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Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2011-000548
Article Type:	Protocol
Date Submitted by the Author:	27-Oct-2011
Complete List of Authors:	Vinogradova, Yana; University of Nottingham, Division of Primary Care Coupland, Carol; University of Nottingham, Division of Primary Care Hippisley-Cox, Julia; University of Nottingham, Division of Primary Care
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Oncology, Pharmacology & therapeutics, Public health
Keywords:	Epidemiology < ONCOLOGY, STATISTICS & RESEARCH METHODS, Bone diseases < ORTHOPAEDIC & TRAUMA SURGERY

Title

Exposure to bisphosphonates and risk of cancer: a protocol for nested case-control studies using the QResearch data.

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Keywords: diphosphonates, neoplasms, case-control studies, osteoporosis/ drug therapy, risk factors.

Word count: 3253

ABSTRACT

Introduction: Bisphosphonates are becoming a common treatment for osteoporosis particularly after discovery of the association between hormone replacement therapy and increased risk of breast cancer. As osteoporosis develops with age, treatment is a long-term intervention. Randomised control trials typically have limited follow-up times, which restricts investigation of the effects of the drugs on risk of primary cancers. A few observational studies have demonstrated a reduced risk of breast cancer and possibly of endometrial cancer in bisphosphonate users. Two epidemiological studies have studied the effect of the drugs on oesophageal cancer but did not reach any definite conclusions. So far, no effects on colorectal and stomach cancer have been shown. This study will investigate the association of bisphosphonates with risks of the 10 most common primary cancers.

Methods and analysis: A series of nested case-control studies will be based on the general population using records from 660 UK general practices within the QResearch database. Cases will be patients with primary cancers diagnosed between 1996 and 2011. Each case will be matched by age, sex, practice and calendar year to 5 controls, who are alive and registered with the practice at the time of diagnosis of the case. Exposure to bisphosphonates will be defined as at least one prescription during the study period. For the most common cancers with substantial numbers of observations, the effect of the duration of the treatment and different types of bisphosphonates will be studied. Conditional logistic regression will be applied to produce odds ratios adjusted for smoking status, socio-economic status, ethnicity, cancer-specific co-morbidities and use of other medications.

Ethics and dissemination: The protocol has been reviewed by the QResearch Scientific Board. The results will be published in a peer-reviewed journal.

INTRODUCTION

Osteoporosis amongst the elderly is a major problem leading to increased mortality and morbidity, and high costs for health services. Thirty-five per cent of the European population aged 50 and over suffer from fractures caused by osteoporosis.[1] Between 1980 and 1990, the use of hormone replacement therapy (HRT) was considered a preventive measure for post-menopausal osteoporotic fractures in women but, after a Women's Health Initiative trial report about increased risk of breast cancer, use of HRT fell significantly.[2]

As a treatment for post-menopausal osteoporosis, bisphosphonates were introduced in the 1990s, and prescribing of them has increased substantially and continually. Hormone replacement therapy (raloxifene) and the use of calcitonin and strontium ranelate [3] are still considered to be options for the treatment of osteoporosis, but according to the UK National Institute for Health and Clinical Excellence (NICE) guidelines[4, 5] recommending bisphosphonates as a first-line therapy for osteoporosis bisphosphonates have become the most commonly prescribed drug.

The proportion of the female population in the UK eligible for treatment varies between 24% and 47%, depending on age.[6] The drugs increase bone mass and reduce the risk of fracture, but these effects become significant only after 6 to 36 months of use depending on the type of drug.[7] The drug binds to bone and after treatment ends[8] is released for up to ten years, depending on which bisphosphonate is used.

The first use of bisphosphonates in the 1970s was in oncology. They were used for the treatment and prevention of skeletal disorders associated with multiple myeloma and bone metastases from breast, prostate, lung and kidney cancers, and other solid tumours. Bisphosphonates have also been used for glucocorticoid-induced osteoporosis.[7]

There is preclinical evidence for the anti-tumour effects of bisphosphonates because of their anti-resorptive properties.[9] Bone is a good environment for tumour cells because of a number of growth factors. Osteoclasts affect release of soluble growth factors and so promote tumour cells. Bisphosphonates accumulated in bones inhibit osteoclast-mediating bone resorption with significant clinical effect. The drugs also demonstrate anti-tumour effects *in vitro* by inhibiting angiogenesis (adhesion, invasion, proliferation) and inducing apoptosis. The cancers studied in vitro were breast, prostate, myeloma, pancreatic and osteosarcoma.[10] These preclinical studies, however, were conducted with concentrations far higher than those used for treating patients with bone metastates.[11]

Although the anti-tumour properties of bisphosphonates are being considered for prevention of bone metastases and a few clinical trials have demonstrated the efficacy of bisphosphonates in women with early-stage breast cancer,[12] they have been little studied in relation to the development of other primary cancers. Four epidemiological studies concentrating on breast cancer have shown positive effects for bisphosphonates: 32 per cent relative risk reduction in post-menopausal women (HR 0.68, 95%CI 0.52 to 0.88),[13] 33 per cent decreased risk in current users, women aged 20-69 years (OR 0.67, 95%CI 0.51 to 0.89),[14] 39 per cent risk reduction in patients taking bisphosphonates for at least one year (OR 0.61, 95%CI 0.50 to 0.76)[15] and 47 per cent risk reduction after start of alendronate (HR 0.53, 95%CI 0.38 to 0.73) and 20 per cent for etidronate (HR 0.80, 95%CI 0.73 to 0.89).[16] A study looking at the risk of endometrial cancer has also shown a 30 per cent decrease associated with bisphosphonate use, but it was not statistically significant (OR 0.7, 95%CI 0.4 to 1.2).[17]

Because bisphosphonates are associated with short-term gastrointestinal adverse effects,[8] an adverse effect on risk of oesophageal cancer might be expected. The first publication about the association was from the US Food and Drug Administration (FDA) Adverse Event

Reporting System, which listed 23 cases of oesophageal cancer in users of oral alendronate between 1995 and 2008.[18] A further observational study, based on 13,678 bisphosphonate users matched to 27,365 non-users, identified 37 oesophageal cancers and 48 gastric cancers and showed reduced risks for oesophageal and gastric cancers (HR 0.35, 95%CI 0.14 to 0.85 and 1.23, 0.68 to 2.22 respectively).[19]

A case-control study looking at 2954 cases of oesophageal, 2018 cases of gastric and 10641 cases of colorectal cancers, based on the General Practice Research Database (GPRD), demonstrated a 30 per cent increased risk of oesophageal cancer in patients with at least one prescription for bisphosphonates (OR 1.30, 95%CI 1.02 to 1.66)[20] but did not find a significant effect on risk of gastric or colorectal cancers (OR's 0.87, 95%CI 0.64 to 1.19 and 0.87, 95%CI 0.77 to 1.00 respectively). A cohort study based on the GPRD did not find any significant association between bisphosphonate use and risk of gastric or oesophageal cancers[21] (combined HR 0.96, 95%CI 0.74 to 1.25, for oesophageal cancer only HR 1.07, 95%CI 0.77 to 1.49). As for colorectal cancer, an Israeli study showed a significantly decreased risk in patients taking bisphosphonates for more an year (RR 0.50, 95% 0.25 to 0.67).[22] A Danish study looked at gastrointestinal cancers and reported an excess risk of oesophageal cancer associated with use of alendronate (HR 2.10, 95%CI 1.01 to 4.35) and etidronate (HR 1.99, 95%CI 1.24 to 3.18) and a possible protective effect of higher doses for colorectal cancer (HR 0.29, 95%CI 0.14 to 0.62).[23] So far no epidemiological studies have investigated associations with risks of other common cancers for bisphosphonate users. A few randomised-controlled trials – the longest for up to 10 years [24-26] – have studied the effect of the drugs on skeletal properties and general adverse effects, but none of them have considered cancer as a consequence of osteoporotic therapy. A cohort study in patients treated for osteoporosis including bisphosphonates is currently enrolling participants to

explore a number of adverse events in the next five years.[27] This is the only study where malignancies form part of the secondary outcome measures.

Our aim is to examine possible associations between use of bisphosphonates and risk of a range of common cancers in a large community sample, including the effect of dose, duration and type of drug.

METHODS AND ANALYSIS

Sample selection

This will be a study using the QResearch primary care research database, which consists of routinely collected data from general practitioner clinical computer systems. The contributing practices, which comprise around 7% of all UK general practices, use the Egton Medical Information System (EMIS). QResearch is one of the largest general practice databases, containing anonymised clinical records for over 13 million patients registered with 660 UK general practices. The information recorded on the database includes patient demographics (year of birth, sex, socio-demographic data derived from UK census 2001), characteristics (height, weight, smoking status), clinical diagnoses, symptoms, and prescribed medications (including repeat prescriptions). Detailed analyses, including age and sex distribution, birth rates and death rates, have been undertaken, and have shown good correspondence with other sources[28] and demonstrated the accuracy and completeness of the data.[29]

An open cohort of patients will be identified, 30 years or older, registered with the study practices during the study period, between 1st Jan 1996 and 1st July 2011. Temporary residents will be excluded. Cases will be incident cases of cancer identified during the study period and these will include the 10 most common cancers. Cases with any previous cancer diagnosis will be excluded. Cases with secondary cancers (READ codes: B56, B57, B58) will be excluded. The right censor date will be the earliest of the following: date of diagnosis of cancer, date of death, date of leaving the practice, date of the latest download of data, the study end date.

Cases and controls

Each case will be matched to 5 controls, who are alive and registered with the practice at the time of diagnosis of the case. Controls will be matched on age, sex, practice and calendar year using incidence density sampling. Controls will be allocated an index date, which is the date on which their matched case was first diagnosed with cancer. Controls with a diagnosis of any cancer before the index date will be excluded.

Cases and controls with a record of mastectomy before their first prescription of bisphosphonates will be excluded, since this treatment is likely to indicate a previous diagnosis of breast cancer with further bone metastases. For breast cancer, only female patients will be included. All patients with Paget's disease will be excluded as the treatment for this condition is administered in higher doses and for much longer periods (typically 2 weeks for osteoporosis against 6 months for Paget's). Patients with prescriptions for the bisphosphonates licensed not for osteoporosis but for malignancies (zolendronic acid, clodronate and daily use of ibandronate) will also be excluded.

For the main analysis, cases and controls will be included if they have complete records for at least 2 years before the index date. A subset of cases and controls with at least 6 years of records will be used for further analyses.

The risks of any cancer and of the 10 most common cancers will be determined for patients prescribed bisphosphonates and compared with the risks for patients not prescribed these drugs. The "most common" cancers have been selected because they have this status in the UK.[30] They are Breast cancer (women, B34), Prostate cancer (men, B46), Lung cancer (B22), Colorectal cancer (B13, B14), Haematological malignancies (B6), Bladder cancer (B49), Melanoma (B32), Gastric cancer (B11), Pancreatic cancer (B17) and Oesophageal cancer (B10). As osteoporosis might be an early symptom of possible myeloma, it will be

analysed separately from lymphoma and leukaemia. The commoner female cancers (Ovary (B44), Uterus (B43) and Cervix (B41)) will also be considered.

Interventions

Exposure to drugs for osteoporosis will be determined based on all prescriptions for bisphosphonates and other drugs before the index date (date of diagnosis or equivalent date for controls) within the observation period (from the date of entry into QResearch to the index date). The bisphosphonates to be included are identified in the British National Formulary section 6.6.2 as treatment for osteoporosis:[3] alendronate (5-10mg daily or 70mg weekly), etidronate (400mg daily for 14 days in 90 day cycles), ibandronate (150mg a month or intravenous 3mg per 3 months) and risedronate (5mg daily).

The cumulative exposure to bisphosphonates will be assessed by extracting duration of the prescribed days' supply and summarising it for each patient. For drugs prescribed in cycles, the length of a cycle will be considered as duration of a prescription, e.g. etidronate prescription for 2 weeks will be assessed as a 90 day prescription duration. The same approach will be applied to intravenous infusion, considering the recommended interval between injections as the duration of a prescription (e.g. 3 months for ibandronate). The cumulative exposure to bisphosphonates will be estimated by extracting the duration for every prescription and, for groups of prescriptions with inter-prescription gaps of less than 60 days, overall course times will be calculated from the start of the first prescription to the end of the last prescription.

As bisphosphonates can be released for months after a treatment, total exposure to bisphosphonates will be estimated as the time between the first prescription and the end-time for the last prescription.

Because bisphosphonates and other osteoporosis treatment drugs are prescribed for years long-term users and short-term users will be distinguished, as treatment of the latter might have been for accidental or clinical fractures, or for better integration of biomaterial or implants. The effect of bisphosphonates on treating fractures varies from 6 to 36 months, e.g. 12 months for risedronate and 24 months for alendronate.[7]

There are three regimens for bisphosphonate use: daily; once-weekly; once-monthly. Daily use has been shown to have lower adherence than weekly use.[31] Another reason for investigating regimens is that, particularly for gastro-intestinal organs, there might be a marked difference between the effects of daily and weekly exposure to bisphosphonates, with associated effects on risks for oesophageal, gastric and colorectal cancers.

Bisphosphonate use will be categorised in a number of ways. The main analyses will compare patients having no prescriptions for the drugs with patients with at least one prescription for any bisphosphonate. The effect of prescribing for short (less than 12 months) and long term (at least 12 months) periods will then be analysed, as well as the effect of regimen: daily or weekly/monthly.

If there are a sufficient number of observations, further analyses will be run for the cumulative exposure (cumulative duration of all prescriptions) and the exposure time to bisphosphonate (the time period between the first prescription and the end-time for the last prescription). The subset of data with at least six years of records will be analysed using following categorisations: no use, less than 180 days, 180 days up to 12 months, 12 to 24 months, 25 or more months. A test for trend will be performed using the actual number of months.

Timing will be categorised as: no use before diagnosis; used within 1-2 years before the index date; used more than two years before the index date. The interaction of timing and

terms of treatment will also be examined, categorised as: no use before diagnosis; used within 1-2 years before the index date, short-term use; used within 1-2 years before the index date, long-term use; used more than two years before the index date, short-term use; used more than two years before the index date, long-term use.

If there are any variations in dose of bisphosphonates, it will be categorised as low (<67% of dose recommended by dose) and normal/high (>66% of recommended dose).

The two main types of bisphosphonates – simple bisphosphonates (etidronate) and nitrogen-containing[7] – will be analysed as there are two different mechanisms of action for the drugs. If there are sufficient numbers, the data will also be analysed by individual drug.

Because prescriptions in the year before the index date might be associated with an early symptom of cancer before a recorded diagnosis, sensitivity analyses ignoring all prescriptions in the last year before the index date will be run. The results from these analyses will highlight any attenuation of the protective effects of bisphosphonates or any increases in magnitudes of harmful effects. A sensitivity analysis on the main analysis will also be run, defining the use of bisphosphonates as at least two prescriptions within the observation period. The analyses will be repeated on a subgroup of patients with at least six years of records to estimate the long-term effect of bisphosphonate use.

The other drugs for osteoporosis to be included are strontium ranelate, raloxifene and calcitonin. As there will not be enough observations to analyse each drug individually they will be combined and included in the analyses as other treatment for osteoporosis. A patient will be considered as a user if they have at least one prescription of any of those drugs in their records before the index date.

Confounding factors

All the analyses will include potential confounders which are established as risk factors for cancer: body mass index (BMI)[32] (continuous variable, at the date closest to one year before the diagnosis and recorded before the index date); smoking status[33] (current smoker – light [1 to 9 cigarettes/day], medium [10 to 19], heavy [20 or more], ex smoker, non smoker); excessive alcohol consumption[34] using Read codes for alcohol status (only if it is a significant confounder for the sample); socio-economic status[35] (Townsend score in fifths); ethnicity[36] (White, Black, Asian, Other). The analysis will also adjust for osteoporosis history,[37] including diagnosis of osteoporosis or osteopenia or previous fractures; use of drugs increasing risk of fracture (systemic corticosteroids and proton-pump inhibitors[38]); use of anti-inflammatory drugs[39] (traditional non-steroidal, cyclo-oxigenase 2 inhibitors and aspirin);[40] use of vitamin D.[41]

Co-morbidities which affect risks of cancer will also be included: rheumatoid arthritis[42] for any cancer; hypertension[43] for uterine cancer; diabetes and glucose intolerance for pancreatic,[44] uterine[45] and colorectal[46] cancers. Analyses of colorectal, oesophageal, gastric and pancreatic cancers will be adjusted for gastro-intestinal disorders[47] if diagnosed before the first use of bisphosphonates or 12 months before the index date, whichever is earlier: upper gastrointestinal disease (dysphagia, oesophagitis, gastro-oesophageal reflux disease, hiatus hernia, oesophageal ulcers, Barrett's oesophagus, gastritis, duodenitis, peptic ulcers, dyspepsia); Crohn's disease, ulcerative colitis; pancreatitis. Bladder cancer analyses will include renal impairment[48] (diagnostic code for chronic kidney disease) if diagnosed before the first use of bisphosphonates or 12 months before the index date, whichever is earlier. Breast cancer analyses will also include previous benign breast disease (fibrocystic disease, intraductal papilloma or fibroadenoma).[49] The results will also be adjusted for family history of cancer[50] (this will vary according to the cancer under consideration) if

recorded six months before the index date. This is to reduce family recall bias as cases are more likely to report a family history of cancer around the time of diagnosis.[51]

Because use of some drugs might be associated with increased risk of some cancers use of HRT[52] and oral contraceptive pill[53] for breast, uterine, ovarian and cervical cancers will also be included. Use of acid suppression drugs[54] (including H2 antagonists (BNF 1.3.1), proton pump inhibitors (BNF 1.3.5) and antacids (BNF 1.1.1)) will be added for gastro-intestinal cancer analyses. If there are enough observations, use of those drugs will be categorised by the number of prescriptions within the observation period: none; fewer than 12 prescriptions; 12 to 24 prescriptions; 25 to 48 prescriptions; more than 49 prescriptions.

Statistical analysis

Conditional logistic regression will be used to estimate odds ratio with 95% confidence intervals for cancer of any site and each of the ten most common cancers and three additional female cancers and their matched controls. The initial analysis model will determine the unadjusted odds ratios for each cancer associated with bisphosphonate prescriptions. A multivariable model will determine the odds ratio for each cancer associated with bisphosphonate prescriptions, adjusted for the potential confounding effects of the variables listed above.

As BMI, smoking status and alcohol consumption may be important confounders but have non-negligible numbers of missing data, multiple imputation will be used to impute the missing values. Ten imputed datasets will be created. Index year, case/control status, years of records, potential confounders, and exposure to bisphosphonates and other drugs, will be included. For comparison, analyses with missing data treated as separate categories will also be carried out.

Stata v 11 will be used for all the analyses. A 1% significance level will be used to account for the multiple outcomes.

Sample size calculation

As different types of cancer may have different risks associated with bisphosphonate use, analyses will require number of cases to relate to each type of cancer. All available data from QResearch will be used. Our calculations are based on the exposure to bisphosphonates in the proposed data extraction for 6.8% of women and 1.8% of men. For non-gender-specific cancers, the total proportion of users is estimated as 4.2%. To detect an odds ratio of 0.87 (for colorectal or stomach cancers[20]) 22322 cases will be needed. To detect an odds ratio of 1.3 (for oesophageal cancer[20]) 5208 cases will be needed. To detect an odds ratio of 0.70 (for breast[14] or uterus[17] cancers) 2382 female cases will be needed. For prostate cancer, to detect 30% increase (or decrease) in risk 11773 (or 8686) male cases will be needed. For other cancers, a detection of 30% risk decrease will require 3785 cases. All calculations are done for matched sets of cases and controls, with 4.5 matched controls per case, an estimated coefficient for exposure between matched cases and controls of 0.2, a power of 80% and a significance level of 1%.

ETHICS AND DISSEMINATION

This protocol has been independently peer reviewed by the QResearch Scientific Board and has been reported to Trent Research Ethics Committee in accordance with the agreed procedure. A full report containing the study findings will be prepared and a paper based on the report will be submitted to a peer reviewed journal.

Authors' contribution

JHC had the original idea for this study. CC contributed to the development of the idea. YV reviewed the literature, contributed to the study design and wrote the draft of the manuscript. JHC and CC critically reviewed the paper. YV is the guarantor of the study.

Funding

This work has been funded by the Division of Primary Care of University of Nottingham. Apart from that, this research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any additional organisation for the submitted work. JHC is professor of clinical epidemiology at the University of Nottingham and unpaid director of QResearch, a not-for-profit organisation which is a joint partnership between the University of Nottingham and EMIS (commercial IT supplier for 60% of general practices in the UK). JHC is also a paid director of ClinRisk Limited, which produces open and closed source software to ensure

the reliable and updatable implementation of clinical risk algorithms within clinical computer systems to help improve patient care. CC is associate professor of medical statistics at the University of Nottingham and a paid consultant statistician for ClinRisk Limited; no other relationships or activities that could appear to have influenced the submitted work.

Acknowledgements

We acknowledge the contribution of EMIS and the University of Nottingham for expertise in creating and maintaining QRESEARCH and to the EMIS practices which contribute data without whom this research would not be possible.

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BMJ open

Exposure to bisphosphonates and risk of cancer: a protocol for nested case-control studies using the QResearch® primary care data.

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2011-000548.R1
Article Type:	Protocol
Date Submitted by the Author:	24-Nov-2011
Complete List of Authors:	Vinogradova, Yana; University of Nottingham, Division of Primary Care Coupland, Carol; University of Nottingham, Division of Primary Care Hippisley-Cox, Julia; University of Nottingham, Division of Primary Care
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Oncology, Pharmacology & therapeutics, Public health
Keywords:	Epidemiology < ONCOLOGY, STATISTICS & RESEARCH METHODS, Bone diseases < ORTHOPAEDIC & TRAUMA SURGERY

Title

Exposure to bisphosphonates and risk of cancer: a protocol for nested case-control studies using the QResearch® primary care database.

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Keywords: bisphosphonates, neoplasms, case-control studies, osteoporosis/ drug therapy, risk factors.

Word count: 3769

ABSTRACT

Introduction: Bisphosphonates are becoming a common treatment for osteoporosis particularly after discovery of the association between hormone replacement therapy and increased risk of breast cancer. As osteoporosis develops with age, treatment is a long-term intervention. Randomised control trials typically have limited follow-up times, which restricts investigation of the effects of the drugs on risk of primary cancers. A few observational studies have demonstrated a reduced risk of breast cancer and possibly of endometrial cancer in bisphosphonate users. Two epidemiological studies have studied the association of the drugs with oesophageal cancer but did not reach any definite conclusions. So far, only borderline associations with colorectal and stomach cancer have been shown. This study will investigate the association of bisphosphonates with risks of the 10 most common primary cancers.

Methods and analysis: A series of nested case-control studies will be based on the general population using records from approximately 600 UK general practices within the QResearch® database. Cases will be patients with primary cancers diagnosed between 1996 and 2011. Each case will be matched by age, sex, practice and calendar year to 5 controls, who are alive and registered with the practice at the time of diagnosis of the case. Exposure to bisphosphonates will be defined as at least one prescription during the study period. For the most common cancers with substantial numbers of observations, the effect of the duration of the treatment and different types of bisphosphonates will be studied. Conditional logistic regression will be applied to produce odds ratios adjusted for smoking status, socio-economic status, ethnicity, cancer-specific co-morbidities and use of other medications.

Ethics and dissemination: The protocol has been reviewed by the QResearch® Scientific Board. The results will be published in a peer-reviewed journal.

INTRODUCTION

Osteoporosis amongst the elderly is a major problem leading to increased mortality and morbidity, and high costs for health services. Thirty-five per cent of the European population aged 50 and over suffer from fractures caused by osteoporosis.[1] Between 1980 and 1990, the use of hormone replacement therapy (HRT) was considered a preventive measure for post-menopausal osteoporotic fractures in women but, after a Women's Health Initiative trial report about increased risk of breast cancer, use of HRT fell significantly.[2]

As a treatment for post-menopausal osteoporosis, bisphosphonates were introduced in the 1990s, and prescribing of them has increased substantially and continually. Hormone replacement therapy (raloxifene) and the use of calcitonin and strontium ranelate [3] are still considered to be options for the treatment of osteoporosis, but according to the UK National Institute for Health and Clinical Excellence (NICE) guidelines[4, 5] recommending bisphosphonates as a first-line therapy for osteoporosis bisphosphonates have become the most commonly prescribed drug.

The proportion of the female population in the UK eligible for treatment varies between 24% and 47%, depending on age.[6] The drugs increase bone mass and reduce the risk of fracture, but these effects become significant only after 6 to 36 months of use depending on the type of drug.[7] The drug binds to bone and after treatment ends[8] is released for up to ten years, depending on which bisphosphonate is used.

The first use of bisphosphonates in the 1970s was in oncology. They were used for the treatment and prevention of skeletal disorders associated with multiple myeloma and bone metastases from breast, prostate, lung and kidney cancers, and other solid tumours. Bisphosphonates have also been used for glucocorticoid-induced osteoporosis.[7]

There is preclinical evidence for the anti-tumour effects of bisphosphonates because of their anti-resorptive properties.[9] Bone is a good environment for tumour cells because of a number of growth factors. Osteoclasts affect release of soluble growth factors and so promote tumour cells. Bisphosphonates accumulated in bones inhibit osteoclast-mediating bone resorption with significant clinical effect. The drugs also demonstrate anti-tumour effects *in vitro* by inhibiting angiogenesis (adhesion, invasion, proliferation) and inducing apoptosis. The cancers studied in vitro were breast, prostate, myeloma, pancreatic and osteosarcoma.[10] These preclinical studies, however, were conducted with concentrations far higher than those used for treating patients with bone metastases.[11]

Although the anti-tumour properties of bisphosphonates are being considered for prevention of bone metastases and a few clinical trials have demonstrated the efficacy of bisphosphonates in women with early-stage breast cancer,[12] they have been little studied in relation to the development of other primary cancers. Four epidemiological studies concentrating on breast cancer have shown positive effects for bisphosphonates: 32 per cent relative risk reduction in post-menopausal women (HR 0.68, 95%CI 0.52 to 0.88),[13] 33 per cent decreased risk in current users, women aged 20-69 years (OR 0.67, 95%CI 0.51 to 0.89),[14] 39 per cent risk reduction in patients taking bisphosphonates for at least one year (OR 0.61, 95%CI 0.50 to 0.76)[15] and 47 per cent risk reduction after start of alendronate (HR 0.53, 95%CI 0.38 to 0.73) and 20 per cent for etidronate (HR 0.80, 95%CI 0.73 to 0.89).[16] A study looking at the risk of endometrial cancer has also shown a 30 per cent decrease associated with bisphosphonate use, but it was not statistically significant (OR 0.7, 95%CI 0.4 to 1.2).[17]

Because bisphosphonates are associated with short-term gastrointestinal adverse effects,[8] an adverse effect on risk of oesophageal cancer might be expected. The first publication about the association was from the US Food and Drug Administration (FDA) Adverse Event

Reporting System, which listed 23 cases of oesophageal cancer in users of oral alendronate between 1995 and 2008.[18] A further observational study, based on 13,678 bisphosphonate users matched to 27,365 non-users, identified 37 oesophageal cancers and 48 gastric cancers and showed reduced risk only for oesophageal but not gastric cancers (HR 0.35, 95%CI 0.14 to 0.85 and 1.23, 0.68 to 2.22 respectively).[19]

A case-control study looking at 2954 cases of oesophageal, 2018 cases of gastric and 10641 cases of colorectal cancers, based on the General Practice Research Database (GPRD), demonstrated a 30 per cent increased risk of oesophageal cancer in patients with at least one prescription for bisphosphonates (OR 1.30, 95%CI 1.02 to 1.66)[20] but did not find a significant association with risk of gastric or colorectal cancers (OR's 0.87, 95%CI 0.64 to 1.19 and 0.87, 95%CI 0.77 to 1.00 respectively). A cohort study based on the GPRD did not find any significant association between bisphosphonate use and risk of gastric or oesophageal cancers[21] (combined HR 0.96, 95%CI 0.74 to 1.25, for oesophageal cancer only HR 1.07, 95%CI 0.77 to 1.49). As for colorectal cancer, an Israeli study showed a significantly decreased risk in patients taking bisphosphonates for more an year (RR 0.50, 95% 0.25 to 0.67).[22] A Danish study looked at gastrointestinal cancers and reported an excess risk of oesophageal cancer associated with use of alendronate (HR 2.10, 95%CI 1.01 to 4.35) and etidronate (HR 1.99, 95%CI 1.24 to 3.18) and a possible protective effect of higher doses for colorectal cancer (HR 0.29, 95%CI 0.14 to 0.62).[23] So far no epidemiological studies have investigated associations with risks of other common cancers for bisphosphonate users. A few randomised-controlled trials – the longest for up to 10 years [24-26] – have studied the effect of the drugs on skeletal properties and general adverse effects, but none of them have considered cancer as a consequence of osteoporotic therapy. A cohort study in patients treated for osteoporosis including bisphosphonates is currently enrolling participants to explore a number of adverse events in the next five years.[27]

Our aim is to examine possible associations between use of bisphosphonates and risk of a range of common cancers in a large community sample, including the effect of dose, duration and type of drug.

METHODS AND ANALYSIS

Sample selection

This will be a study using the QResearch® primary care research database, which consists of routinely collected data from general practitioner clinical computer systems. The contributing practices, which comprise around 7% of all UK general practices, use the Egton Medical Information System (EMIS). QResearch® is one of the largest general practice databases, containing anonymised clinical records for over 13 million patients registered with more than 600 UK general practices. The information recorded on the database includes patient demographics (year of birth, sex, socio-demographic data derived from UK census 2001), characteristics (height, weight, smoking status), clinical diagnoses, symptoms, and prescribed medications (including repeat prescriptions). Detailed analyses, including age and sex distribution, birth rates and death rates, have been undertaken, and have shown good correspondence with other sources[28] and demonstrated the accuracy and completeness of the data.[29]

An open cohort of patients will be identified, 30 years or older, registered with the study practices during the study period, between 1st Jan 1996 and 1st July 2011. Temporary residents and those who did not have a valid postcode related Townsend deprivation score (about 3% of the population) will be excluded. Cases will be incident cases of cancer identified during the study period and these will include the 10 most common cancers. Cases with any previous cancer diagnosis will be excluded. Cases with secondary cancers (READ codes: B56, B57, B58) will be excluded. The right censor date will be the earliest of the following: date of diagnosis of cancer, date of death, date of leaving the practice, date of the latest download of data, the study end date.

Cases and controls

Each case will be matched to 5 controls, who are alive and registered with the practice at the time of diagnosis of the case. Controls will be matched on age, sex, practice and calendar year using incidence density sampling. Controls will be allocated an index date, which is the date on which their matched case was first diagnosed with cancer. Controls with a diagnosis of any cancer before the index date will be excluded. Cases and controls will be included if they have records for at least 2 years of follow-up within the QResearch® database before the index date to ensure completeness of the data. Cases and controls with a record of mastectomy before their first prescription of bisphosphonates will be excluded, since this treatment is likely to indicate a previous diagnosis of breast cancer with further bone metastases. For breast cancer, only female patients will be included. All patients with Paget's disease will be excluded as the treatment for this condition is administered in higher doses and for much longer periods (typically 2 weeks for osteoporosis against 6 months for Paget's). Patients with prescriptions for the bisphosphonates licensed not for osteoporosis but for malignancies (zoledronic acid if there was more than one prescription in a year, any use of clodronate and daily use of ibandronate) will also be excluded.

The risks of the most common cancers will be compared between patients prescribed bisphosphonates and patients not prescribed these drugs. The "most common" cancers have been selected because they have this status in the UK.[30] They are Breast cancer (women, B34), Prostate cancer (men, B46), Lung cancer (B22), Colorectal cancer (B13, B14), Haematological malignancies (B6), Bladder cancer (B49), Melanoma (B32), Gastric cancer (B11), Pancreatic cancer (B17) and Oesophageal cancer (B10). As osteoporosis might be an early symptom of possible myeloma, it will be analysed separately from lymphoma and leukaemia. The commoner female cancers (Ovary (B44), Uterus (B43) and Cervix (B41)) will also be considered.

Interventions

The observation period for assessing exposure for each patient will be defined as the time between the date of entry into the QResearch® database and six months prior to the date of diagnosis or the equivalent date for controls. Exposure to drugs for osteoporosis will be determined based on all prescriptions for bisphosphonates and other drugs within the observation period. Prescriptions in the last 6 months before the index date will not be used in the analysis to remove potential reverse causality bias as patients might be prescribed bisphosphonates to treat early symptoms of not yet diagnosed cancer[31]. The bisphosphonates to be included are identified in the British National Formulary section 6.6.2 as treatment for osteoporosis:[3] alendronate (5-10mg daily or 70mg weekly), etidronate (400mg daily for 14 days in 90 day cycles), ibandronate (150mg a month or intravenous 3mg per 3 months) and risedronate (5mg daily and 35mg weekly), zoledronic acid (5mg intravenous once a year). Other bisphosphonates such as pamidronate and tiludronate could be used for treatment of osteoporosis[8] but they are not licensed for this in the UK and therefore no data are available for the study.

The exposure to bisphosphonates will be assessed by extracting duration of the prescribed days' supply. For drugs prescribed in cycles, the length of a cycle will be considered as duration of a prescription, e.g. etidronate prescription for 2 weeks will be assessed as a 90 day prescription duration. The same approach will be applied to intravenous infusion, considering the recommended interval between injections as the duration of a prescription (e.g. 3 months for ibandronate). For groups of prescriptions with inter-prescription gaps of less than 60 days, overall course times will be calculated from the start of the first prescription to the end of the last prescription. The cumulative exposure to bisphosphonates will be estimated by calculating the sum of all overall course times for each patient.

Because bisphosphonates and other osteoporosis treatment drugs can be prescribed for many years long-term users and short-term users will be distinguished, as treatment of the latter might have been for accidental or clinical fractures, or for better integration of biomaterial or implants. The effect of bisphosphonates on treating fractures varies from 6 to 36 months, e.g. 12 months for risedronate and 24 months for alendronate.[7]

There are a few different regimens for bisphosphonate use: daily; daily for two weeks taken in 90-days cycles, once-weekly; once-monthly; injections once in three months and once a year. Daily use has been shown to have lower adherence than weekly use with one of the possible reasons being inconvenience.[32] Another reason for investigating regimens is that, particularly for gastro-intestinal organs, there might be a marked difference between the effects of daily and other exposures to bisphosphonates, with associated effects on risks for oesophageal, gastric and colorectal cancers.

Bisphosphonate use will be categorised in a number of ways. The main analyses will compare patients having no prescriptions for the drugs with patients with at least one prescription for any bisphosphonate. The effect of prescribing for short (less than 12 months) and long term (at least 12 months) periods will then be analysed, as well as the effect of regimen (daily use or other regimen).

If there are a sufficient number of observations, further analyses will be run for the cumulative duration of all prescriptions. Duration of use of bisphosphonates will be analysed using the following categorisations: no use; less than 6 months; 7 to 36 months; 37 to 72 months; 73 months or more. A test for trend will be performed using the actual number of months.

Timing will be categorised as: no use within the observation period; used within six months to two years before the index date; last used more than two years before the index date. The

combination of timing and duration of treatment will also be examined, categorised as: no use within the observation period; used within six months to two years before the index date, short-term use; used within six months to two years before the index date, long-term use; last used more than two years before the index date, short-term use; last used more than two years before the index date, long-term use.

If there is sufficient variation in dose of bisphosphonates, it will be categorised as low (<67% of dose recommended by dose) and normal/high (>66% of recommended dose).

The two main types of bisphosphonates – simple bisphosphonates (etidronate) and nitrogen-containing[7] – will be analysed as there are two different mechanisms of action for the drugs. If there are sufficient numbers, the data will also be analysed by individual drug.

The other drugs for osteoporosis to be included are strontium ranelate, raloxifene, teriparatide, calcitonin and parathyroid hormone. As there are unlikely to be enough observations to analyse each drug individually they will be combined and included in the analyses as other treatment for osteoporosis. A patient will be considered as a user if they have at least one prescription of any of those drugs in their records in the observation period.

Confounding factors

All the analyses will include potential confounders which are established as risk factors for cancer: body mass index (BMI)[33] (continuous variable, at the date closest to one year before the diagnosis and recorded before the index date); smoking status[34] (current smoker – light [1 to 9 cigarettes/day], medium [10 to 19], heavy [20 or more], ex smoker, non smoker); excessive alcohol consumption[35] using Read codes for alcohol status (only if it is a significant confounder for the sample); socio-economic status[36] (Townsend score in fifths); ethnicity[37] (White, Black, Asian, Other). The analysis will also adjust for osteoporosis history,[38] including diagnosis of osteoporosis or osteopenia or previous fractures; use of drugs increasing risk of fracture such as systemic corticosteroids and acid-suppressive medications (including H2 antagonists (BNF 1.3.1), proton pump inhibitors (BNF 1.3.5) and antacids (BNF 1.1.1));[39] use of anti-inflammatory drugs[40] (traditional non-steroidal, cyclo-oxigenase 2 inhibitors and aspirin);[41] use of vitamin D.[42]

Co-morbidities which affect risks of cancer will also be included: rheumatoid arthritis[43] for any cancer; hypertension[44] for uterine cancer; diabetes and glucose intolerance for pancreatic,[45] uterine[46] and colorectal[47] cancers. Analyses of colorectal, oesophageal, gastric and pancreatic cancers will be adjusted for gastro-intestinal disorders[48] if diagnosed before the first use of bisphosphonates or 12 months before the index date, whichever is earlier: upper gastrointestinal disease (dysphagia, oesophagitis, gastro-oesophageal reflux disease, hiatus hernia, oesophageal ulcers, Barrett's oesophagus, gastritis, duodenitis, peptic ulcers, dyspepsia); Crohn's disease, ulcerative colitis; pancreatitis. Bladder cancer analyses will include renal impairment[49] (diagnostic code for chronic kidney disease) if diagnosed before the first use of bisphosphonates or 12 months before the index date, whichever is earlier. Breast cancer analyses will also include previous benign breast disease (fibrocystic disease, intraductal papilloma or fibroadenoma).[50] The results will also be adjusted for

family history of cancer[51] (this will vary according to the cancer under consideration) if recorded at least six months before the index date. This is to reduce family recall bias as cases are more likely to report a family history of cancer around the time of diagnosis.[52]

Because use of some drugs might be associated with increased risk of some cancers use of HRT[53] and oral contraceptive pill[54] for breast, uterine, ovarian and cervical cancers will also be included. Use of acid suppression drugs[55] will be added for gastro-intestinal cancer analyses and if there are enough observations, use of those drugs will be categorised by the number of prescriptions within the observation period: none; fewer than 12 prescriptions; 12 to 24 prescriptions; 25 to 48 prescriptions; more than 49 prescriptions.

Statistical analysis

Conditional logistic regression will be used to estimate odds ratio with 95% confidence intervals for cancer of any site and each of the ten most common cancers and the three additional female cancers. If there are enough observations blood cancers (myeloma, lymphoma and leukaemia) will be analysed separately. The initial analysis model will determine the unadjusted odds ratios for each cancer associated with bisphosphonate prescriptions. A multivariable model will determine the odds ratio for each cancer associated with bisphosphonate prescriptions, adjusted for the potential confounding effects of the variables listed above.

A sensitivity analysis on the main analysis will also be run, defining the use of bisphosphonates as at least two prescriptions within the observation period. The analyses will be repeated on a subgroup of patients with at least six years of records and will only analyse the prescriptions in the last 6 years excluding the last 6 months to ensure the completeness of data in estimating the long-term effect of bisphosphonate use.

As BMI, smoking status and alcohol consumption may be important confounders but have non-negligible numbers of missing data, multiple imputation will be used to impute the missing values[56]. Ten imputed datasets will be created. Index year, case/control status, years of records, potential confounders, and exposure to bisphosphonates and other drugs, will be included in the imputation model. For comparison, analyses with missing data treated as separate categories will also be carried out.

Stata v 11 will be used for all the analyses. A 1% significance level will be used to account for the multiple outcomes.

Sample size calculation

As different types of cancer may have different risks associated with bisphosphonate use, analyses will require the number of cases to relate to each type of cancer. All eligible cases from QResearch® will be used. Our calculations are based on the exposure to bisphosphonates in the preliminary data extraction for 4.5% of women and 1.7% of men for gender-specific cancers. For non-gender-specific cancers, the total proportion of users is estimated as 4.2%. To detect an odds ratio of 0.87 (for colorectal or stomach cancers[20]) 22,322 cases will be needed. To detect an odds ratio of 1.3 (for oesophageal cancer[20]) 5208 cases will be needed. To detect an odds ratio of 0.70 (for breast[14] or uterus[17] cancers) 3540 female cases will be needed. For prostate cancer, to detect a 30% increase (or decrease) in risk 12,449 (or 9190) male cases will be needed. For other cancers, detection of a 30% risk increase (or decrease) will require 5208 cases (or 3785 cases). All calculations are done for matched sets of cases and controls, with 4.5 matched controls per case, an estimated coefficient for exposure between matched cases and controls of 0.2, a power of 80% and a significance level of 1%.

DISCUSSION

This is an observational study based on routinely collected data from a large primary care research database and will have strengths and limitations similar to such studies. It will be substantially larger and will have greater statistical power than any previous studies. It will allow analyses to be carried out investigating the effects of the duration of treatment for the commonest cancers. As the data on prescriptions and potential confounding variables are routinely and prospectively collected and recorded before the index date the study will be free from recall bias, and as all eligible cases and randomly selected controls will be included this will ensure there is no selection bias.

The limitations of the study will include possible uncertainty in cancer diagnosis. A systematic review based on GPRD validation studies reported that, on average, 95% of diagnoses of neoplasms recorded on the GP electronic record were confirmed from other data sources.[57] However it has been found that one in five of all primary care patients with cancer were not identified through electronic searches for malignancies in general practice electronic records, although this was based on data from 1990–1999.[58] Any such misclassification will result in underestimating any association with bisphosphonates shifting odds ratios toward unity. As the selection of the cases will be based on the first record of a cancer the exact site of origin might be determined only later and therefore will not be used in the analyses. Information about cancer stage or results of histological investigations is not consistently recorded in general practice and will not be used.

Another limitation is potential overestimation of bisphosphonate use. The analysis will be based on prescriptions not on actual use and no data are available on adherence to the medications. However, there is no reason for non-adherence to systematically differ between cases and controls.

Other limitations are also common to any general practice databases. Information on certain risk factors such as level of physical activity, diet and cancer screening tests (mammography, prostate-specific antigen test, colonoscopy) is not reliably recorded so these factors will not be included in the analyses. Also results of any bone mineral density tests are not recorded consistently and will not be used in the analysis so there may be some residual confounding.

Important confounders such as smoking or body mass index have a certain amount of missing data and they will be imputed.

ETHICS AND DISSEMINATION

This protocol has been independently peer reviewed by the QResearch® Scientific Board and has been reported to Trent Research Ethics Committee in accordance with the agreed procedure, reference number MREC/03/4/021. To guarantee the confidentiality of personal and health information only the authors will have access to the data during the study. It will be possible to access the data after the publication of the results but only on premises of the University of Nottingham. The full protocol and statistical code will be available from the authors after the publication of the results.

Authors' contribution

JHC had the original idea for this study. CC contributed to the development of the idea and the study design. YV reviewed the literature, contributed to the study design and wrote the draft of the manuscript. JHC and CC critically reviewed the paper. YV is the guarantor of the study. All authors approved the submitted version.

Funding

This work has been funded by the Division of Primary Care of University of Nottingham. Apart from that, this research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. Only the authors will be responsible for analysis, interpretation of the data and writing the report for publication.

Competing interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and

declare no support from any additional organisation for the submitted work. JHC is professor of clinical epidemiology at the University of Nottingham and unpaid director of QResearch®, a not-for-profit organisation which is a joint partnership between the University of Nottingham and EMIS (commercial IT supplier for 60% of general practices in the UK). JHC is also a paid director of ClinRisk Limited, which produces open and closed source software to ensure the reliable and updatable implementation of clinical risk algorithms within clinical computer systems to help improve patient care. There were no other relationships or activities that could appear to have influenced the submitted work.

Acknowledgements

We acknowledge the contribution of EMIS and the University of Nottingham for expertise in creating and maintaining QResearch® and to the EMIS practices which contribute data without whom this research would not be possible.

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