby, F. Thompson, A. Thurston, N. Vine, N.O.G.G. (NOGG), UK clinical guideline for the prevention and treatment of osteoporosis, Arch. Osteoporos. 12 (1) (2017) 43.
[38] E. McCloskey, J.A. Kanis, H. Johansson, N. Harvey, A. Odén, A. Cooper, C. Cooper, R.M. Francis, D.M. Reid, D. Marsh, P. Selby, F. Thompson, S. Hewitt, J. Compston, FRAX-based assessment and intervention thresholds—an exploration of thresholds in women aged 50 years and older in the UK, Osteoporos. Int. 26 (8) (2015) 2091–2099.