VOLUME 33 · NUMBER 10 · APRIL 1 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Oral Bisphosphonate Use and Risk of Postmenopausal Endometrial Cancer

Polly A. Newcomb, Michael N. Passarelli, Amanda I. Phipps, Garnet L. Anderson, Jean Wactawski-Wende, Gloria Y.F. Ho, Mary Jo O'Sullivan, and Rowan T. Chlebowski

Polly A. Newcomb, Michael N. Passarelli, Amanda I. Phipps, and Garnet L. Anderson, Fred Hutchinson Cancer Research Center; Polly A. Newcomb, Michael N. Passarelli, Amanda I. Phipps, and Garnet L. Anderson, School of Public Health, University of Washington, Seattle, WA; Jean Wactawski-Wende, School of Public Health and Health Professions, University at Buffalo, The State University of New York, Buffalo; Gloria Y.F. Ho, Albert Einstein College of Medicine, Bronx, NY; Mary Jo O'Sullivan, University of Miami, Miami, FL; and Rowan T. Chlebowski, Los Angeles Biomedical Research Institute at Harbor–University of California Los Angeles Medical Center, Torrance, CA.

Published online ahead of print at www.jco.org on February 23, 2015.

The Women's Health Initiative program is supported by the National Heart, Lung, and Blood Institute; National Institutes of Health; and US Department of Health and Human Services through Contracts No. HHSN268201100046C, HHSN268201100001C, HHSN268201100002C, HHSN268201100003C, HHSN268201100004C, and HHSN271201100004C. P.A.N., M.N.P., and A.I.P. were additionally supported by the National Cancer Institute at the National Institutes of Health (Grants No. K05 CA152705, T32 CA009168, and K07 CA172298, respectively).

Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

Corresponding author: Polly A. Newcomb, PhD, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave N, M4-B402, Seattle, WA 98109; e-mail: pnewcomb@fhcrc.org.

0732-183X/15/3310w-1186w/$20.00

DOI: 10.1200/JCO.2014.58.6842

ABSTRACT

Purpose
Bisphosphonates are common medications used for the treatment of osteoporosis and are also used to reduce metastases to bone in patients with cancer. Several studies, including the Women's Health Initiative (WHI), have found that use of bisphosphonates is associated with reduced risk of developing breast cancer, but less is known about associations with other common malignancies. This study was aimed at examining the effects of bisphosphonates on the risk of endometrial cancer.

Methods
We evaluated the relationship between use of oral bisphosphonates and endometrial cancer risk in a cohort of 89,918 postmenopausal women participating in the WHI. A detailed health interview was conducted at baseline, and bisphosphonate use was ascertained from an inventory of regularly used medications at baseline and over follow-up. All women had an intact uterus at the time of study entry.

Results
During a median follow-up of 12.5 years, 1,123 women were diagnosed with incident invasive endometrial cancer. Ever use of bisphosphonates was associated with reduced endometrial cancer risk (adjusted hazard ratio, 0.80; 95% CI, 0.64 to 1.00; $P = .05$), with no interactions observed with age, body mass index, or indication for use.

Conclusion
In this large prospective cohort of postmenopausal women, bisphosphonate use was associated with a statistically significant reduction in endometrial cancer risk.

J Clin Oncol 33:1186-1190. © 2015 by American Society of Clinical Oncology

INTRODUCTION

Bisphosphonates are widely used for the prevention and treatment of osteoporosis; in 2007, nearly 6 million patients received prescriptions for this indication.[1] Aminobisphosphonates, the most active of these drugs, also have cytostatic, proapoptotic, and antimetastatic properties[2] and have been inversely associated with breast cancer risk in some,[3-6] but not all,[7] studies. Hormonally mediated endometrial cancer shares many risk factors with breast cancer,[8] and previous studies have reported reduced risk of endometrial cancer in women with a history of fractures,[9,10] providing support for this thesis. A few small retrospective studies of bisphosphonate use and endometrial cancer have been published with inconsistent findings.[11-13] We examined this association in the well-annotated Women's Health Initiative (WHI), a prospective cohort involving four randomized clinical trials (WHI-CT) and a large observational study (WHI-OS). Use of oral bisphosphonates was ascertained for WHI participants at baseline and over the follow-up period.

METHODS

Study Population

WHI enrolled 161,808 postmenopausal women, age 50 to 79 years, from 40 clinical sites across the United States between 1993 and 1998. WHI-OS participants were generally similar to those of WHI-CT but were ineligible or unwilling to be included in a randomized trial. Details of the WHI recruitment, eligibility criteria, and protocols have been published elsewhere.[14-17] All participants provided informed consent. The institutional review boards at all WHI institutions approved the protocols and procedures.

Measurement of Health Characteristics and Oral Bisphosphonate Use

All women were personally interviewed regarding general health information at baseline. An inventory of all

current, regularly used medications, including oral bisphosphonates, was taken at baseline and at 1, 3, and 6 years after random assignment for WHI-CT components. The same inventory was performed at baseline and 3 years after for WHI-OS. Participants were instructed to provide medication bottles or packaging for drugs taken at least twice per week during the previous 2 weeks. All medications were matched to the Medi-Span (Indianapolis, IN) Master Drug Data Base to ascertain detailed ingredient information. Intravenous bisphosphonates were not included.

Follow-Up for Endometrial Cancer Diagnoses

WHI participants reported diagnoses of invasive endometrial cancer, or hysterectomy for any reason, semi-annually (WHI-CT) or annually (WHI-OS). Incident endometrial cancers were adjudicated centrally by physicians through medical and pathology records review.[15] Follow-up was censored at the earliest of the following events: time of hysterectomy, last known follow-up, or August 2010. The vast majority of endometrial cancers (81%) were diagnosed at local stage.

Study Exclusions

Women reporting a history of endometrial or breast cancer, hysterectomy, antiestrogen use, or hormone therapy specifically to treat bone fracture before study entry were excluded from analyses, as were women with missing information on endometrial cancer or hysterectomy at baseline or during follow-up. Requiring women to have an intact uterus at baseline led to the exclusion of all 10,739 women who participated in an estrogen-alone randomized trial. The final analytic study population included 89,918 WHI participants.

Statistical Analyses

We estimated adjusted hazard ratios (HRs) with 95% CIs from Cox regression models comparing bisphosphonate users to nonusers, treating bisphosphonate use as a time-varying never/ever variable, with baseline hazard stratified by WHI study component and adjustment for the following baseline covariates: age, 5-year hip fracture probability,[18] body mass index (BMI), race, education, smoking status, estrogen-only use, estrogen-progestin use, oral contraceptive use, parity, and mammography. The 5-year hip fracture probability considers age, race, weight, height, self-reported health, diabetes, physical activity, bone fracture after age 54 years, parental hip fracture, smoking, and corticosteroid use. We considered further stratification by intervention arm of WHI-CT in sensitivity analyses. The proportional hazards assumption was assessed by testing for interactions with log-transformed time on study.

Bisphosphonate use was treated as a time-varying never/ever variable by updating baseline use at years 1, 3, and 6 for women in WHI-CT and at year 3 for women in WHI-OS. We permitted nonusers to become users over follow-up, but users could not become nonusers. We assessed interactions in the association between bisphosphonate use and endometrial cancer by age, BMI, and hip fracture probability score, each measured at baseline. All statistical tests were performed using SAS version 9.2 (SAS Institute, Cary, NC) and were two-sided, with $P \leq .05$ considered statistically significant.

RESULTS

Of the 89,918 women included in our analyses, 39,261 (44%) were enrolled onto one or more of the three randomized trials, and 50,657 (56%) were exclusively in the WHI-OS. Bisphosphonate use at baseline was uncommon (2%) but had markedly increased by year 6 (10%). Alendronate was the most common type of bisphosphonate, accounting for more than 90% of use.

Users of any type of bisphosphonate at baseline were slightly older, more highly educated, less likely to be current smokers, and leaner than nonusers (Table 1). Users and nonusers were not that different in their use of hormone therapy before enrollment. Compared with nonusers, however, a lower percentage of bisphosphonate users at baseline participated in the combined estrogen plus progestin randomized trial (19% of nonusers and 11% of users, but treatment and placebo arms were well-balanced between users and nonusers).

During study follow-up, 1,123 women were diagnosed with incident endometrial cancer (1,070 nonusers and 53 users of bisphosphonates). The crude incidence of endometrial cancer was 12 per 10,000 person-years of follow-up among nonusers and eight per 10,000 person-years among users of any type of bisphosphonate (seven per 10,000 person-years among alendronate users). Bisphosphonate use was inversely associated with age-adjusted endometrial cancer risk (HR, 0.76; 95% CI, 0.61 to 0.94; $P = .01$; Table 2). The inclusion of confounders, selected a priori, left the association largely unchanged (bisphosphonate users: HR, 0.80; 95% CI, 0.64 to 1.00; $P = .05$; alendronate users: HR, 0.77; 95% CI, 0.61 to 0.98; $P = .03$). In models without adjustment for variables already accounted for in the Robbin's fracture probability (age, race, smoking, and BMI), the HR for bisphosphonate use changed from 0.80 (95% CI, 0.64 to 1.00) to 0.74 (95% CI, 0.59 to 0.92).

The magnitude of HRs was similar for different durations of use, but the HRs were less precise than the estimate ignoring duration of use. Results were largely unchanged in models that also stratified the baseline hazard by intervention arm of each randomized trial. We found no statistically significant interactions with BMI ($P = .41$), age at baseline ($P = .21$), or hip fracture probability score ($P = .83$).

DISCUSSION

In this large cohort of postmenopausal women, oral bisphosphonate use was associated with a statistically significant reduction in endometrial cancer risk. The mechanisms underlying the observed relationship are unclear. Bisphosphonates prevent metastasis to bone,[19] and numerous in vivo studies have demonstrated their proapoptotic and antiangiogenic properties.[20,21] This association might be hormonally mediated, especially given that bisphosphonate history is most strongly, if not exclusively, associated with lower risk of hormone receptor–positive breast cancer as shown in the study of contralateral breast cancer by Monsees et al.[6]

To our knowledge, this is the first prospective study to evaluate bisphosphonate use and endometrial cancer risk. The relationship has been evaluated in the United Kingdom General Practice Database, where the findings were inconsistent,[11,12] and the Cancer in the Ovary and Uterus Study (CITOUS), which found that the use of bisphosphonates was associated with reduced risk of endometrial cancer.[13] The 20% reduction in risk we observed is far more modest than the 60% reduction reported in CITOUS. Although CITOUS determined bisphosphonate use from pharmacy records, limiting the potential for recall bias, this bias could have been introduced from the measurement of other covariates, which were collected retrospectively from self-report.

The results presented here have limitations. This analytic study design is observational rather than randomized.[22] Therefore, confounding is a possibility because women using oral bisphosphonates may have done so because of their high fracture risk as a result of low endogenous estrogen, perhaps as a consequence of low weight, which could place them at low endometrial cancer risk.[23] We carefully controlled for weight and considered various approaches to define this

Table 1. Baseline Demographics and Clinical Characteristics of Women's Health Initiative Participants According to Use of Oral Bisphosphonates (1993 to 2010)

	Oral Bisphosphonate User							
	At Baseline				At Baseline, Year 1, or Year 3*			
	No (n = 88,073)		Yes (n = 1,845)		No (n = 76,993)		Yes (n = 6,293)	
Characteristic	No.	%	No.	%	No.	%	No.	%
Age at eligibility screening, years								
Mean	62.9		67.2		62.8		66.1	
SD	7.2		6.4		7.1		6.6	
50-59	31,084	35.3	229	12.4	27,627	35.9	1,091	17.3
60-69	39,009	44.3	887	48.1	34,119	44.3	3,144	50.0
≥ 70	17,980	20.4	729	39.5	15,247	19.8	2,058	32.7
Race/ethnicity								
White	74,459	85.7	1,671	91.5	65,447	86.2	5,700	91.8
Black/African American	6,177	7.1	19	1.0	5,286	7.0	101	1.6
Hispanic/Latino	3,354	3.9	40	2.2	2,780	3.7	113	1.8
Asian/Pacific Islander	2,536	2.9	97	5.3	2160	2.8	290	4.7
American Indian/Alaskan native	319	0.4	0	0.0	269	0.4	6	0.1
Other/missing	1,228	—	18	—	1,051	—	83	—
Education								
Less than high school	3,998	4.6	59	3.2	3,345	4.4	179	2.9
High school/vocational	22,129	25.3	425	23.2	19,428	25.4	1,433	23.0
Some college	23,097	26.4	398	21.7	20,157	26.4	1,475	23.6
College	10,561	12.1	278	15.2	9,305	12.2	868	13.9
Graduate/professional	27,656	31.6	671	36.6	24,233	31.7	2,285	36.6
Missing	632	—	14	—	525	—	53	—
Body mass index, kg/m^2								
Mean	27.6		25.1		27.7		25.1	
SD	5.9		4.8		5.8		4.6	
< 25	32,749	37.2	1,052	57.0	28,160	36.6	3,549	56.4
25 to < 30	29,939	34.0	562	30.5	26,343	34.2	1,939	30.8
≥ 30	24,576	27.9	222	12.0	21,794	28.3	753	12.0
Missing	809	—	9	—	696	—	52	—
Smoking								
Never	43,833	50.4	990	54.3	38,564	50.7	3,309	53.3
Former	36,961	42.5	747	41.0	32,291	42.5	2,584	41.6
Current	6,145	7.1	85	4.7	5,195	6.8	316	5.1
Missing	1,134	—	23	—	943	—	84	—
Parity, No. of children								
Nulliparous	11,131	12.7	284	15.5	9,639	12.6	906	14.5
1	7,718	8.8	148	8.1	6,658	8.7	512	8.2
2	22,040	25.2	472	25.7	19,245	25.2	1,625	25.9
3	21,026	24.0	434	23.7	18,464	24.1	1,539	24.6
≥ 4	25,598	29.3	497	27.1	22,514	29.4	1,681	26.8
Missing	560	—	10	—	473	—	30	—
Mammography in prior 2 years								
No	14,929	17.5	152	8.5	12,966	17.4	617	10.1
Yes	70,410	82.5	1,644	91.5	61,739	82.6	5,503	89.9
Missing	2,734	—	49	—	2,288	—	173	—
Oral contraceptive use								
Never	50,407	57.3	1,281	69.4	43,446	56.4	4,182	66.5
< 1 year	7,658	8.7	127	6.9	6,769	8.8	479	7.6
1 to < 3 years	7,865	8.9	129	7.0	6,972	9.1	452	7.2
≥ 3 years	22,115	25.1	308	16.7	19,784	25.7	1,180	18.8
Missing	28	—	0	—	22	—	0	—
E-alone use								
Never	77,834	88.4	1,593	86.3	68,091	88.4	5,445	86.5
< 5 years	6,714	7.6	167	9.1	5,820	7.6	585	9.3
5 to < 10 years	1,763	2.0	44	2.4	1,551	2.0	129	2.0
≥ 10 years	1,761	2.0	41	2.2	1,530	2.0	134	2.1
Missing	1	—	0	—	1	—	0	—

(continued on following page)

Table 1. Baseline Demographics and Clinical Characteristics of Women's Health Initiative Participants According to Use of Oral Bisphosphonates (1993 to 2010) (continued)

Characteristic	Oral Bisphosphonate User							
	At Baseline				At Baseline, Year 1, or Year 3*			
	No (n = 88,073)		Yes (n = 1,845)		No (n = 76,993)		Yes (n = 6,293)	
	No.	%	No.	%	No.	%	No.	%
E+P use								
Never	54,057	61.4	1,162	63.0	46,709	60.7	4,001	63.6
< 5 years	17,097	19.4	353	19.1	15,154	19.7	1,134	18.0
5 to < 10 years	9,418	10.7	152	8.2	8,451	11.0	587	9.3
≥ 10 years	7,500	8.5	178	9.6	6,678	8.7	571	9.1
Missing	1	—	0	—	1	—	0	—
5-Year predicted probability of hip fracture, %†								
< 0.5	63,449	72.0	757	41.0	56,157	72.9	3,213	51.1
0.5 to 1	13,334	15.1	481	26.1	11,511	15.0	1,459	23.2
≥ 1	11,290	12.8	607	32.9	9,325	12.1	1,621	25.8
Missing	0	—	0	—	0	—	0	—
Women's Health Initiative study components‡								
Observational study	49,349	56.0	1,308	70.9	42,587	55.3	4,145	65.9
Calcium/vitamin D CT	20,844	23.7	226	12.2	19,211	25.0	1,008	16.0
Dietary modification CT	26,999	30.7	364	19.7	23,873	31.0	1,491	23.7
Hormone CT	16,329	18.5	200	10.8	14,670	19.1	818	13.0
Hormone CT arm								
Not included in hormone CT	71,744	81.5	1,645	89.2	62,323	80.9	5,475	87.0
Placebo	7,960	9.0	105	5.7	7,076	9.2	479	7.6
E+P	8,369	9.5	95	5.1	7,594	9.9	339	5.4

Abbreviations: CT, clinical trial; E, estrogen; E+P, estrogen plus progestin; SD, standard deviation.
*Among those remaining at risk of endometrial cancer at year 3.
†Calculated as described in Robbins et al.[18]
‡Percentages do not sum to 100% as a result of overlap of study components.

risk factor; all seemed to provide similar control for any residual confounding with little change in our measures of association. We also took fracture risk, as summarized by the index of Robbins et al,[18] into account. This fracture probability has proved to be a valid measure of fracture risk, although it does not include measured bone mineral density. Thus, our full-adjustment approach to protect against residual confounding leads us to be conservative about the strength of the association. Finally, although this is a large study, our numbers were

Table 2. Relative Risk of Endometrial Cancer Comparing Oral Bisphosphonate Users to Nonusers, Women's Health Initiative (1993 to 2010)

Oral Bisphosphonate Use*	Person-Years at Risk†	No. of Endometrial Cancer Events	Age-Adjusted Analysis			Multivariable-Adjusted Analysis		
			HR‡	95% CI	*P*	HR‡§	95% CI	*P*
Any use								
No	871,495	1,070	1.00		.01	1.00		.05
Yes	68,602	53	0.76	0.61 to 0.94		0.80	0.64 to 1.00	
Type								
Alendronate sodium	63,297	47	0.72	0.57 to 0.90	.005	0.77	0.61 to 0.98	.03
Risedronate sodium	3,349	5	1.33	0.73 to 2.42	.34	1.44	0.77 to 2.70	.25
Other‖	1,956	1	0.37	0.05 to 2.59	.31	0.40	0.06 to 2.82	.36
Duration of use, years								
< 1	22,101	17	0.73	0.50 to 1.08	.11	0.85	0.57 to 1.25	.40
1 to 3	27,817	19	0.75	0.54 to 1.05	.09	0.81	0.58 to 1.15	.24
≥ 3	18,684	17	0.77	0.53 to 1.11	.16	0.76	0.51 to 1.13	.17

Abbreviations: HR, hazard ratio; WHI-CT, Women's Health Initiative clinical trials; WHI-OS, Women's Health Initiative observational study.
*Users reported at least 2 weeks of use; nonusers include never-users and those who used for < 2 weeks. Baseline oral bisphosphonate use was updated at years 1, 3, and 6 for women in WHI-CT and at year 3 for women in WHI-OS.
†Median follow-up time of 12.5 years.
‡Baseline hazard stratified by Women's Health Initiative study component.
§Adjusted for age, 5-year hip fracture probability, body mass index, race, education, smoking status, estrogen-only use, estrogen-progestin use, oral contraceptive use, parity, and mammography, all measured at baseline.
‖Other includes etidronate disodium and tiludronate disodium.

limited to explore heterogeneity in associations according to endometrial cancer subtypes. Given that type II endometrial tumors are less likely to be hormonally mediated than type I tumors,[24] it is plausible that bisphosphonate use would be most relevant to risk of type I tumors; however, the modest number of type II tumors in the study population (approximately 10%) precluded separate evaluation by tumor type.

The prevalence of bisphosphonate use was initially low in this cohort. However, we were able to incorporate the substantial increase in use with a time-varying variable. All study participants were instructed to present regularly used medications during the scheduled drug inventories. Any misclassification or under-reporting of exposure history is unlikely to differ between women who developed endometrial cancer during follow-up and those who did not; nondifferential misclassification would have yielded attenuated measures of the true association.[25]

The strengths of our large study include the prospective collection of detailed data on endometrial cancer risk factors, accounting for prior and incident hysterectomy, and centralized adjudication of endometrial cancer diagnoses. In summary, our findings suggest that use of bisphosphonates is modestly associated with reduced endometrial cancer risk, a finding consistent with the inverse association between use of this medication and breast cancer risk.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Polly A. Newcomb
Financial support: Polly A. Newcomb
Administrative support: Polly A. Newcomb, Jean Wactawski-Wende
Provision of study materials or patients: Jean Wactawski-Wende
Collection and assembly of data: Polly A. Newcomb, Garnet L. Anderson, Jean Wactawski-Wende, Rowan T. Chlebowski
Data analysis and interpretation: Polly A. Newcomb, Michael N. Passarelli, Amanda I. Phipps, Garnet L. Anderson, Gloria Y.F. Ho, Mary Jo O'Sullivan, Rowan T. Chlebowski
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. Wysowski DK, Greene P: Trends in osteoporosis treatment with oral and intravenous bisphosphonates in the United States, 2002-2012. Bone 57:423-428, 2013
2. Neville-Webbe HL, Holen I, Coleman RE: The anti-tumour activity of bisphosphonates. Cancer Treat Rev 28:305-319, 2002
3. Newcomb PA, Trentham-Dietz A, Hampton JM: Bisphosphonates for osteoporosis treatment are associated with reduced breast cancer risk. Br J Cancer 102:799-802, 2010
4. Rennert G, Pinchev M, Rennert HS: Use of bisphosphonates and risk of postmenopausal breast cancer. J Clin Oncol 28:3577-3581, 2010
5. Chlebowski RT, Chen Z, Cauley JA, et al: Oral bisphosphonate use and breast cancer incidence in postmenopausal women. J Clin Oncol 28:3582-3590, 2010
6. Monsees GM, Malone KE, Tang MT, et al: Bisphosphonate use after estrogen receptor-positive breast cancer and risk of contralateral breast cancer. J Natl Cancer Inst 103:1752-1760, 2011
7. Hue TF, Cummings SR, Cauley JA, et al: Effect of bisphosphonate use on risk of postmenopausal breast cancer: Results from the randomized clinical trials of alendronate and zoledronic acid. JAMA Intern Med 174:1550-1557, 2014
8. Brinton LA, Berman ML, Mortel R, et al: Reproductive, menstrual, and medical risk factors for endometrial cancer: Results from a case-control study. Am J Obstet Gynecol 167:1317-1325, 1992
9. Newcomb PA, Trentham-Dietz A, Egan KM, et al: Fracture history and risk of breast and endometrial cancer. Am J Epidemiol 153:1071-1078, 2001
10. Persson I, Adami HO, McLaughlin JK, et al: Reduced risk of breast and endometrial cancer among women with hip fractures (Sweden). Cancer Causes Control 5:523-528, 1994
11. Cardwell CR, Abnet CC, Veal P, et al: Exposure to oral bisphosphonates and risk of cancer. Int J Cancer 131:E717-E725, 2012
12. Vinogradova Y, Coupland C, Hippisley-Cox J: Exposure to bisphosphonates and risk of common non-gastrointestinal cancers: Series of nested case-control studies using two primary-care databases. Br J Cancer 109:795-806, 2013
13. Rennert G, Rennert HS, Pinchev M, et al: The effect of bisphosphonates on the risk of endometrial and ovarian malignancies. Gynecol Oncol 133:309-313, 2014
14. Anderson GL, Manson J, Wallace R, et al: Implementation of the Women's Health Initiative study design. Ann Epidemiol 13:S5-S17, 2003 (suppl 9)
15. Curb JD, McTiernan A, Heckbert SR, et al: Outcomes ascertainment and adjudication methods in the Women's Health Initiative. Ann Epidemiol 13:S122-S128, 2003 (suppl 9)
16. Hays J, Hunt JR, Hubbell FA, et al: The Women's Health Initiative recruitment methods and results. Ann Epidemiol 13:S18-S77, 2003 (suppl 9)
17. Stefanick ML, Cochrane BB, Hsia J, et al: The Women's Health Initiative postmenopausal hormone trials: Overview and baseline characteristics of participants. Ann Epidemiol 13:S78-S86, 2003 (suppl 9)
18. Robbins J, Aragaki AK, Kooperberg C, et al: Factors associated with 5-year risk of hip fracture in postmenopausal women. JAMA 298:2389-2398, 2007
19. Lipton A: Emerging role of bisphosphonates in the clinic: Antitumor activity and prevention of metastasis to bone. Cancer Treat Rev 34:S25-S30, 2008 (suppl 1)
20. Clézardin P: Bisphosphonates' antitumor activity: An unravelled side of a multifaceted drug class. Bone 48:71-79, 2011
21. Caraglia M, Santini D, Marra M, et al: Emerging anti-cancer molecular mechanisms of aminobisphosphonates. Endocr Relat Cancer 13:7-26, 2006
22. Anglemyer A, Horvath HT, Bero L: Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials. Cochrane Database Syst Rev 4:MR000034, 2014
23. Kaaks R, Lukanova A, Kurzer MS: Obesity, endogenous hormones, and endometrial cancer risk: A synthetic review. Cancer Epidemiol Biomarkers Prev 11:1531-1543, 2002
24. Amant F, Moerman P, Neven P, et al: Endometrial cancer. Lancet 366:491-505, 2005
25. Flegal KM, Keyl PM, Nieto FJ: Differential misclassification arising from nondifferential errors in exposure measurement. Am J Epidemiol 134: 1233-1244, 1991

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Oral Bisphosphonate Use and Risk of Postmenopausal Endometrial Cancer

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or jco.ascopubs.org/site/ifc.

Polly A. Newcomb
No relationship to disclose

Michael N. Passarelli
No relationship to disclose

Amanda I. Phipps
No relationship to disclose

Garnet L. Anderson
No relationship to disclose

Jean Wactawski-Wende
No relationship to disclose

Gloria Y.F. Ho
No relationship to disclose

Mary Jo O'Sullivan
No relationship to disclose

Rowan T. Chlebowski
Consulting or Advisory Role: Novartis, Pfizer, Genentech, Novo Nordisk, Genomic Health
Speakers' Bureau: Novartis
Travel, Accommodations, Expenses: Novartis, Pfizer, Genentech, Novo Nordisk, Genomic Health

Acknowledgment

We thank the Women's Health Initiative (WHI) investigators and staff for their skill and dedication and the study participants for making the program possible. A listing of WHI investigators can be found at https://cleo.whi.org/researchers/Documents%20%20Write%20a%20Paper/WHI%20Investigator%20Short%20List.pdf.