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ORIGINAL RESEARCH

Occurrence of Gastrointestinal Cancer in Users of Bisphosphonates and Other Antiresorptive Drugs Against Osteoporosis

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Abstract We studied the association between bisphosphonate use and risk of gastrointestinal (GI) cancers in a nationwide retrospective cohort from Denmark. All users of bisphosphonates and other drugs against osteoporosis between 1996 and 2006 ($n = 103{,}562$) were used as the exposed group, with three age- and gender-matched controls from the general population ($n = 310{,}683$) as the nonexposed group. The main outcome was occurrence of cancer of the esophagus, ventricle, small intestine, colon, pancreas, gallbladder or bile duct, or liver. Except for colon cancer, most of the GI cancers were rare. For clodronate and raloxifene, no excess risk was present for any of the GI cancers. For alendronate, an excess risk of esophageal and liver cancer was observed; however, the excess risk was most pronounced at low doses and short duration of observation. No dose–response relationship was present except for colon cancer with alendronate, where a decrease was seen with increasing dose so that at high doses a seemingly protective effect was present (≥1 defined daily dose, HR = 0.29, 95% CI 0.14–0.62). For etidronate, an excess risk of esophageal, liver, pancreas, and gallbladder and bile duct cancers was seen. Again, no relationship with dose or duration of observation was present. An excess risk of esophageal and liver cancers may be seen with alendronate and etidronate. However, the association may not be causal as no dose–response or time relationship was present. For colon cancer, the decline with increasing alendronate dose may be due to a "healthy user" effect.

Keywords Bisphosphonate · Alendronate · Etidronate · Raloxifene · Esophagus · Liver · Pancreas · Colon · Small intestine · Stomach · Gallbladder · Bile duct · Cancer

Case reports have linked esophageal cancer to bisphosphonate exposure [1, 2]. The rationale for a link has been induction of esophagitis and ulcerations by the bisphosphonates [3, 4] in the same way as esophagitis and esophageal reflux in general have been associated with esophageal cancer [5–7]. However, an association between bisphosphonates and esophageal cancer has been refuted by most [8–11], but not all [12], observational studies. Green et al. [12] reported an excess risk of esophageal cancer with ≥10 prescriptions of bisphosphonates or use for ≥3 years.

For cancer of the stomach (ventricle), a similar effect as that of ulcerations in the esophagus may be hypothesized for the bisphosphonated. However, no association with stomach cancer has been demonstrated [12].

In vitro, bisphosphonates may inhibit the growth of colon cancer cells [13]. However, in observational studies, no association between colon cancer and bisphosphonates has been observed [12].

No reports exist for other gastrointestinal (GI) cancers (small bowel, liver, gallbladder and bile duct, or pancreas). Bisphosphonates may be used to treat hypercalcemia resulting from GI tumors or metastases from these [14, 15], but per se no reports on tumorigenesis or antitumor effects on small bowel, liver, pancreas or gallbladder or bile duct tumors exist.

The purpose of the current study thus was to study if an association existed between use of drugs against osteoporosis, especially the bisphosphonates, and GI cancer risk (esophagus, ventricle, small bowel, colon, liver, gallbladder and bile duct, or pancreas).

The author has stated that there is no conflict of interest.

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Materials and Methods

Study Design

The study was designed as a cohort, with patients exposed to drugs against osteoporosis being compared to an age- and gender-matched control group of subjects not exposed to such drugs. The main outcome was occurrence of GI cancers (esophagus, ventricle, small bowel, colon, pancreas, gallbladder and bile duct, or liver).

Patients Exposed to Drugs against Osteoporosis

All patients who had filed a prescription for any antiresorptive drug between January 1, 1996, and December 31, 2006, were included. These included polyphosphates (ATC codes M05BA01 [etidronate], M05BA02 [clodronate], M05BA03 [pamidronate], M05BA04 [alendronate], M05BA06 [ibandronate], M05BA07 [risedronate], M05BA08 [zoledronate], M05BB01 [etidronate plus calcium], M05BB03 [alendronate plus vitamin D]) and raloxifene (ATC code G03XC01). All drugs were administered orally except zoledronate and pamidronate, which were administered intravenously.

Controls

For each subject exposed to a drug against osteoporosis, three control subjects of the same age (same birth year) and gender were randomly selected from the background population from the same period as the exposed patients. A dummy baseline date was assigned to each control subject based on the date of first use of a drug against osteoporosis among the corresponding patient exposed to a drug against osteoporosis.

Registers Used

Information on occurrence of diabetes and occurrence of other diseases such as alcoholism came from the National Hospital Discharge Register [16]. The National Hospital Discharge Register was founded in 1977 [16]. It covers all inpatient contacts from 1977 to 1994 and from 1995 also all outpatient visits to hospitals, outpatient clinics, and emergency rooms [16]. Upon discharge, the physician codes the reason for the contact using the ICD system. The code used is at the discretion of the individual physician. The register has a nationwide coverage and an almost 100% capture of contacts [16]. In general, the validity of registrations is high [17].

The Danish Medicines Agency keeps a nationwide register of all drugs sold at pharmacies throughout the country from 1996 onward (The National Pharmacological Database run by the Danish Medicines Agency, http://www.dkma.dk). Any drugs bought are registered with an ATC code, dosage sold, form of medication (tablets, injections, etc.), and date of sale.

The date of start of exposure was the first date of prescription of a drug against osteoporosis and an exactly matched dummy date in the controls (each exposed patient was matched to three controls, who were then given the same dummy date of start of exposure), thus minimizing the effects of immortal time bias [18].

Cause of death was retrieved from the register of deaths under the National Board of Health.

Exposure was calculated as the average daily dose (number of defined daily dosages [DDDs], equal to average normal dose of a drug per day). This average dose was calculated as the sum of all redeemed prescriptions from first prescription to the date of censoring divided by the time in days from first prescription to the date of censoring. Information on vital status and migrations came from the National Person Register. All subjects were followed up until time of death, migration, any defined event, or December 31, 2006, whichever came first. It is possible to link these sources of information through the Central Person Register number, which is a unique registration code given to every inhabitant, to some degree similar to the American Social Security number, that allows registration on an individual basis. The project was approved and controlled by the National Board of Health and the Danish Data Protection Agency.

Confounders

Adjustments were made for potential confounders associated with GI cancers. Alcoholism was included as alcohol is associated with esophageal, stomach, colon, and liver cancers [19]. Reflux from the stomach to the esophagus is linked to esophageal cancer; adjustments were thus performed for use of antacid drugs [5–7]. Acetylsalicylic acid (ASA) and non-steroidal anti-inflammatory drugs (NSAIDs) have been associated with ulcerations of the esophagus and ventricle but also with a decreased risk of colon cancer [20]. Furthermore, adjustments were made for age, gender, and use of inhaled corticosteroids and beta-agonists as a proxy for smoking.

Statistics

Mean and standard deviation were used as descriptive statistics. A Cox regression analysis for matched design was applied for risk of the outcome after initiation of any drug against osteoporosis or the corresponding dummy baseline date among the controls. The assumption for proportional hazards was evaluated using inspection of the survival curves and hazards. Further testing for log-time interaction did not reveal violations of the proportional

hazard assumption. Adjustments were made for age, gender, alcoholism, use of inhaled bronchodilator or corticosteroid drug (proxy for smoking), antacid drugs, ASA or NSAID, prior gastric surgery, and socioeconomic status (income, working or not, married or unmarried). Only incident cases were included; i.e., patients with prior GI malignancies were excluded from the analyses. Analyses were performed using STATA 9.0 (StataCorp, College Station, TX) and SPSS 19.0 (SPSS, Inc., Chicago, IL), both in the UNIX version.

Results

Table 1 shows the baseline characteristics of the patients who had used a drug against osteoporosis and controls.

Table 1 Baseline characteristics of patients exposed to drugs against osteoporosis (cases) and matched controls

Variable	Cases (n = 103,562)	Controls (n = 310,683)	P
Age (years)	70.5 ± 11.4	70.5 ± 11.4	–
Men	15,820 (15.3%)	47,460 (15.3%)	–
Women	87,742 (84.7%)	263,223 (84.7%)	
Raloxifene (mean treatment time)	4,831 (4.9 years)	–	–
Teriparatide (mean treatment time)	303 (1.1 years)	–	–
Etidronate (mean treatment time)	39,724 (5.5 years)	–	–
Clodronate (mean treatment time)	566 (2.4 years)	–	–
Pamidronate (mean treatment time)	45 (1.3 years)	–	–
Alendronate (mean treatment time)	55,090 (2.8 years)	–	–
Ibandronate (mean treatment time)	612 (0.4 years)	–	–
Risedronate (mean treatment time)	1,452 (1.4 years)	–	–
Zoledronate (mean treatment time)	22 (0.6 years)	–	–
Strontium ranelate (mean treatment time)	917 (0.9 years)	–	–
Systemic HT before	14,276 (13.8%)	41,131 (13.2%)	<0.01
Systemic HT after	5,498 (5.3%)	24,346 (7.8%)	<0.01
Bronchodilator drugs or corticosteroids before	25,861 (25.0%)	43,938 (14.1%)	<0.01
Bronchodilator drugs or corticosteroids after	25,786 (24.9%)	38,752 (12.5%)	<0.01
Alcoholism before	3,637 (3.5%)	6,048 (1.9%)	<0.01
Alcoholism after	1,391 (1.3%)	2,361 (0.8%)	<0.01
NSAID or ASA before	73,591 (71.1%)	166,554 (53.6%)	<0.01
NSAID or ASA after	55,558 (53.7%)	138,621 (44.6%)	<0.01
Antiulcer drugs before	40,080 (38.7%)	78,205 (25.2%)	<0.01
Antiulcer drugs after	45,531 (44.0%)	82,840 (26.7%)	<0.01
Prior GI cancer	1,865 (1.8%)	6,328 (2.0%)	<0.01
Prior gastric surgery	2,055 (2.0%)	4,348 (1.4%)	<0.01
Income in the index year (Danish crowns)	143,198 ± 127,472	145,791 ± 130,227	<0.01
Widowed	26,819 (25.9%)	80,128 (25.8%)	<0.01
Divorced	11,901 (11.5%)	33,651 (10.8%)	
Married	57,121 (55.2%)	173,268 (55.8%)	
Unmarried	7,335 (7.1%)	22,090 (7.1%)	
Other	386 (0.4%)	1,546 (0.5%)	
Working	24,109 (23.3%)	85,377 (27.5%)	<0.01
Unemployed	2,406 (2.3%)	7,721 (2.5%)	
Retired	76,551 (73.9%)	215,826 (69.5%)	
Other	496 (0.5%)	1,759 (0.6%)	

Number of patients unless otherwise stated. Age data are mean ± standard deviation (SD)

The terms "before" and "after" refer to before and after initiation of drugs against osteoporosis among the patients using such drugs and for the controls before and after the corresponding matched dummy date of initiation of drugs against osteoporosis

ASA acetylsalicylic acid, *COPD* chronic obstructive pulmonary disease, *HT* hormone therapy (i.e., *ET* estrogen therapy, or *EPT* estrogen/progestogen therapy), *NSAID* non-steroidal anti-inflammatory drug

Patients and controls were well matched concerning age and gender. The patients in general had more comorbid factors and more often had used drugs for various conditions than the controls. Few had had prior GI cancers. In general, socioeconomic parameters differed little in absolute terms between exposed and nonexposed subjects except for a larger percentage of the exposed being retired. However, due to the large numbers, statistical significance was obtained.

Table 2 shows the crude risk of GI cancers with use of drugs against osteoporosis compared to nonexposed controls. Only for alendronate, clodronate, etidronate, and raloxifene were sufficient number of users and end points present for analysis. For alendronate, an excess risk was seen for esophageal and liver cancers. For clodronate, no significant changes in cancer risk were observed. With etidronate an excess risk of esophageal, ventricle, liver, and pancreatic cancers was seen. For raloxifene, no excess risk of any GI cancer was seen. Changing the analyses to cause of death as the end point changed the results little with the exception that death from colon cancer obtained statistical significance for alendronate and death from cancer of the small bowel achieved statistical significance for etidronate.

Table 2 Crude relative risk (RR) of GI cancers after start of drugs against osteoporosis

Drug	GI cancer	Exposed/nonexposed	RR	HR cause of death
Alendronate	No GI cancer	53,935/161,207	Reference	Reference
	Esophagus	14/18	2.32 (1.18–4.58)*	1.71 (1.13–2.57)*
	Gallbladder and bile duct	8/13	1.84 (0.77–4.38)	0.97 (0.49–1.90)
	Liver	11/13	2.53 (1.17–5.49)*	2.12 (1.40–3.19)*
	Pancreas	22/50	1.32 (0.78–2.17)	1.13 (0.89–1.44)
	Colon	108/329	0.98 (0.79–1.22)	1.28 (1.06–1.54)*
	Small bowel	3/4	2.24 (0.52–9.62)	2.31 (0.73–7.31)
	Ventricle	10/22	1.36 (0.65–2.85)	1.02 (0.68–1.54)
Clodronate	No GI cancer	533/1,663	Reference	Reference
	Esophagus	0/0	–	–
	Gallbladder and bile duct	1/1	3.12 (0.23–43.2)	–
	Liver	1/0	–(NS)	–
	Pancreas	1/2	1.56 (0.14–16.9)	2.82 (0.52–15.3)
	Colon	2/13	0.48 (0.11–2.05)	1.76 (0.20–15.5)
	Small bowel	0/0	–	–
	Ventricle	0/0	–	–
Etidronate	No GI cancer	38,461/115,633	Reference	Reference
	Esophagus	32/48	2.00 (1.29–3.11)*	2.23 (1.62–3.07)*
	Gallbladder and bile duct	16/39	1.23 (0.69–2.20)	0.99 (0.59–1.64)
	Liver	24/32	2.25 (1.35–3.77)*	1.76 (1.20–2.57)*
	Pancreas	78/137	1.71 (1.30–2.25)*	1.56 (1.28–1.90)*
	Colon	301/929	0.97 (0.86–1.11)	1.12 (0.96–1.30)
	Small bowel	6/11	1.64 (0.61–4.39)	2.72 (1.01–7.31)*
	Ventricle	33/64	1.55 (1.02–2.35)*	1.14 (0.79–1.62)
Raloxifene	No GI cancer	4,767/14,244	Reference	Reference
	Esophagus	1/0	–(NS)	–
	Gallbladder and bile duct	2/1	5.98 (0.73–49.2)	2.98 (0.42–21.2)
	Liver	0/1	0.00 (NS)	–
	Pancreas	0/9	0.00 (NS)	–
	Colon	10/30	1.00 (0.49–2.04)	1.31 (0.71–2.41)
	Small bowel	0/0	–	–
	Ventricle	0/2	0.00 (NS)	–

A separate analysis using a crude Cox regression analysis was performed using certificates of death and the cause of death registered on these

HR hazard ratio, *NS* nonsignificant

*$2P < 0.05$

Table 3 shows the same as Table 2 but adjusted for confounders in a Cox proportional hazard regression analysis. In general, the results were similar to those shown in Table 2, with no excess risks being observed for clodronate and raloxifene. With alendronate an excess risk of esophageal and liver cancers was observed, while for etidronate an excess risk of esophageal, liver, pancreatic, and ventricular cancers was present after adjustment.

Table 4 shows the adjusted risk of GI cancers by dose of drug against osteoporosis. Only for alendronate and etidronate were sufficient numbers of exposed present for analysis. For alendronate, a significant excess risk of

Table 3 Risk of various cancers of the GI tract after start of drugs against osteoporosis: hazard ratio in a Cox proportional hazard regression analysis

GI cancer	Alendronate	Clodronate	Etidronate	Raloxifene
Esophagus	2.10 (1.01–4.35)*	–	1.99 (1.24–3.18)*	–
Bile duct	1.88 (0.76–4.68)	16.0 (0.72–357)	1.29 (0.71–2.35)	6.93 (0.61–78.4)
Liver	2.55 (1.10–5.89)*	–	2.14 (1.23–3.71)*	–
Pancreas	1.36 (0.81–2.29)	5.50 (0.36–83.6)	1.73 (1.30–2.31)*	–
Colon	1.16 (0.93–1.45)	1.31 (0.28–6.10)	1.05 (0.92–1.20)	0.97 (0.47–2.00)
Small intestine	2.19 (0.46–10.4)	–	1.56 (0.56–4.38)	–
Ventricle	1.16 (0.54–2.53)	–	1.57 (1.01–2.43)*	–

Adjusted for age, gender, alcoholism, use of inhaled bronchodilator or corticosteroid drug (proxy for smoking), antacid drugs, ASA or NSAID drugs, working or not, married or not, income above vs. below median (112,000 DKK/year), and gastric surgery before. Only incident cases, prior GI malignancies excluded

ASA acetylsalicylic acid, *DDD* defined daily dose, *GI* gastrointestinal, *NSAID* non-steroidal anti-inflammatory drug

*$2P < 0.05$

Table 4 Dose response of various cancers of the GI tract after start of drugs against osteoporosis: hazard ratio (HR) in a Cox proportional hazard regression analysis

GI cancer	Alendronate (DDD)			Etidronate (DDD)		
	≤0.66	0.67–0.99	≥1	≤0.66	0.67–0.99	≥1
Esophagus	3.19 (1.40–7.29)*	1.36 (0.39–4.70)	1.24 (0.28–5.48)	–	1.21 (0.17–8.76)	4.59 (1.67–12.6)*
Bile duct	2.80 (0.98–8.05)	1.41 (0.31–6.36)	0.98 (0.13–7.60)	1.26 (0.17–9.15)	–	1.64 (0.23–11.9)
Liver	4.13 (1.66–10.3)*	2.08 (0.58–7.48)	–	2.44 (0.59–10.1)	–	5.10 (1.58–16.4)*
Pancreas	1.79 (0.94–3.41)	1.34 (0.60–2.99)	0.73 (0.22–2.36)	0.94 (0.30–2.94)	0.83 (0.21–3.34)	0.83 (0.21–3.35)
Colon	1.44 (1.08–1.93)*	1.49 (1.08–2.04)*	0.30 (0.14–0.63)*	0.90 (0.54–1.50)	1.19 (0.71–1.98)	1.26 (0.77–2.06)
Small intestine	3.35 (0.59–19.1)	2.22 (0.24–20.7)	–	–	11.6 (2.62–51.4)	–
Ventricle	2.21 (0.96–5.10)	0.73 (0.17–3.14)	–	1.39 (0.34–5.65)	–	1.93 (0.47–7.85)
	≤365 DDD	366–730 DDD	>730 DDD	≤160 DDD[#]	161–330 DDD[#]	>330 DDD[#]
Esophagus	4.45 (1.93–10.3)*	3.21 (0.91–11.3)	0.57 (0.13–2.48)	2.23 (0.54–9.15)	1.98 (0.48–8.08)	1.03 (0.14–7.44)
Bile duct	3.27 (1.04–10.3)*	3.45 (0.75–15.7)	0.83 (0.18–3.73)	1.71 (0.23–12.4)	1.41 (0.19–10.2)	–
Liver	5.53 (2.13–14.3)*	–	1.68 (0.54–5.28)	4.77 (1.47–15.4)*	1.41 (0.19–10.2)	1.52 (0.21–11.1)
Pancreas	2.23 (1.14–4.36)*	2.82 (1.25–6.35)*	0.48 (0.17–1.33)	2.10 (0.86–5.10)	0.70 (0.17–2.82)	–
Colon	1.49 (1.07–2.06)*	0.85 (0.48–1.53)	1.08 (0.81–1.45)	2.01 (1.35–2.99)*	0.73 (0.40–1.33)	0.69 (0.37–1.28)
Small intestine	2.42 (0.26–22.6)	10.5 (1.75–63.2)*	–	–	9.80 (2.21–43.5)*	–
Ventricle	1.83 (0.67–4.98)	3.11 (1.03–9.34)*	0.23 (0.03–1.73)	1.91 (0.47–7.79)	1.62 (0.40–6.60)	–

Adjusted for age, gender, alcoholism, use of inhaled bronchodilator or corticosteroid drug (proxy for smoking), antacid drugs, ASA or NSAID drugs, working or not, married or not, income above vs. below median (112,000 DKK/year), and gastric surgery before. Only incident cases, prior GI malignancies excluded

ASA acetylsalicylic acid, *DDD* defined daily dose, *GI* gastrointestinal, *NSAID* non-steroidal anti-inflammatory drug

*$2P < 0.05$

[#] For etidronate 1 DDD is 400 mg; however, etidronate is administered with 400 mg/day for 2 weeks followed by a pause for 11 weeks; i.e., due to the pauses, the seemingly low DDD covers a long treatment period as the drug is administered in a cyclic manner (e.g., 160, DDD which should usually equal 160 days, equals 6.5 * 160 = 1,040 days, or approximately 2.8 years of use at 100% adherence)

esophageal, gallbladder and bile duct, colon, ventricular, and liver cancers was seen but only with the lowest daily dose. In general, no dose response could be demonstrated due to wide confidence intervals. However, for colon cancer an interesting inverse dose response was observed with an increased risk at low doses but a seemingly protective effect at high doses (P for trend < 0.05). For etidronate, a significant excess risk of esophageal, liver, and gallbladder and bile duct cancers was seen at the highest doses, but no statistically significant dose–response relationship was present. Changing the analyses from daily dose to cumulated dose in general did not change the results except for etidronate, where the significance for liver and colon cancers was seen with the lowest doses.

Table 5 shows the time-divided risk of GI cancer. In general, no time trend was present. For alendronate, a significant excess risk of esophageal and gallbladder and bile duct cancers was present for the shortest duration, but no trend with time was present due to wide confidence intervals. For etidronate, a decreased risk of colon cancer was present at most time intervals, even the shortest.

Figure 1 shows the hazard for esophageal and liver cancers. In general, the cancers occurred throughout the observation period, with a higher frequency in the exposed than in the nonexposed.

Discussion

In this large-scale nationwide cohort study, excess risk of esophageal and liver cancers was seen in users of alendronate and etidronate. However, no dose–response or time relationship was present, and the cancers were rare.

The fact that esophageal and liver cancers occurred throughout the observation period with a higher frequency points against an early effect of cancers already in progress being detected upon starting bisphosphonates as such patients may be more likely to undergo upper endoscopy due to the expected risk of ulcerations from the bisphosphonates. However, the absence of a time and dose dependence points against a causal relationship. The incubation period for the GI cancers studied here is rather long, with 3–5 years perhaps being a short period for inducing new cancers. In this study an excess risk of GI cancers was seen with short duration of observation, and this may further point against a causal relationship.

Some studies have indicated that supplemental calcium may have some protective potential against colon cancer [21]. Calcium supplements are usually administered alongside antiresorptive drugs. However, despite this, no time trend in risk of colon cancer development was present, although at the highest doses some decrease in the risk of colon cancer may be seen but only for alendronate and not for etidronate or raloxifene. This decrease may be the result of adherence to calcium supplements. However, the decreased risk of colon cancer with increasing dose of alendronate may also be a "healthy user" effect as reported in randomized controlled trials, where reduced risks of death and coronary events were seen even in the placebo group with increasing adherence to the drugs [22].

In the present study, use of beta-agonists was included as a proxy for smoking. In Denmark smoking prevalence is relatively high. In the study period, smoking prevalence was around 30% among those aged 40–69 years and around 20% among those aged 70 years or more (http://www.sst.dk/~/media/Sundhed%20og%20forebyggelse/Tobak/Tal%20og%20undersoegelser/Danskernes%20rygevaner/2004/monitorering_krydstabeller_%202004.ashx). As almost all cases of COPD are related to smoking and as COPD accounts for approximately 75% of all users of inhaled bronchodilators and/or beta-agnoists, it seems that among the users of these drugs around 3/4 × 16% (the estimated prevalence of use of such drugs) = 12% are smokers; i.e., around 12/20 = 60% are captured.

Table 5 Time-dependent risk of various cancers of the GI tract after start of drugs against osteoporosis: crude RR

GI cancer	Alendronate			Etidronate		
	≤2 years 25,407/75,754	2.1–5 years 20,937/57,687	>5 years 7,767/28,215	≤2 years 5,948/13,028	2.1–5 years 10,974/25,891	>5 years 22,029/77,974
Esophagus	3.41 (1.31–8.85)*	1.72 (0.57–5.20)*	1.21 (0.13–11.6)	1.64 (0.85–3.18)	1.23 (0.61–2.46)	3.54 (1.11–11.3)*
Bile duct	3.73 (1.10–12.7)*	1.03 (0.27–3.89)	0.00	1.31 (0.58–2.99)	0.87 (0.36–2.06)	0.00
Liver	2.24 (0.52–9.61)	1.53 (0.52–4.53)	–*	1.87 (0.88–4.00)	1.38 (0.64–3.01)	7.08 (0.91–55.3)
Pancreas	0.39 (0.12–1.24)	1.84 (0.32–10.7)	1.60 (0.97–2.63)	1.41 (0.95–2.09)	1.27 (0.83–1.94)	1.26 (0.46–3.50)
Colon	1.07 (0.77–1.47)	0.55 (0.19–1.59)	1.19 (0.96–1.48)	0.80 (0.67–0.95)*	0.72 (0.59–0.88)*	0.66 (0.38–1.13)
Small intestine	0.99 (0.10–9.56)	–	2.73 (0.65–11.5)	0.27 (0.04–1.90)	5.88 (1.39–24.9)*	0.00
Ventricle	1.09 (0.35–3.41)	–	1.65 (0.79–3.46)	1.52 (0.81–2.86)	1.10 (0.58–2.07)	0.97 (0.27–3.46)

Numbers in column heads are number of exposed users of the drug in question versus number of nonexposed controls

*$2P < 0.05$

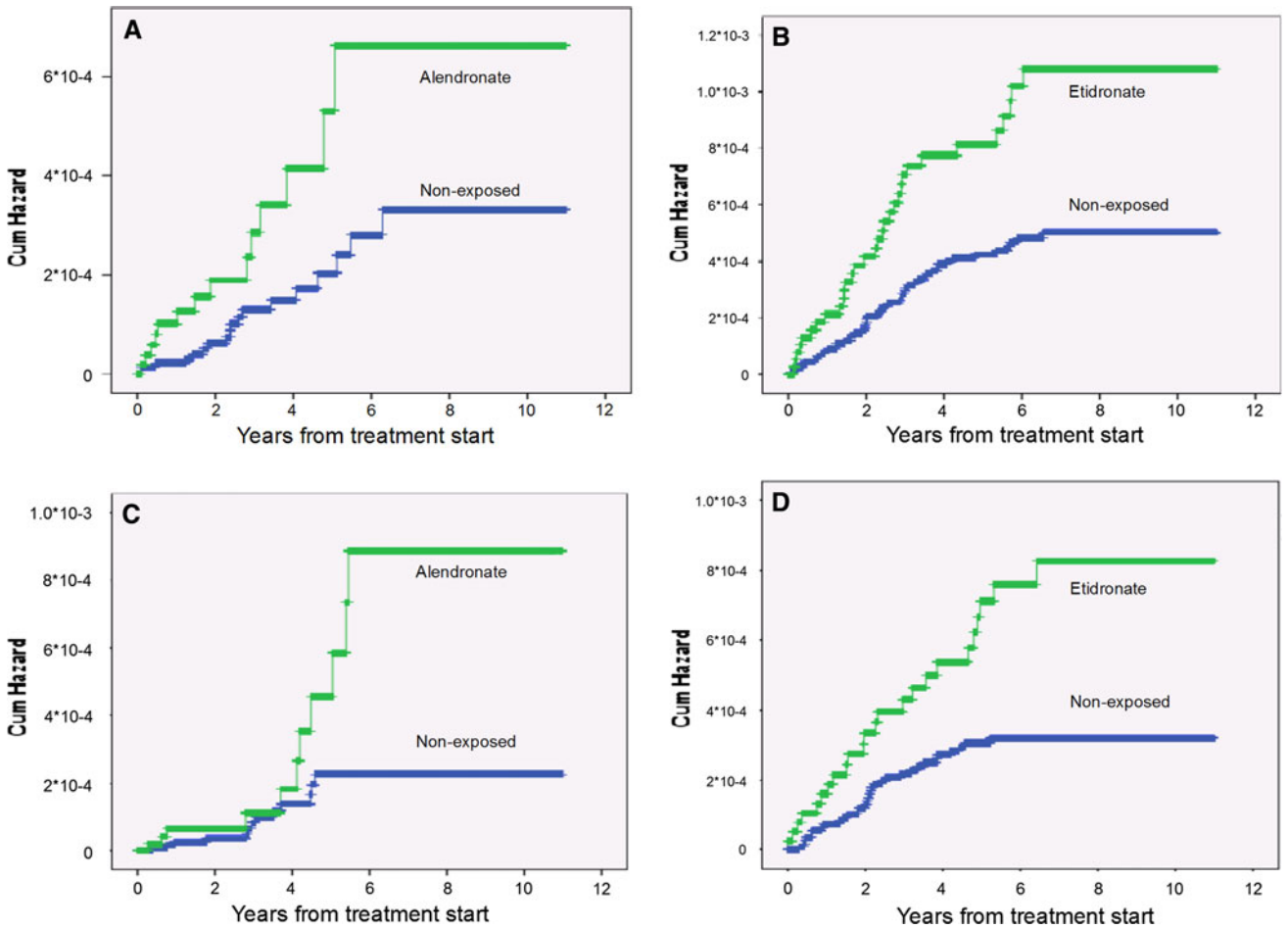

Fig. 1 Risk of esophageal and liver cancers expressed as hazard plots. Ordinate is cumulated hazard, i.e., absolute risk (2×10^{-4} is, e.g., a risk of 2 out of 10,000 and 1×10^{-3} is a risk of 1 in 1,000). **a** Alendronate and risk of esophageal cancer. **b** Etidronate and risk of esophageal cancer. **c** Alendronate and risk of liver cancer. **d** Etidronate and risk of liver cancer

The advantages of the present study are the large sample size, the extended duration of follow-up, and the completeness and validity of registrations. A further advantage was the ability to adjust for ASA/NSAID use and exposure to corticosteroids, the first being associated with colon cancer and the risk of upper GI ulcerations and the latter also being associated with upper GI ulcerations, increasing the likelihood of undergoing endoscopy. The major drawbacks are lack of individual information on smoking, body mass index, use of calcium supplements, and dietary habits.

In conclusion, an excess risk of esophageal and liver cancers may be seen with alendronate and etidronate. However, the association may not be causal as no dose–response or time relationship was present. For colon cancer, the decline with increasing alendronate dose may be due to a "healthy user" effect.

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References

1. Wysowski DK (2009) Reports of esophageal cancer with oral bisphosphonate use. N Engl J Med 360:89–90
2. Terashima T, Hiramatsu K, Shimatani A, Matsuda M, Ogino H, Satomura Y, Noda Y (2006) An esophageal ulcer mimicking advanced esophageal cancer in a patient on alendronate sodium treatment for osteoporosis. Endoscopy 38(2):E37
3. Ribeiro A, DeVault KR, Wolfe JT, Stark ME (1998) Alendronate-associated esophagitis: endoscopic and pathologic features. Gastrointest Endosc. 47:525–528
4. de Groen P, Lubbe D, Hirsch L, Daifotis A, Stephenson W, Freedholm D, Pryor-Tillotson S, Seleznick M, Pinkas H, Wang K (1996) Esophagitis associated with the use of alendronate. N Engl J Med 335:1016–1021
5. Chow WH, Finkle WD, McLaughlin JK, Frankl H, Ziel HK, Fraumeni JFJ (1995) The relation of gastroesophageal reflux disease and its treatment to adenocarcinomas of the esophagus and gastric cardia. JAMA 274:474–477

6. Lagergren J, Bergström R, Lindgren A, Nyrén O (1999) Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med 340:825–831
7. Lassen A, Hallas J, de Muckadell OBS (2006) Esophagitis: incidence and risk of esophageal adenocarcinoma—a population-based cohort study. Am J Gastroenterol 101:1193–1199
8. Cardwell CR, Abnet CC, Cantwell MM, Murray LJ (2010) Exposure to oral bisphosphonates and risk of esophageal cancer. JAMA 304:657–663
9. Nguyen DM, Schwartz J, Richardson P, El-Serag HB (2010) Oral bisphosphonate prescriptions and the risk of esophageal adenocarcinoma in patients with Barrett's esophagus. Dig Dis Sci 55: 3404–3407
10. Solomon DH, Patrick A, Brookhart MA (2009) More on reports of esophageal cancer with oral bisphosphonate use. N Engl J Med 360:1789–1792
11. Abrahamsen B, Eiken P, Eastell R (2009) Subtrochanteric and diaphyseal femur fractures in patients treated with alendronate: a register-based national cohort study. J Bone Miner Res 24: 1095–1102
12. Green J, Czanner G, Reeves G, Watson J, Wise L, Beral V (2010) Oral bisphosphonates and risk of cancer of oesophagus, stomach, and colorectum: case–control analysis within a UK primary care cohort. BMJ 341:c4444
13. Sewing L, Steinberg F, Schmidt H, Göke R (2008) The bisphosphonate zoledronic acid inhibits the growth of HCT-116 colon carcinoma cells and induces tumor cell apoptosis. Apoptosis 13:782–789
14. Montella L, Addeo R, Palmieri G, Caraglia M, Cennamo G, Vincenzi B, Guarrasi R, Mamone R, Faiola V, Frega N, Capasso E, Maiorino L, Leopardo D, Pizza C, Montesarchio V, Del Prete S (2010) Zoledronic acid in the treatment of bone metastases by hepatocellular carcinoma: a case series. Cancer Chemother Pharmacol 65:1137–1143
15. Penel N, Dewas S, Doutrelant P, Clisant S, Yazdanpanah Y, Adenis A (2008) Cancer-associated hypercalcemia treated with intravenous diphosphonates: a survival and prognostic factor analysis. Support Care Cancer 16:387–392
16. Andersen T, Madsen M, Jørgensen J, Mellemkjær L, Olsen J (1999) The Danish National Hospital Register. Dan Med Bull 46:263–268
17. Mosbech J, Jørgensen J, Madsen M, Rostgaard K, Thornberg K, Poulsen T (1995) The Danish National Patient Register: evaluation of data quality [in Danish]. Ugeskr Laeger 157:3741–3745
18. Lévesque LE, Hanley JA, Kezouh A, Suissa S (2010) Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. BMJ 340:b5087
19. Bagnardi V, Blangiardo M, La Vecchia C, Corrao G (2001) Alcohol consumption and the risk of cancer: a meta-analysis. Alcohol Res Health 25:263–270
20. Ruder EH, Laiyemo AO, Graubard BI, Hollenbeck AR, Schatzkin A, Cross AJ (2011) Non-steroidal anti-inflammatory drugs and colorectal cancer risk in a large, prospective cohort. Am J Gastroenterol 106:1340–1350
21. Carroll C, Cooper K, Papaioannou D, Hind D, Pilgrim H, Tappenden P (2010) Supplemental calcium in the chemoprevention of colorectal cancer: a systematic review and meta-analysis. Clin Ther 32:789–803
22. Curtis JR, Larson JC, Delzell E, Brookhart MA, Cadarette SM, Chlebowski R, Judd S, Safford M, Solomon DH, Lacroix AZ (2011) Placebo adherence, clinical outcomes, and mortality in the women's health initiative randomized hormone therapy trials. Med Care 49:427–435