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.

Bisphophonates, 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 bisphophonates may influence cancer survival. Trials of bisphophonates 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 bisphophonates 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 NCADR 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 (Lèvesque 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. NCADR 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 treatment. Smoking, alcohol consumption and body mass index reflect end of life treatment. Smoking, alcohol consumption and body mass index were determined from GP records before CRC treatment. Smoking, alcohol consumption and body mass index were determined from GP records before CRC treatment.

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 to calculate hazard ratios (HRs) for cancer-specific deaths and 95% confidence intervals (CIs) for bisphosphonate users. Analyses were also conducted adjusting for potential confounders. Analyses were also conducted adjusting for potential confounders.

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)                | 1647 (41.6)                  |         |
| **Year of CRC**|                           |                               |         |
| 1998–2000      | 72 (20.8)                 | 980 (22.1)                   |         |
| 2001–2003      | 123 (35.6)                | 1532 (34.5)                  |         |
| 2004–2006      | 151 (43.6)                | 1933 (43.5)                  |         |
| **Age at CRC diagnosis (years)** | | | |
| 60–69          | 2 (0.6)                   | 59 (1.3)                     |         |
| 60–69          | 2 (0.6)                   | 220 (5.0)                    |         |
| 60–69          | 39 (5.5)                  | 707 (15.9)                   | <0.001  |
| 60–69          | 12 (17.9)                 | 1224 (27.5)                  |         |
| 60–69          | 165 (47.7)                | 1460 (32.9)                  |         |
| 60–69          | 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)                | 2524 (57.2)                  | 0.01    |
| Rectum (including rectosigmoid junction) | 124 (35.7) | 1903 (42.8) |         |
| **Stages**     |                           |                               |         |
| 1              | 55 (15.7)                 | 498 (11.2)                   | <0.001  |
| 2              | 125 (36.1)                | 1298 (29.2)                  |         |
| 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)                  | 278 (6.7)                    | 0.3     |
| Moderately     | 240 (69.4)                | 2908 (65.4)                  |         |
| 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)                  | 0.05    |
| Former smoker  | 102 (29.5)                | 1135 (25.5)                  |         |
| 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)                   | 0.002   |
| Alcohol consumer | 211 (61.0) | 2781 (62.6) |         |
| Unknown        | 80 (23.1)                 | 1214 (27.4)                  |         |
| **BMI (kg m−2) before CRC** | | | |
| Underweight (<18.5) | 12 (3.5) | 54 (1.2) | <0.001  |
| 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 drug.
| Medication usage after diagnosis | User | Non-user |
|---------------------------------|------|---------|
| Cancer-specific mortality       | All patients | Person years | All patients | Person years | All patients |
| Bisphosphonate user vs non-user | 60   | 346     | 1145         | 1516         | 4445         | 20,423       | 0.94 (0.73, 1.22) | 0.65 |
| 1–12 prescriptions              | 37   | 145     | 563          | 1516         | 4445         | 20,423       | 0.98 (0.71, 1.36) | 0.91 |
| >12 prescriptions               | 23   | 201     | 582          | —            | —            | —            | 0.88 (0.58, 1.34) | 0.56 |
| 1 to 365 DDDs                   | 37   | 144     | 536          | 1516         | 4445         | 20,423       | 1.04 (0.75, 1.44) | 0.83 |
| ≥365 DDDs                      | 23   | 202     | 610          | —            | —            | —            | 0.82 (0.54, 1.24) | 0.35 |
| Nitrogen-containing bisphosphonate user vs non-user | 54   | 322     | 1019         | 1522         | 4469         | 20,549       | 0.98 (0.74, 1.28) | 0.87 |
| Alendronate user vs non-user    | 44   | 273     | 837          | 1532         | 4518         | 20,731       | 1.02 (0.76, 1.38) | 0.92 |

**Subgroup analysis**

| Colon cancer | 36   | 222     | 761          | 828          | 2542         | 11,758       | 0.92 (0.66, 1.29) | 0.64 |
| Rectal cancer (including rectosigmoid junction) | 24   | 124     | 384          | 688          | 1903         | 8665         | 1.02 (0.68, 1.53) | 0.94 |
| Female ≥ 60 years old             | 42   | 246     | 854          | 477          | 1,413        | 6622         | 0.94 (0.68, 1.29) | 0.7 |
| Stages 1 and 2                   | 23   | 180     | 630          | 321          | 1,796        | 10,038       | 1.29 (0.84, 1.97) | 0.24 |
| Stages 3 and 4                   | 19   | 82      | 233          | 727          | 1,539        | 5,900        | 0.88 (0.56, 1.39) | 0.58 |
| Prediagnostic non-users<sup>d</sup> | 27   | 234     | 729          | 1,370        | 4,077        | 18,713       | 0.80 (0.55, 1.18) | 0.26 |

**Sensitivity analysis**

| Increasing lag to 1 year | 49   | 312     | 1012         | 1,527        | 4,479        | 20,556       | 0.92 (0.69, 1.22) | 0.55 |
| Propensity score matched analysis<sup>f</sup> | 32   | 113     | 565          | 37           | 113          | 577          | 0.97 (0.72, 1.31) | 0.86 |
| User vs non-user 1 year before diagnosis<sup>f</sup> | 35   | 109     | 540          | 1,397        | 4,311        | 23,752       | 1.04 (0.75, 1.43) | 0.81 |

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<sup>a</sup>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.

<sup>b</sup>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).

<sup>c</sup>Cohort restricted to those with available stage and grade information and analysis additionally adjusted for stage and grade.

<sup>d</sup>Analysis restricted to non-users in the year before diagnosis, restricted to individuals with at least 1 year of records before colorectal cancer diagnosis.

<sup>e</sup>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.

<sup>f</sup>On the basis of one 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.
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 ≥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).

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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