Use of Bisphosphonates and Reduced Risk of Colorectal Cancer

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ABSTRACT

Purpose

Bisphosphonates are commonly used for the treatment of osteoporosis and bone metastases caused by breast cancer and were recently reported to be associated with a reduced risk of breast cancer, possibly acting through the mevalonate pathway, but their association with risk of other cancers is unknown.

Patients and Methods

The Molecular Epidemiology of Colorectal Cancer study is a population-based, case-control study in northern Israel of patients with colorectal cancer and age-, sex-, clinic-, and ethnic group-matched controls. Long-term use of bisphosphonates before diagnosis was assessed in a subset of 933 pairs of postmenopausal female patients and controls, enrolled in Clalit Health Services, using computerized pharmacy records.

Results

The use of bisphosphonates for more than 1 year before diagnosis, but not for less than 1 year, was associated with a significantly reduced relative risk (RR) of colorectal cancer (RR, 0.50; 95% CI, 0.35 to 0.71). This association remained statistically significant after adjustment in a model for vegetable consumption, sports activity, family history of colorectal cancer, body mass index, and use of low-dose aspirin, statins, vitamin D, and postmenopausal hormones (RR, 0.41; 95% CI, 0.25 to 0.67). Concomitant use of bisphosphonates and statins did not further reduce the risk.

Conclusion

The use of oral bisphosphonates for more than 1 year was associated with a 59% relative reduction in the risk of colorectal cancer, similar to the recently reported association of this drug class with reduction in breast cancer risk.

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INTRODUCTION

Bisphosphonates are widely used in the treatment of osteoporosis¹ and of bone metastases in patients with breast cancer and are being considered for prevention of skeletal lesions caused by malignancy.^{2,3} This class of drugs has recently been associated with reduced risk of breast cancer.⁴⁻⁶ Nitrogen-containing bisphosphonates inhibit protein prenylation through inhibition of the mevalonate pathway.⁷ Isoprenoid biosynthesis is required for a variety of cancer cell growth-related cellular processes and for development of metastasis; its inhibition by bisphosphonates is associated with anticancer activity.⁸⁻¹² Inhibition of angiogenesis and of tumor cell adhesion and promotion of apoptosis are other antitumor mechanisms that have been suggested for bisphosphonates.^{13,14} Demonstrating an association with other tumors sites could point at a possible global, rather than site-specific,

effect. Thus far, no association has been reported regarding bisphosphonate use and the risk of colorectal cancer.

PATIENTS AND METHODS

Participants

The Molecular Epidemiology of Colorectal Cancer study is a population-based, case-control study of incident colorectal cancer in northern Israel. Recruitment to this ongoing study started on March 31, 1998. Controls were identified from the same source population with the use of the Clalit Health Services (CHS) database. CHS is the largest health care provider in Israel and covered, during the study years, approximately 70% of the older population (persons at least 60 years of age). Health care coverage in Israel is mandatory and is provided by four groups akin to not-for-profit health maintenance organizations. Thus, all study participants (patients and controls) had a similar basic health insurance plan and similar access to health services. Controls were individually matched to patients according to the year of birth, sex, residence as defined by

primary clinic location, and ethnic group (Jewish *v* non-Jewish). If the potential control refused, another potential control was chosen according to the same matching criteria. Potential controls were excluded if they had a history of colorectal cancer, as were patients. Participants provided written informed consent at the time of enrollment and were interviewed to obtain information about their personal and family history of cancer, reproductive history, medical history, medication use, and health habits.¹⁵ A validated food frequency questionnaire adapted to the Israeli diet¹⁶ was used to study the association of various dietary components with the risk of colorectal cancer. Diagnoses of colorectal cancer were made independently by the diagnosing hospitals and were confirmed by means of a standardized pathologic review by one pathologist. Included in this analysis are women (patients and controls) who reported being postmenopausal at time of diagnosis (for patients) or interview (for controls) or were over the age of 55 years and only CHS insurees (for all of whom prescription data were available). The institutional review boards at the Carmel Medical Center (Haifa, Israel) and the University of Michigan (Ann Arbor, MI) approved all procedures.

Exposure Data

The use of bisphosphonates was determined based on CHS pharmacy records that were available for all study participants included in this analysis. Detailed prescription information enabled us to evaluate the dose-response relationship between duration of bisphosphonate use and the risk of colorectal cancer. Because of the low copayment, it is unlikely that prescription medications were purchased in private, non-CHS pharmacies.

Relevant exposure variables known to be associated with colorectal cancer risk were tested as possible confounders or effect modifiers. These variables included the following: family history, which was defined as the report of colorectal cancer in at least one first-degree relative; self-reported engagement in sports activity (dichotomous variable); Jewish ethnic group, which was determined by self-described ethnic group and country of birth of parents and grandparents and analyzed as Ashkenazi or Eastern European compared with all others; vegetable consumption, which was categorized into two groups based on the median number of servings consumed per day in the control group ($< v \geq$ five servings per day); body mass index (BMI; calculated from self-reported height and weight) categorized into normal and overweight versus obese (≥ 30 kg/m²); and statin use, which was taken from the CHS pharmacy records. Use of low-dose aspirin at least once per day for at least 3 years, use of calcium supplements and vitamin D supplements for at least 1 year, and use of any postmenopausal hormones were self-reported because they could be purchased over the counter in any pharmacy. Red meat consumption, categorized into portions per day, was recorded but was not used in the analysis because only 8% of the participants reported consuming more than one portion per week.

Statistical Analysis

Statistical analyses were performed using SPSS (version 15.0; SPSS, Chicago, IL), with reported two-sided *P* values. A contingency table was used to assess crude associations between bisphosphonate use and the risk of colorectal cancer. Analyses were performed using all controls and only first chosen controls to evaluate possible selection bias. Conditional logistic regression was used to assess the main association between bisphosphonate use and the risk of colorectal cancer, adjusting for other known risk factors.

RESULTS

Findings reported here are based on data from 933 pairs of CHS postmenopausal women enrolled on this ongoing study, recruited between 2000 and 2006, for whom all data sources (questionnaires and pharmacy data) were available at time of analysis. The overall study response rate was 75.5% of all eligible patients. Among patients who were located and approached, 83.3% agreed to participate, 2.2% were unable to participate because of medical or language problems, and 14.5% declined to participate. The median time between patient diagnosis and interview was 1 week, and median time between patient

interview and the interview of the patient's matched control was 5 months. Of all randomly chosen population controls invited to participate, 57.6% consented.

Corresponding with the known epidemiology patterns for colorectal cancer in Israel, Ashkenazi Jews were over-represented among the patients compared with non-Ashkenazi Jews and Arabs.¹⁷ First-degree family history of colorectal cancer, low vegetable consumption, and low level of physical activity were all positively associated with colorectal cancer risk, whereas use of low-dose daily aspirin for more than 3 years, use of statins for more than 1 year, and use of postmenopausal hormones were inversely related to colorectal cancer risk (Table 1). Being obese (BMI ≥ 30 kg/m²) was inversely associated with colorectal cancer risk.

Using pharmacy records to include all bisphosphonate users who filled at least three prescriptions before diagnosis of colorectal cancer (138 controls, 14.8%; 97 patients, 10.4%), a significant reduction in risk of colorectal cancer was found, with a relative risk (RR) of 0.67 (95% CI, 0.51 to 0.88). Similar associations were achieved when the analysis was restricted to first chosen controls and also when all potential participants (CHS patients and controls, including nonresponders) were included (unadjusted RR, 0.61; 95% CI, 0.47 to 0.80).

Duration of use and type of medication were available from pharmacy records. Alendronate was used by 94.7% of the bisphosphonate users in our study. Of these users, 60% used 10 mg daily, and 40% used 70 mg weekly. Compliance with daily use was estimated at 89%, and compliance with use of weekly agents was estimated at 96%. A significant negative association with colorectal cancer risk was demonstrated only in those who used bisphosphonates for more than 1 year (Table 2). Because bisphosphonates and statins both act through blocking the same mevalonate pathway, we studied the effects of concomitant use of both drugs on risk of colorectal cancer. Although bisphosphonate use and statin use each demonstrated a strong negative association, the combined use was not associated with further risk reduction (data not shown).

The association between bisphosphonate use for more than 1 year and colorectal cancer risk did not change significantly in a conditional regression model including the following variables from the study questionnaire: family history, BMI, sports participation, vegetable consumption, and use of low-dose aspirin, statins, vitamin D, and postmenopausal hormones (RR, 0.41; 95% CI, 0.25 to 0.67; Table 3). The degree of risk reduction with use of bisphosphonates for a year or more was similar for the right colon (odds ratio [OR], 0.49; 95% CI, 0.29 to 0.85), left colon (OR, 0.50; 95% CI, 0.29 to 0.86), and rectum (OR, 0.50; 95% CI, 0.23 to 1.08).

DISCUSSION

These data show a significant negative association between use of bisphosphonates and colorectal cancer risk, possibly suggesting a protective effect against colorectal cancer development. This study follows previous reports of similar negative association between bisphosphonate use and breast cancer risk.⁴⁻⁶ However, although the negative association with breast cancer could not be fully separated from the known negative association between low bone density (which could have led to the use of bisphosphonates) and lower risk of breast cancer, in the case of colorectal cancer, low bone density has never been proven to be a risk factor for colorectal

Table 1. Comparison of Major Self-Reported Study Variables Between Postmenopausal Patients and Controls From the CHS

Variable	Patients (n = 933)		Controls (n = 933)		P for Difference
	No.	%	No.	%	
Mean age, years	71.1		72.0		NS
Ethnicity					.02
Arab	107	11.5	108	11.6	
Ashkenazi Jew	638	67.3	573	61.4	
Sephardi Jew	166	17.8	222	23.8	
Mixed/other Jew	16	1.7	11	1.2	
Non-Jew, non-Arab	16	1.7	19	2.0	
Family history of colorectal cancer in first-degree relative	120	13.3	75	8.1	< .001
Sports activity (yes)	221	24.6	342	36.7	< .001
Vegetables (≥ 5 portions/day)	461	53.3	538	57.9	.05
BMI (≥ 30 kg/m ²)	167	20.9	234	27.5	.002
Aspirin use (low dose, once a day for at least 3 years)	110	12.3	190	20.5	< .001
Statin use (≥ 1 year)	234	25.1	360	38.6	< .001
Postmenopausal hormone use (any)	76	8.5	131	14.3	< .001
Calcium supplement use (≥ 1 year)	75	8.0	154	16.5	< .001
Vitamin D supplement use (≥ 1 year)	54	5.8	134	14.4	< .001
Bisphosphonate use (≥ 3 prescriptions)	97	10.4	138	14.8	.004
Bisphosphonate use (> 1 year)	53	5.7	100	10.7	< .001

Abbreviations: CHS, Clalit Health Services; NS, not significant; BMI, body mass index.

cancer, with some studies suggesting that osteoporosis increases the risk of colorectal cancer^{18,19} and another suggesting a possible negative association in postmenopausal women.²⁰ Recent data have raised the possibility that bisphosphonate use is associated with increased risk of esophageal cancer, but the findings were conflicting, limited to long-term use, and different for various types of bisphosphonates used.^{21,22} Our findings in users of oral bisphosphonate preparations are consistent with preclinical data suggesting biologic plausibility through a variety of anticancer effects of this drug group, none of which, however, were described in colon tissue.⁸⁻¹² In addition, the intravenous use of a member of this drug class for bone metastasis control in patients with breast cancer was associated in randomized controlled trials with reduction in risk of contralateral breast cancers⁵ and reduction in risk of bone metastases.^{3,23,24}

Bisphosphonates, as inhibitors of isoprenoid biosynthesis, have been shown to exert direct antitumor effects in vitro (inhibit tumor cell adhesion and invasion of the extracellular matrix) and in cell lines (reduce proliferation and induce apoptosis) and have antiangiogenic

properties as evidenced by reduced vascular endothelial growth factor levels.^{14,25,26} In addition, bisphosphonates have been shown to reduce skeletal tumor burden in a variety of animal models,²⁷⁻²⁹ either by direct antitumor activity or indirect effects via osteoclast inhibition and alteration of the bone microenvironment. Recently, it was shown that ibandronate, a member of the nitro-bisphosphonate class, reduced the incidence of colorectal dysplasia and reduced expression of thymidine kinase mRNA in the colorectum of mice with induced ulcerative colitis.³⁰

Bisphosphonates inhibit the same mevalonate pathway as do statins, and the combined effect of these two drug groups has been demonstrated, both by increased bone density in hypercholesterolemic osteoporotic women who added statins to their bisphosphonate treatment^{31,32} and by reduced lipid levels with the addition of

Table 2. Association Between Use of Bisphosphonates and Risk of Postmenopausal Colorectal Cancer by Number of Years of Bisphosphonate Use

Bisphosphonate Use	No. of Patients (n = 933)	No. of Controls (n = 933)	OR	95% CI
No use	836	795	1.00	
Any use	97	138	0.67	0.51 to 0.88
< 1 year of use	44	38	1.10	0.71 to 1.72
≥ 1 year of use	53	100	0.50	0.36 to 0.71
> 2 years of use	34	64	0.51	0.34 to 0.79
> 3 years of use	18	45	0.39	0.22 to 0.68

Abbreviation: OR, odds ratio.

Table 3. Final Conditional Logistic Regression Model of the Association of Use of Bisphosphonates With Colorectal Cancer Risk in Postmenopausal Women in the MECC Study (N = 1,866 CHS participants)

Variable	RR	95% CI
Bisphosphonate use (> 1 year)	0.41	0.25 to 0.67
Family history of colorectal cancer in first-degree relative	1.89	1.25 to 2.86
Sports activity (yes)	0.57	0.43 to 0.75
BMI (≥ 30 kg/m ²)	0.57	0.43 to 0.76
Aspirin use (low dose, once a day for at least 3 years)	0.64	0.45 to 0.90
Statin use (≥ 1 year)	0.59	0.45 to 0.78
Postmenopausal hormone use (any)	0.49	0.33 to 0.74
Vitamin D supplement use (≥ 1 year)	0.44	0.25 to 0.78
Vegetables (≥ 5 portions/day)	0.82	0.63 to 1.06
Calcium supplement use (≥ 1 year)	0.66	0.40 to 1.10

Abbreviations: MECC, Molecular Epidemiology of Colorectal Cancer; CHS, Clalit Health Services; RR, relative risk; BMI, body mass index.

bisphosphonates.³³⁻³⁵ In our data, the protective association of bisphosphonates was demonstrated separately from the significant protective association of statins, but no additive protection was demonstrated in users of both drugs concomitantly. Similarly, the protective effect of use of aspirin against colorectal cancer, which has also been shown to reduce estrogen levels and possibly affect the risk of osteoporosis and breast cancer,³⁶ was demonstrated independently of the effect of bisphosphonates.

Bisphosphonates are widely used to treat osteoporosis¹ and bone metastases.³⁷ Their adverse effects profile, although not fully clear,^{38,39} includes the rare adverse effect of osteonecrosis of the jaw⁴⁰ and a possibility of higher risk of fractures after prolonged treatment periods.⁴¹ The adverse effects profile is of major importance if bisphosphonates are to be recommended for cancer prevention in healthy people. Similar to the case with breast cancer, the protective effect of bisphosphonates in our study was demonstrated after only 1 year of use and did not change meaningfully with extended periods of use. Because this class of medications is known to be stable in the bone for many years after its administration,⁴² further research should focus on the optimal length of intervention needed to achieve cancer risk reduction.

This study has several limitations. Participation in the study was partial, mainly because of candidate refusal to participate. This phenomenon was more minor in patients than in controls, which could lead to participation bias. However, the participation rate among the identified patients was within commonly described rates in case-control studies, whereas the controls were randomly selected from a population register and replaced if they refused by another randomly selected control, aiming at minimized selection bias. To evaluate possible selection bias, we also analyzed the data by first chosen controls and, to a limited extent, for nonparticipants for whom we had access to pharmacy records. These analyses yielded similar point estimates and CIs as those shown in the tables. Data on possible risk factors were collected retrospectively and, therefore, could be prone to recall bias. However, all risk factors for colorectal cancer reported in this study behaved according to expectation based on other studies reported in the literature, with the exception of obesity. However, obesity has been

shown not to be associated with risk of colorectal cancer in postmenopausal hormone replacement therapy users.⁴³ Being able to assess a large variety of potential confounders helped us demonstrate the strength of the association between bisphosphonates and colorectal cancer risk in a multivariate model. Because the main effect of bisphosphonate use was ascertained through pharmacy records, no recall bias was involved. We could not evaluate the degree of compliance of the study participants with the doses recommended in the filled prescriptions. One way of doing so could be by observing changes in bone density, but such data were not available in this study. However, these results should serve as hypothesis generating only, because it cannot be excluded that unknown confounding factors, associated with healthy behavior, both trigger bisphosphonate use and lower colorectal cancer risk.

Overall, these data provide evidence that oral bisphosphonates may be effective for prevention of colorectal cancer in postmenopausal women. The study demonstrated a 59% reduction in risk after adjustment for many known risk factors for colorectal cancer. This significant negative association, as seen with breast cancer, calls for consideration of bisphosphonates for future chemoprevention studies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Gad Rennert, Stephen B. Gruber

Collection and assembly of data: Gad Rennert, Mila Pinchev, Hedy S. Rennert, Stephen B. Gruber

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