Exposure to Oral Bisphosphonates and Risk of Esophageal Cancer

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Context Use of oral bisphosphonates has increased dramatically in the United States and elsewhere. Esophagitis is a known adverse effect of bisphosphonate use, and recent reports suggest a link between bisphosphonate use and esophageal cancer, but this has not been robustly investigated.

Objective To investigate the association between bisphosphonate use and esophageal cancer.

Design, Setting, and Participants Data were extracted from the UK General Practice Research Database to compare the incidence of esophageal and gastric cancer in a cohort of patients treated with oral bisphosphonates between January 1996 and December 2006 with incidence in a control cohort. Cancers were identified from relevant Read/Oxford Medical Information System codes in the patient's clinical files. Cox proportional hazards modeling was used to calculate hazard ratios and 95% confidence intervals for risk of esophageal and gastric cancer in bisphosphonate users compared with nonusers, with adjustment for potential confounders.

Main Outcome Measure Hazard ratio for the risk of esophageal and gastric cancer in the bisphosphonate users compared with the bisphosphonate nonusers.

Results Mean follow-up time was 4.5 and 4.4 years in the bisphosphonate and control cohorts, respectively. Excluding patients with less than 6 months' follow-up, there were 41 826 members in each cohort (81% women; mean age, 70.0 (SD, 11.4) years). One hundred sixteen esophageal or gastric cancers (79 esophageal) occurred in the bisphosphonate cohort and 115 (72 esophageal) in the control cohort. The incidence of esophageal and gastric cancer combined was 0.7 per 1000 person-years of risk in both the bisphosphonate and control cohorts; the incidence of esophageal cancer alone in the bisphosphonate and control cohorts was 0.48 and 0.44 per 1000 person-years of risk, respectively. There was no difference in risk of esophageal and gastric cancer combined between the cohorts for any bisphosphonate use (adjusted hazard ratio, 0.96 [95% confidence interval, 0.74-1.25]) or risk of esophageal cancer only (adjusted hazard ratio, 1.07 [95% confidence interval, 0.77-1.49]). There also was no difference in risk of esophageal or gastric cancer by duration of bisphosphonate intake.

Conclusion Among patients in the UK General Practice Research Database, the use of oral bisphosphonates was not significantly associated with incident esophageal or gastric cancer.

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Bisphosphonates inhibit osteoclast-mediated bone resorption and are mainly used to prevent or treat osteoporosis, especially in postmenopausal women. Bisphosphonate use has increased dramatically in recent years in the United States and other Western populations,[1,2] and bisphosphonates are now commonly prescribed in elderly women; eg, in 2005, approximately 10% of UK women older than 70 years received a bisphosphonate prescription.[3]

Oral bisphosphonates are known to cause serious esophagitis in some users.[4,5] Crystalline material that resembles ground alendronate tablets has been found on biopsy in patients with bisphosphonate-related esophagitis, and follow-up endoscopies have shown that abnormalities remain after the esophagitis heals.[6] Reflux esophagitis is an established risk factor for esophageal cancer through the Barrett pathway.[7-9] It is not known whether bisphosphonate-related esophagitis can also increase esophageal cancer risk. However, the US Food and Drug Administration recently reported 23 cases of esophageal cancer (between 1995 and 2008) in patients using the bisphosphonate alendronate and a further 31 cases in patients using bisphosphonates in Europe and Japan,[10] possibly indicating risk of malignancy associated with bisphosphonate use.

See also Patient Page.

Large studies with appropriate comparison groups, adequate follow-up, robust characterization of bisphosphonate exposure, and information on relevant confounders are required to determine whether bisphosphonates increase esophageal cancer risk. We undertook such a study within the UK General Practice Research Database (GPRD).

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METHODS

The GPRD is the world's largest computerized database of anonymized longitudinal patient records and includes 500 general practices comprising approximately 6% of the UK population. Participating practices follow protocols to record and transfer data[11] and are assessed for completeness, continuity, and plausibility. Practices meeting predefined standards are registered as "up to standard." The information recorded includes demographic information, clinical diagnoses, referral and hospital discharge information, and details of all prescriptions issued. Read/Oxford Medical Information System codes are used to classify medical diagnoses.[12] The high quality of GPRD prescription and diagnosis information has been documented.[13] In a recent review of validation studies, the median proportion of GPRD cancer cases confirmed (by general practice record request, algorithm, or manual review) was 95%.[14] Ethical approval for all observational research using GPRD data has been obtained from a multicenter research ethics committee.

Study Population

We undertook a cohort study within up-to-standard practices of the GPRD. 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 from this initial cohort if they were younger than 40 years on their index date or if they had a cancer diagnosis (excluding nonmelanoma skin cancer) in the 3 years prior to their index date.

In sequential order (by date of first prescription for bisphosphonates), 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 control cohort who received bisphosphonates for treatment of cancer-related osteoporosis/metastasis, thereby artificially reducing the risk of cancer in the control cohort). Therefore, some control participants were members of the initial bisphosphonate cohort (with a later date of first bisphosphonate prescription than their match)—but once selected as control participants, they were excluded from the bisphosphonate cohort. A sensitivity analysis is presented excluding pairs of individuals in which the control was a bisphosphonate user.

The incidence of esophageal and gastric cancer was compared in the bisphosphonate and control cohorts prior to the date on which data were downloaded from each contributing general practice (more than 90% by August 1, 2008). Cancers were identified from relevant Read/Oxford Medical Information System codes in the patients' clinical files. All cancer codes recorded for potential esophageal and gastric cancer cases were examined by a physician epidemiologist (L.J.M.) blinded to whether the patient was in the bisphosphonate or control cohort. Only patients with consistently recorded codes for these cancers were accepted. The date of the first recorded esophageal or gastric cancer code was considered the diagnosis date. Participants with codes for Barrett esophagus and gastroesophageal reflux disease were also identified.

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). The DDD system is a validated measure of drug consumption maintained by the World Health Organization.[15] Defined daily dose is 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.

In the bisphosphonate cohort, the total number of DDDs of oral bisphosphonates received was divided by the number of days of follow-up and categorized by approximate tertiles into high, medium, and low use. The bisphosphonate cohort was also subdivided according to whether the first oral bisphosphonate received was a nitrogen-containing bisphosphonate (eg, alendronate, risedronate, and ibandronate), alendronate, or a non–nitrogen-containing bisphosphonate (eg, etidronate, tiludronate, and clodronate).

Data Extraction Relating to Potential Confounders

Data on smoking, alcohol consumption, and body mass index (BMI; opportunistically collected within the GPRD) in the 3-year period before the index date were extracted; where several records were available, that closest to the index date was used. Data on use of hormone therapy, nonsteroidal anti-inflammatory drugs, H_2 receptor antagonists, and proton pump inhibitors prior to the index date were also extracted.

Statistical Analysis

The expected number of esophageal and gastric cancers was determined 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.[16] A standardized incidence ratio (SIR) was then calculated and exact methods used to produce 95% confidence intervals (CIs).

The main survival analysis was conducted on the time from index date to the first esophageal or gastric cancer diagnosis. 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. Participants were censored at the first of the following outcomes: date of other cancer diagnosis, date of death, date of leaving general practice, or date of last data download from general practice by GPRD.

Kaplan-Meier curves were plotted to investigate survival in the 2 groups and

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to check the assumption of proportional hazards. The Cox proportional hazards model was used to calculate hazard ratios (HRs) and 95% CIs and to adjust for confounding variables. Confounders with missing data were included using a missing data category, and a complete case analysis was also conducted (not shown, because estimates were little altered).

To investigate dose response, separate analyses were conducted including only time after the bisphosphonate user had received specified numbers of DDDs (ie, 182, 365, 730, and 1095 DDDs, equivalent to a 6-month, 1-year, 2-year, and 3-year supply, respectively). In these analyses the start of follow-up for each bisphosphonate user and matched control was moved from the index date to the date at which the bisphosphonate user had received the specified number of DDDs. Similar analyses were conducted for nitrogen-containing bisphosphonates and alendronate. Because the control cohort may have included some bisphosphonate users, a reanalysis was conducted excluding pairs of individuals in which the control was a bisphosphonate user.

All analyses were conducted using Stata version 9.0 (StataCorp, College Station, Texas), and all analyses were performed at the 5% significance level.

Sample-Size Calculation

Prior to conducting the study, and using incidence rates from England in 2005,[16] we estimated there would be approximately 60 cases of esophageal cancer in the control cohort, allowing more than 80% power to detect a 60% increase in esophageal cancer incidence in the bisphosphonate cohort.[17]

RESULTS

Data were received from the GPRD for 46 036 oral bisphosphonate users and 46 036 matched controls. Three hundred fourteen cohort members had esophageal or gastric cancer codes recorded during follow-up. In 27 cases (8.6%), the codes were inconsistent and the diagnosis was not accepted, leaving a total of 287 diagnoses of incident esophageal or gastric cancer (0.34% of the combined cohorts; 181 esophageal cancers [92 in the control cohort] and 106 gastric cancers [57 in the control cohort]). Data on cancer histological subtypes were unavailable.

The SIRs of esophageal and gastric cancer in the control cohort were 1.18 (95% CI, 0.95-1.45) and 0.70 (95% CI, 0.53-0.91), respectively, showing underrecording of gastric cancer. The SIR for esophageal and gastric cancer combined was 0.94 (95% CI, 0.79-1.10). These SIRs suggest that tumors arising at the gastroesophageal junction or in the gastric cardia may have been classified as esophageal cancers rather than gastric cancers. Our principal analysis was therefore for gastric and esophageal cancers combined.

Of the bisphosphonate users, 41 826 had at least 6 months of follow-up, and further analyses were restricted to these patients and their matched controls. Eighty-one percent of both cohorts were women, and the mean age was 70.0 (SD, 11.4) years (TABLE 1). Mean follow-up was 4.5 (SD, 2.6) years and 4.4 (SD, 2.6) years in the bisphosphonate and control cohorts, respectively, and both had a maximum follow-up period of 12.9 years. All of the bisphosphonate cohort and 9% of the control cohort received at least 1 prescription for oral bisphosphonates during the follow-up period. The mean number of bisphosphonate DDDs prescribed per day in the bisphosphonate and con-

Table 1. Participant Characteristics in Bisphosphonate Cohort and Matched Control Cohort[a]

Characteristic	No. (%) Bisphosphonate (n = 41 826)	No. (%) Control (n = 41 826)
Age, mean (SD), y	70.0 (11.4)	70.0 (11.4)
Sex		
Men	7777 (19)	7777 (19)
Women	34 049 (81)	34 049 (81)
Any bisphosphonate prescription (during follow-up period)	41 826 (100)	3705 (9)
Bisphosphonate use, mean (SD), DDDs/d (during follow-up period)	0.59 (0.49)	0.03 (0.16)
Follow-up, mean (SD), y	4.5 (2.6)	4.4 (2.6)
BMI, mean (SD)[b]	25.5 (2.25)	27.1 (2.25)
Smoking		
Never	12 609 (30)	11 871 (28)
Former	6916 (17)	5689 (14)
Current	4328 (10)	3531 (8)
Missing	17 973 (43)	20 735 (50)
Alcohol		
Never	3619 (9)	3178 (8)
Former	534 (1)	369 (1)
Current	11 146 (27)	10 406 (25)
Missing	26 527 (63)	27 873 (67)
Prescribed therapy (ever, before index date)		
Hormone therapy	10 281 (25)	7774 (19)
NSAIDs	34 113 (82)	29 287 (70)
PPIs	12 961 (31)	8847 (21)
H_2 receptor antagonists	14 495 (35)	9098 (22)
Barrett esophagus diagnosis (ever, before index date)	198 (0.5)	145 (0.4)
GERD diagnosis (ever, before index date)	5016 (12)	3657 (9)

Abbreviations: BMI, body mass index; DDD, defined daily dose; GERD, gastroesophageal reflux disease; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor.
[a] Includes only individuals with more than 6 months' follow-up.
[b] Calculated as weight in kilograms divided by height in meters squared. Data were available for 20 199 patients (48.3%) in the bisphosphonate cohort and for 17 513 (41.9%) in the control cohort.

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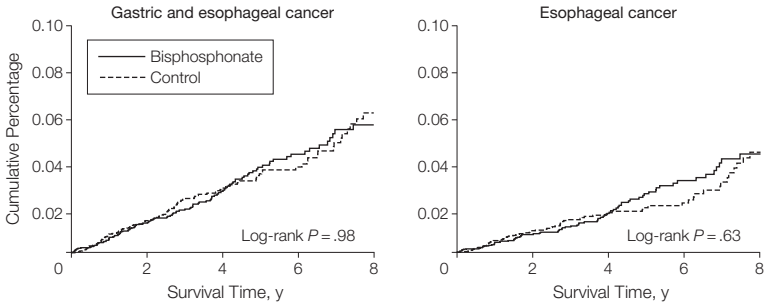
Figure. Kaplan-Meier Curves Comparing Time to Esophageal and Gastric Cancer Combined or Esophageal Cancer Alone in the Bisphosphonate and Control Cohorts



No. at risk

Control	41 826	31 119	17 317	7956	3493	41 826	31 119	17 317	7956	3493
Bisphosphonate	41 826	31 224	17 564	8288	3695	41 826	31 224	17 564	8288	3695

First 6 months of follow-up were removed for every participant, because cancer incidence during this period is unlikely to be attributable to bisphosphonate usage.

trol cohorts during this period was 0.59 (SD, 0.49) and 0.03 (SD, 0.16), respectively. Data on BMI were available for 48.3% of the bisphosphonate and 41.9% of the control cohort members: mean BMI was higher in the control cohort than the bisphosphonate cohort (27.1 vs 25.5, calculated as weight in kilograms divided by height in meters squared). There were only small differences in smoking and alcohol status between the cohorts. Ever use of hormone therapy, nonsteroidal anti-inflammatory drugs, H_2 receptor antagonists, and proton pump inhibitors before the index date was higher in the bisphosphonate cohort than in the control cohort.

Any Bisphosphonate Use

The FIGURE shows the cumulative incidences of esophageal and gastric cancers combined and esophageal cancers alone in the cohorts. There was no difference in combined esophageal and gastric cancer risk between the cohorts before or after adjustments for potential confounders (HR, 1.00 [95% CI, 0.77-1.29] and 0.96 [95% CI, 0.74-1.25], respectively) (TABLE 2). Similarly, there was no difference in esophageal cancer risk between the cohorts (adjusted HR, 1.07 [95% CI, 0.77-1.49]) (TABLE 3).

Tables 2 and 3 also show that after receipt of specified amounts of bisphosphonate DDDs there was no evidence of an increase in risk of esophageal and gastric cancer combined (or esophageal cancer alone). For instance, after receipt of 365 bisphosphonate DDDs (equivalent to a 1-year supply), the risk of esophageal and gastric cancer combined (or esophageal cancer alone) were similar in the bisphosphonate and control cohorts (unadjusted HR, 0.94 [95% CI, 0.64-1.39] and 0.88 [95% CI, 0.55-1.43], respectively). Table 3 also shows no increase in risk of esophageal and gastric cancer combined (or esophageal cancer alone) in the groups with higher use of bisphosphonates based on DDDs per day. There was no association between any bisphosphonate use and risk of these cancers when members of the control cohort who were prescribed bisphosphonates subsequent to the index date (and their matched bisphosphonate cohort member) were excluded from the analysis (adjusted HR, 0.92 [95% CI, 0.70-1.21] and 1.01 [95% CI, 0.72-1.42] for risk of esophageal and gastric cancer combined and esophageal cancer alone, respectively).

When, to maximize follow-up, we restricted the analysis to patients whose date of first receipt of bisphosphonates was before January 1, 2000 (and their matched controls), the adjusted HRs for risk of esophageal and gastric cancer combined and for risk of esophageal cancer alone were 1.19 (95% CI, 0.69-2.05) and 1.23 (95% CI, 0.66-2.30), respectively, for any bisphosphonate use. This analysis included 7082 members (17%) from each cohort; mean follow-up was 6.8 (SD, 3.7) years. Stratifying the analysis by sex revealed no evidence of an association in men or women between bisphosphonate use and risk of esophageal and gastric cancer combined (adjusted HR, 0.94 [95% CI, 0.69-1.30] in women and 1.01 [95% CI, 0.62-1.64] in men) or risk of esophageal cancer alone (adjusted HR, 1.02 [95% CI, 0.68-1.52] in women and 1.22 [95% CI, 0.68-2.20] in men).

Bisphosphonate Subtypes

Tables 2 and 3 show that there was no association between the risk of esophageal and gastric cancer combined or esophageal cancer alone and use of nitrogen-containing bisphosphonates (adjusted HRs, 0.91 and 0.96, respectively), alendronate (adjusted HRs, 0.79 and 0.77) or non–nitrogen-containing bisphosphonates (adjusted HRs, 1.04 and 1.25). Similarly, there was no evidence of an association with risk of these cancers after receiving more than 1 year (or 2 years) of prescriptions for either nitrogen-containing bisphosphonates or alendronate.

Cancer Risk and History of Gastroesophageal Reflux Disease or Barrett Esophagus

In the bisphosphonate and control cohorts, 5016 (12%) and 3657 (9%) patients, respectively, had gastroesophageal reflux disease (GERD) codes recorded prior to their index date (Table 1). The association between GERD and incidence of esophageal and gastric cancer combined, or esophageal cancer alone, did not differ between the bisphosphonate and control cohorts ($P = .74$ and $P = .99$, respectively, for interaction term). Specifically, GERD diagnosis was associated with a 49% increase in the incidence of esophageal and gastric cancer combined (HR, 1.49 [95% CI, 0.85-2.61]) in the bisphosphonate cohort and a 69% increase in the control co-

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hort (HR, 1.69 [95% CI, 1.06-2.71]), with similar increases in risk seen for esophageal cancer alone. In the bisphosphonate and control cohorts, 198 (0.47%) and 145 (0.35%) patients, respectively, had Barrett esophagus codes recorded prior to their index date (Table 1). Only 1 of these (in the control cohort) developed esophageal or gastric cancer.

COMMENT

In this study we found no difference in the incidence of esophageal and gastric cancer combined (or esophageal cancer alone) in a large cohort of mainly elderly women exposed to oral bisphosphonates compared with an age- and sex-matched unexposed population. There was no increase in the risk of these cancers in patients who had ever been prescribed bisphosphonates or in those who had been prescribed nitrogen-containing bisphosphonates, alendronate, or non–nitrogen-containing bisphosphonates. There was also no association with cancer risk by duration of use of these drugs. Incidence of esophageal and gastric cancer in patients with a history of GERD was not different in those exposed to bisphosphonates compared with those not exposed to these drugs.

Strengths of our study were its large size, substantial period of follow-up, and the use of recorded prescription data rather than self-reported drug use, which may misclassify exposure. Additionally, underestimation of bisphosphonate usage would seem unlikely, because these drugs cannot be obtained without prescription in the United Kingdom. However, based on the CIs of the HRs, a modest (<30%) increase in risk of esophageal and gastric cancer in bisphosphonate users cannot be excluded, and a modest protective effect (20%-25% decrease in risk) is also possible. Data from preclinical studies indicate that bisphosphonates, especially nitrogen-containing bisphosphonates, may affect tumor proliferation, invasion, and angiogenesis, potentially reducing cancer risk.[18-21]

Our findings agree with those of reports from the United States and Denmark that showed no increase in esophageal cancer risk in users of oral bisphosphonates.[22,23] The US study was based on data from the US Medicare

Table 2. Esophageal and Gastric Cancer Incidence in the Bisphosphonate and Matched Control Cohorts

	Bisphosphonate		Control		Risk			
					Unadjusted		Adjusted[a]	
Bisphosphonate Category	Cases	Person-Years	Cases	Person-Years	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Any bisphosphonate								
Prescribed	116	165 400	115	163 479	1.00 (0.77-1.29)	.98	0.96 (0.74-1.25)	.77
Incidence after cumulative prescriptions greater than (in DDDs)[b]								
183	75	104 678	75	104 104	1.00 (0.72-1.37)	.98	1.01 (0.73-1.40)	.96
365	50	73 364	53	73 171	0.94 (0.64-1.39)	.76	0.98 (0.66-1.45)	.90
730	28	40 326	29	40 491	0.97 (0.58-1.63)	.91	0.96 (0.56-1.63)	.87
1095	16	22 813	17	22 891	0.95 (0.48-1.87)	.88	0.90 (0.44-1.81)	.76
Total bisphosphonate intake during follow-up (in DDDs/d)[c]								
Low (0-<0.24)	48	62 922	45	63 648	1.08 (0.72-1.62)	.71	0.95 (0.63-1.45)	.83
Medium (≥0.24-<0.89)	35	58 161	36	55 334	0.93 (0.58-1.48)	.74	0.96 (0.59-1.54)	.86
High (≥0.89)	33	44 316	34	44 497	0.98 (0.60-1.58)	.92	0.96 (0.59-1.58)	.89
Nitrogen-containing bisphosphonates								
First prescribed	71	106 480	77	106 412	0.92 (0.67-1.27)	.63	0.91 (0.65-1.27)	.59
Incidence after cumulative prescriptions greater than (in DDDs)[b]								
365	48	70 251	51	69 935	0.94 (0.63-1.39)	.75	0.98 (0.65-1.47)	.92
730	27	39 022	29	39 187	0.94 (0.55-1.58)	.81	0.92 (0.54-1.58)	.77
Alendronate								
First prescribed	55	81 369	67	80 837	0.82 (0.57-1.17)	.27	0.79 (0.55-1.15)	.22
Incidence after cumulative prescriptions greater than (in DDDs)[b]								
365	34	52 308	45	51 741	0.75 (0.48-1.17)	.20	0.75 (0.48-1.19)	.23
730	22	28 898	28	28 904	0.79 (0.45-1.38)	.40	0.76 (0.43-1.35)	.35
Non–nitrogen-containing bisphosphonates								
First prescribed	45	58 920	38	57 068	1.14 (0.74-1.76)	.55	1.04 (0.67-1.62)	.87

Abbreviations: CI, confidence interval; DDD, defined daily dose; HR, hazard ratio.

[a] Adjusted for body mass index, alcohol, smoking, hormone therapy prescription (before index date), nonsteroidal anti-inflammatory drug prescription (before index date), Barrett esophagus diagnosis (before index date), gastroesophageal reflux disease diagnosis (before index date), H_2 receptor antagonist prescription (before index date), and proton pump inhibitor prescription (before index date).

[b] Person-years and cancer cases occurring after the date of specified bisphosphonate prescriptions received for each bisphosphonate cohort member and their matched control. Daily divided dose equivalents: 183 DDDs are equivalent to a 6-month supply; 365 DDDs to a 1-year supply; 730 DDDs to a 2-year supply; and 1095 DDDs to a 3-year supply.

[c] In bisphosphonate cohort (see "Methods" for details of selection of cohorts).

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program but contained few cases. Consequently, the CIs around the estimates were wide, so findings were consistent with either a 74% reduction or a 384% increase in esophageal cancer risk in bisphosphonate users.[22] A Danish report also demonstrated no increase in esophageal cancer risk in bisphosphonate users, but that study was based on only 37 cases of esophageal cancer with very short follow-up (median, 2 years) and included only a select group of individuals who had sustained fractures.[23] In addition, neither study adjusted for potential confounders or investigated bisphosphonates by type, dosage, or duration.

Our study also has several limitations. Because exposure was determined from recorded prescriptions, overestimation of usage is possible, as compliance with bisphosphonate prescribing is known to be suboptimal.[24] A further weakness was the ascertainment of cancer incidence, because our GPRD data were not linked to cancer registries; therefore, we relied on relevant diagnostic codes from patients' clinical files. Some inaccuracy is therefore inevitable, although the recording of cancer outcomes within the GPRD has been shown to be high,[25] and in this data set, less than 10% of cases with esophageal or gastric cancer had inconsistently recorded cancer codes. The lack of information on histological subtype of esophageal cancers is also a weakness, and it is possible that an association with either esophageal adenocarcinoma or squamous cell carcinoma was obscured. However, we did not see an increased risk of esophageal or gastric cancer in patients with a prior history of GERD who received bisphosphonates compared with those who did not receive these drugs. Too few patients had a history of Barrett esophagus to examine esophageal or gastric cancer rates in this subgroup, which is predisposed to esophageal adenocarcinoma.

Another limitation of our study was the relatively high proportion of missing data on potential confounders. It is possible that residual confounding by poorly measured or unmeasured confounders may have masked an association between the use of bisphosphonates and esophageal and gastric cancer risk, but the estimates seen in an analy-

Table 3. Esophageal (Only) Cancer Incidence in the Bisphosphonate and Matched Control Cohorts

	Bisphosphonate		Control		Risk			
					Unadjusted		Adjusted[a]	
Bisphosphonate Category	Cases	Person-Years	Cases	Person-Years	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Any bisphosphonate								
Prescribed	79	165 400	72	163 480	1.08 (0.79-1.49)	.63	1.07 (0.77-1.49)	.67
Incidence after cumulative prescriptions greater than (in DDDs)[b]								
183	51	104 676	49	104 104	1.04 (0.70-1.53)	.86	1.05 (0.70-1.57)	.82
365	31	73 364	35	73 170	0.88 (0.55-1.43)	.62	0.92 (0.56-1.51)	.74
730	22	40 326	22	40 492	1.00 (0.56-1.81)	.99	0.98 (0.53-1.81)	.95
1095	15	22 813	14	22 891	1.08 (0.52-2.23)	.84	1.01 (0.48-2.12)	.99
Total bisphosphonate intake during follow-up (in DDDs/d)[c]								
Low (0-<0.24)	35	62 922	27	63 648	1.31 (0.80-2.17)	.29	1.24 (0.74-2.09)	.41
Medium (≥0.24-<0.89)	24	58 162	23	55 334	0.98 (0.55-1.74)	.94	1.03 (0.57-1.86)	.92
High (≥0.89)	20	44 316	22	44 497	0.91 (0.50-1.67)	.78	0.90 (0.48-1.68)	.74
Nitrogen-containing bisphosphonates								
First prescribed	44	106 480	47	106 412	0.94 (0.62-1.41)	.75	0.96 (0.63-1.47)	.86
Incidence after cumulative prescriptions greater than (in DDDs)[b]								
365	30	70 251	34	69 935	0.88 (0.54-1.44)	.61	0.93 (0.56-1.54)	.78
730	22	39 022	22	39 187	1.01 (0.56-1.82)	.99	0.98 (0.53-1.80)	.95
Alendronate								
First prescribed	33	81 369	42	80 837	0.78 (0.50-1.23)	.29	0.77 (0.48-1.23)	.27
Incidence after cumulative prescriptions greater than (in DDDs)[b]								
365	22	52 308	31	51 741	0.70 (0.41-1.21)	.20	0.68 (0.39-1.19)	.18
730	19	28 898	21	28 904	0.91 (0.49-1.68)	.75	0.85 (0.45-1.61)	.62
Non–nitrogen-containing bisphosphonates								
First prescribed	35	58 920	25	57 068	1.35 (0.81-2.25)	.25	1.25 (0.73-2.12)	.37

Abbreviations: CI, confidence interval; DDD, defined daily dose; HR, hazard ratio.

[a] Adjusted for body mass index, alcohol, smoking, hormone therapy prescription (before index date), nonsteroidal anti-inflammatory drug prescription (before index date), Barrett esophagus diagnosis (before index date), gastroesophageal reflux disease diagnosis (before index date), H_2 receptor antagonist prescription (before index date), and proton pump inhibitor prescription (before index date).

[b] Person-years and cancer cases occurring after the date of specified prescriptions received for each bisphosphonate cohort member and their matched control. Daily divided dose equivalents: 183 DDDs are equivalent to a 6-month supply; 365 DDDs to a 1-year supply; 730 DDDs to a 2-year supply; and 1095 DDDs to a 3-year supply.

[c] In bisphosphonate cohort (see "Methods" for details of selection of cohorts).

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sis involving only participants with complete data on confounders were not different from those in the principal analyses. Exposures that increase risk of both esophageal cancer and osteoporosis (eg, smoking and low BMI) would artificially increase risk of esophageal cancer in bisphosphonate users, but exposures that increase risk of esophageal cancer but decrease risk of osteoporosis (eg, high BMI) could potentially mask any increase in esophageal cancer risk in bisphosphonate users. However, the observed differences in BMI between the groups were not large.

In conclusion, in the UK GPRD patient population we found no evidence for a substantially increased risk of esophageal (or gastric) cancer in persons using oral bisphosphonates. These drugs should not be withheld, on the basis of possible esophageal cancer risk, from patients with a genuine clinical indication for their use.

Author Contributions: Dr Cardwell had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Cardwell, Abnet, Cantwell, Murray.
Acquisition of data: Cardwell, Murray.
Analysis and interpretation of data: Cardwell, Abnet, Murray.
Drafting of the manuscript: Cardwell, Abnet, Murray.
Critical revision of the manuscript for important intellectual content: Cardwell, Abnet, Cantwell, Murray.
Statistical analysis: Cardwell, Abnet.
Obtained funding: Murray.
Administrative, technical, or material support: Cardwell, Cantwell.
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REFERENCES

1. Usher C, Teeling M, Bennett K, Feely J. Effect of clinical trial publicity on HRT prescribing in Ireland. *Eur J Clin Pharmacol*. 2006;62(4):307-310.
2. Udell JA, Fischer MA, Brookhart MA, Solomon DH, Choudhry NK. Effect of the Women's Health Initiative on osteoporosis therapy and expenditure in Medicaid. *J Bone Miner Res*. 2006;21(5):765-771.
3. Watson J, Wise L, Green J. Prescribing of hormone therapy for menopause, tibolone, and bisphosphonates in women in the UK between 1991 and 2005. *Eur J Clin Pharmacol*. 2007;63(9):843-849.
4. Ryan JM, Kelsey P, Ryan BM, Mueller PR. Alendronate-induced esophagitis: case report of a recently recognized form of severe esophagitis with esophageal stricture—radiographic features. *Radiology*. 1998;206(2):389-391.
5. de Groen PC, Lubbe DF, Hirsch LJ, et al. Esophagitis associated with the use of alendronate. *N Engl J Med*. 1996;335(14):1016-1021.
6. Ribeiro A, DeVault KR, Wolfe JT III, Stark ME. Alendronate-associated esophagitis: endoscopic and pathologic features. *Gastrointest Endosc*. 1998;47(6):525-528.
7. Chow WH, Finkle WD, McLaughlin JK, Frankl H, Ziel HK, Fraumeni JF Jr. The relation of gastroesophageal reflux disease and its treatment to adenocarcinomas of the esophagus and gastric cardia. *JAMA*. 1995;274(6):474-477.
8. Lagergren J, Bergström R, Lindgren A, Nyrén O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N Engl J Med*. 1999;340(11):825-831.
9. Lassen A, Hallas J, de Muckadell OB. Esophagitis: incidence and risk of esophageal adenocarcinoma—a population-based cohort study. *Am J Gastroenterol*. 2006;101(6):1193-1199.
10. Wysowski DK. Reports of esophageal cancer with oral bisphosphonate use. *N Engl J Med*. 2009;360(1):89-90.
11. Hollowell J. The General Practice Research Database: quality of morbidity data. *Popul Trends*. 1997;(87):36-40.
12. Kinn S, Lee N, Millman A. ABC of medical computing: using computers in clinical audit. *BMJ*. 1995;311(7007):739-742.
13. Jick H, Jick SS, Derby LE. Validation of information recorded on general practitioner based computerised data resource in the United Kingdom. *BMJ*. 1991;302(6779):766-768.
14. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. *Br J Clin Pharmacol*. 2010;69(1):4-14.
15. The Anatomical Therapeutic Chemical Classification System With Defined Daily Doses. World Health Organization Web site. http://www.who.int/classifications/atcddd/en/. Accessed July 15, 2010.
16. Office for National Statistics Web site. http://www.ons.gov.uk. Accessed July 15, 2010.
17. Breslow NE, Day NE. *The Design and Analysis of Cohort Studies*. Oxford, England: Oxford University Press; 1987. *Statistical Methods in Cancer Research*; vol 2.
18. Shipman CM, Rogers MJ, Apperley JF, Russell RG, Croucher PI. Bisphosphonates induce apoptosis in human myeloma cell lines: a novel anti-tumour activity. *Br J Haematol*. 1997;98(3):665-672.
19. Giraudo E, Inoue M, Hanahan D. An aminobisphosphonate targets MMP-9-expressing macrophages and angiogenesis to impair cervical carcinogenesis. *J Clin Invest*. 2004;114(5):623-633.
20. Coxon JP, Oades GM, Kirby RS, Colston KW. Zoledronic acid induces apoptosis and inhibits adhesion to mineralized matrix in prostate cancer cells via inhibition of protein prenylation. *BJU Int*. 2004;94(1):164-170.
21. Guise TA. Antitumor effects of bisphosphonates: promising preclinical evidence. *Cancer Treat Rev*. 2008;34(suppl 1):S19-S24.
22. Solomon DH, Patrick A, Brookhart MA. More on reports of esophageal cancer with oral bisphosphonate use [letter]. *N Engl J Med*. 2009;360(17):1789-1790.
23. Abrahamsen B, Eiken P, Eastell R. More on reports of esophageal cancer with oral bisphosphonate use [letter]. *N Engl J Med*. 2009;360(17):1791-1792.
24. Cramer JA, Gold DT, Silverman SL, Lewiecki EM. A systematic review of persistence and compliance with bisphosphonates for osteoporosis. *Osteoporos Int*. 2007;18(8):1023-1031.
25. Jick H, Jick S, Derby LE, Vasilakis C, Myers MW, Meier CR. Calcium-channel blockers and risk of cancer. *Lancet*. 1997;349(9051):525-528.

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