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Exposure to oral bisphosphonates and risk of cancer

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Recently, oral bisphosphonate use has increased markedly in the United States and elsewhere. Little is known about cancer risks associated with these drugs. A few studies have observed associations between bisphosphonates and the risk of breast, colorectal and esophageal cancer. However, the risk of all cancer and the risk of other cancers have not been investigated. In our study, we examined the risk of all cancer and site specific cancers in individuals taking bisphosphonates. Data were extracted from the UK General Practice Research Database to compare site-specific cancer incidence in a cohort of oral bisphosphonate users and a control cohort. Hazard ratios (HRs) were calculated using Cox regression modeling. The bisphosphonate and control cohort contained 41,826 participants (mean age 70, 81% female). Overall, the bisphosphonate cohort compared with the control cohort had a reduced risk of all cancer after any bisphosphonate usage [HR = 0.87, 95% confidence interval (CI) 0.82, 0.92]. In the bisphosphonate cohort, compared with the control cohort, there was no evidence of a difference in the risk of lung (HR = 1.03, 95% CI 0.88, 1.20) or prostate cancer (HR = 0.86, 95% CI 0.67, 1.09) but breast (HR = 0.71, 95% CI 0.62, 0.81) and colorectal cancer (HR = 0.74, 95% CI, 0.60–0.91) were both reduced. Our findings indicate that bisphosphonates do not appear to increase cancer risk. Although reductions in breast and colorectal cancer incidence were observed in bisphosphonate users it is unclear, particularly for breast cancer, to what extent confounding by low bone density may explain the association.

Bisphosphonates inhibit osteoclast-mediated bone resorption and are established in the prevention or treatment of osteoporosis. Bisphosphonate use has increased dramatically in recent years in Western populations[1–3] but the long-term cancer risks associated with these drugs are unknown. Preclinical data suggest that bisphosphonates may exert antitumor activity through mechanisms including inhibition of angiogenesis and cellular proliferation, cell-cycle arrest, induction of apoptosis in cancer cell lines, prevention of tumor cell adhesion and extravasation as well as activation of immune cells with anticancer activity.[4–7] Clinical trials also support an anti-neoplastic role for bisphosphonates. Some,[8,9] but not all,[10] trials of early generation oral bisphosphonate clodronate as adjuvant therapy in breast cancer patients showed improvements in overall survival and bone metastasis free survival. Trials of zoledronate in endocrine-responsive breast cancer patients have also shown increased disease free survival, decreased loco-regional recurrences and contralateral breast cancer.[11–13] Few epidemiological studies investigating the risk of cancer in bisphosphonate users have been conducted. Three studies[14–16] have investigated bisphosphonate use and breast cancer risk, two studies[17,18] have investigated bisphosphonate use and colorectal cancer risk and two studies,[17,19] including an earlier report from this cohort,[19] have investigated bisphosphonate use and esophageal cancer risk. However, there have not been any studies that have investigated the entire cancer burden in bisphosphonate users or studies which have investigated the risk of cancer at other sites (including lung, prostate, ovarian, etc.) in bisphosphonate users. The main aim of our study was to investigate the risk of all cancer and cancer by site in a cohort of bisphosphonate users. These analyses will better allow the risks and benefits of bisphosphonate use on all cancer incidence to be determined. Also, the investigation of previously unstudied cancer sites may identify additional cancers, which may be influenced by bisphosphonate usage.

Key words: cancer, risk, bisphosphonates, cohort, epidemiology
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Material and Methods

The study cohorts have previously been described in detail.[19] Cohorts were identified within United Kingdom General Practice Research Database (UK GPRD), the world's largest computerized database of anonymized longitudinal patient records including ~6% of the UK population. The high quality of General Practice Research Database (GPRD) prescription and diagnosis information has been documented.[20] Ethical

approval for all observational research using GPRD data has been obtained from a multicenter research ethics committee.

We established an initial bisphosphonate cohort of all patients receiving a prescription for oral bisphosphonates (from January 1, 1996 to December 31, 2006). The date of first oral bisphosphonate prescription was taken as the index date. Participants were excluded if they were younger than 40 years on their initial index date or if they had a prior cancer diagnosis (excluding nonmelanoma skin cancer) recorded within GPRD. In sequential order (by date of first bisphosphonate prescription), each bisphosphonate user was matched to a single control (who was allocated their index date) randomly selected from individuals of the same sex, year of birth and general practice, regardless of bisphosphonate use (to avoid removing patients from the cohort who received bisphosphonates for cancer-related osteoporosis/metastasis, thereby artificially reducing the risk of cancer in the control cohort). Therefore, some control participants used bisphosphonates, but once selected as control participants, they were excluded from the bisphosphonate cohort. All bisphosphonate and control cohort members had to have at least 3 years of data within GPRD before the index date.

Cancers were identified from Read/Oxford Medical Information System codes in patients' clinical files. All cancer codes were examined by a physician/epidemiologist (L.J.M.) blinded to whether the patient was in the bisphosphonate or control cohort. Cancer codes were categorized into: breast, lung, colorectal, prostate, ovarian, endometrial, unspecified female reproductive tract, lymphoma/leukemia, gastro-esophageal, bladder, malignant melanoma, myeloma, pancreas and other sites or site unclear. Date of first cancer code was considered the diagnosis date. Cancer incidence was compared in the bisphosphonate and control cohorts before the date on which data were downloaded from each general practice (more than 90% by August 1, 2008).

Classification of bisphosphonate exposure

All prescriptions for oral bisphosphonates were identified. Data on the preparations prescribed, the date of prescription, and the number of packs/tablets prescribed were extracted and converted to defined daily doses (DDDs), which are the assumed average maintenance dose per day of a drug used for its main indication in adults, which for oral bisphosphonates is the prevention or treatment of osteoporosis.

Data extraction relating to potential confounders

Data on smoking, alcohol consumption and body mass index (BMI) in the 3-year period before the index date were extracted, and the record closest to the index date was used. Subjects with a recorded code for osteoporosis or osteopenia at any time, or who had a code for any fracture recorded in the 3-year period before the index date, were identified. Subjects who had received five or more prescriptions for hormone replacement therapy (HRT) or oral steroids or ten or more prescriptions for nonsteroidal anti-inflammatory drugs (NSAIDs) in the 3-year period before the index date were identified, as were subjects who received one or more prescriptions for calcium and/or vitamin D supplements in the 6-month period after the index date. Smoking, alcohol, BMI and HRT use were considered confounders as they are associated with both low bone density and cancer risk. Receipt of NSAIDs, calcium and/or vitamin D are associated with reduced cancer risk and are potential confounders.[21–24]

Statistical analysis

The ascertainment of cancer within GPRD was estimated by calculating the expected number of cancers in the control cohort using the person-years of follow up in the cohort and the age and sex specific incidence rates from England in 2005 (http://www.ons.gov.uk/ons/rel/vsob1/cancer-statistics-registrations–england–series-mb1-/no–36–2005/index.html). A standardized incidence ratio (SIR) was then calculated and exact methods used to calculate 95% confidence intervals (CIs).

Survival analysis was conducted separately for each cancer site/group of sites on the time from index date to the specific cancer diagnosis of interest or to the date of censoring. Participants were censored at the first of the following outcomes: date of other cancer diagnosis (except for the all cancer diagnosis analysis), date of death, date of leaving general practice or date of last data download from general practice by GPRD. The first 6 months of follow-up was removed for every participant, because cancer incidence in this period is unlikely to be attributable to bisphosphonate usage. Kaplan-Meier curves were plotted to investigate time to cancer diagnosis in the two cohorts and to check the assumption of proportional hazards. The Cox proportional hazards model was used to calculate all hazard ratios (HRs) and 95% CIs and to adjust for potential confounding variables. The assumption of proportional hazards was checked by inspection of survival curves and within the proportional hazards model by tests of the interaction between the co-variate with time. Confounders with missing data were included using a missing data category, and a complete case analysis was also conducted (not shown, as estimates were little altered). Separate analyses were conducted comparing the risk of the common cancers in the bisphosphonate and control cohort after adjustment for BMI only, alcohol consumption only and smoking status only (not shown, as estimates were little altered), allowing larger numbers of individuals to contribute as these variables were missing for the greatest proportion of individuals. Analyses were repeated for users of nitrogen-containing bisphosphonates and alendronate.

To investigate dose response, separate analyses were conducted, for breast and colorectal cancer, including only follow-up time after the bisphosphonate user had received 1, 2, 3 and 4 years DDDs (follow-up from the same date for matched controls). To explore potential confounding by indication, subgroup analyses[25] were conducted for breast and colorectal cancer including only pairs of bisphosphonate users and controls in which the control was diagnosed with osteoporosis/osteopenia before the index date or a fracture in

Table 1. Cancer ascertainment in the control cohort ($n = 46,036$)

Site	Observed cases	Expected cases[1]	Standardized incidence ratio (95% CI)
Males and females			
All cancers[2]	3,126	2866.35	1.09 (1.05, 1.13)
Lung cancer	382	401.21	0.95 (0.86, 1.14)
Colorectal cancer	414	397.07	1.04 (0.94, 1.15)
Lymphoma or leukemia	180	169.3	1.06 (0.91, 1.23)
Gastro-esophageal	149	159.53	0.93 (0.79, 1.10)
Malignant melanoma	101	68.81	1.47 (1.20, 1.78)
Bladder cancer	146	100.64	1.45 (1.23, 1.71)
Pancreas cancer	71	94.60	0.75 (0.59, 0.95)
Myeloma	60	44	1.37 (1.04, 1.76)
Females only			
Breast cancer	588	560.54	1.05 (0.97, 1.14)
Ovary	85	92.45	0.92 (0.73, 1.14)
Endometrial	73	91.07	0.80 (0.63, 1.01)
Males only			
Prostate cancer	188	188.83	1.00 (0.86, 1.15)

[1]Expected number of cases in the control cohort by age and sex distribution based upon incidence rates from England in 2005.
[2]Excludes nonmelanoma skin cancer.

the 3-year period before the index date. Unpaired analyses (with adjustment for age and sex) that included only members of the bisphosphonate and control cohorts with a prior diagnosis of osteoporosis/osteopenia or fracture were also conducted. All conducted hypothesis tests were two sided. All statistical analyses were conducted using STATA version 9 (StataCorp, College Station, TX).

Results

Data were extracted from GPRD for 46,036 oral bisphosphonate users and 46,036 matched controls. During follow-up, 5,956 cancers were recorded in the bisphosphonate and control cohorts. To estimate completeness of ascertainment of cancers in the GPRD, SIRs for cancers in the control cohort compared with age and sex specific incidence rates from England in 2005 are shown in Table 1. The SIR for all cancers in the control cohort was slightly elevated (SIR = 1.09, 95% CI 1.05, 1.13). SIRs for most cancers were similar to those expected from national rates but rates of bladder cancer (SIR = 1.45), myeloma (SIR = 1.37) and malignant melanoma (SIR = 1.47) were significantly higher than expected, whereas the pancreas cancer rate (SIR = 0.75) was significantly lower.

In bisphosphonate cohort, 41,826 participants had at least 6 months of follow-up and analyses were restricted to these participants and their matched controls. The mean age was 70 (standard deviation (SD) = 11.4) in the two cohorts (Table 2). The follow-up in the bisphosphonate and control cohorts was similar (mean 4.5 and 4.4 years and maximum 12.9 and 12.9, respectively). All of the bisphosphonate cohort and 9% of the control cohort received at least one prescription for oral bisphosphonates during the follow-up period. Mean BMI was higher in the control cohort than the bisphosphonate cohort (27.1 kg/m^2 *vs.* 25.5 kg/m^2, respectively). A similar proportion of the bisphosphonate and control cohorts were smokers or reported alcohol consumption. HRT, NSAIDs, steroids and calcium and vitamin D supplements were all more commonly prescribed in the bisphosphonate cohort. The majority of subjects in the bisphosphonate cohort had used nitrogen containing bisphosphonates (87%) or alendronate (70%).

Overall cancer incidence

Table 3 contains a comparison of cancer incidence in the bisphosphonate and control cohorts. Overall, in the bisphosphonate cohort compared with the control cohort, there was a reduction in the risk of all cancer after any usage (HR = 0.87, 95% CI 0.82, 0.92) and after 1 year of prescriptions (HR = 0.87, 95% CI 0.80, 0.95). Adjustments for potential confounders had little impact on these associations. There were no substantial differences in cancer risk when the analyses were restricted to users of nitrogen containing bisphosphonates or alendronate (data not shown).

Cancer incidence by site

There was little evidence of a difference in the risk of most site-specific cancers in the bisphosphonate cohort compared with the control cohort (Table 3). There was evidence of reductions in breast and colorectal cancer risk in the bisphosphonate cohort after any usage (adjusted HR = 0.75, 95% CI 0.63, 0.89; $p = < 0.001$ and adjusted HR = 0.74, 95% CI 0.60, 0.91; $p = 0.01$, respectively) and after 1 year of prescriptions (adjusted HR = 0.79, 95% CI 0.62, 1.01; $p = 0.06$ and adjusted HR = 0.72, 95% CI 0.53, 0.98; $p = 0.04$, respectively). Further analysis of these cancers is shown below. There was some evidence, although not significant, of an increase in the risk of myeloma (adjusted HR = 1.76, 95% CI 0.91, 3.37; $p = 0.09$), and decreases in the risk of endometrial (adjusted HR = 0.55, 95% CI 0.28, 1.10; $p = 0.09$), prostate (adjusted HR = 0.68, 95% CI 0.41, 1.13; $p = 0.14$) and bladder cancer (adjusted HR = 0.67, 95% CI 0.41, 1.10; $p = 0.11$). However, these estimates were based on small numbers of incident events (27, 19, 50 and 41 in the bisphosphonate cohort, respectively) and further reliable analysis was not possible

Breast cancer incidence

Survival curves (Fig. 1) indicate that the difference in breast cancer risk in the bisphosphonate and control cohorts seems to attenuate slightly over time. This is also indicated by evidence ($p = 0.01$) of an interaction between the effect of bisphosphonate usage and time in the proportional hazards model. Dose-response analysis (Table 4) also demonstrated that the association between bisphosphonates and breast cancer risk was less apparent after 3 years (HR = 0.81, 95% CI 0.57, 1.16; $p = 0.25$) and after 4 years of bisphosphonate prescriptions (HR = 0.94, 95% CI 0.57, 1.54; $p = 0.79$). Subgroup

Table 2. Participant characteristics in bisphosphonate cohort and matched control cohort including only individuals with more than 6 months follow-up

	Bisphosphonate cohort		Matched control cohort	
Characteristic	***n* (%)**	**Mean (SD)**	***n* (%)**	**Mean (SD)**
Age (at index date)	41,826 (100%)	70.0 (11.4)	41,826 (100%)	70.0 (11.4)
40–49.9	2,057 (5%)		2,057 (5%)	
50–59.9	6,600 (16%)		6,600 (16%)	
60–69.9	10,772 (26%)		10,772 (26%)	
70–79.9	13,753 (33%)		13,753 (33%)	
80–89.9	7,715 (18%)		7,715 (18%)	
90 or greater	894 (2%)		894 (2%)	
Sex				
Male	7,777 (19%)		7,777 (19%)	
Female	34,049 (81%)		34,049 (81%)	
Any bisphosphonate prescription (during follow-up period)	41,826 (100%)		3,705 (9%)	
Bisphosphonate in DDDs per day (during follow-up period)	41,826	0.59 (0.49)	41,826	0.03 (0.16)
Follow-up (years)	41,826 (100%)	4.5 (2.6)	41,826 (100%)	4.4 (2.6)
BMI	20,199 (48%)	25.5 (2.25)	17,513 (42%)	27.1 (2.25)
Missing	21,627 (52%)		24,313 (58%)	
Smoking				
Never	12,609 (30%)		11,871 (28%)	
Ex	6,916 (17%)		5,689 (14%)	
Current	4,328 (10%)		3,531 (8%)	
Missing	17,973 (43%)		20,735 (50%)	
Alcohol				
Never	3,619 (9%)		3,178 (8%)	
Ex	534 (1%)		369 (1%)	
Current	11,146 (27%)		10,406 (25%)	
Missing	26,527 (63%)		27,873 (67%)	
HRT prescription, in females ($\geq$5 prescriptions, in 3 years before index date)	4,513 (13%)		3,167 (9%)	
NSAID prescription ($\geq$10 prescriptions, in 3 years before index date)	11,319 (27%)		8,989 (21%)	
Steroid prescription ($\geq$5 prescriptions, in 3 years before index date)	9,085 (22%)		1,170 (3%)	
Vitamin D supplementation ($\geq$1 prescription, in 6 months after index date)	14,919 (36%)		1,490 (4%)	
Calcium supplementation ($\geq$1 prescription, in 6 months after index date)	23,493 (56%)		1,905 (5%)	

analysis was conducted by identifying members of the control cohort with a diagnosis for osteoporosis/osteopenia or fracture before the index date and comparing the risk of breast cancer in these participants to their matched bisphosphonate users (*i.e.,* retaining the matching). In these analyses, the association between bisphosphonate usage and breast cancer were attenuated in analyses defined by osteoporosis/osteopenia codes (HR = 0.90, 95% CI 0.52, 1.57; $p = 0.72$) and fracture codes (HR = 0.91, 95% CI 0.54, 1.52; $p = 0.71$). Subgroup analyses were also conducted that included any member of either cohort with a diagnosis for osteoporosis\osteopenia or fracture (ignoring the matching). In these analyses, the associations between bisphosphonate usage and breast cancer remained (HR = 0.70, 95% CI 0.46, 1.06; $p = 0.09$ and HR = 0.56, 95% CI 0.36, 0.87; $p = 0.01$, respectively). The breast cancer association was similar in different BMI categories.

Table 3. Overall cancer incidence in the bisphosphonate and control cohorts by cancer site

	Any usage						After 1 year of DDDs[1]					
	Bis. cases	Control cases	HR (95% CI)	*p*	Adjusted[2] HR (95% CI)	*p*	Bis. cases	Control cases	HR (95% CI)	*p*	Adjusted[2] HR (95% CI)	*p*
Males and females [person years]	[165,677]	[163,771]					[71,920]	[71,685]				
All cancers	2,273	2,599	0.87 (0.82, 0.92)	<0.001	0.82 (0.76, 0.88)	<0.001	941	1,074	0.87 (0.80, 0.95)	0.002	0.85 (0.77, 0.95)	0.004
Lung cancer	329	317	1.03 (0.88, 1.20)	0.74	0.85 (0.70, 1.03)	0.10	131	125	1.05 (0.82, 1.34)	0.72	0.86 (0.63, 1.17)	0.34
Colorectal	264	344	0.76 (0.65, 0.89)	0.001	0.74 (0.60, 0.91)	0.01	115	154	0.74 (0.58, 0.95)	0.02	0.72 (0.53, 0.98)	0.04
Lymphoma or leukemia	181	153	1.17 (0.94, 1.45)	0.15	1.03 (0.79, 1.36)	0.81	75	59	1.27 (0.90, 1.78)	0.17	1.11 (0.73, 1.69)	0.63
Gastro-esophageal	116	115	1.00 (0.77, 1.29)	0.98	0.85 (0.61, 1.19)	0.35	48	50	0.96 (0.64, 1.42)	0.83	1.05 (0.65, 1.70)	0.83
Malignant melanoma	64	83	0.76 (0.55, 1.06)	0.10	0.80 (0.53, 1.20)	0.28	28	33	0.85 (0.51, 1.40)	0.51	0.82 (0.44, 1.52)	0.53
Bladder cancer	101	119	0.84 (0.64, 1.09)	0.19	0.80 (0.57, 1.12)	0.20	41	58	0.70 (0.47, 1.05)	0.09	0.67 (0.41, 1.10)	0.11
Pancreas cancer	62	60	1.02 (0.72, 1.46)	0.91	0.84 (0.53, 1.35)	0.48	23	21	1.09 (0.60, 1.97)	0.78	1.14 (0.56, 2.35)	0.96
Myeloma	72	53	1.35 (0.95, 1.92)	0.10	1.39 (0.89, 2.15)	0.14	27	21	1.28 (0.73, 2.27)	0.39	1.76 (0.91, 3.37)	0.09
Other sites or site unclear	501	546	0.91 (0.80, 1.02)	0.12	0.83 (0.71, 0.97)	0.02	182	201	0.90 (0.74, 1.10)	0.31	0.87 (0.68, 1.11)	0.26
Females only [person years]	[138,850]	[133,959]					[60,214]	[59,135]				
All cancers	1,698	2,012	0.82 (0.76, 0.87)	<0.001	0.80 (0.73, 0.86)	<0.001	705	824	0.84 (0.76, 0.93)	0.001	0.84 (0.74, 0.96)	0.006
Breast cancer	369	501	0.71 (0.62, 0.81)	<0.001	0.75 (0.63, 0.89)	<0.001	165	218	0.74 (0.61, 0.91)	0.004	0.79 (0.62, 1.01)	0.06
Ovarian cancer	43	69	0.60 (0.41, 0.88)	0.01	0.64 (0.40, 1.03)	0.07	25	27	0.91 (0.53, 1.57)	0.74	0.88 (0.45, 1.71)	0.71
Endometrial	33	64	0.50 (0.33, 0.76)	0.001	0.64 (0.38, 1.08)	0.10	19	29	0.64 (0.36, 1.15)	0.14	0.55 (0.28, 1.10)	0.09
Unspecified female reproductive tract	23	26	0.85 (0.49, 1.49)	0.58	1.29 (0.67, 2.50)	0.45	12	11	1.07 (0.47, 2.43)	0.87	1.38 (0.53, 3.58)	0.51
Males only [person years]	[26,826]	[29,812]					[11,705]	[12,550]				
All cancers	575	587	1.09 (0.97, 1.22)	0.16	0.97 (0.83, 1.14)	0.70	235	250	1.01 (0.84, 1.20)	0.93	0.94 (0.75, 1.19)	0.62
Prostate cancer	115	149	0.86 (0.67, 1.09)	0.21	0.71 (0.50, 1.01)	0.05	50	67	0.80 (0.55, 1.15)	0.22	0.68 (0.41, 1.13)	0.14

[1]Follow-up after 365 DDDs in the bisphosphonate cohort (or 365 days if 365 DDDs received in under 365 days). [2]Adjusted for BMI, alcohol, smoking, NSAID prescription (≥10 prescriptions, in 3 years before index date), glucocorticoid steroid (≥5 prescriptions, in 3 years before index date), vitamin D prescription (any, in the 6 months after index date) and calcium (any, in the 6 months after index date) in the male and female combined analyses and male only analyses, additionally adjusted for HRT prescription (≥5 prescriptions, in 3 years before index date) in the female only analyses.

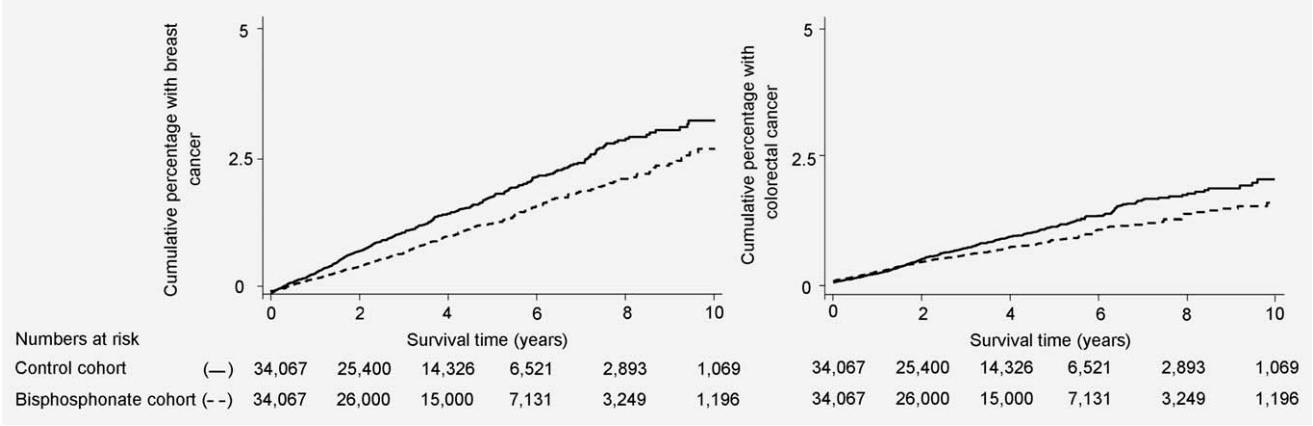

Figure 1. Time to breast and colorectal cancer in the bisphosphonate and control cohort.

Colorectal cancer incidence

Survival curves (Fig. 1) indicate that the difference in colorectal cancer risk in the bisphosphonate and control cohorts seems to increase slightly over time but there was no interaction between the effect of bisphosphonate usage and time ($p = 0.17$) in the proportional hazards model. Table 4 demonstrates that the association between bisphosphonate usage and colorectal cancer risk was more marked with increasing duration of exposure; after 3 years (HR = 0.65, 95% CI 0.39, 1.08; $p = 0.10$) and after 4 years of prescriptions (HR = 0.48, 95% CI 0.22, 1.01; $p = 0.05$). The association was similar in males (after 1 year of prescriptions HR 0.78, 95% CI 0.47, 1.28) and females (after 1 year of prescriptions HR 0.74, 95% CI 0.56, 0.97). Subgroup analyses (retaining the matching) indicated that the association between bisphosphonate usage and colorectal cancer was attenuated in controls with osteoporosis/osteopenia codes and their matched bisphosphonate users (HR = 1.18, 95% CI 0.60, 2.33; $p = 0.63$) and controls with fracture codes and their matched bisphosphonate users (HR = 0.95, 95% CI 0.45, 2.00; $p = 0.90$), but these estimates were based on small numbers. In subgroup analyses (ignoring the matching), there was some attenuation of the association between bisphosphonate usage and colorectal cancer in participants with an osteoporosis/osteopenia diagnosis (HR = 0.82, 95% CI 0.48, 1.40; $p = 0.46$) and more marked attenuation in participants with a fracture diagnosis (HR = 1.05, 95% CI 0.58, 1.89; $p = 0.87$). The association appeared similar in different BMI categories.

Discussion

This cohort study of mainly elderly women found a reduction in overall cancer risk in bisphosphonate users. There was little evidence of an increase in any site-specific cancers in the bisphosphonate users. There was evidence of 20% and 25% reductions in breast cancer and colorectal cancer risk in bisphosponate users, respectively. The observed reduction in breast cancer risk was attenuated with increasing use of bisphosphonates, unlike for colorectal cancer where stronger associations were seen with increasing use. In subgroup analyses where members of the unexposed cohort with a history of osteoporosis/osteopenia or a fracture were compared to their matched control, the associations for breast and colorectal cancer were attenuated.

The association between bisphosphonate use and all cancer risk or cancer risk by site has not been examined, with the exception of breast,[14–16] colorectal[17,18] and esophageal cancer.[17,19] Importantly, we observed no increase in cancers overall or site specific cancers. The magnitude of the reduction in breast cancer risk we observed was similar to three previous studies.[14–16] However, two of these studies were breast cancer case–control studies[14,15] and have various weaknesses including low response rates,[14,15] differential response rates between cases and controls[15] and potential for recall bias related to bisphosphonate exposure.[14] Interestingly, the only previous cohort study[16] demonstrated a reduction in breast cancer risk after less than 2 years of bisphosphonate usage but not after longer usage, which is similar to the attenuation of the breast cancer association with increasing usage that we observed.

There is substantial preclinical evidence indicating that bisphosphonates may reduce cancer risk[4,6,26,27] and trials of clodronate[8] and, particularly, zoledronate[11–13] in breast cancer patients demonstrate that bisphosphosphonates positively influence cancer outcomes that are unrelated to skeletal metastases. Although these studies address cancer progression, they provide support for bisphosphonate related anti-breast cancer activity and suggest that the reduction in breast cancer risk we observed may be real. An alternative explanation is that the estimate of breast cancer risk is confounded by cumulative estrogen exposure or other factors that influence both bone density and cancer risk. Previous studies of postmenopausal women have confirmed that higher bone mineral density is associated with increased breast cancer risk.[28–30] The pattern of reduction in the incidence of estrogen related cancers (breast and endometrial) in our study, together with attenuation of the breast cancer association with increasing use of bisphosphonates, and when the matched analysis was

Table 4. Breast and colorectal cancer incidence in the bisphosphonate and control cohorts by duration of use and in subgroups

	Bisphosphonate cohort		Control cohort		Hazard ratio (95% CI)	*p*
	Cases	Person years	Cases	Person years		
Breast cancer						
Any bisphosphonate	369	138,850	501	133,959	0.71 (0.62, 0.81)	<0.001
After cumulative bisphosphonate prescriptions greater than[1]:						
365 DDDs (~1 year supply)	165	60,214	218	59,135	0.74 (0.61, 0.91)	0.004
730 DDDs (~2 years supply)	90	32,936	125	32,632	0.71 (0.54, 0.94)	0.02
1,095 DDDs (~3 years supply)	55	21,137	68	21,136	0.81 (0.57, 1.16)	0.25
1,460 DDDs (~4 years supply)	30	9,108	32	9,064	0.94 (0.57, 1.54)	0.79
Subgroup analyses by diagnosis code before index date, retaining matching[2]						
Osteoporosis\osteopenia	25	7,357	26	6,829	0.90 (0.52, 1.57)	0.72
Fracture (in 3 years before index)	28	6,750	29	6,337	0.91 (0.54, 1.52)	0.71
Subgroup analyses by diagnosis code\BMI category before index date, ignoring matching[3]						
Osteoporosis\osteopenia	216	84,983	26	6,829	0.70 (0.46, 1.06)	0.09
Fracture (in 3 years before index)	62	24,344	29	6,337	0.56 (0.36, 0.87)	0.01
BMI under or normal	94	33,056	78	20,491	0.75 (0.56, 1.02)	0.06
BMI overweight	92	30,359	139	33,292	0.70 (0.60, 0.81)	0.02
Colorectal cancer						
Any bisphosphonate	264	165,577	344	163,771	0.76 (0.65, 0.89)	0.001
After cumulative bisphosphonate prescriptions greater than[1]:						
365 DDDs (~1 year supply)	115	71,920	154	71,685	0.74 (0.58, 0.95)	0.02
730 DDDs (~2 years supply)	53	38,822	83	38,877	0.64 (0.45, 0.90)	0.01
1,095 DDDs (~3 years supply)	24	21,138	37	21,135	0.65 (0.39, 1.08)	0.10
1,460 DDDs (~4 years supply)	10	10,615	21	10,634	0.48 (0.22, 1.01)	0.05
Subgroup analyses by diagnosis code before index date, retaining matching[2]						
Osteoporosis\osteopenia	19	7,551	15	7,016	1.18 (0.60, 2.33)	0.63
Fracture (in 3 years before index)	14	7,315	14	6,958	0.95 (0.45, 2.00)	0.90
Subgroup analyses by diagnosis code\BMI category before index date, ignoring matching[4]						
Osteoporosis\osteopenia	142	96,034	15	7,016	0.82 (0.48, 1.40)	0.46
Fracture (in 3 years before index)	54	27,238	14	6,958	1.05 (0.58, 1.89)	0.87
BMI under or normal	62	38,201	49	23,868	0.84 (0.58, 1.22)	0.37
BMI overweight	72	37,023	102	40,923	0.75 (0.63, 0.90)	0.002

[1]Person years and cancer cases occurring after the date of specified bisphosphonate prescriptions received for each bisphosphonate cohort member and their matched control. If DDDs received before expected date used, *e.g.,* if 365 DDDs of prescriptions received in under 365 day then 365 days used as exposure date. [2]Analysis of control cohort members with a diagnosis of osteoporosis\fracture before their index date and their matched bisphosphonate cohort member, regardless of whether they also have a diagnosis of osteoporosis\fracture. [3]Analysis of bisphosphonate cohort and control cohort members with a diagnosis of osteoporosis/osteopenia (or a diagnosis of fracture or with BMI $<$ 25 or with BMI $\geq$ 25) before their index date, adjusted for age as matching not retained. [4]Analysis of bisphosphonate cohort and control cohort members with a diagnosis of osteoporosis/osteopenia (or a diagnosis of fracture or with BMI $<$ 25 or with BMI $\geq$ 25) before their index date, adjusted for age (as continuous) and sex as matching not retained.

restricted to subjects who were similar in terms of history of osteoporosis/osteopenia or fracture, suggests that confounding by indication may underlie the reductions in breast cancer incidence we observed. However, in subgroup analyses where matching was not retained the reductions in breast cancer incidence remained, although the subjects included in the unexposed and exposed cohorts in this analysis may be less comparable than in the analysis that retained the matching.

This is the first cohort study to observe a reduction in colorectal cancer risk in bisphosphonate users and we show that the association was more marked with increasing bisphosphonate use, although it was attenuated in subjects with a history of osteoporosis/osteopenia or fracture. A recent case–control study,[17] also within the UK GPRD, showed a 13% reduction colorectal cancer risk in individuals with one or more prescriptions for bisphosphonates. Also a 33% reduction in risk with three or more prescriptions for

bisphosphonates has also recently been described in a case–control study from Israel.[18] Confounding by low bone density may be less of a problem in our colorectal analyses because, colorectal cancer is not generally considered to be a hormone related malignancy to the same extent as breast cancer[31] and high bone density has been associated with reduced rather than increased colorectal cancer risk.[32–34] Our estimate of the association between bisphosphonate use and colorectal cancer risk may remain confounded by body mass, alcohol and smoking, as data on these parameters were substantially incomplete. Data on physical activity were also too incomplete to use. Our results provide only qualified support for a protective effect of bisphosphonate use against colorectal cancer development and further investigations are required.

This study has some strengths and limitations. Strengths include the large size, reasonable period of follow-up, exclusion of prior cancers and the use of recorded prescription data. Underestimation of bisphosphonate usage is unlikely, because these drugs cannot be obtained without prescription in the UK but overestimation of usage is possible, as compliance with bisphosphonate prescribing is suboptimal.[35] A further weakness was the ascertainment of cancer incidence as linkage to cancer registries was not available, although the recording of cancer outcomes within the GPRD has been shown to be high,[20] and it is reassuring that the incidences of most cancers in the control cohort were similar to population rates for England. Although it is possible that early cancer symptoms could lead to an increased likelihood of bisphosphonate prescriptions, particularly for cancer symptoms related to weight loss and low bone mineral density, this would lead to an increased cancer risk in the bisphosphonate cohort and could not explain our findings for either breast or colorectal cancer. Other limitations include the relatively high proportion of missing data on potential confounders such as weight, potential for residual confounding and multiple comparisons.

In conclusion, this analysis of a large population based sample of bisphosphonate users and matched controls showed a decrease in breast and colorectal cancer risk. There was also some evidence of decreases in bladder, endometrial and prostate cancer risk. Further studies are required to examine the relationship between use of bisphosphonates and cancer incidence but it is reassuring that cancer risk was not increased in users of these drugs.

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