BMJ

RESEARCH

Oral bisphosphonates and risk of cancer of oesophagus, stomach, and colorectum: case-control analysis within a UK primary care cohort

Jane Green, clinical epidemiologist,[1] Gabriela Czanner, statistician,[1] Gillian Reeves, statistical epidemiologist,[1] Joanna Watson, epidemiologist,[1] Lesley Wise, manager, Pharmacoepidemiology Research and Intelligence Unit,[2] Valerie Beral, professor of cancer epidemiology[1]

[1]Cancer Epidemiology Unit, University of Oxford, Oxford OX3 7LF

[2]Medicines and Healthcare products Regulatory Agency, Pharmacoepidemiology Research Unit, London SW8 5NQ

Correspondence to: J Green
jane.green@ceu.ox.ac.uk

Cite this as: *BMJ* 2010;341:c4444
doi:10.1136/bmj.c4444

ABSTRACT

Objective To examine the hypothesis that risk of oesophageal, but not of gastric or colorectal, cancer is increased in users of oral bisphosphonates.

Design Nested case-control analysis within a primary care cohort of about 6 million people in the UK, with prospectively recorded information on prescribing of bisphosphonates.

Setting UK General Practice Research Database cohort.

Participants Men and women aged 40 years or over—2954 with oesophageal cancer, 2018 with gastric cancer, and 10 641 with colorectal cancer, diagnosed in 1995-2005; five controls per case matched for age, sex, general practice, and observation time.

Main outcome measures Relative risks for incident invasive cancers of the oesophagus, stomach, and colorectum, adjusted for smoking, alcohol, and body mass index.

Results The incidence of oesophageal cancer was increased in people with one or more previous prescriptions for oral bisphosphonates compared with those with no such prescriptions (relative risk 1.30, 95% confidence interval 1.02 to1.66; P=0.02). Risk of oesophageal cancer was significantly higher for 10 or more prescriptions (1.93, 1.37 to 2.70) than for one to nine prescriptions (0.93, 0.66 to 1.31) (P for heterogeneity=0.002), and for use for over 3 years (on average, about 5 years: relative risk *v* no prescription, 2.24, 1.47 to 3.43). Risk of oesophageal cancer did not differ significantly by bisphosphonate type, and risk in those with 10 or more bisphosphonate prescriptions did not vary by age, sex, smoking, alcohol intake, or body mass index; by diagnosis of osteoporosis, fracture, or upper gastrointestinal disease; or by prescription of acid suppressants, non-steroidal anti-inflammatory drugs, or corticosteroids. Cancers of the stomach and colorectum were not associated with prescription of bisphosphonate: relative risks for one or more versus no prescriptions were 0.87 (0.64 to 1.19) and 0.87 (0.77 to 1.00). The specificity of the association for oesophageal cancer argues against methodological problems in the selection of cases and controls or in the analysis.

Conclusions The risk of oesophageal cancer increased with 10 or more prescriptions for oral bisphosphonates and with prescriptions over about a five year period. In Europe and North America, the incidence of oesophageal cancer at age 60-79 is typically 1 per 1000 population over five years, and this is estimated to increase to about 2 per 1000 with five years' use of oral bisphosphonates.

INTRODUCTION

Adverse gastrointestinal effects are common among people who take oral bisphosphonates for the prevention and treatment of osteoporosis; they range from dyspepsia, nausea, and abdominal pain to erosive oesophagitis and oesophageal ulcers.[1] Recent case reports have suggested a possible increase in the risk of oesophageal cancer with use of such bisphosphonate preparations.[2] We report here on the relation between prospectively recorded prescribing information for oral bisphosphonates and the subsequent incidence of cancers of the oesophagus, stomach, and colorectum, using data from the UK General Practice Research Database cohort.

METHODS

The General Practice Research Database is a computerised database containing anonymised patient records for about 6 million people in the United Kingdom registered with a National Health Service primary care physician (general practitioner).[3] Every prescription issued by the general practitioner, all consultations with the general practitioner, test results and diagnoses from primary and secondary care, referrals to outpatient clinics, hospital admissions, and deaths are coded by the general practitioner and entered into the database, as are basic demographic data and certain lifestyle data. General Practice Research Database prescription data have been shown to be virtually complete, and the data on incidence of cancer (based on hospital records) are around 95% valid and complete.[4 5] Individual patients are recorded as entering the General Practice Research Database when they are registered with a participating general practice and

leave the database when they move to a non-participating general practice, leave the NHS (for example, through emigration), or die. The database thus consists of longitudinal medical records in which patients' length of follow-up is the time between entering and leaving the database.

We did a nested case-control study of gastrointestinal cancer in the General Practice Research Database. We defined cases as men and women aged at least 40 years with a diagnosis of incident invasive cancer of the oesophagus (ICD-10 code C15), stomach (C16), or colorectum (C18-20) recorded between 1995 and 2005 and with at least 12 months of follow-up within the General Practice Research Database before the date of diagnosis. For each case, we selected five controls with no record of gastrointestinal cancer before the index date (defined as the date of diagnosis of the case) matched on age at index date (to within 2 years), sex, participating general practice, and observation period in the database. The observation period for this study was, for both cases and their matched controls, the period between the date of entry of the case into the General Practice Research Database and the date of diagnosis (that is, patients were eligible as controls only if their follow-up time in the database included the observation period of their matched case, and for the analyses we set the observation period of the controls to match that of the cases exactly). We defined patients as exposed to bisphosphonates if they had a record within the observation period of at least one prescription for any oral bisphosphonate preparation that is licensed in the UK for use in osteoporosis (*British National Formulary* section 6.6.2). We excluded patients with prescriptions for bisphosphonates licensed to treat Paget's disease or bone metastases. We estimated duration of use of bisphosphonates as the time between the first prescription and last prescription within the observation period.

We used conditional logistic regression to calculate relative risks and 95% confidence intervals for oesophageal, stomach, and colorectal cancer in relation to prescription of oral bisphosphonates. We used the Stata computing package (release 10.1) for all analyses. We adjusted the main analyses for smoking status (latest record before index date: never, past, current, missing), alcohol intake (latest record before index date: non-drinker, drinker, missing), and body mass index (latest record at least two years before index date: <25, 25-30, ≥30, missing). We assigned missing values for the confounding variables to a separate category.

We did three sensitivity analyses: defining bisphosphonate exposure as two or more prescriptions; restricting analyses to patients with complete data on smoking, alcohol, and body mass index (complete case analysis); and restricting data on bisphosphonate prescription, smoking, and alcohol use to that recorded more than one year before the index date. The results of sensitivity analyses, including the complete case analysis, suggested that use of a multiple imputation method for dealing with missing data was not necessary in this dataset and may in any case not be appropriate, given the association between bisphosphonate use and the extent of missing data on potential confounding variables.

We also did analyses of the risk of cancer associated with prescription of bisphosphonates within groups defined by various factors that may be related to prescription of bisphosphonates and to risk of gastrointestinal cancer. In addition to age at diagnosis, sex, smoking status, alcohol drinking, and body mass index, these included diagnosis of osteoporosis or osteopenia within the observation period (yes or no); diagnosis of fracture (any site) recorded before the first bisphosphonate prescription (yes or no: analysis restricted to those with at least 12 months' observation before the first bisphosphonate prescription); diagnosis of upper gastrointestinal disease (including oesophagitis, gastro-oesophageal reflux disease, hiatus hernia, oesophageal ulcers, Barrett's oesophagus, gastritis, duodenitis, peptic ulcers, and dyspepsia) recorded before the first bisphosphonate prescription (yes or no: analysis restricted to those with at least 12 months' observation before the first bisphosphonate prescription); and prescription of non-steroidal anti-inflammatory drugs (*British National Formulary* section 10.1.1, including aspirin), corticosteroids (sections 6.3.2 and 10.1.2), or acid suppressant drugs (including H_2 receptor agonists, section 1.3.1, and proton pump inhibitors, section 1.3.5) (yes or no; either at any time during the observation period or before the first bisphosphonate prescription).

We calculated estimates of the absolute risk of oesophageal cancer in bisphosphonate users from the relative risks obtained here, applied to incidences of oesophageal cancer typical for men and women aged 60-79 years in Europe and North America.[6]

RESULTS

The nested case-control study included 2954 men and women with cancer of the oesophagus, 2018 with stomach cancer, 10 641 with colorectal cancer, and a total of 77 750 matched controls. The mean observation period was (by design) identical for cases and their matched controls and was 7.5 years, on average. Table 1 shows the characteristics of cases and controls for the three cancer sites. Overall, cases had a mean age at diagnosis of 72 (SD 11) years, and 6744 (43%) were female. Oesophageal and gastric cancer cases were more likely to be smokers than were their matched controls, whereas smoking status was similar for colorectal cases and controls.

About 3% of the study population (415 cases and 2170 controls) had at least one prescription for an oral bisphosphonate during the observation period. Among the controls, those prescribed bisphosphonates were, as expected, older (44% (952/2170) of those prescribed bisphosphonates were aged over 80, compared with 26% (19 419/75 580) of those not prescribed bisphosphonates) and more likely to be female (80% (1732/2170) of those prescribed bisphosphonates compared with 42% (31 885/75 580) of those not prescribed bisphosphonates). Differences in the

Table 1 | Characteristics of gastrointestinal cancer cases and controls*. Values are numbers (percentages) unless stated otherwise

Characteristics	Oesophageal cancer		Gastric cancer		Colorectal cancer	
	Cases (n=2954)	Controls (n=14 721)	Cases (n=2018)	Controls (n=10 007)	Cases (n=10 641)	Controls (n=53 022)
Mean years of observation	7.7	7.7	7.5	7.5	7.5	7.5
Female sex	1074 (36)	5345 (36)	770 (38)	3822 (38)	4900 (46)	24 450 (46)
Age (years) at index date:						
40-59	489 (17)	2446 (17)	194 (10)	965 (10)	1764 (17)	8820 (17)
60-79	1706 (58)	8523 (58)	1163 (58)	5818 (58)	6162 (58)	30 807 (58)
≥80	759 (25)	3752 (25)	661 (33)	3224 (32)	2715 (26)	13 395 (25)
Smoking status:						
Never	1208 (41)	7164 (49)	897 (44)	4937 (49)	5356 (50)	26 825 (51)
Past	680 (23)	2970 (20)	494 (25)	1958 (20)	2409 (23)	10 464 (20)
Current	729 (25)	2405 (16)	396 (20)	1544 (15)	1665 (16)	8123 (15)
Missing	337 (11)	2182 (15)	231 (11)	1568 (16)	1211 (11)	7610 (14)
Alcohol intake:						
Non-drinker	466 (16)	2256 (15)	389 (19)	1664 (17)	1649 (15)	8277 (16)
Drinker	1893 (64)	8909 (61)	1206 (60)	5777 (58)	6777 (64)	31 958 (60)
Missing	595 (20)	3556 (24)	423 (21)	2556 (26)	2215 (21)	12 757 (24)
Body mass index (kg/m^2):						
<25.0	811 (27)	3883 (26)	548 (27)	2631 (26)	2840 (27)	14 573 (27)
25.0-29.9	864 (29)	4459 (30)	567 (28)	2873 (29)	3203 (30)	15 694 (30)
≥30.0	403 (14)	1906 (13)	258 (13)	1203 (12)	1472 (14)	6808 (13)
Missing	876 (30)	4473 (30)	645 (32)	3300 (33)	3126 (29)	15 947 (30)
Prescribed oral bisphosphonate	90 (3.0)	345 (2.3)	49 (2.4)	270 (2.7)	276 (2.6)	1555 (2.9)

*Five controls matched to each case by age at diagnosis of case (index date) to within 2 years, sex, general practice, and observation period in General Practice Research Database.

age and sex composition of the cases, and so of their matched controls, account for the small differences in the proportion of controls for each cancer site prescribed bisphosphonates. Before 2000, the most commonly prescribed bisphosphonate in both women and men was etidronate. However, use of etidronate declined markedly after the introduction of a weekly formulation of alendronate in 2000, and by 2005 the weekly formulations of alendronate and risedronate accounted for almost all prescriptions.

Table 2 shows details of bisphosphonate prescribing in cases and controls. Those with at least one prescription for oral bisphosphonates had a significantly increased risk of cancer of the oesophagus (adjusted relative risk for one or more prescriptions *v* no such prescription 1.30, 95% confidence interval 1.02 to 1.66; P=0.02) but not of cancer of the stomach (relative risk 0.87, 0.64 to 1.19) or colorectum (0.87, 0.77 to 1.00). The risk of oesophageal cancer was significantly higher in people with 10 or more prescriptions for bisphosphonate than in those with one to nine prescriptions (mean number of prescriptions in cases 21.6 *v* 3.6; relative risks 1.93, 1.37 to 2.70 *v* 0.93, 0.66 to 1.31; P for heterogeneity by number of prescriptions=0.002). Estimated duration of use of bisphosphonates was similarly related to risk of oesophageal cancer: for use for less than one year, one to three years and more than three years versus no prescriptions, the relative risks were 0.98 (0.66 to 1.46), 1.12 (0.73 to 1.73), and 2.24 (1.47 to 3.43). The mean duration of use in cases with more than three years of use was 4.6 years. For the large majority of oesophageal cancer cases and their controls with bisphosphonate prescriptions, the first prescription within the follow-up period was at least 12 months after the start of follow-up (75/90 (83%) cases; 290/345 (84%) controls). In these patients, the relation between prescription of bisphosphonate and risk of cancer was similar to the overall findings (relative risk for any *v* no prescription 1.28, 0.98 to 1.67; for ≥10 *v* no prescriptions 2.01, 1.37 to 2.94; for more than three years' duration v no prescription 2.48, 1.54 to 3.98). Most people prescribed bisphosphonates had their last prescription less than a year before their index date; the study had insufficient power to assess the separate effects of duration of use and time since last use of bisphosphonates.

Table 2 shows relative risks adjusted for smoking, alcohol, and body mass index. Unadjusted and adjusted relative risks are given in web table A, which shows that the effect of adjustment for these factors was minimal. The bisphosphonate related risks were also similar when we restricted analyses to the 1883 people who died during the year after being diagnosed with oesophageal cancer (relative risk for 1-9 *v* no prescriptions 0.87, 0.56 to 1.34; for ≥10 *v* no prescriptions 2.29, 1.51 to 3.47; for more than three years of use *v* no prescription 2.23, 1.26 to 3.95).

Risk of oesophageal cancer did not vary significantly by type of bisphosphonate prescribed. Compared with people with no prescriptions for bisphosphonates, the

Table 2 | Relative risks (RRs) and 95% confidence intervals (CIs) for incident gastrointestinal cancer at specified sites, in relation to prescription of oral bisphosphonates

	Oesophagus			Stomach			Colorectum		
Oral bisphosphonates	Prescriptions*	Cases/ controls	RR† (95% CI)	Prescriptions*	Cases/ controls	RR† (95% CI)	Prescriptions*	Cases/ controls	RR† (95% CI)
Not prescribed	NA	2864/14 376	1.00	NA	1969/9737	1.00	NA	10 365/51 467	1.00
Prescribed	13.6/2.4	90/345	1.30 (1.02 to 1.66)	8.9/1.4	49/270	0.87 (0.64 to 1.19)	11.0/1.9	276/1555	0.87 (0.77 to 1.00)
No of prescriptions:									
1-9	3.6/1.0	40/214	0.93 (0.66 to 1.31)	3.0/0.4	28/160	0.84 (0.56 to 1.27)	3.8/0.8	164/880	0.92 (0.77 to 1.09)
≥10	21.6/3.5	50/131	1.93 (1.37 to 2.70)	16.6/2.8	21/110	0.91 (0.57 to 1.47)	21.6/3.7	112/675	0.82 (0.67 to 1.00)
Estimated duration of use‡:									
≤1 year	4.9/0.3	31/155	0.98 (0.66 to 1.46)	3.5/0.3	26/123	1.03 (0.67 to 1.59)	3.3/0.3	120/647	0.91 (0.75 to 1.11)
1-3 years	13.0/2.0	26/114	1.12 (0.73 to 1.73)	11.9/1.8	16/86	0.89 (0.52 to 1.53)	11.6/1.8	91/544	0.83 (0.66 to 1.04)
≥3 years	22.2/4.6	33/76	2.24 (1.47 to 3.43)	21.6/4.9	7/61	0.54 (0.24 to 1.18)	24.3/5.1	65/364	0.88 (0.67 to 1.15)

NA=not applicable.
*Prescriptions of bisphosphonates in cases; reported as mean number/mean years.
†All relative risks adjusted for smoking status, alcohol intake, and body mass index.
‡Time between first and last prescription.

relative risks were 1.38 (1.02 to 1.88) for any prescription for etidronate (57 exposed cases), 1.28 (0.88 to 1.86) for any prescription for alendronate (37 exposed cases), and 1.67 (0.94 to 2.95) for any prescription for risedronate (17 exposed cases) (P for heterogeneity by type=0.7). Numbers were too small to allow comparison between daily and weekly preparations of alendronate or risedronate.

Bisphosphonate associated risk also did not vary materially between groups of patients categorised by age, sex, smoking status, alcohol intake, or body mass index; by diagnosis of osteoporosis/osteopenia; or by diagnosis of fracture or of upper gastrointestinal disease before prescription of bisphosphonate (figure). The risk was also similar within groups defined by prescription of acid suppressant drugs, non-steroidal anti-inflammatory drugs, or corticosteroids, either at any time during the observation period (as shown in the figure) or before the first bisphosphonate prescription (data not shown). We found no material differences between the results reported here and those from the three sensitivity analyses described in the Methods section (table 3). For the complete case analysis, unadjusted and adjusted relative risks were 1.08 (0.70 to 1.67) and 1.05 (0.68 to1.63) for one to nine versus no prescriptions, and 1.99 (1.32 to 3.01) and 1.88 (1.24 to 2.86) for 10 or more versus no prescriptions.

Information on histological type was available for only 20% (593/2954) of the oesophageal cancers. When we used these data, the adjusted relative risks for one or more bisphosphonate prescriptions versus no prescription were 2.02 (1.02 to 4.01) among 437 cases of adenocarcinoma and 2183 matched controls and 0.83 (0.36 to 1.93) among 156 cases of squamous cell carcinoma and 776 matched controls (P for heterogeneity by tumour histology=0.1).

DISCUSSION

In this large nested case-control study within a UK cohort with prospectively recorded information on prescribing of bisphosphonates, we found a significantly increased risk of oesophageal cancer in people with previous prescriptions for oral bisphosphonates. The increased risk was largely restricted to those with 10 or more prescriptions and with prescriptions spanning many years. For example, prescribing of bisphosphonates over a period of about five years was associated with a doubling of the risk of oesophageal cancer. The association did not vary materially within subgroups defined by age, sex, smoking status, alcohol drinking, or body mass index; diagnosis of osteoporosis, previous fracture, or previous upper gastrointestinal disease; or prescription of non-steroidal anti-inflammatory drugs, corticosteroids, or acid suppressant drugs. In contrast to the findings for oesophageal cancer, risks for cancer of the stomach and cancer of the colorectum were not significantly increased after prescription of bisphosphonates.

Strengths and limitations of study

This study has the advantage of large size, with nearly 3000 cases of oesophageal cancer, and of reliable and complete prospectively recorded data on all prescriptions. Participants with oesophageal cancer and their matched controls were observed for an average of almost eight years, and we had enough cases and controls with 10 or more bisphosphonate prescriptions to allow analysis by number of prescriptions and estimated duration of use. Data were available for most of the study participants on the main factors that have been associated with risk of oesophageal cancer, including smoking, alcohol intake, and body mass index. Adjustment for these minimised the scope for

Table 3 | Sensitivity analyses comparing relative risks for oesophageal cancer in relation to prescription of oral bisphosphonates, using varying criteria for definition of exposure and inclusion of adjustment variables

Sensitivity analyses	No of exposed cases of oesophageal cancer	Relative risk* (95% CI) 1-1-9 *v* 0 prescriptions	Relative risk* (95% CI) ≥10 *v* 0 prescriptions
Main analysis: bisphosphonate exposure defined as ≥1 prescription within observation period; missing data on adjustment variables assigned to separate category	90	0.93 (0.66 to 1.31)	1.93 (1.37 to 2.70)
Bisphosphonate exposure defined as ≥2 prescriptions	80	0.93 (0.63 to 1.39)	1.93 (1.37 to 2.70)
Restricted to those with full information on adjustment variables	68	1.05 (0.68 to 1.63)	1.88 (1.24 to 2.86)
All exposure and adjustment data recorded at least 12 months before index date, and restricted to those with full information on adjustment variables	52	1.09 (0.67 to 1.79)	2.00 (1.23 to 3.27)

*Adjusted for smoking status, alcohol intake, and body mass index.

confounding by known risk factors, and sensitivity analyses that excluded participants with missing data on any of the adjustment variables gave results virtually identical to those in the overall analysis. The General Practice Research Database is based on a representative sample (about 7%) of the UK population,[3] and the results of this study, which includes men and women across a wide age range and with varying backgrounds, should be generalisable to other populations.

Limitations of the study include the fact that the General Practice Research Database records prescriptions issued but not whether the drugs were used or whether the instructions on taking these drugs, designed to minimise the risk of oesophageal irritation, were followed.[7] Not everyone prescribed bisphosphonates will use them,[8] but this is less likely to be true among people with many prescriptions—for example, with 10 or more bisphosphonate prescriptions—or with prescriptions over many years. Furthermore, low compliance would result in underestimation of the risk associated with bisphosphonate use and should not produce spurious associations. We had no information on bisphosphonate prescriptions before a patient's entry into the database, but bisphosphonate associated risks were similar when analyses were restricted to those with their first bisphosphonate prescription at least a year after the start of their period of observation in the General Practice Research Database.

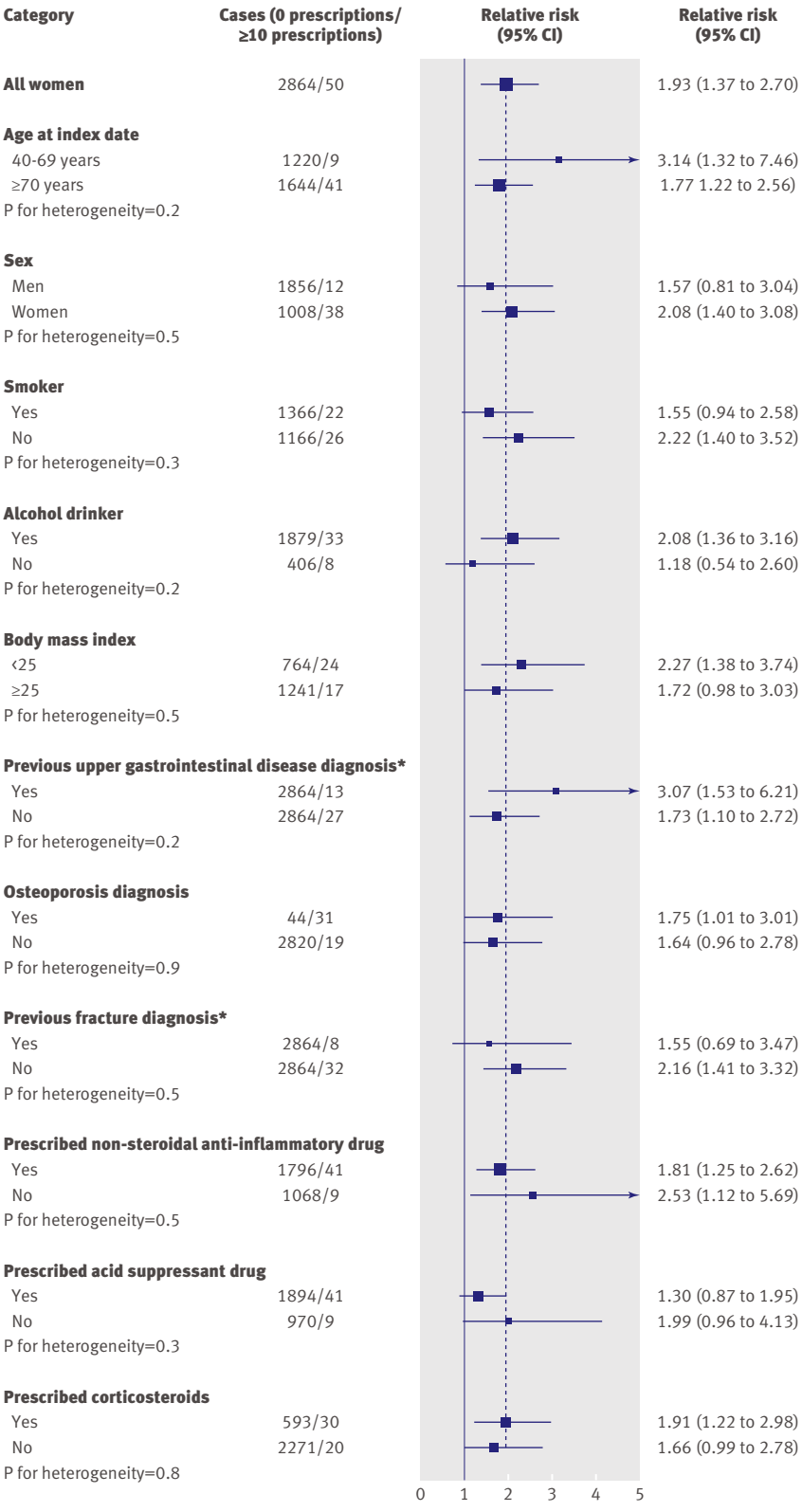
Data in the General Practice Research Database on incidence of cancer by site are reliable,[4] but information on tumour histology is incomplete. Oesophageal squamous cell carcinomas and adenocarcinomas differ with regard to some risk factors,[9] including the effect of alcohol and body mass index.[10 11] Although we found no significant difference in bisphosphonate associated relative risk by histological type, our analyses were limited by small numbers of exposed cases with relevant data.

We did our analyses to test the specific hypothesis that oral bisphosphonates increase the risk of oesophageal cancer. We included gastric and colorectal cancers in our analyses to compare the findings for these two other gastrointestinal cancers (for which no prior hypothesis existed) with those for oesophageal cancer. We used identical criteria to select cases and controls for the three cancers and did identical analyses for each. The specificity of the association for oesophageal cancer argues against methodological problems in the selection of cases and controls or in the analysis. As bisphosphonate users may be more likely to be investigated for upper gastrointestinal tract symptoms and thus be diagnosed as having early oesophageal cancer, we did an analysis restricted to people who died within a year of diagnosis of oesophageal cancer (as they are less likely to have had an early diagnosis), and the results were similar to those of the main analysis. Nor is the association likely to be due to a higher underlying risk of oesophageal cancer in people prescribed bisphosphonates; if anything, symptoms of oesophageal disease might be expected to result in the avoidance of bisphosphonates (and thus to an underestimation of risk). The effect of previous gastrointestinal disease on bisphosphonate prescribing is, however, probably more complex than this.[12] All the cases in this study were diagnosed several years before the publication of a possible link between bisphosphonates and oesophageal cancer, so the association cannot to be due to selective surveillance after publication of recent reports.

We found similar risks for oesophageal cancer associated with prescription of bisphosphonates in people with and without a recorded diagnosis of osteoporosis and in those with and without a fracture recorded before prescription of bisphosphonates. The risk also did not vary significantly within groups defined by previous upper gastrointestinal disease or by prescription of other drugs for which use may be related to risk of osteoporosis or gastrointestinal disease, including cancer, and to prescription of, as well as side effects from, oral bisphosphonates. We cannot rule out the possibility that the associations observed reflect other, unknown, factors that are linked to prolonged use of bisphosphonates and that also increase the risk of oesophageal cancer.

Comparison with other studies

In early 2009 the possibility of a link with oesophageal cancer was raised by a report of 54 adverse reaction case reports received by the US Food and Drug Administration from the United States, Europe, and Japan.[2] A causal association is plausible: upper gastrointestinal side effects, including oesophagitis, are clinically recognised with oral bisphosphonates,[1] and inflammation of the oesophagus is a risk factor for both squamous cell carcinoma and adenocarcinoma of the oesophagus. Two brief reports were published



Relative risks of incident oesophageal cancer in people with ≥10 prescriptions for oral bisphosphonates, compared with those with no prescriptions, by various factors. Relative risks adjusted for smoking status, alcohol intake, and body mass index, as appropriate. *Diagnosis before prescription of bisphosphonates: analyses restricted to those with ≥12 months' observation before first bisphosphonate prescription

as correspondence in response to the case reports' publication. Solomon and colleagues reported no significant difference in incidences of oesophageal cancer between people in a US Medicare health plan database prescribed bisphosphonates for osteoporosis and those prescribed other drugs for osteoporosis (incidence rate ratio 0.55, 95% confidence interval 0.06 to 4.72) or between bisphosphonate users and the general population (incidence rate ratio 1.12, 0.26 to 4.84).[13] The value of this study is difficult to assess, as the publication provided no information on numbers of exposed or unexposed cases or on details of the analysis. Abrahamsen and colleagues examined risk of incident upper gastrointestinal cancer in people with previous fracture identified from national registers in Denmark.[14] They found a reduced risk of oesophageal cancer in people with prescriptions for oral bisphosphonates, compared with those with no such prescriptions, over a mean of 2.8 years' follow-up (hazard ratio 0.35, 95% confidence interval 0.14 to 0.85, based on 37 cases). No data were available on long term exposure to bisphosphonates.[14] Similarly, no significant association between prescription of oral bisphosphonates and incidence of oesophageal adenocarcinoma was found in a recent US nested case-control study of patients with Barrett's oesophagus (relative risk 0.92, 95% confidence interval 0.21 to 4.15), but this study included only two exposed cases and lacked information on potential confounders.[15]

Between acceptance and publication of this paper, another report on oral bisphosphonates and risk of oesophageal cancer, also using data from the General Practice Research Database, was published.[16] Although that study, by Cardwell et al, and ours used the same database, with prospectively recorded information on prescribing of bisphosphonates, the observation time is nearly twice as long in our analysis as in Cardwell et al's analysis (on average 7.7 *v* 4.5 years). Our study thus had the potential to include people with longer durations of bisphosphonate use and also had greater statistical power, with five matched controls per case compared with equal numbers in the exposed and comparison groups in Cardwell et al's study.

In our study, the excess risk of oesophageal cancer was largely restricted to people with 10 or more bisphosphonate prescriptions and to those with prescriptions over more than three years. In Cardwell et al's report, people with greater than 1095 defined daily doses of bisphosphonates, which is broadly equivalent to more than three years of use, had an incidence of oesophageal cancer of 6.6 per 10 000 person years, based on only 15 cases; those with fewer defined daily doses had an incidence of 4.5 per 10 000 person years, giving an unadjusted relative risk for more than 1095 versus fewer defined daily doses of bisphosphonates of 1.46 (95% confidence interval 0.78 to 2.60). Cardwell et al report an unadjusted relative risk of 1.08 (0.52 to 2.23) in bisphosphonate users with more than 1095 defined daily doses compared with their matched controls. For both of these estimates the confidence intervals are wide, however, and the relative

WHAT IS ALREADY KNOWN ON THIS TOPIC

Case reports suggest an association between use of oral bisphosphonates for osteoporosis and increased risk of oesophageal cancer

The epidemiological evidence is limited, and no adequately large prospective study with information on potential confounding factors and long follow-up has been published

WHAT THIS STUDY ADDS

Within a large UK cohort, people with 10 or more prescriptions for oral bisphosphonates had an increased risk of oesophageal cancer but not of gastric or colorectal cancers

risks are not significantly different from our more stable estimate of 2.24 (1.47 to 3.43) for more than three years versus no prescriptions. Thus, as would be expected, when broadly equivalent exposures are compared, the results from our analyses and those of Cardwell et al do not differ significantly.

Conclusions and policy implications

Oral bisphosphonates are the recommended first line treatment for primary and secondary prevention of osteoporotic fracture in both men and women in Europe and in North America.[17-19] Osteoporosis is common, especially among postmenopausal women, and is associated with considerable morbidity and mortality. Prescribing of bisphosphonates is increasing; in the UK, for example, about 3% of women aged over 70 received a prescription for oral bisphosphonates in 2000, rising to 10% in 2005.[20] Evidence from randomised controlled trials suggests that the oral bisphosphonates most commonly prescribed in this study (alendronate, etidronate, and risedronate) reduce the risk of fracture in postmenopausal women at high risk of fracture,[21-23] but little evidence for such a benefit exists in women at low risk of fracture, in men,[24] or among those with more than four years' use. No randomised trial of bisphosphonates was large enough or continued for long enough to have detected a doubling of risk for oesophageal cancer. Concerns have been raised about other adverse effects of long term use of oral bisphosphonates; these include osteonecrosis of the jaw, severe musculoskeletal pain, atrial fibrillation, and bone micro-damage caused by long term suppression of bone turnover, leading to increased risk of atypical fracture.[25] Although bisphosphonate use has been reported to be associated with a reduced risk of breast cancer,[26] this association is unlikely to be causal as risk of breast cancer is known to be reduced in women with osteoporosis.[27]

Oesophageal cancer is not common in Western countries, but it has a high morbidity and is often fatal. On the basis of incidences for Europe and North America published by the World Health Organization in 2007,[6] a doubling of risk of oesophageal cancer associated with about five years' use of oral bisphosphonates would mean an estimated overall increase in incidence of oesophageal cancer in people aged 60-79 years from 1 case per 1000 population over five years in both sexes combined (in women 0.5 and in men 1.5 per 1000) in non-users to 2 cases per 1000 over five years (in women 1 case and in men 3 cases per 1000) in users.

If confirmed, an association between use of oral bisphosphonates and risk of oesophageal cancer would add to our knowledge of the risks and benefits of use of oral bisphosphonates. Treatment and prevention of osteoporotic fracture is a subject of increasing public health importance with large scale clinical and economic implications. Further research is warranted to confirm or refute our findings and in particular to examine the associations between use of different types and formulations of bisphosphonates and risk of the different histological types of oesophageal cancer.

We are grateful to patients and general practitioners participating in the General Practice Research Database and to General Practice Research Database staff for help and advice.

Contributors: All authors participated in the design of the study, the interpretation of the analysis, and the writing of the report. All authors have seen and approved the final version of the report. GC did the analyses. VB and JG are the guarantors.

Funding: The General Practice Research Database dataset for this study was obtained under the collaborative research licence funded by the Medical Research Council, and the study was approved by the Independent Scientific Advisory Committee of the General Practice Research Database (protocol number 06_090). Cancer Research UK provided further funding for the study. The funders had no role in study design, in the analysis and interpretation of data, in the writing of the report, or in the decision to submit the article for publication.

Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that they have no financial or non-financial interests that may be relevant to the submitted work.

Ethical approval: Not needed.

EData sharing:E No additional data available.

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Accepted: 23 June 2010