SHORT COMMUNICATION

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Post-diagnostic oral bisphosphonate use and colorectal cancer mortality: a population-based cohort study within the UK Clinical Practice Research Datalink

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Background: We conducted the first study to investigate post-diagnostic oral bisphosphonates use and colorectal cancer-specific mortality.

Methods: Colorectal cancer patients were identified from the National Cancer Data Repository (1998–2007) and linked to the UK Clinical Practice Research Datalink, providing prescription records, and Office of National Statistics mortality data. Time-dependent Cox regression models investigated colorectal cancer-specific mortality in post-diagnostic bisphosphonate users.

Results: Overall, in 4791 colorectal cancer patients, there was no evidence of an association between bisphosphonate use and colorectal cancer-specific mortality (adjusted hazard ratio = 1.11; 95% confidence interval 0.80, 1.54) or with drug frequency or type.

Conclusions: In this novel population-based cohort study, post-diagnostic bisphosphonate use was not associated with longer rates of colorectal cancer survival.

Bisphosphonates, in particular those containing nitrogen, may act on tumour cells directly protecting against visceral metastases. Studies have reported antiproliferative effects and proapoptotic effects, as well as reductions in tumour cell adhesion, invasion, angiogenesis and immune system modulation (Neville-Webbe *et al*, 2002). Studies in colorectal cancer (CRC) found similar results reporting decreased cell proliferation (Suri *et al*, 2001; Sassa *et al*, 2009) and increased apoptosis (Suri *et al*, 2001; Sewing *et al*, 2008).

Clinical trials also suggest bisphosphonates may influence cancer survival. Trials of bisphosphonates as adjuvant therapy in breast cancer patients reported improved survival outcomes, however, evidence is inconsistent (Neville-Webbe *et al*, 2002). In CRC, studies have shown reductions in risk (Yang *et al*, 2013), but no epidemiological studies have investigated the effect of bisphosphonates on cancer outcomes in patients diagnosed with CRC.

This was the first study to investigate the effect of post-diagnostic oral bisphosphonate usage on CRC-specific mortality in a large prospective UK population-based cohort of CRC patients.

MATERIALS AND METHODS

Study design. The UK Clinical Practice Research Datalink (CPRD) contains demographic information, clinical diagnoses and details of issued prescriptions. This was linked to the National Cancer Data Repository (NCDR), comprising data from all English cancer registries including date, site of primary cancer diagnosis, stage and treatment data and to the Office of National Statistics (ONS) mortality data up to January 2011. Ethical approval for observational research using CPRD has been obtained from a

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multicentre research ethics committee. CRC cases were identified from CPRD, based on a primary diagnosis of CRC, confirmed by a NCDR CRC diagnosis (ICD codes C18 for colon and C19/C20 for rectum) from 1998 to 2007. Individuals with a history of cancer were excluded (except *in situ* neoplasms and non-melanoma skin). Patients were excluded if the date of cancer diagnosis predated their date of registration at a CPRD practice or predated CPRD quality records or occurred after the last date of data collection. One patient recorded as having a prescription for an intravenous bisphosphonate was excluded. Deaths were classified as CRC-specific if the underlying cause of death was C18, C19, C20, C21 or C26. Follow-up started 1 year after a cancer diagnosis, as it is unlikely that post-diagnostic medication use could influence deaths in this time period. Other studies have utilised similar methods (Yu *et al*, 2014). Patients were followed up to death, end of registration with the GP, last date of data collection from the GP or end of follow-up.

Exposure data. Oral bisphosphonate use was determined from GP prescription records. Prescription data were converted to defined daily doses (DDD) based on quantity and strength in milligrams. Bisphosphonate use was investigated as a time varying covariate (Lévesque *et al*, 2010), with individuals considered non-users until 6 months after their first prescription. This lag of 6 months removed prescriptions in 6 months before death as these may reflect end of life treatment.

Confounders. NCDR provided data on cancer stage, grade and treatment. Smoking, alcohol consumption and body mass index (BMI) were determined from the closest GP record before a CRC diagnosis (records >10 years were ignored). Pre-diagnostic comorbidities were determined from GP diagnosis codes. Post-diagnostic use of low-dose aspirin, β-blockers, non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme (ACE) inhibitors and statins (modelled as time varying covariates with a 6 month lag), was determined from GP prescribing data.

Data analysis. Time-dependent Cox regression models were used to calculate hazard ratios (HRs) for cancer-specific deaths and 95% confidence intervals (CIs) for bisphosphonate users *vs* non-users, adjusting for potential confounders. Analyses were also conducted by DDDs and number of prescriptions, as well as in alendronate users and users of nitrogen-containing bisphosphonates. Analyses were repeated restricting to patients with available stage and grade information and additionally adjusting for these covariates.

Subgroup analyses were conducted by site, stage and among females >60 years. Sensitivity analyses were conducted increasing the lag to 1 year and investigating pre-diagnostic bisphosphonate use in the year before diagnosis, not excluding deaths in the year after diagnosis. Additional analysis investigated post-diagnostic use among new users of bisphosphonates. A propensity score matched analysis was conducted using a simplified analysis based upon use in the first year after diagnosis. Logistic regression was used to create a propensity score for bisphosphonate use in the first year after diagnosis using previously mentioned potential confounders. Matching was implemented by PSMATCH2 (Leuven, 2013) using single nearest neighbour matching. Cox regression compared CRC-specific mortality in bisphosphonate users and propensity score matched control group using a robust variance estimator to account for lack of independence within matched pairs, as recommended (Austin, 2013). All analyses were conducted using STATA 11 (StatCorp, College Station, TX, USA).

On the basis of the observed cohort of 4800 colorectal patients and 1550 cancer-specific deaths and the observed bisphosphonate usage of 7% of individuals, the study would have over 80% power to detect as statistically significant a HR of ~0.75, using a method based upon Schoenfeld's log rank test method implemented in STATA 11.

Table 1. Characteristics of colorectal cancer patients by post-diagnostic bisphosphonate use

Characteristics	Bisphosphonate user, *n* (%)	Bisphosphonate non-user, *n* (%)	*P*-value
Sex			
Male	84 (24.3)	2598 (58.5)	<0.001
Female	262 (75.7)	1847 (41.6)	
Year of CRC			
1998–2000	72 (20.8)	980 (22.1)	
2001–2003	123 (35.6)	1532 (34.5)	0.85
2004–2006	151 (43.6)	1933 (43.5)	
Age at CRC diagnosis (years)			
<40	2 (0.6)	59 (1.3)	
40–49	2 (0.6)	220 (5.0)	
50–59	19 (5.5)	707 (15.9)	
60–69	62 (17.9)	1224 (27.5)	<0.001
70–79	165 (47.7)	1460 (32.9)	
80–89	94 (27.2)	714 (16.1)	
⩾90	2 (0.6)	61 (1.4)	
Mean (s.d.)	74.0 (8.8)	68.5 (11.6)	
Site			
Colon	223 (64.3)	2542 (57.2)	0.01
Rectum (including rectosigmoid junction)	124 (35.7)	1903 (42.8)	
Stages			
1	55 (15.9)	498 (11.2)	
2	125 (36.1)	1298(29.2)	<0.001
3	77 (22.3)	1313 (29.5)	
4	5 (1.5)	226 (5.1)	
Unknown	84 (24.3)	1110 (25.0)	
Grade			
Well	25 (7.2)	298 (6.7)	
Moderately	240 (69.4)	2908 (65.4)	0.3
Poorly	38 (11.0)	531 (12.0)	
Unknown	43 (12.4)	708 (15.9)	
Treatment within 6 months of CRC			
Surgery	300 (86.7)	3869 (87.0)	0.86
Radiotherapy	34 (9.8)	724 (16.3)	0.002
Chemotherapy	59 (17.1)	1382 (31.1)	<0.001
Smoking before CRC			
Non-smoker	160 (46.2)	1919 (43.2)	
Former smoker	102 (29.5)	1135 (25.5)	0.05
Current smoker	37 (10.7)	655 (14.7)	
Unknown	47 (13.6)	736 (16.6)	
Alcohol before CRC			
Non-drinker	55 (15.9)	448 (10.1)	
Alcohol consumer	211 (61.0)	2781 (62.6)	0.002
Unknown	80 (23.1)	1216 (27.4)	
BMI (kg m^{-2}) before CRC			
Underweight (<18.5)	12 (3.5)	54 (1.2)	
Normal (18.5–25)	121 (35.0)	1251 (28.1)	
Overweight (25–30)	103 (29.8)	1367 (30.8)	<0.001
Obese (>30)	37 (10.7)	658 (14.8)	
Missing	73 (21.1)	1115 (25.1)	
Comorbidity pre and post CRC			
Cerebrovascular disease	22 (6.4)	268 (6.0)	0.81
Chronic pulmonary disease	92 (26.6)	674 (15.2)	<0.001
Congestive heart disease	22 (6.4)	171 (3.9)	0.02
Diabetes	31 (9.0)	439 (9.9)	0.58
Myocardial infarction	14 (4.1)	257 (5.8)	0.18
Peptic ulcer disease	21 (6.1)	268 (6.0)	0.98
Peripheral vascular disease	9 (2.6)	164 (3.7)	0.3
Rheumatological disease	53 (15.3)	118 (2.7)	<0.001
Renal disease	5 (1.5)	77 (1.7)	0.69
Statin use (in exposure period)	146 (42.2)	1424 (32.0)	<0.001
Low-dose aspirin use (in exposure period)	145 (41.9)	1481 (33.3)	0.001
ACE inhibitor use (in exposure period)	149 (43.1)	1334 (30.0)	<0.001
Beta-blocker use (in exposure period)	121 (35.0)	1177 (26.5)	<0.001
NSAID use (in exposure period)	213 (61.6)	1998 (45.0)	<0.001

Abbreviations: ACE = angiotensin-converting enzyme; CRC = colorectal cancer; NSAID = non-steroidal anti-inflammatory drugs.

Table 2. Association between post-diagnostic bisphosphonate use and colorectal cancer-specific death

	User			Non-user								
Medication usage after diagnosis[a]	Cancer-specific mortality	All patients	Person years	Cancer-specific mortality	All patients	Person years	Unadjusted HR (95% CI), ($n=4792$)	*P*-value	Adjusted[b] HR (95% CI), ($n=4792$)	*P*-value	Fully Adjusted[c] HR (95% CI), ($n=3466$)	*P*-value
Bisphosphonate user *vs* non-user	60	346	1145	1516	4445	20 423	0.94 (0.73, 1.22)	0.65	1.00 (0.77, 1.31)	1	1.11 (0.80, 1.54)	0.54
1–12 prescriptions	37	145	563	1516	4445	20,423	0.98 (0.71, 1.36)	0.91	1.03 (0.74, 1.43)	0.89	1.07 (0.70, 1.64)	0.76
>12 prescriptions	23	201	582	—	—	—	0.88 (0.58, 1.34)	0.56	0.96 (0.63, 1.47)	0.86	1.16 (0.72, 1.88)	0.54
1 to 365 DDDs	37	144	536	1516	4445	20,423	1.04 (0.75, 1.44)	0.83	1.08 (0.77, 1.50)	0.66	1.12 (0.73, 1.71)	0.6
⩾365 DDDs	23	202	610	—	—	—	0.82 (0.54, 1.24)	0.35	0.92 (0.61, 1.41)	0.71	1.09 (0.67, 1.77)	0.74
Nitrogen-containing bisphosphonate user *vs* non-user	54	322	1019	1522	4469	20,549	0.98 (0.74, 1.28)	0.87	1.09 (0.82, 1.44)	0.56	1.13 (0.80, 1.61)	0.48
Alendronate user *vs* non-user	44	273	837	1532	4518	20,731	1.02 (0.76, 1.38)	0.9	1.15 (0.84, 1.56)	0.38	1.25 (0.85, 1.84)	0.27
Subgroup analysis												
Colon cancer	36	222	761	828	2542	11,758	0.92 (0.66, 1.29)	0.64	1.05 (0.74,1.49)	0.79	1.10 (0.72, 1.69)	0.7
Rectal cancer (including rectosigmoid junction)	24	124	384	688	1903	8665	1.02 (0.68, 1.53)	0.94	0.96 (0.63, 1.45)	0.83	1.18 (0.70, 1.98)	0.53
Female ⩾60 years old	42	246	854	477	1,413	6622	0.94 (0.68, 1.29)	0.7	1.05 (0.75, 1.46)	0.79	1.14 (0.75, 1.74)	0.53
Stages 1 and 2	23	180	630	321	1796	10,038	1.29 (0.84, 1.97)	0.24	1.42 (0.91, 2.21)	0.12	1.36 (0.86, 2.14)	0.19
Stages 3 and 4	19	82	233	727	1539	5800	0.88 (0.56, 1.39)	0.58	0.92 (0.58, 1.48)	0.73	0.92 (0.56, ,1.49)	0.73
Pre-diagnostic non-users[d]	27	234	729	1370	4077	18,713	0.80 (0.55, 1.18)	0.26	0.82 (0.56,1.21)	0.32	0.84 (0.51, 1.39)	0.5
Sensitivity analysis												
Increasing lag to 1 year	49	312	1012	1527	4479	20,556	0.92 (0.69, 1.22)	0.55	0.97 (0.72, 1.31)	0.86	1.12 (0.78, 1.59)	0.54
Propensity score matched analysis[e]	32	113	565	37	113	577	—	—	0.88 (0.54, 1.42)	0.6	1.13 (0.62, 2.07)	0.68
User *vs* non-user 1 year before diagnosis[f]	35	109	540	1397	4311	23,752	1.04 (0. 75, 1.50)	0.81	1.08 (0.77, 1.52)	0.65	1.35 (0.90, 2.02)	0.14

[a]Medication use modelled as a time varying covariate with an individual considered a non-user before 6 months after first medication usage (or 12th prescription) and user after this time, excluding deaths in the year after cancer diagnosis.

[b]Adjusted for year of diagnosis, age at diagnosis, sex , site (colon/rectum for colorectal cancer) , surgery within 6 months, chemotherapy within 6 months, radiotherapy within 6 months, pre-diagnostic comorbidities (including myocardial infarction, cerebrovascular disease, congestive heart disease, chronic pulmonary disease, peripheral vascular disease, peptic ulcer disease, diabetes, renal disease and rheumatoid arthritis) pre-diagnostic smoking (missing category included), low-dose aspirin use, statin use, ACE inhibitor use, β-blocker use and NSAID use (all in the exposure period).

[c]Cohort restricted to those with available stage and grade information and analysis additionally adjusted for stage and grade.

[d]Analysis restricted to non-users in the year before diagnosis, restricted to individuals with at least 1 year of records before colorectal cancer diagnosis.

[e]Propensity score calculated using logistic regression with bisphosphonate use as the outcome and the following exposure variables: low-dose aspirin use, statin use, ACE inhibitor use, β-blocker use, NSAID use (in first year after diagnosis), age, year, gender, surgery, radiotherapy, chemotherapy, cancer site (colon or rectum), comorbidities (before diagnosis, including cerebrovascular disease, chronic pulmonary disease, congestive heart disease, diabetes, myocardial infarction, peptic ulcer disease, peripheral vascular disease and renal disease) and smoking before diagnosis. Fully adjusted estimate model also includes stage and grade.

[f]On the basis ofone or more prescription in the year before cancer diagnosis, restricted to individuals with at least 1 year of records before a cancer diagnosis, does not exclude deaths in the first year after diagnosis. Adjusted analysis includes all variables used in footnote a with the exception of other medication usage that are adjusted for in the year before diagnosis.

RESULTS

The final cohort consisted of 4791 CRC patients with 1576 CRC-specific deaths. The average follow-up was 3.3 years with a range in follow-up from 1 to 12.9 years. Bisphosphonate users were more likely to be female, to have colon cancer, be older at diagnosis, to be non-drinkers and to have certain comorbidities including chronic obstructive pulmonary disease, congestive heart disease and rheumatological disease (Table 1). In addition, bisphosphonate users were less likely to undergo radiotherapy or chemotherapy compared with non-users and less likely to be current smokers or have a high BMI. Patients using bisphosphonates were also more likely to present with lower-stage disease and were more likely to take other medications (including statins, low-dose aspirin, ACE inhibitors, NSAIDs and β-blockers).

Post-diagnostic bisphosphonate use and colorectal cancer-specific mortality. There was no evidence of an association between CRC-specific death and post-diagnostic bisphosphonate use before (HR = 0.94; 95% CI 0.73, 1.22) or after adjustment for potential confounders (fully adjusted HR = 1.11 95%; CI 0.80, 1.54) (Table 2). There was no evidence of a dose–response relationship in users of >12 prescriptions (adjusted HR = 1.16 95%; CI 0.72, 1.88) or those $\geqslant 365$ DDDs (adjusted HR = 1.09 95%; CI 0.67, 1.77). The observed association remained similar in users of nitrogen-containing bisphosphonates and was slightly attenuated in those using alendronate (adjusted HR = 1.25 95%; CI 0.85, 1.84).

Sensitivity analyses. In most subgroup and sensitivity analyses the observed associations were similar (Table 2). In particular, associations with CRC-specific mortality were similar when propensity score matched analyses were conducted on all confounders (HR = 1.13 95%; CI 0.62, 2.07). Use of bisphosphonates in the year before diagnosis gave a more marked estimate (adjusted HR = 1.35; 95% CI 0.90, 2.02).

DISCUSSION

This study of a large population-based CRC cohort, found no association between post-diagnostic bisphosphonate use and CRC-specific mortality.

No studies have investigated bisphosphonate use and survival in a cohort of CRC patients. Although previous studies have reported reductions in CRC risk among bisphosphonate users (Yang *et al*, 2013), these protective associations do not appear to translate to CRC survival. However, a study of post-menopausal women reported that users of alendronate had a reduced risk of dying from colon cancer (adjusted HR = 0.62 95%; CI 0.52, 0.72) (Pazianas *et al*, 2012), but as this cohort was not restricted to colon cancer patients this estimate is likely to largely reflect incidence rather than survival. The authors also reported that alendronate users who developed colon cancer had reduced all-cause mortality compared with alendronate non-users who developed colon cancer (adjusted HR = 0.82; 95% CI 0.70, 0.97). However, this estimate will have been influenced by non-cancer mortality and this estimate is based upon alendronate use determined years before colon cancer diagnosis (potentially up to 10 years).

Our study utilised a large cohort of CRC patients and linkage with NCDR and ONS data allowed robust verification of cancer diagnosis and death data, respectively. Using GP prescribing data should capture almost all usage as bisphosphonates are not available over the counter in the UK as well as eliminating any recall bias that exists in questionnaire-based studies and allowing temporal relationships to be investigated. Although consumption cannot be guaranteed, similar findings were observed when assessing increasing number of prescriptions and DDDs, thus reducing the likelihood that compliance is affecting our results. It is possible however, that bias due to misclassification of cancer-specific death could occur. Although we adjusted for important confounders such as sex, stage and treatment, the possibility of residual confounding remains as we were unable to adjust for other confounders such as socioeconomic status. Although bone metastasis is an indication for intravenous bisphosphonates use in the UK (Joint Formulary Committee, 2014), this seems unlikely to bias our results because we investigated only oral bisphosphonates and bone metastases is rare in CRC cancer patients (Roth *et al*, 2009). Additionally, bisphosphonate users had lower stage at presentation and analysis of bisphosphonate use before diagnosis revealed similar results.

In conclusion, this large population-based study of CRC patients found no association between bisphosphonate use and CRC-specific mortality. Our findings do not support preclinical evidence suggesting bisphosphonates may protect against visceral metastases (Neville-Webbe *et al*, 2002).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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