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ORIGINAL REPORT

A Prospective Study of Bisphosphonate Use and Risk of Colorectal Cancer

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ABSTRACT

Purpose
Bisphosphonates are used for the treatment of bone metastases and have been associated with a lower risk of breast cancer. A recent case-control study showed an inverse association between bisphosphonate use and colorectal cancer. Data from prospective cohorts are lacking.

Patients and Methods
We prospectively examined the relationship between bisphosphonate use and risk of colorectal cancer among 86,277 women enrolled onto the Nurses Health Study (NHS). Since 1998, participants have returned biennial questionnaires in which they were specifically queried about the regular use of bisphosphonates. We used Cox proportional hazards models to calculate hazard ratios (HRs) and 95% CIs for risk of colorectal cancer.

Results
Through 2008, we documented 801 cases of colorectal cancer over 814,406 person-years of follow-up. The age-adjusted HR for women who regularly used bisphosphonates was 0.92 (95% CI, 0.73 to 1.14) and was further attenuated after adjustment for other risk factors (multivariate HR, 1.04; 95% CI, 0.82 to 1.33). The risk was not influenced by duration of use (P_{trend} = 0.79). Compared with nonusers, the multivariate-adjusted HRs of colorectal cancer were 1.24 (95% CI, 0.94 to 1.64) for women with 1 to 2 years of use, 1.16 (95% CI, 0.79 to 1.69) for 3 to 4 years of use, and 0.97 (95% CI, 0.60 to 1.56) for ≥ 5 years of use. There was no association between bisphosphonate use and colorectal cancer within strata of other risk factors.

Conclusion
In a large prospective cohort, we did not observe an association between long-term use of bisphosphonates and risk of colorectal cancer.

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INTRODUCTION

Primarily used for treatment of osteoporosis, bisphosphonates are among the most commonly prescribed medications among women. Bisphosphonates inhibit bone breakdown by promoting osteoclast apoptosis and are also widely used for treatment of bone metastases in patients with breast cancer.[1,2] Bisphosphonates have been hypothesized to have direct anticancer activity through several mechanisms, including inhibition of isoprenoid biosynthesis through the mevalonate pathway. In experimental studies, bisphosphonates inhibit angiogenesis,[3] tumor adhesion, and metastasis,[4,5] and they promote apoptosis.[6] A few studies have shown an association between bisphosphonates and reduced risk of breast cancer.[7-10] Most recently, in a population-based case-control study,[11] bisphosphonate use for at least 1 year was associated with a 59% reduction in risk of colorectal cancer (CRC) among postmenopausal women.

We therefore sought to examine the association between use of bisphosphonates and risk of CRC among women enrolled in a large prospective cohort—the Nurses' Health Study (NHS)—in which detailed information about medication use, diet, and lifestyle are collected biennially. This cohort offered us a unique opportunity to prospectively examine bisphosphonate use in the context of other detailed data on dietary and lifestyle risk factors that may either confound or modify its association with CRC.

PATIENTS AND METHODS

Study Population

The NHS is a prospective cohort that began in 1976 when 121,700 US female registered nurses age 30 to 55 years completed a mailed health questionnaire. We have mailed questionnaires every 2 years to update information and identify new cases of cancer; follow-up has consistently exceeded 90%. A validated assessment of physical

activity is administered every 2 years,[12] and a validated semiquantitative food frequency questionnaire (SFFQ) is administered every 4 years.[13,14] The institutional review board at the Brigham and Women's Hospital approved this study.

Outcome Ascertainment

In the NHS, when a participant (or next of kin for decedents) reported a diagnosis of CRC on a biennial questionnaire, we obtained the patient's hospital records and pathology reports. Study physicians, blinded to exposure data, reviewed all medical records to confirm self-reported diagnoses and identify the anatomic site of the cancer. We also identified deaths through the National Death Index and next of kin. Mortality follow-up was more than 98% complete.[15] For all deaths, we sought information to determine the cause of death and, when appropriate, requested permission from next-of-kin to review medical records.

Assessment of Bisphosphonate Use

In 1998, participants were asked whether they were currently using "Fosamax (alendronate) or Didronel" for osteoporosis or any other reasons. Similarly, on the 2002, 2004, and 2006 questionnaires, participants were asked whether over the past 2 years they regularly used "Fosamax, Actonel, or other bisphosphonate."

Assessment of Other Covariates

On each biennial questionnaire, women were asked about their menopause status, weight, time spent in recreational and leisure-time activities, smoking status, family history of colon cancer, alcohol intake, smoking history, use of hormone replacement therapy (HRT), regular use of aspirin, regular use of statins, history of osteoporosis, history of polyps, and prior lower endoscopy. Participants' self-report of body weight and physical activity have been previously validated.[16] By using a validated SFFQ administered every 4 years,[13,14] total intake of calcium, vitamin D, and folate were calculated from the reported consumption of foods and use of multivitamins and specific vitamin and mineral supplements. As in previous analyses, nutrient intake and physical activity were updated with the cumulative average of the current and all previous assessments to reduce within-person variation and to reflect long-term exposure.[17]

Statistical Analysis

At baseline, we included women who returned the 1998 biennial questionnaire in which they were first specifically queried about their use of bisphosphonates. We excluded participants who had previously reported cancer or ulcerative colitis. After these exclusions, 86,277 women were eligible for analysis. Person-time for each participant was calculated from the date of return of the baseline questionnaire to the date of diagnosis of CRC, date of last questionnaire report, death from any cause, or June 1, 2008, whichever came first. Women were defined as bisphosphonate users if they responded that they regularly used bisphosphonate in the past 2 years. We also assessed duration of use by assigning 2 years of use for each report of bisphosphonate use on a questionnaire and updating this variable biennially (eg, women who reported use on one biennial questionnaire were assigned a duration of use of 2 years; women who reported use on two biennial questionnaires were assigned a duration of 4 years, and so on). We used Cox proportional hazards modeling with time-varying variables with the most updated information for bisphosphonate use and other covariates before each 2-year interval to calculate adjusted hazard ratios (HRs) and 95% CIs. The proportional hazards assumption was evaluated by using the Wald test to assess significance of the interaction between time and categories of bisphosphonate use. We evaluated effect modification by using cross-classified categories of CRC risk factors and bisphosphonate use. We tested significance of interactions by using the log likelihood ratio test to compare the model with cross-classified categories with a model that included the risk factors as independent variables. We used SAS version 9.1.3 (SAS Institute, Cary, NC) for these analyses. All *P* values were two-sided, and *P* values less than .05 were considered statistically significant.

Table 1. Baseline Characteristics of the Cohort According to Bisphosphonate Use

Characteristic	Nonuser (n = 82,035)			Bisphosphonate User (n = 4,242)		
	%	Mean	SD	%	Mean	SD
Age, years		64.5	7.1		67.7	6.5
White race	97.4			98.0		
Body mass index (kg/m^2)		26.8	5.3		24.4	4.4
Smoking						
Never	44.0			44.6		
Previous/current	56.0			55.6		
Family history of colorectal cancer	13.6			15.2		
History of osteoporosis	14.4			79.4		
Regular aspirin use*	45.5			48.1		
Hormone replacement therapy						
Premenopausal	3.1			0.5		
Never	23.7			25.2		
Previous/current	73.2			74.3		
Regular use of statin	16.0			19.9		
Total calcium intake (mg/d)†		1,011	364		1,196	404
Vitamin D intake (IU/d)		437	271		536	295
Folate intake (quantiles)†		4.5	2.9		5.2	2.8
Alcohol intake (g/d)		4.9	9.1		4.9	8.6
Physical activity (METs/wk)		17.7	16.2		17.8	15.7
History of polyps	10.8			12.9		
History of lower endoscopy	32.7			42.3		

NOTE. Baseline information is based on 1998 questionnaire.
Abbreviations: SD, standard deviation; MET, metabolic equivalent.
*Defined as ≥ two standard (325 mg) tablets per week.
†Energy-adjusted intake from diet and supplements.

RESULTS

Among 86,277 women, we documented 801 incident CRC cases over 814,406 person-years of follow-up. At baseline, in 1998, 4.9% of women regularly used bisphosphonates, increasing to 19.8% by 2008. Compared with participants who did not regularly use bisphosphonates, regular bisphosphonate users had a lower body mass index (BMI), consumed significantly more calcium and vitamin D, and were more likely to have a history of osteoporosis and to have undergone endoscopic screening for CRC (Table 1).

We observed a modest, nonsignificant reduction in the risk of developing CRC among bisphosphonate users compared with nonusers in the age-adjusted model (HR, 0.92; 95% CI, 0.73 to 1.14; Table 2). This association was significantly attenuated after adjusting for total intake of calcium or endoscopic screening. In a fully adjusted analysis, accounting for known or putative risk factors for CRC, the risk was further attenuated (multivariate-adjusted HR, 1.04; 95% CI, 0.82 to 1.33).

We also assessed the effect of duration of bisphosphonate use and risk of CRC. There remained no significant association with risk of CRC even among women with a longer duration of use (Table 3). Compared with nonusers of bisphosphonate, the multivariate-adjusted HRs of CRC were 1.24 (95% CI, 0.94 to 1.64) for women with 2 years of use, 1.16 (95% CI, 0.79 to 1.69) for 4 years of use, and 0.97 (95% CI, 0.60 to 1.56) for 6 to 10 years of use.

Table 2. Risk of Colorectal Cancer According to Bisphosphonate Use

Variable	Nonuser (706/712,802)* HR	Bisphosphonate User (95/101,604)* HR	95% CI
Age adjusted	Ref.	0.92	0.73 to 1.14
Age + calcium intake adjusted	Ref.	0.99	0.79 to 1.24
Age + screening adjusted	Ref.	0.96	0.77 to 1.20
Multivariate adjusted†	Ref.	1.04	0.82 to 1.33

Abbreviation: HR, hazard ratio; Ref., reference.
*No. of cases/No. of person-years.
†Adjusted for age (years), race (white, nonwhite), body mass index (< 21, 21-22.9, 23-24.9, 25-29.9, ≥ 30 kg/m^2), smoking status (current, past, never), family history (sibling, mother, or father) of colon cancer (yes, no), history of osteoporosis (yes, no), regular aspirin use (≥ two standard tablets per week), hormone replacement therapy (never, past, current), regular statin use (yes, no), total daily calcium intake (< 600, 600-899, 900-1,200, > 1,200 mg/d), vitamin D intake (< 400, 400-600, > 600 IU/d), folate intake (quintiles), red meat intake (< two per week, two to four per week, five to six per week, at least one per day), total daily alcohol intake (< 5, 5-15, > 15 g/d), level of physical activity (< 1.7, 1.7-4.5, 4.6-10.5, 10.6-22.1, > 22.1 metabolic equivalents per week), history of polyps (yes, no), and history of screening (yes, no).

We evaluated potential differences in the influence of bisphosphonate use according to strata of known risk factors (Table 4). The effect of bisphosphonate was not modified by strata defined by age, BMI, smoking history, use of postmenopausal hormones, regular use of aspirin, regular use of statins, screening, or dietary intake of calcium (all $P_{interaction} > .10$). We considered the possibility that any influence of bisphosphonates on risk of CRC may be confined to postmenopausal women. The multivariate-adjusted HR of CRC with regular use of bisphosphonate was 1.04 (95% CI, 0.82 to 1.33) among postmenopausal women.

We explored the influence of the primary indication for the use of bisphosphonates—osteoporosis—on the association between regular use of bisphosphonates and risk of CRC. The HR for development of incident CRC was significantly attenuated after additionally adjusting for osteoporosis (multivariate HR, 1.00; 95% CI, 0.79 to 1.27). In addition, although osteoporosis was inversely associated with risk of CRC (age-adjusted HR, 0.84; 95% CI, 0.72 to 0.99), further adjusting for calcium and vitamin D significantly attenuated this association (multivariate HR, 0.91; 95% CI, 0.77 to 1.06). This risk was further attenuated after fully adjusting for additional CRC risk factors (multivariate HR, 0.94; 95% CI, 0.79 to 1.10).

DISCUSSION

In this large, prospective study, which included 801 cases of CRC, we did not observe an association between regular use of bisphosphonates and risk of CRC over 10 years of follow-up. Although our results cannot exclude a protective effect of bisphosphonates with longer follow-up, we did not observe any evidence of a trend with increasing duration of use. Bisphosphonate-mediated inhibition of the mevalonate pathway is proposed as an anticancer mechanism shared with statins. However, we did not observe any association between bisphosphonate use and CRC within strata defined by statin use or other risk factors.

Our results are consistent with a previous case-control study[11] of 63,663 individuals nested in the United Kingdom General Practice Research Database, which showed no significant association between bisphosphonate use and risk of CRC, although their risk estimates were compatible with a possible weak inverse association (relative risk [RR], 0.87; 95% CI, 0.77 to 1.00).

Our findings notably differ with recent data from the Molecular Epidemiology of Colorectal Cancer (MECC) case-control study[11] conducted in Northern Israel, which observed that use of bisphosphonates for at least 1 year was associated with a 59% significant reduction in the risk of CRC. However, the MECC study had limited information on key potential confounders, including physical activity (assessed as participation in sports activities) and calcium or vitamin D intake (assessed only as use of supplements). Our study was able to more fully adjust for these factors by using validated instruments of leisure-time physical activity and dietary and supplemental calcium and vitamin D intake.[12,13] We were also able to account for the diagnosis of osteoporosis and the use of endoscopic screening, which were not assessed in the MECC study. In our analysis, adjustment for dietary intake of calcium or vitamin D, use of endoscopic screening, or a diagnosis of osteoporosis did attenuate the weak, nonsignificant association we observed in age-adjusted models (HR, 0.92). Thus, inadequate control for healthy behaviors associated with the primary indication for use of bisphosphonates (osteoporosis) could account for the inverse association observed in the MECC study. Our prospective cohort design also minimized bias related to differential recall of

Table 3. Risk of Colorectal Cancer According to Duration of Bisphosphonate Use

Variable	No. of Years of Regular Bisphosphonate Use: 0 (686/698,986)*	1-2 (63/63,563)* HR	1-2 (63/63,563)* 95% CI	3-4 (32/31,124)* HR	3-4 (32/31,124)* 95% CI	≥5 (20/27,004)* HR	≥5 (20/27,004)* 95% CI	P_{trend}
Age adjusted	1.00	1.10	0.85 to 1.44	0.99	0.68 to 1.42	0.78	0.49 to 1.23	.44
Multivariable adjusted†	1.00	1.24	0.94 to 1.64	1.16	0.79 to 1.69	0.97	0.60 to 1.56	.79

Abbreviation: HR, hazard ratio.
*No. of cases/No. of person-years.
†Adjusted for age (years), race (white, nonwhite), body mass index (< 21, 21-22.9, 23-24.9, 25-29.9, ≥ 30 kg/m^2), smoking status (current, past, never), family history (sibling, mother, or father) of colon cancer (yes, no), history of osteoporosis (yes, no), regular aspirin use (≥ two standard tablets per week), hormone replacement therapy (never, past, current), regular statin use (yes, no), total daily calcium intake (< 600, 600-899, 900-1,200, > 1,200 mg/d), vitamin D intake (< 400, 400-600, > 600 IU/d), folate intake (quintiles), red meat intake (< two per week, two to four per week, five to six per week, at least one per day), total daily alcohol intake (< 5, 5-15, > 15 g/d), level of physical activity (< 1.7, 1.7-4.5, 4.6-10.5, 10.6-22.1, > 22.1 metabolic equivalents per week), history of polyps (yes, no), and history of screening (yes, no).

Table 4. Risk of Colorectal Cancer According to Use of Bisphosphonate in Selected Strata

Variable	Nonuser		Bisphosphonate User			$P_{interaction}$
	No. of Cases/No. of Person-Years	HR	No. of Cases/No. of Person-Years	HR	95% CI	
Age ≤ 65 years	249/388,320		29/43,209			.26
Age adjusted		Ref.		1.12	0.75 to 1.67	
Multivariate adjusted*		Ref.		1.29	0.83 to 2.00	
Age > 65 years	324,482		66/58,395			
Age adjusted		Ref.		0.85	0.65 to 1.10	
Multivariate adjusted*		Ref.		0.95	0.71 to 1.27	
Body mass index ≤ 25 kg/m^2	309/328,845		60/64,378			.67
Age adjusted		Ref.		0.96	0.72 to 1.28	
Multivariate adjusted*		Ref.		1.04	0.76 to 1.43	
Body mass index > 25 kg/m^2	397/383,958		35/37,225			
Age adjusted		Ref.		0.88	0.62 to 1.26	
Multivariate adjusted*		Ref.		1.00	0.69 to 1.48	
Calcium intake < 900 mg/d	342/261,738		28/21,341			.57
Age adjusted		Ref.		1.03	0.69 to 1.54	
Multivariate adjusted*		Ref.		1.07	0.70 to 1.65	
Calcium intake ≥ 900 mg/d	392/451,064		67/80,262			
Age adjusted		Ref.		0.95	0.73 to 1.24	
Multivariate adjusted*		Ref.		1.05	0.78 to 1.41	
Hormonal replacement therapy, current/previous use	417/483,952		33/30,237			.62
Age adjusted		Ref.		1.00	0.76 to 1.32	
Multivariate adjusted*		Ref.		1.11	0.82 to 1.51	
Hormone replacement therapy, never used	289/188,850		62/71,367			
Age adjusted		Ref.		0.80	0.55 to 1.15	
Multivariate adjusted*		Ref.		0.95	0.63 to 1.43	
Regular user of aspirin	264/321,881		34/46,709			.78
Age adjusted		Ref.		0.92	0.64 to 1.33	
Multivariate adjusted*		Ref.		1.05	0.71 to 1.57	
Nonuser of aspirin	442/390,921		61/54,895			
Age adjusted		Ref.		0.91	0.69 to 1.20	
Multivariate adjusted*		Ref.		1.04	0.77 to 1.42	
Current or previous smoker	443/394,356		58/55,237			.85
Age adjusted		Ref.		0.92	0.70 to 1.23	
Multivariate adjusted*		Ref.		1.02	0.75 to 1.39	
Never smoker	263/318,445		37/46,367			
Age adjusted		Ref.		0.93	0.65 to 1.33	
Multivariate adjusted*		Ref.		1.12	0.76 to 1.65	
History of screening	460/384,048		48/37,653			.90
Age adjusted		Ref.		0.98	0.71 to 1.35	
Multivariate adjusted*		Ref.		1.08	0.75 to 1.54	
No history of screening	246/328,753		47/63,950			
Age adjusted		Ref.		0.94	0.69 to 1.28	
Multivariate adjusted*		Ref.		1.03	0.74 to 1.43	
Regular user of statin	188/172,740		30/33,647			.45
Age adjusted		Ref.		0.78	0.52 to 1.17	
Multivariate adjusted*		Ref.		0.97	0.62 to 1.51	
Nonuser of statin	476/479,806		62/60,524			
Age adjusted		Ref.		1.00	0.76 to 1.31	
Multivariate adjusted*		Ref.		1.10	0.81 to 1.48	

Abbreviation: HR, hazard ratio; Ref., reference.
*Adjusted for same variables as Table 5 minus the strata covariate.

potentially confounding lifestyle and dietary risk factors and the selection or participation biases inherent in case-control designs. Such biases may, in part, explain other protective associations between high BMI (≥ 30 kg/m^2), statin use, and CRC observed in the MECC case-control study that have not been corroborated by prospective cohort studies.[18-22]

Our results also contrast with a recent case-control analysis nested in Manitoba's population database in which Singh et al[23] concluded that bisphosphonate use was associated with a lower risk of CRC. However, a borderline statistically significant inverse association was observed only in a multivariate model, which adjusted for age, sex, socioeconomic status, number of ambulatory care visits,

prior exposure to lower endoscopy, nonsteroidal anti-inflammatory drug use, and Charlson comorbidity index score (RR, 0.84; 95% CI, 0.71 to 1.00).[23] A strong inverse association with bisphosphonate use was restricted to risedronic acid, the least commonly used agent in the class (9%). The age-adjusted association with alendronate, the most commonly used agent (79%; RR, 0.91; 95% CI, 0.78 to 1.05) was strikingly similar to our results (RR, 0.92). However, as with the MECC study, the analysis of the Manitoba database was unable to account for physical activity and vitamin D and calcium intake that confounded the association between bisphosphonate use and CRC in our analysis.

Our study has several limitations. First, we did not have information about bisphosphonate use in participants before 1998. However, the prevalence of use in 1998 was low (4.9%) and steadily increased through 2008, reflecting secular trends in the use of these drugs over time. Thus, misclassification of use before 1998 was likely extremely low. Second, we did not have specific information on the type or brand of bisphosphonate and the doses used or use of intravenous formulations. Thus, we cannot completely exclude the possibility that use of higher doses or specific types of bisphosphonates may have a differential association as was suggested by the Manitoba case-control study that observed a strong inverse association with risedronic acid, the least commonly used agent of the class. Third, our follow-up was limited to 10 years and it remains possible that longer-term use is protective. Last, we cannot exclude the possibility of a modest inverse association between bisphosphonates and CRC within the lower limit of our confidence bounds. However, on the basis of the number of cases of CRC and prevalence of bisphosphonate use, our study had greater than 80% power at a significance level of 0.05 to detect an RR of 0.75, a far more modest association than that observed in the MECC study.

In summary, although bisphosphonates are recommended for many individuals with osteoporosis and skeletal metastases, in this prospective cohort study, we found no support for the hypothesis that bisphosphonates prevent CRC. As with statin drugs, additional prospective studies may not confirm the promising results of case-control studies.[18,19]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
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