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Exposure to bisphosphonates and risk of common non-gastrointestinal cancers: series of nested case–control studies using two primary-care databases

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Background: Bisphosphonates are the most commonly prescribed osteoporosis drugs but long-term effects are unclear, although antitumour properties are known from preclinical studies.

Methods: Nested case–control studies were conducted to investigate bisphosphonate use and risks of common non-gastrointestinal cancers (breast, prostate, lung, bladder, melanoma, ovarian, pancreas, uterus and cervical). Patients 50 years and older, diagnosed with primary cancers between 1997 and 2011, were matched to five controls using the UK practice-based QResearch and Clinical Practice Research Datalink (CPRD) databases. The databases were analysed separately and the results combined.

Results: A total of 91 556 and 88 845 cases were identified from QResearch and CPRD, respectively. Bisphosphonate use was associated with reduced risks of breast (odds ratio (OR): 0.92, 95% confidence interval (CI): 0.87–0.97), prostate (OR: 0.87, 95% CI: 0.79–0.96) and pancreatic (OR: 0.79, 95% CI: 0.68–0.93) cancers in the combined analyses, but no significant trends with duration. For alendronate, reduced risk associations were found for prostate cancer in the QResearch (OR: 0.81, 95% CI: 0.70–0.93) and combined (OR: 0.84, 95% CI: 0.75–0.93) analyses (trend with duration P-values 0.009 and 0.001). There were no significant associations from any of the other analyses.

Conclusion: In this series of large population-based case–control studies, bisphosphonate use was not associated with increased risks for any common non-gastrointestinal cancers.

Bisphosphonates were introduced as a treatment for postmenopausal osteoporosis (National Institute for Health and Clinical Excellence, 2008a, b) in the 1990s, and prescribing has substantially increased (Kanis et al, 2008). The effects of bisphosphonates are long term as the drugs accumulate in bones and are released for several years after treatment ends (Watts and Diab, 2010). It is a relatively new treatment and very few studies have looked at the long-term effect of bisphosphonates on risks of different cancers in the general population.

Although antitumour properties of bisphosphonates have been discovered in preclinical studies (Croucher et al, 2003; Guise, 2008)

and reaffirmed in the treatment of bone metastases (Gnant, 2010), no long-term randomised clinical trials have been run to determine the effect of bisphosphonates on cancer incidence. Epidemiological studies have consistently reported a reduced risk of breast cancer in bisphosphonate users (Chlebowski et al, 2010; Newcomb et al, 2010; Rennert et al, 2010; Vestergaard et al, 2011; Cardwell et al, 2012), but the effects of bisphosphonates on other common non-gastrointestinal cancers are still uncertain, having been investigated in only one up-to-date observational study using the Clinical Practice Research Datalink (CPRD) (Cardwell et al, 2012). Previous studies have generally been insufficiently powered to

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detect associations for other types of cancer, and few have looked at associations with individual types of bisphosphonate drugs, and so there is little data to establish definitive conclusions. Our aim, therefore, was to investigate the associations between bisphosphonates and risks of common cancers in the general population using a nested case–control design and including all available data from two large primary-care databases – both the QResearch and the CPRD.

MATERIALS AND METHODS

Data source. The two largest primary-care databases in the UK, QResearch and CPRD, were used. Each database covers around 6% of the UK population from more than 600 general practices, and contains electronic records including patient demographics, referrals, tests and prescriptions. Both are representative of the general population in the United Kingdom, have been rigorously validated using other sources of information (Jick *et al*, 2003; Hippisley-Cox *et al*, 2004) and have been used for a range of safety studies involving commonly prescribed medications (Green *et al*, 2010; Hippisley-Cox and Coupland, 2010; Parker *et al*, 2010; Walker *et al*, 2011). The protocol for this study was published in Vinogradova *et al* (2012) and, although originally based on QResearch, a replicate study has also been conducted using CPRD to examine any possible differences between the two and further increase in the statistical power by running analyses to derive combined results from both data sources.

Study design. Open cohorts of patients were identified in each database: patients were aged 50 years and older and registered with the practice at some time during the study period between January 1997 and July 2011. For this paper, we selected the most common solid, non-gastrointestinal cancers (breast, prostate, lung, bladder, pancreatic, ovarian and melanoma) as the outcomes and identified incident cases from the cohorts. Less common female cancers (cervix and uterus) were also considered. Each case was matched to up to five controls by age, sex, practice and calendar year. All controls were alive and registered with the practice at the date of the first recorded diagnosis of cancer in their matched case, which we defined as the index date for each case and their matched controls. For cases and controls, patients were included only if they had at least 2 years of data before their index date. Cases and controls with bisphosphonate prescriptions licensed for any malignancies before the index date (date of diagnosis for cases or equivalent date for controls) were excluded. For breast cancer, male patients and patients with a record of mastectomy before their first prescription of bisphosphonates were excluded. Patients with Paget's disease were also excluded.

Exposure to bisphosphonates. Exposure to bisphosphonates was assessed, including prescriptions for alendronate, etidronate, ibandronate and risedronate as the nationally licensed drugs for the treatment of osteoporosis (BNF 6.6.2) (British Medical Association and Royal Pharmaceutical Society of Great Britain, 2008). Information was extracted on all prescriptions for bisphosphonates during the observation period – defined as a period between the date of patient registration with the general practice and 6 months before the index date. Prescriptions in the past 6 months before the index date were not used to reduce protopathic bias because early symptoms of cancer such as low weight or bone ache could lead to bisphosphonate treatments. For the main analyses, a patient was considered to be a bisphosphonate user if they had at least one prescription during the observation period. Cumulative exposure was estimated by summing the durations of all bisphosphonate prescriptions for each patient, considering gaps of fewer than 90 days between two prescriptions as continuous therapy. Duration of exposure to bisphosphonates was analysed

using the following categorisations: no use; short-term use (used for <1 year); long-term use (used for >1 year). For analyses of the most common cancers (breast, prostate, lung, bladder and melanoma), finer categories for duration of use of bisphosphonates were considered: no use, <6 months; 7–36 months; 37–72 months; and 73 months or more. A test for trend was performed using the actual number of months.

Confounding variables. All the analyses included potential confounders established as risk factors for cancer. Body mass index (BMI) (Henderson and Bernstein, 2008), a continuous variable, was based on values recorded at the date closest to 1 year before the index date. Using Read codes, smoking status (Hecht, 2008) (current smoker – light (1–9 cigarettes per day), medium (10–19), heavy (20 or more), ex-smoker, non-smoker); alcohol consumption (Schütze *et al*, 2011); and ethnicity (Ferlay *et al*, 2010) (White or not recorded, Black, Asian, Other) used values recorded at the closest date before the index date. The analysis also adjusted for history of osteoporosis (McGlynn *et al*, 2008), including diagnosis of osteoporosis or osteopenia or previous fractures (recorded before the index date); use of drugs increasing risks of fracture and cancer 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)); (Corley *et al*, 2010) use of anti-inflammatory drugs (Coussens and Werb, 2002) (traditional non-steroidal anti-inflammatory drugs, cyclo-oxygenase 2 inhibitors and aspirin); (Gonzalez-Perez *et al*, 2003) and use of vitamin D (Mocellin, 2011) if they were prescribed at least 1 year before the index date. For female cancer patients, use of hormone replacement therapy and oral contraceptive pills were also added to the analyses.

If they were diagnosed at least a year before the index date, comorbidities, which affect risks of cancer, were also included: rheumatoid arthritis (Thomas *et al*, 2000) for any cancer; benign breast disease for breast cancer; diabetes for pancreatic (Vincent *et al*, 2011) and uterine (Burbos *et al*, 2010) cancers; hypertension for uterine cancer (Bangalore *et al*, 2011); and gastrointestinal disorders for pancreatic cancer (Vinogradova *et al*, 2012). The results were also adjusted for cancer-specific family histories of cancer (Mai *et al*, 2011) (to reduce recall bias in cases only if recorded at least 6 months before the index date; Chang *et al*, 2006).

Statistical analysis. This study used conditional logistic regression to estimate odds ratios with 95% CIs for cancers at each selected site. The Wald test was used for estimating the effects of duration and testing for differences between bisphosphonate types. Missing values for the confounding factors (BMI, smoking status and alcohol intake) were imputed using ICE multiple imputation program in Stata (StataCorp LP, College Station, TX, USA) (Royston, 2005) where all the confounding variables and exposure to bisphosphonates were included into the models. Ten imputed data sets were created and the results were combined using Rubin's rules (Royston, 2004).

Each database was analysed separately and the results combined using the method of Mantel and Haenszel for fixed-effect models.

The primary analyses were based on bisphosphonate exposure excluding prescriptions in the 6 months before the index date. Five sensitivity analyses were carried out for each data set. The first was to eliminate possible bias by redefining bisphosphonate exposure as at least two prescriptions and considering patients with one prescription only as non-users. Such patients might never have started treatment or have soon stopped it because of adverse gastrointestinal effects. The second sensitivity analysis was based on all prescriptions before the index date including the ones issued in the past 6 months. This aimed to eliminate another form of bias caused by a possible oversampling of unexposed cases and controls in the main analyses. The third sensitivity analysis was run on

patients with at least 6 years of medical records and redefined exposure based on prescription information only between 72 and 6 months before the index date. This was to eliminate possible bias arising from the different observation times for patients in the main analyses.

Townsend scores, a measure of deprivation, were available for only 49% of CPRD practices, and only 36% of CPRD patients had it recorded. Deprivation, therefore, was not included as a confounding variable in any of the main analyses. The fourth sensitivity analysis included Townsend scores as a confounding variable, but was run only on patients with a valid code. The fifth and final sensitivity analysis was run on observations with recorded values for BMI, smoking status and alcohol consumption. For the fourth and fifth sensitivity analyses, the definitions for use of bisphosphonates and years of medical records were identical to the main analysis.

Although sample size calculations were carried out and presented in the protocol (Vinogradova *et al*, 2012), all available data were used in the analyses. We considered a 1% level as statistically significant to allow for multiple comparisons, but have presented 95% CIs in our results to create parity with other studies. Stata Version 12 was used for all analyses.

RESULTS

Study population. Within the study period, we identified 91 556 and 88 845 cases of cancers of interest in people aged 50 years and older from QResearch and CPRD, respectively. These were matched to 427 674 and 415 583 controls, respectively, all with at least 2 years of medical records (Figure 1). Median years of available records was 17 (interquartile range 10–28 in QResearch cases and controls, 10–29 in CPRD cases and 10–30 CPRD controls), and it was consistent both for cancer sites and for cases and controls. Table 1 shows the numbers of cases and controls for each cancer site and also the characteristics of the study population. QResearch and CPRD provided similar samples from the general population. The QResearch cases and controls were about the same age (mean 69.4 years, standard deviation 9.8 in cases; 69.4 years, 9.7 in controls) as CPRD (69.9 years, 10.4 in cases; 69.7 years, 10.2 in controls) but included fewer women (48% *vs* 51%), and so had slightly different incidences in cancers of interest.

The proportion of bisphosphonate users (4.2%) was the same in both databases and in cases and controls, with similar proportions of patients prescribed different types of bisphosphonates. Figure 2 shows that in both databases the proportion of cases and controls with at least one bisphosphonate prescription consistently grew from 1% in 1997 to 7% in 2011. Use of etidronate decreased but use of alendronate and risedronate increased, for alendronate reaching over 80% for bisphosphonate users with at least one prescription. Most bisphosphonate users were older than 60 years (92% in both databases) and their median duration of use was 20 months (interquartile range 7–43) in cases and controls in QResearch and 19 months (6–40 in cases and 6–41 in controls) in CPRD. The median duration varied slightly between the cancer sites, from 16.5 months for cervix cases and 27 for melanoma cases in QResearch, and 17 for lung cancer cases to 22.5 for melanoma cases in CPRD. A much higher proportion of women were users than men (6.6% women *vs* 2.0% men in cases, 6.8% women *vs* 1.7% men in controls for QResearch, 6.5% women *vs* 1.9% men in cases and 6.6% women *vs* 1.7% men in controls for CPRD). Use of bisphosphonates did not necessarily follow a recorded diagnosis of osteoporosis/osteopenia or a history of fractures; over 30% of bisphosphonate users did not have either factor recorded

(38% cases and 36% controls in QResearch and 36% cases and 34% controls for CPRD).

Table 2 shows the number and proportion of cases and controls who were bisphosphonate users for each cancer site and overall use of the drug by database. Figure 3 contains the results of combined analyses for overall bisphosphonate use. Table 3 presents trend test results along with odds ratios for short- and long-term use for the seven most common cancers. Table 4 shows further analyses for the associations of different types of bisphosphonate use with breast, prostate and lung cancer risks.

Breast cancer. Overall use of bisphosphonates was associated with a reduced risk of breast cancer but it was only significant in QResearch analyses (adjusted odds ratio (AOR): 0.89, 95% CI: 0.82–0.97) and the combined analyses (AOR: 0.92, 95% CI: 0.87–0.98). Clinical Practice Research Datalink analyses demonstrated a similar direction of the association (AOR: 0.95, 95% CI: 0.88–1.03), but it was not statistically significant ($P = 0.2$). None of the associations were duration-dependent, with the only statistically significantly decreased risk for QResearch ($P = 0.008$) in the subcategory between 7 and 36 months (AOR: 0.87, 95% CI: 0.78–0.96 for QResearch; 0.95, 0.86–1.05 for CPRD; 0.91, 0.85–0.98 for combined). The risks did not vary between bisphosphonate types and none of them had statistically significant associations with breast cancer risk.

The sensitivity analysis, which defined bisphosphonate use as at least two prescriptions, demonstrated an even stronger reduced association with breast cancer risk (AOR: 0.87, 95% CI: 0.80–0.94, $P < 0.001$ for QResearch; 0.94, 0.87–1.01, $P = 0.1$ for CPRD; 0.90, 0.85–0.96, $P < 0.001$ for combined), but it remained statistically significant only for short-term use, and only for QResearch and combined (AOR: 0.80, 95% CI: 0.71–0.91, $P < 0.001$ for QResearch; 0.87, 0.80–0.94, $P < 0.001$ for combined) but not for CPRD (AOR: 0.92, 95% CI: 0.82–.03). There was no significant association with long-term use for any analyses.

Other female cancers. Although QResearch analyses for ovarian cancer showed an almost 20% increased, but not statistically significant, risk (AOR: 1.19, 95% CI: 0.96–1.47), CPRD analyses had an opposite, and also not statistically significant, association (AOR: 0.84, 95% CI: 0.67–1.04), with combined results showing no association at all (AOR: 1.00, 95% CI: 0.86–1.16). None of the results from the different databases were duration-dependent.

There was a significant association between risedronate use and ovarian cancer risk for QResearch (24 exposed cases) and the combined analyses (56 exposed cases) (AOR: 0.48, 95% CI: 0.31–0.75, $P = 0.001$ for QResearch; 0.62, 0.46–0.84, $P = 0.002$ for combined). The CPRD analysis (32 exposed cases) showed a reduced risk but not statistically significantly (AOR: 0.77, 95% CI: 0.52–1.16). The trend tests were not statistically significant ($P = 0.013$ for QResearch; $P = 0.6$ for CPRD; $P = 0.07$ for combined) and this was consistent across all sensitivity analyses.

Overall use of bisphosphonates was not associated with cervical or uterine cancer risk for either database or for the combined analyses. Further analyses demonstrated no associations with duration of use.

Prostate cancer. Adjusted analyses in both databases demonstrated a reduced risk associated with bisphosphonate use but not significant (AOR: 0.90, 95% CI: 0.79–1.02 for QResearch; 0.84, 0.73–0.96 for CPRD), but contributing to a significant association in the combined analysis (AOR: 0.87; 95% CI: 0.79–0.96). Although neither of the databases showed a significant duration-dependent association (QResearch $P_{trend} = 0.064$; CPRD $P_{trend} = 0.03$), the combined analyses did ($P_{trend} = 0.005$), with a 15% reduced risk associated with long-term use of bisphosphonates (AOR: 0.85,; 95% CI: 0.76–0.95).

QRESEARCH

Cancers of interest 1997–2011, cases and controls with at least 2 years of data
Total: 92 159 and 431 730
Breast: 24 891 and 116 355
Prostate: 26 656 and 125 046
Lung: 18 019 and 84 428
Bladder: 7485 and 34 971
Melanoma: 5008 and 23 489
Ovary: 3431 and 16 127
Pancreas: 3597 and 16 870
Uterus: 2250 and 10 595
Cervix: 822 and 3849

Excluded from breast cancer sample because of mastectomy:
392 controls (any time before index date)
337 cases (more than a year before the diagnosis)
3 cases with bisphosphonate use after the mastectomy in the last year

Excluded from all cancers because of Paget's disease:
224 cases, 817 controls

Excluded from all cancers because of bisphosphonate prescription not for osteoporosis:
39 cases, 50 controls

Excluded from all cancers because of absence of a case or control:
2 cases, 2795 controls

Remained cases and controls
Total: 91 556 and 427 674
Breast: 24 489 and 113 945
Prostate: 26 554 and 124 230
Lung: 17 961 and 83 992
Bladder: 7464 and 34 786
Melanoma: 4998 and 23 399
Ovary: 3427 and 16 089
Pancreas: 3593 and 16 818
Uterus: 2248 and 10 570
Cervix: 822 and 3845

CPRD

Cancers of interest 1997–2011, cases and controls with at least 2 years of data
Total: 89 470 and 419 666
Breast: 25 860 and 121 331
Prostate: 23 268 and 108 865
Lung: 19 121 and 90 018
Bladder: 7106 and 33 179
Melanoma: 4631 and 21 734
Ovary: 3094 and 14 586
Pancreas: 3496 and 16 299
Uterus: 2153 and 10 159
Cervix: 741 and 3495

Excluded from breast cancer sample because of mastectomy:
442 controls (any time before index date)
365 cases (more than a year before the diagnosis)
54 cases with bisphosphonate use after the mastectomy in the last year

Excluded from all cancers because of Paget's disease:
218 cases, 884 controls

Excluded from all cancers because of bisphosphonate prescription not for osteoporosis:
27 cases, 37 controls

Excluded from all cancers because of absence of a case or control:
4 cases, 2877 controls

Remained cases and controls
Total: 88 845 and 415 383
Breast: 25 444 and 118 835
Prostate: 23 176 and 108 102
Lung: 19 059 and 89 471
Bladder: 7084 and 32 984
Melanoma: 4621 and 21 654
Ovary: 3088 and 14 532
Pancreas: 3485 and 16 200
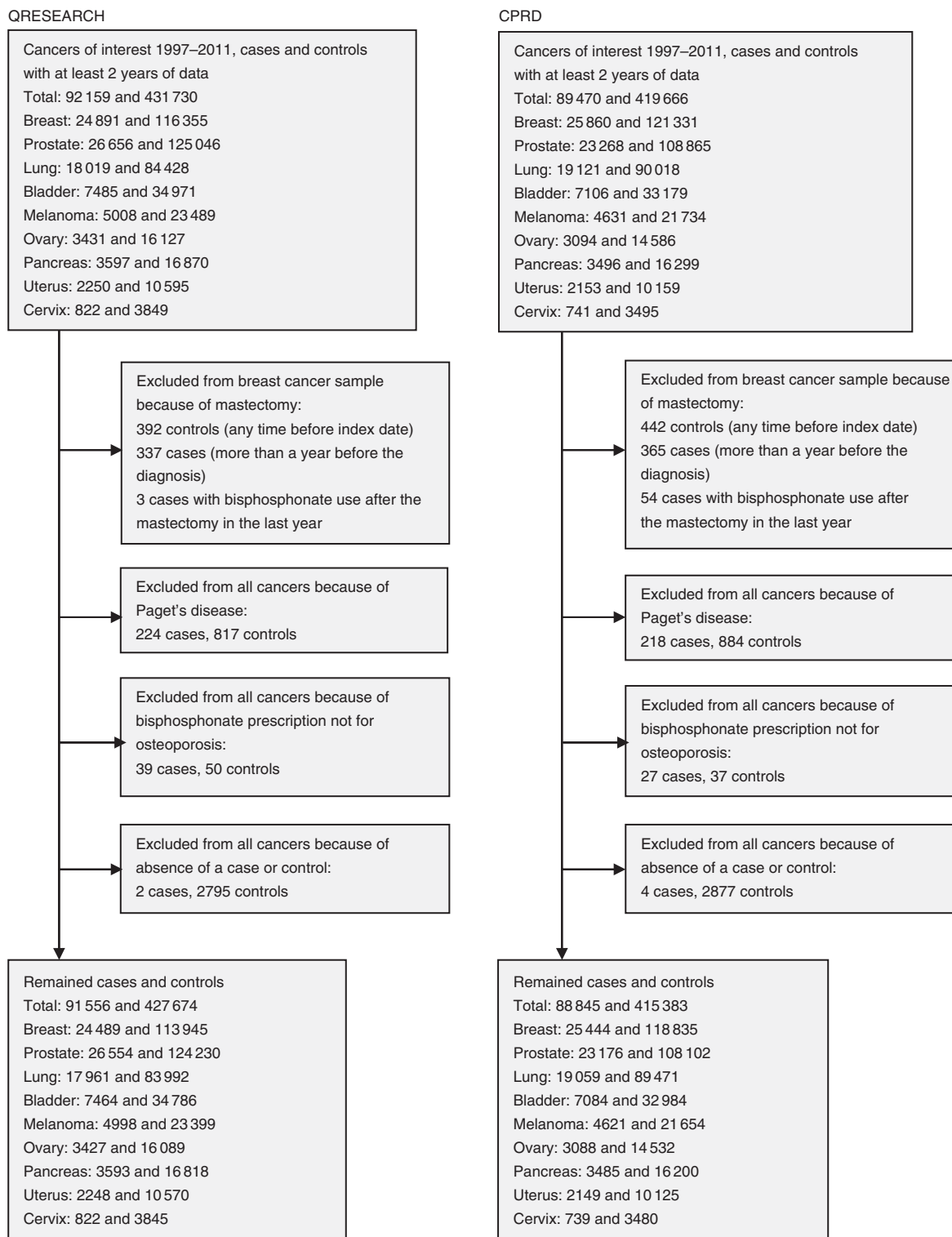Uterus: 2149 and 10 125
Cervix: 739 and 3480

Figure 1. **Flow of the included patients for QResearch and CPRD analyses.**

Further analyses showed significantly reduced risks for alendronate users in QResearch, with a greater reduced risk for long-term users (AOR: 0.75; 95% CI: 0.62–0.92), which was duration-dependent ($P_{trend} = 0.009$). Clinical Practice Research Datalink associations were directionally similar to QResearch but not significant and also with lower risk for long-term users (AOR: 0.86; 95% CI: 0.70–1.05) and not duration-dependent

($P_{trend} = 0.05$), although contributing to a significant association (AOR: 0.80; 95% CI: 0.70–0.92) and duration dependency ($P_{trend} = 0.001$) in the combined analysis.

All sensitivity analyses with other definitions of use were consistent in showing a reduced risk in long-term alendronate users apart from the one including prescriptions from the past 6 months before the index date. This analysis also

Table 1. Baseline characteristics in cases and all matched controls by database (QResearch or CPRD)				
	QResearch		CPRD	
	Cases	Controls	Cases	Controls
Total	91 556	427 674	88 845	415 383
Breast	24 489	113 945	25 444	118 835
Prostate	26 554	124 230	23 176	108 102
Lung	17 961	83 992	19 059	89 471
Bladder	7464	34 786	7084	32 984
Skin	4998	23 399	4621	21 654
Ovary	3427	16 089	3088	14 532
Pancreas	3593	16 818	3485	16 200
Uterus	2248	10 570	2149	10 125
Cervix	822	3845	739	3480
Sex				
Male	47 193 (51.5)	220 492 (51.6)	43 596 (49.1)	203 487 (49.0)
Female	44 363 (48.5)	207 182 (48.4)	45 249 (50.9)	211 896 (51.0)
Age band (years)				
30–54	7345 (8.0)	34 000 (7.9)	6998 (7.9)	32 749 (7.9)
55–64	22 786 (24.9)	106 266 (24.8)	22 071 (24.8)	104 095 (25.1)
65–74	30 410 (33.2)	143 528 (33.6)	28 407 (32.0)	134 902 (32.5)
75–84	26 177 (28.6)	122 798 (28.7)	23 864 (26.9)	112 533 (27.1)
85 +	4838 (5.3)	21 082 (4.9)	7505 (8.4)	31 104 (7.5)
Ethnicity				
White	21 477 (23.5)	90 874 (21.2)	7034 (7.9)	30 294 (7.3)
Not recorded[a]	69 131 (75.5)	331 241 (77.5)	78 841 (88.7)	371 491 (89.4)
Non-white	948 (1.0)	5559 (1.3)	2970 (3.3)	13 598 (3.3)
Asian[b]	364 (0.4)	2726 (0.6)	194 (0.2)	1516 (0.4)
Black[b]	397 (0.4)	1834 (0.4)	166 (0.2)	649 (0.2)
Other[b]	187 (0.2)	999 (0.2)	2610 (2.9)	11 433 (2.8)
Deprivation, Townsend quintile				
1, most affluent[c]	23 442 (26.3)	110 919 (26.7)	9753 (30.5)	45 736 (30.6)
2[c]	19 959 (22.4)	94 167 (22.7)	7695 (24.0)	36 203 (24.2)
3[c]	18 032 (20.2)	84 427 (20.3)	6253 (19.5)	29 740 (19.9)
4[c]	15 768 (17.7)	72 202 (17.4)	5007 (15.6)	23 075 (15.4)
5, most deprived[c]	12 075 (13.5)	53 799 (12.9)	3290 (10.3)	14 914 (10.0)
Not recorded	2280 (2.5)	12 160 (2.8)	56 847 (64.0)	265 715 (64.0)
BMI (kg m^{-2})				
15–24[c]	27 225 (38.0)	120 028 (37.3)	29 310 (39.1)	131 726 (38.3)
25–29[c]	28 956 (40.4)	130 874 (40.7)	29 808 (39.7)	138 713 (40.3)
30–49[c]	15 409 (21.5)	70 904 (22.0)	15 913 (21.2)	73 554 (21.4)
Not recorded	19 966 (21.8)	105 868 (24.8)	13 814 (15.5)	71 390 (17.2)
Smoking status				
Non-smoker[c]	34 949 (41.4)	182 349 (48.0)	40 128 (47.6)	21 2180 (55.4)
Ex-smoker[c]	31 475 (37.3)	136 575 (36.0)	26 958 (32.0)	112 142 (29.3)
Current light smoker[c]	5633 (6.7)	20 787 (5.5)	3966 (4.7)	13 871 (3.6)
Current moderate smoker[c]	7825 (9.3)	26 747 (7.0)	8838 (10.5)	30 846 (8.1)
Current heavy smoker[c]	4467 (5.3)	13 187 (3.5)	4382 (5.2)	13 646 (3.6)
Not recorded	7207 (7.9)	48 029 (11.2)	4573 (5.1)	32 698 (7.9)
Use of alcohol				
No use[c]	22 061 (29.9)	101 997 (30.5)	19 714 (25.8)	92 647 (26.6)
Ex use[c]			2030 (2.7)	7672 (2.2)
Light[c]	44 809 (60.7)	203 342 (60.8)	44 448 (58.1)	204 556 (58.8)
Moderate and more[c]	7009 (9.5)	29 036 (8.7)	10 250 (13.4)	42 911 (12.3)
Not recorded	17 677 (19.3)	93 299 (21.8)	12 403 (14.0)	67 597 (16.3)

Table 1. (Continued)

	QResearch		CPRD	
	Cases	Controls	Cases	Controls
Comorbidities				
Upper GI	19 250 (21.0)	83 377 (19.5)	24 302 (27.4)	107 660 (25.9)
Diabetes	8140 (8.9)	36 769 (8.6)	7990 (9.0)	37 011 (8.9)
Pancreatitis	492 (0.5)	1981 (0.5)	552 (0.6)	2102 (0.5)
Hypertension	31 466 (34.4)	142 577 (33.3)	31 169 (35.1)	142 474 (34.3)
Chronic kidney disease	3444 (3.8)	15 558 (3.6)	3710 (4.2)	16 425 (4.0)
Rheumatoid arthritis	1424 (1.6)	6591 (1.5)	1673 (1.9)	7310 (1.8)
Benign breast disease	2727 (3.0)	10 077 (2.4)	2761 (3.1)	9653 (2.3)
History of osteoporosis				
Osteoporosis/osteopenia	3682 (4.0)	16 998 (4.0)	4023 (4.5)	18 474 (4.4)
Osteoporotic fractures	3322 (3.6)	16 013 (3.7)	2375 (2.7)	10 342 (2.5)
Family history of cancer	2841 (3.1)	11 756 (2.7)	2836 (3.2)	11 364 (2.7)
Medications (excluding past 6 months)				
Acid-lowering drugs	32 523 (35.5)	14 0637 (32.9)	33 531 (37.7)	145 409 (35.0)
NSAIDs	52 422 (57.3)	233 143 (54.5)	55 106 (62.0)	248 518 (59.8)
Corticosteroids	14 156 (15.5)	57 106 (13.4)	13 908 (15.7)	54 233 (13.1)
Calcium	1023 (1.1)	4816 (1.1)	6286 (7.1)	28 984 (7.0)
Vitamin D	4891 (5.3)	22 582 (5.3)	4960 (5.6)	23 035 (5.5)
Hormone replacement[d]	12 071 (13.2)	51 861 (12.1)	12 633 (14.2)	55 666 (13.4)
Oral contraceptives[d]	773 (0.8)	3551 (0.8)	1236 (1.4)	5490 (1.3)
Bisphosphonates				
Any	3827 (4.2)	17 883 (4.2)	3769 (4.2)	17 490 (4.2)
Alendronate	2589 (2.8)	12 010 (2.8)	2538 (2.9)	11 969 (2.9)
Etidronate	1286 (1.4)	5949 (1.4)	1170 (1.3)	5471 (1.3)
Risedronate	851 (0.9)	3985 (0.9)	806 (0.9)	3715 (0.9)
Ibandronate	74 (0.1)	435 (0.1)	75 (0.1)	353 (0.1)
Other osteoporosis drugs				
Any	319 (0.3)	1641 (0.4)	333 (0.4)	1685 (0.4)
Raloxifen	192 (0.2)	1032 (0.2)	217 (0.2)	1081 (0.3)
Strontium	95 (0.1)	456 (0.1)	97 (0.1)	509 (0.1)
Calcitonin	38 (0.0)	207 (0.0)	34 (0.0)	162 (0.0)

Abbreviations: CPRD = Clinical Practice Research Datalink; GI = gastrointestinal; NSAID = non-steroidal anti-inflammatory drugs. Values are numbers and %.
[a]Assumed White for the analyses.
[b]Broken down categories for non-White group.
[c]Proportion only within recorded data.
[d]Only for women cancers.

demonstrated an increased risk for very short-term use (up to 6 months) but only in QResearch (AOR: 1.29; 95% CI: 1.08–1.53, $P = 0.004$). As for overall bisphosphonate use, the sensitivity analysis for at least two prescriptions reached a statistically significant level in CPRD (AOR: 0.83, 95% CI: 0.72–0.95, $P = 0.008$).

Lung cancer. After adjusting for confounders, there was no significant association with bisphosphonate use (AOR: 0.97, 95% CI: 0.88–1.08 in QResearch; 1.12, 1.01–1.23 in CPRD; 1.04, 0.97–1.12 for combined). Further analyses demonstrated no associations with duration or type of bisphosphonate.

Results were consistent in sensitivity analyses apart from one – the sensitivity analysis, which included prescriptions from the past 6 months before the index date showed increased risk associated with short-term use in both databases (AOR: 1.34, 95% CI: 1.18–1.52, $P < 0.001$ for QResearch; 1.30, 1.15–1.47, $P < 0.001$ for CPRD).

Bladder cancer. Adjusting for confounders showed no association between bisphosphonate use and risk of bladder cancer (AOR: 0.96, 95% CI: 0.80–1.14 for QResearch; 0.94, 0.79–1.12 for CPRD; 0.95, 0.84–1.08 for combined). Sensitivity analyses also showed no associations.

Melanoma. There was no association between overall bisphosphonate use and risk of melanoma in either database (AOR: 1.05, 95% CI: 0.87–1.28 for QResearch; 0.95, 0.77–1.19 for CPRD; 1.01, 0.87–1.17 for combined), and analyses did not show statistically significantly increased risk with longer use in either database or the combined ($P_{trend} = 0.013$ for QResearch; $P_{trend} = 0.5$ for CPRD; $P_{trend} = 0.02$ for combined). The results were consistent across the sensitivity analyses, except for the one defining use as at least one prescription between 6 and 72 months.
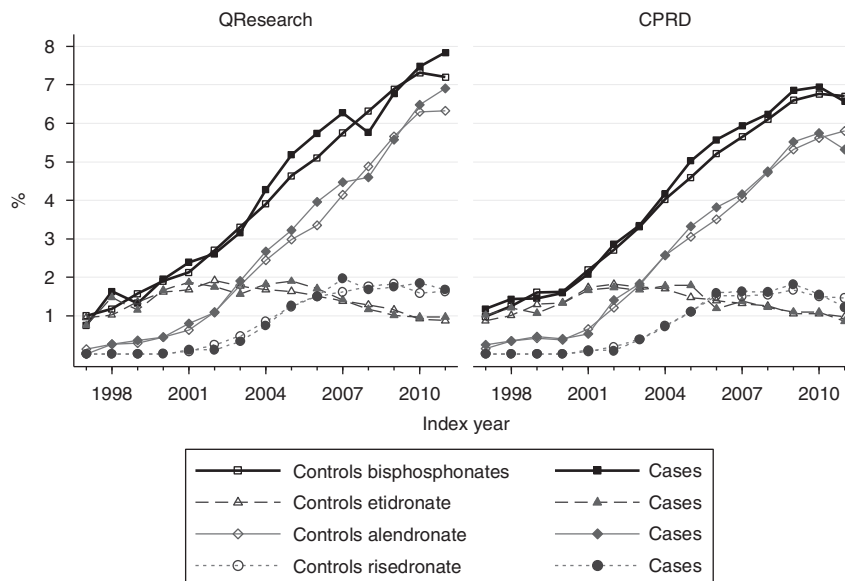
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Figure 2. **Proportion of cases and controls in QResearch and CPRD with at least one prescription of bisphosphonate by index year.**

Table 2. Bisphosphonate use in cancer cases and controls, numbers and odds ratios (95% CIs) compared with non-use by database

Cancer site	QResearch			CPRD			Combined analysis	
	Cases/controls	Adjusted*odds ratio (95% CI)	*P*-value	Cases/controls	Adjusted*odds ratio (95% CI)	*P*-value	Pooled odds ratio (95% CI)	*P*-value
Breast[a]	1304/6923	0.89 (0.82–0.97)	0.005	1324/6847	0.95 (0.88–1.03)	0.2	0.92 (0.87–0.97)	0.004
Prostate[b]	460/2150	0.90 (0.79–1.02)	0.1	376/1901	0.84 (0.73–0.96)	0.012	0.87 (0.79–0.96)	0.003
Lung[c]	1035/3809	0.97 (0.88–1.08)	0.6	1114/3911	1.12 (1.01–1.23)	0.03	1.04 (0.97–1.12)	0.2
Bladder[d]	274/1219	0.96 (0.80–1.14)	0.6	280/1263	0.94 (0.79–1.12)	0.5	0.95 (0.84–1.08)	0.4
Melanoma[e]	241/1067	1.05 (0.87–1.28)	0.6	178/881	0.95 (0.77–1.19)	0.7	1.01 (0.87–1.17)	0.9
Ovary[f]	204/939	1.19 (0.96–1.47)	0.1	170/937	0.84 (0.67–1.04)	0.1	1.00 (0.86–1.16)	1.0
Pancreas[g]	178/886	0.81 (0.64–1.01)	0.06	196/918	0.78 (0.63–0.97)	0.03	0.79 (0.68–0.93)	0.003
Uterus[h]	99/671	1.07 (0.79–1.44)	0.7	96/636	0.95 (0.71–1.27)	0.7	1.00 (0.81–1.24)	1.0
Cervix[i]	32/219	0.78 (0.48–1.27)	0.3	35/196	1.21 (0.76–1.93)	0.4	0.98 (0.70–1.37)	0.9

Abbreviations: BMI = body mass index; CI = confidence interval; CPRD = Clinical Practice Research Datalink; GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drugs. *Adjusted for BMI, smoking status, alcohol consumption, ethnicity, rheumatoid arthritis, osteoporosis and fractures, use of other osteoporosis drugs, vitamin D, NSAIDs, corticosteroids, acid-lowering drugs and years of data.
[a]Also adjusted for family history of breast cancer, benign breast disease, use of oral contraceptives and hormone replacement therapy.
[b]Also adjusted for family history of prostate cancer.
[c]Also adjusted for family history of lung cancer.
[d]Also adjusted for family history of cancer and chronic kidney disease.
[e]Also adjusted for family history of cancer.
[f]Also adjusted for family history of ovarian cancer, use of oral contraceptives and hormone replacement therapy.
[g]Also adjusted for family history of GI cancer, GI disease, diabetes and history of pancreatitis.
[h]Also adjusted for family history of cancer, hypertension, diabetes, use of oral contraceptives and hormone replacement therapy.
[i]Also adjusted for family history of cancer, use of oral contraceptives and hormone replacement therapy.

Here use of etidronate in the QResearch analysis was associated with increased risk of melanoma (AOR: 1.67, 95% CI: 1.23–2.26, $P < 0.001$); however, this association was not duration-dependent ($P_{trend} = 0.02$).

Pancreatic cancer. After adjusting for the confounders analyses in both databases showed a reduced risk of pancreatic cancer in bisphosphonate users, although it was not statistically significant (AOR: 0.81, 95% CI: 0.64–1.01 for QResearch; 0.78, 0.63–0.97 for CPRD). The combined analysis, however, demonstrated a statistically significant association (AOR: 0.79, 95% CI: 0.68–0.93). Short-term use was associated with an even lower but not statistically significant risk in all analyses (AOR: 0.78, 95% CI: 0.57–1.06 for QResearch; 0.77, 0.57–1.02 for CPRD; 0.77,
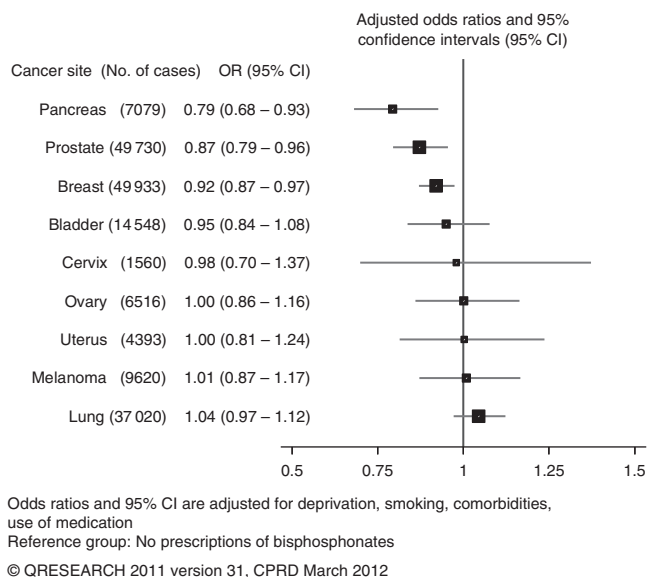
Adjusted odds ratios and 95% confidence intervals (95% CI)

Cancer site (No. of cases)	OR (95% CI)
Pancreas (7079)	0.79 (0.68 – 0.93)
Prostate (49 730)	0.87 (0.79 – 0.96)
Breast (49 933)	0.92 (0.87 – 0.97)
Bladder (14 548)	0.95 (0.84 – 1.08)
Cervix (1560)	0.98 (0.70 – 1.37)
Ovary (6516)	1.00 (0.86 – 1.16)
Uterus (4393)	1.00 (0.81 – 1.24)
Melanoma (9620)	1.01 (0.87 – 1.17)
Lung (37 020)	1.04 (0.97 – 1.12)

Odds ratios and 95% CI are adjusted for deprivation, smoking, comorbidities, use of medication
Reference group: No prescriptions of bisphosphonates
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Figure 3. Risk of cancer in patients prescribed bisphosphonates, combined results for QResearch and CPRD analyses.

0.63–0.96 for combined) and there was also no trend for duration of use.

A sensitivity analysis defining use as at least two prescriptions reached statistically significant level for the CPRD analysis in overall use (0.73, 0.59–0.91, $P = 0.005$) and for short-term use (AOR: 0.65, 95% CI: 0.47–0.89, $P = 0.008$). The other sensitivity analyses did not demonstrate any significant associations.

Additional information. Sensitivity analyses on patients with valid BMI, smoking status and alcohol consumption data and on patients with valid Townsend codes showed similar results, which are available from the authors.

DISCUSSION

Summary. This study, based on medical records from the two largest UK primary-care databases, showed that the use of bisphosphonates was not associated with increased risks for any of the most common solid non-gastrointestinal cancers. Decreased risks of breast, prostate and pancreatic cancers had no duration relationship with bisphosphonate use and were found only in short-term users. Alendronate use, however, was associated with a decreased risk of prostate cancer and this association was duration-dependent.

Strengths and limitations. Based on the two largest primary-care databases, including more recent data than previous studies and covering the period when bisphosphonates have become much more widely prescribed in the general population, our study provides more data for investigating the duration effects of bisphosphonate use and over longer periods than previous studies. All eligible cancer cases and controls, alive or dead, were included into the study. This representativeness of the databases, and the lack of recall, selection and respondent biases, also makes the results more generalisable.

The limitations include possible uncertainties in cancer diagnosis. The selection of cases was based on the first record of a cancer and the exact origin site may have been determined only later, but this level of detail was not available across all records. A systematic review based on GPRD validation studies reported that, on average, 95% of diagnoses of cancer recorded on the GP

electronic record were confirmed by other data sources (Herrett et al, 2010). Information about cancer stage and the results of histological investigations were also not consistently recorded across general practices and so were not used. Another limitation is the potential misclassification of bisphosphonate use. The analyses were based on prescriptions not on actual use and no data were available on adherence to medications. There is no reason, however, to suppose that non-adherence differs systematically between cases and controls.

Other limitations include information bias and missing data. Lack of symptom or family history records might arise simply because the patients have not reported them. Information on certain risk factors such as the level of physical activity, diet and cancer screening tests (mammography, prostate-specific antigen test) was also not reliably recorded, so these factors were not included in the analyses. Further, results of any bone mineral density tests were not consistently recorded and were not used in the analysis, and so there might be some residual confounding. Important confounders such as smoking or BMI had some missing data, so these had to be imputed.

Bisphosphonate users. Comparisons between bisphosphonate users and non-users reflect the recommendations for targeting the group with osteoporosis, and so some characteristics and comorbidities such as low BMI and rheumatoid arthritis in users were expected as these are risk factors for primary osteoporosis. As secondary osteoporosis is more likely to develop in patients with impaired digestion, use of acid-lowering drugs and also use of corticosteroids (Mauck and Clarke, 2006; Hippisley-Cox and Coupland, 2009) were much higher for bisphosphonate users.

Breast cancer. Reduced breast cancer risk associated with bisphosphonates use has been shown in five studies to date, all smaller than the current one (Chlebowski et al, 2010; Newcomb et al, 2010; Rennert et al, 2010; Vestergaard et al, 2011; Cardwell et al, 2012). No relation between risk and duration of use could suggest that osteoporosis is responsible for such reductions (Chen et al, 2008). Adjustments for osteoporosis, however, have demonstrated the independent effect of bisphosphonates. Reduced risk associated with recent, but not remote, use of bisphosphonates might also be explained by a possible bisphosphonate-related prevention of progress for undiagnosed cancers up to an invasive stage. This has already been shown by Chlebowski's study (Chlebowski et al, 2010) and supported by studies in menopausal women with early-stage breast cancer treated with bisphosphonates (Gnant, 2010). Although an Israeli (Rennert et al, 2010) case–control study showed a statistically significantly decreased risk associated with more than a year of bisphosphonate use (AOR: 0.61, 95% CI: 0.50–0.76), the study was subject to recall bias (participants reported their past use of bisphosphonates) and selection bias (all participants were alive at the moment of the interview). Another case–control study (Newcomb et al, 2010) with similar limitations in the design also reported a statistically significant trend ($P_{trend} = 0.01$) for duration of bisphosphonate use. A cohort study of Cardwell et al (2012) showed risk reduction associated with overall bisphosphonate use similar to ours (adjusted hazard ratio (AHR): 0.79, 95% CI: 0.62–1.01), and also becoming not statistically significant for patients with use of more than a year. Although our results for different types of bisphosphonate were in line with Vestergaard et al's study (2011) for alendronate (AHR: 0.91, 95% CI: 0.81–1.03), the risk reduction for etidronate in our study did not reach a statistically significant level.

Prostate cancer. The association between overall use of bisphosphonates and prostate cancer risk was similar to that for breast cancer, also without statistically significant effects for therapy duration. Although the association between alendronate use and

Table 3. Bisphosphonate short- and long-term use in cancer cases and controls, numbers and odds ratios (95% CIs) compared with non-use by database								
Cancer site	**QResearch**			**CPRD**			**Combined analysis**	
Terms of use	Cases/ controls	Adjusted*odds ratio (95% CI)	*P*-value	Cases/ controls	Adjusted*odds ratio (95% CI)	*P*-value	Pooled odds ratio (95% CI)	*P*-value
Breast	Trend		**0.5**	Trend		**0.3**	Trend	**0.2**
Short term (less than a year)	462/2523	0.86 (0.77–0.97)	0.01	508/2620	0.95 (0.86–1.06)	0.4	0.91 (0.84–0.98)	0.02
Long term (at least a year)	842/4400	0.91 (0.83–1.00)	0.05	816/4227	0.95 (0.86–1.04)	0.3	0.93 (0.87–0.99)	0.03
Prostate	Trend		**0.06**	Trend		**0.03**	Trend	**0.005**
Short term (less than a year)	186/838	0.95 (0.80–1.13)	0.6	149/764	0.84 (0.70–1.02)	0.07	0.90 (0.79–1.02)	0.1
Long term (at least a year)	274/1312	0.86 (0.74–1.00)	0.06	227/1137	0.84 (0.71–0.99)	0.04	0.85 (0.76–0.95)	0.005
Lung	Trend		**0.7**	Trend		**1.0**	Trend	**0.8**
Short term (less than a year)	415/1351	1.04 (0.90–1.19)	0.6	467/1507	1.15 (1.01–1.32)	0.03	1.10 (1.00–1.21)	0.06
Long term (at least a year)	620/2458	0.93 (0.82–1.05)	0.2	647/2404	1.09 (0.96–1.23)	0.2	1.01 (0.92–1.10)	0.9
Bladder	Trend		**0.3**	Trend		**0.6**	Trend	**0.3**
Short term (less than a year)	109/455	0.99 (0.79–1.26)	1.0	117/464	1.06 (0.84–1.33)	0.6	1.03 (0.87–1.21)	0.8
Long term (at least a year)	165/764	0.93 (0.76–1.15)	0.5	163/799	0.86 (0.69–1.06)	0.2	0.90 (0.77–1.04)	0.2
Melanoma	Trend		**0.01**	Trend		**0.5**	Trend	**0.02**
Short term (less than a year)	77/400	0.91 (0.70–1.20)	0.5	64/354	0.88 (0.65–1.18)	0.4	0.90 (0.73–1.10)	0.3
Long term (at least a year)	164/667	1.16 (0.92–1.45)	0.2	114/527	1.01 (0.78–1.31)	0.9	1.09 (0.92–1.29)	0.3
Ovaries	Trend		**0.4**	Trend		**0.1**	Trend	**0.7**
Short term (less than a year)	83/322	1.37 (1.04–1.81)	0.02	62/355	0.80 (0.59–1.08)	0.1	1.07 (0.87–1.31)	0.5
Long term (at least a year)	121/617	1.08 (0.84–1.38)	0.6	108/582	0.86 (0.66–1.11)	0.2	0.96 (0.81–1.15)	0.7
Pancreas	Trend		**0.2**	Trend		**0.05**	Trend	**0.02**
Short term (less than a year)	63/316	0.78 (0.57–1.06)	0.1	71/336	0.77 (0.57–1.02)	0.07	0.77 (0.63–0.96)	0.02
Long term (at least a year)	115/570	0.82 (0.63–1.06)	0.1	125/582	0.80 (0.62–1.02)	0.08	0.81 (0.67–0.97)	0.02

Abbreviations: CI = confidence interval; CPRD = Clinical Practice Research Datalink. *Adjusted for the confounders listed in the footnote for Table 2. Bold values indicate statistical significance.

decreased risk appeared to be significant even with a duration relationship, it was found only in the QResearch database and might again suggest a possible suppressing effect of alendronate on an already existing *in situ* cancer (Tuomela *et al*, 2008). In particular in the prostate, *in vitro* studies have observed substantial concentrations of nitrogen-containing bisphosphonates (zolendronic acid and ibandronate) after administration of the drug (Fournier *et al*, 2002), which could result in suppressed angiogenesis in prostate tumours. The only epidemiological study looking at prostate cancer with respect to bisphosphonate use has also demonstrated lower risk for bisphosphonate users, although not statistically significant (AHR: 0.71, 95% CI: 0.50–1.01) (Cardwell *et al*, 2012).

Lung cancer. Our study showed no association between lung cancer risk and bisphosphonate use. This is consistent with the only other epidemiological study (Cardwell *et al*, 2012), which also

found a reduced risk for long-term users (AHR: 0.86, 95% CI: 0.63–1.17) but it was not statistically significant. The antitumour properties of bisphosphonates might not be applicable in the lung because it is not a site where bisphosphonates accumulate (Fournier *et al*, 2002). The sensitivity analysis for all prescriptions including the past 6 months showed a significantly increased risk but without any duration relationship and in particular for short-term users. This may simply suggest that a common symptom of lung cancer, bone pain, is sometimes initially mistaken as osteoporosis.

Pancreas. Although none of the database analyses showed statistically significantly decreased risks associated with bisphosphonate use, the combined analysis did. The findings were consistent with the only other epidemiological study (Cardwell *et al*, 2012) for this cancer site (AHR: 0.84, 95% CI: 0.53–1.35). The effects of bisphosphonates on growth and apoptosis in

Table 4. Bisphosphonate use for individual drugs in cancer cases and controls, numbers and odds ratios (95% CIs) compared with non-use by database							
	QResearch			CPRD			Combined analysis	
	Cases/ controls	Adjusted*odds ratio (95% CI)	*P*-value	Cases/ controls	Adjusted*odds ratio (95% CI)	*P*-value	Pooled odds ratio (95% CI)	*P*-value
Breast, alendronate	Trend		**0.7**	Trend		**0.04**	Trend	**0.3**
Any use	901/4627	0.98 (0.89–1.07)	0.6	892/4648	0.96 (0.88–1.05)	0.3	0.97 (0.91–1.03)	0.3
Short term (less than a year)	409/2148	0.95 (0.85–1.08)	0.4	414/2085	1.00 (0.89–1.13)	0.9	0.98 (0.90–1.06)	0.6
Long term (at least a year)	492/2479	1.00 (0.89–1.12)	1.0	478/2563	0.92 (0.83–1.03)	0.2	0.96 (0.89–1.04)	0.3
Breast, etidronate	Trend		**0.1**	Trend		**0.8**	Trend	**0.2**
Any use	453/2437	0.90 (0.81–1.01)	0.07	412/2246	0.91 (0.81–1.02)	0.1	0.91 (0.84–0.98)	0.02
Short term (less than a year)	176/893	0.95 (0.80–1.13)	0.6	179/1018	0.88 (0.74–1.03)	0.1	0.91 (0.81–1.03)	0.1
Long term (at least a year)	277/1544	0.87 (0.76–1.00)	0.05	233/1228	0.94 (0.81–1.09)	0.4	0.90 (0.82–1.00)	0.04
Breast, risedronate	Trend		**0.9**	Trend		**0.3**	Trend	**0.5**
Any use	281/1537	0.92 (0.80–1.06)	0.2	279/1492	0.96 (0.84–1.11)	0.6	0.94 (0.85–1.04)	0.2
Short term (less than a year)	139/803	0.89 (0.73–1.07)	0.2	118/733	0.83 (0.68–1.02)	0.07	0.86 (0.75–0.99)	0.03
Long term (at least a year)	142/734	0.96 (0.80–1.16)	0.7	161/759	1.08 (0.90–1.29)	0.4	1.02 (0.90–1.17)	0.7
Prostate, alendronate	Trend		**0.009**	Trend		**0.05**	Trend	**0.001**
Any use	292/1506	0.81 (0.70–0.93)	0.004	257/1299	0.88 (0.75–1.03)	0.1	0.84 (0.75–0.93)	0.001
Short term (less than a year)	142/692	0.86 (0.71–1.05)	0.1	120/591	0.91 (0.74–1.13)	0.4	0.89 (0.77–1.02)	0.1
Long term (at least a year)	150/814	0.75 (0.62–0.92)	0.004	137/708	0.86 (0.70–1.05)	0.1	0.80 (0.70–0.92)	0.002
Prostate, etidronate	Trend		**0.9**	Trend		**0.6**	Trend	**0.8**
any use	141/567	1.06 (0.87–1.30)	0.5	104/496	0.88 (0.70–1.10)	0.3	0.98 (0.84–1.14)	0.8
Short term (less than a year)	55/223	1.10 (0.81–1.48)	0.6	34/209	0.69 (0.47–1.00)	0.05	0.91 (0.72–1.15)	0.4
Long term (at least a year)	86/344	1.04 (0.81–1.33)	0.8	70/287	1.02 (0.77–1.34)	0.9	1.03 (0.86–1.24)	0.8
Prostate, risedronate	Trend		**0.9**	Trend		**0.3**	Trend	**0.4**
Any use	99/455	0.98 (0.77–1.23)	0.8	70/374	0.87 (0.66–1.13)	0.3	0.93 (0.78–1.10)	0.4
Short term (less than a year)	38/208	0.83 (0.58–1.18)	0.3	32/165	0.90 (0.61–1.33)	0.6	0.86 (0.66–1.12)	0.3
Long term (at least a year)	61/247	1.09 (0.81–1.46)	0.6	38/209	0.83 (0.58–1.19)	0.3	0.98 (0.78–1.23)	0.8
Lung, alendronate	Trend		**0.5**	Trend		**0.4**	Trend	**0.3**
Any use	696/2542	1.00 (0.89–1.12)	0.9	756/2701	1.05 (0.94–1.18)	0.4	1.03 (0.95–1.11)	0.5
Short term (less than a year)	339/1114	1.07 (0.92–1.24)	0.4	386/1220	1.16 (1.01–1.34)	0.04	1.12 (1.01–1.24)	0.04
Long term (at least a year)	357/1428	0.93 (0.80–1.08)	0.3	370/1481	0.96 (0.83–1.11)	0.6	0.95 (0.85–1.05)	0.3
Lung, etidronate	Trend		**0.8**	Trend		**0.1**	Trend	**0.2**
Any use	338/1262	1.04 (0.90–1.20)	0.6	356/1200	1.13 (0.98–1.31)	0.09	1.09 (0.98–1.20)	0.2
Short term (less than a year)	139/500	1.02 (0.82–1.27)	0.9	161/502	1.15 (0.94–1.42)	0.2	1.09 (0.94–1.27)	0.3
Long term (at least a year)	199/762	1.05 (0.87–1.26)	0.6	195/698	1.12 (0.93–1.35)	0.2	1.08 (0.95–1.24)	0.2
Lung, risedronate			**0.9**	Trend		**0.7**	Trend	**0.7**
Any use	261/848	1.02 (0.86–1.21)	0.8	252/829	1.11 (0.94–1.31)	0.2	1.06 (0.94–1.20)	0.3
Short term (less than a year)	125/380	1.05 (0.83–1.33)	0.7	126/412	1.06 (0.85–1.34)	0.6	1.06 (0.90–1.25)	0.5
Long term (at least a year)	136/468	0.98 (0.78–1.22)	0.8	126/417	1.13 (0.90–1.42)	0.3	1.05 (0.89–1.23)	0.6

Abbreviations: CI = confidence interval; CPRD = Clinical Practice Research Datalink. *Adjusted for the confounders listed in the footnote for Table 2. Bold values indicate statistical significance.

pancreatic cancer cells have been shown *in vitro* (Tassone *et al*, 2003) and *in vivo* (Takiguchi *et al*, 2012). No duration relationship suggests, however, that as with breast and prostate cancers bisphosphonates might inhibit growth only of already existing tumours.

Other cancers. Our study has not shown any significant associations between overall use of bisphosphonates and risk of endometrial, ovarian or cervical cancers, but the numbers for endometrial and cervical cancers were very low and the findings were not consistent across the databases. An association found between ovarian cancer and risedronate use was found only in QResearch data and without a duration relationship. Previous much smaller studies have suggested a possible decreased risk for bisphosphonate users for ovarian (AHR: 0.64, 95% CI: 0.40–1.03) and endometrial cancers (AHR: 0.64, 95% CI: 0.38–1.08 (Cardwell *et al*, 2012) and AOR: 0.7, 95% CI: 0.4–1.2 (Fortuny *et al*, 2009)), but the results also did not reach a statistically significant level. Our finding of a decreased risk for bladder cancer, which was not however statistically significant, was consistent with a previous study (AHR: 0.67, 95% CI: 0.41–1.10, $P = 0.11$) (Cardwell *et al*, 2012). No statistically significant associations between bisphosphonate use and melanoma risk were found, similar to the earlier study (AHR: 0.80, 95% CI: 0.53–1.20) (Cardwell *et al*, 2012).

CONCLUSION

We have conducted a series of large population-based case–control studies in two primary-care databases examining the association of bisphosphonates with risks of common cancers in the general population and found associations with reduced risks for breast, prostate and pancreatic cancers, but with no duration relationship and only in short-term users. A duration-dependent reduced risk associated with alendronate use was found for prostate cancer, but only in the QResearch data. This study does not provide enough evidence to conclude that bisphosphonates have protective effects on cancer, but the results are reassuring regarding the safety of bisphosphonates.

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