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ORIGINAL REPORT

Use of Bisphosphonates and Risk of Breast Cancer in a French Cohort of Postmenopausal Women

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ABSTRACT

Purpose
To assess whether bisphosphonate (BP) use is associated with decreased breast cancer incidence in a cohort of postmenopausal women.

Methods
The study population included 64,438 postmenopausal women participating in the French E3N (Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale) prospective cohort, with data self-reported in biennial questionnaires matched with data from a drug reimbursement database. Exposure to BPs and the use of other osteoporosis treatments during follow-up were determined using reimbursement data. Other covariates (breast cancer risk factors, clinical risk factors for osteoporotic fractures, and bone mineral density surveillance) originated from the questionnaires. Hazard ratios (HRs) of breast cancer were estimated using Cox proportional hazards models, considering exposure as a time-varying variable.

Results
Over an average of 7.2 years of follow-up (2004 to 2011), 2,407 first primary breast cancer cases were identified. The HR of breast cancer associated with exposure to BPs was 0.98 (95% CI, 0.85 to 1.12). We found no effect modification by age, body mass index, time since menopause, use of hormone replacement therapy, use of calcium supplements, or use of vitamin D supplements. There was no heterogeneity across BP molecules and no trend according to cumulative dose, duration of use, or time since last use. We observed a decrease in breast cancer risk restricted to the year after treatment initiation (HR, 0.56; 95% CI, 0.36 to 0.87), which was likely explained by healthy screenee bias. Finally, we did not find any variation in HRs across breast carcinomas defined by their estrogen receptor or invasive or in situ status.

Conclusion
In our observational cohort of postmenopausal women observed from 2004 to 2011, BP use, likely prescribed for the management of osteoporosis, was not associated with decreased breast cancer incidence.

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INTRODUCTION

Bisphosphonates (BPs) inhibit osteoclastic bone resorption and are commonly prescribed for the management of postmenopausal osteoporosis.[1,2]

Preclinical studies have suggested that BPs could also exert some antitumor activities through an effect on tumor apoptosis, proliferation, invasion, or angiogenesis,[3,4] which makes BPs an attractive class of drugs to be studied further for cancer prevention.

In clinical trials, high doses of BPs as adjuvant therapy for breast cancer decreased breast cancer mortality among postmenopausal women, and this was attributed to the prevention of bone metastasis rather than to the prevention of recurrence at other sites.[5] In Europe, this has led recently to the recommendation that high-dose BPs should be considered part of adjuvant breast cancer treatment in postmenopausal women or in those receiving ovarian suppression therapy.[6] Whether BPs could play a role in breast cancer primary prevention has never been evaluated in a clinical trial. It is therefore crucial to provide evidence from observational studies on the potential association between lower-dose BPs used for osteoporosis and breast cancer incidence. To

ASSOCIATED CONTENT

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date, observational studies have been fairly consistent in demonstrating decreased risks, although analyses according to duration of use have yielded inconsistent results.[7-12]

One of the recognized challenges in studying BPs and breast cancer incidence is to adequately control for possible confounding by indication.[13] Indeed, one of the indications for BPs is low bone mineral density (BMD), which in itself has been associated with decreased breast cancer risk.[14] Interestingly, in a recent post hoc analysis of two randomized trials of BPs for postmenopausal fracture prevention, devoid of confounding by indication, 3- to 4-year BP treatments were not associated with decreased breast cancer incidence.[15]

In the French context of a rather large use of low-dose BPs to manage low BMD, and of higher-dose BPs recommended as part of adjuvant breast cancer treatment, we investigated the association between low-dose BPs use and breast cancer incidence in the French prospective Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale (E3N) cohort study. Detailed information on BP use extracted from a drug reimbursement database, as well as on the use of other osteoporosis treatments, on the history of osteoporosis or fractures, and on BMD surveillance, enabled a precise assessment of the association between BP use and breast cancer risk while carefully considering potential prescription biases.

METHODS

E3N Cohort

E3N is a prospective cohort of 98,995 French women born between 1925 and 1950 and insured by a health insurance plan that mostly covers teachers.[16] Participants gave written informed consent and completed self-administered questionnaires that had been sent biennially since 1990. Furthermore, for each cohort member, the health insurance plan provided data that included all outpatient reimbursements for health expenditure since January 1, 2004; these data included brand names, dosages, and dates of drug purchases.

The study was approved by the French National Commission for Data Protection and Privacy.

Identification of Participants With Breast Cancer

The occurrence of cancer was identified from information provided in each follow-up questionnaire, which inquired about any cancer occurrence (including the date of diagnosis and site); next-of-kin spontaneous reports; and the national cause-of-death registry. Pathology reports were obtained for 95% of incident breast cancers. Information on tumor characteristics was extracted from these reports. The main analyses also included participants who reported a breast cancer diagnosis for whom pathology reports had not been obtained because the proportion of false-positive self-reports was low ($< 5\%$).

Population for Analysis and Follow-Up

Follow-up started on January 1, 2004. Participants contributed person-years of follow-up until the date of diagnosis of any malignancy (with the exception of basal cell carcinoma and in situ colorectal tumor), the date of the last completed questionnaire, or December 7, 2011 (the date at which the last considered E3N questionnaire was sent to participants), whichever occurred first.

The study population included 64,438 postmenopausal women who were age 53 to 79 years and free of cancer on January 1, 2004 (Fig 1).

Exposure to BPs

We considered all deliveries of BPs since January 1, 2004, corresponding to the Anatomic Therapeutic Chemical codes M05BA and M05BB, with the exception of BPs licensed for malignancies.

We defined as ever exposed those women who had had at least one BP delivery since January 1, 2004, or who self-reported BP use in the questionnaires sent before January 1, 2004 (ie, those who indicated BP use in the 1993 or 1995 questionnaires inquiring about the names of the drugs they ever used for osteoporosis; those who indicated BP use in the 1997 questionnaire inquiring about the names of the drugs they were taking at least three times a week; and those who ticked the "current use at least three times/week of bisphosphonates" box in the 2000 or 2002 questionnaires). We also assessed exposure according to characteristics of use: molecule, time since last use, time since first delivery, duration of use, and number of defined daily doses (DDDs). The DDD is the assumed average daily maintenance dose for a molecule used for its main indication in adults, available from the WHO Collaborating Centre for Drug Statistics Methodology.[17] We extracted WHO DDDs pertaining to osteoporosis treatment.[18]

For analyses on the basis of characteristics of BP use, we restricted the study sample to BP-naive women by excluding women who self-reported BP use in the questionnaires sent before January 1, 2004, and those with at least one BP delivery between January 1, 2004, and April 1, 2004, because they were likely to have begun BPs before the availability of reimbursement data. For the analyses of BP-naive women (n = 59,822; Fig 1), follow-up began on April 1, 2004.

Covariates

Parameters considered as potential confounders are listed in Table 1. Information on these parameters originated either from the biennial self-administered questionnaires sent before January 1, 2004, with subsequent updates in 2005 and 2008 for most parameters that could change during follow-up, or from the drug reimbursement database, which contains information starting from January 1, 2004 (Data Supplement).

Statistical Analysis

Hazard ratios (HRs) of breast cancer were estimated using Cox proportional hazards models for left-truncated and right-censored data, with age as the time scale.

Covariates included in our final multivariable models were selected following a procedure presented in the Data Supplement.

BP exposure as well as other covariates extracted from the reimbursement database, time since menopause, and covariates originating from the self-administered questionnaires that were updated in the 2005 or 2008 questionnaires were fitted as time-varying variables in our models.

Effect modification was evaluated by including cross-product interaction terms in the Cox models (Data Supplement).

All covariates had $< 5\%$ of missing values, which were replaced either by using the previous nonmissing questionnaire value where appropriate, or with the mode or the median values observed among the subjects with complete data. A complete case analysis was also conducted (not shown, because results were similar).

When studying the risk of different breast cancers characterized by their estrogen receptor (ER) or invasive or in situ status, competing risk analysis was performed using the cause-specific hazards approach.[20] Cases with missing information on ER or in situ or invasive status were excluded from the corresponding analyses.

Model parameters were estimated and compared using likelihood methods and Wald tests.

All tests of statistical significance were two sided, and significance was set at the .05 level. All analyses were performed using the SAS system, version 9.3 (SAS Institute, Cary, NC).

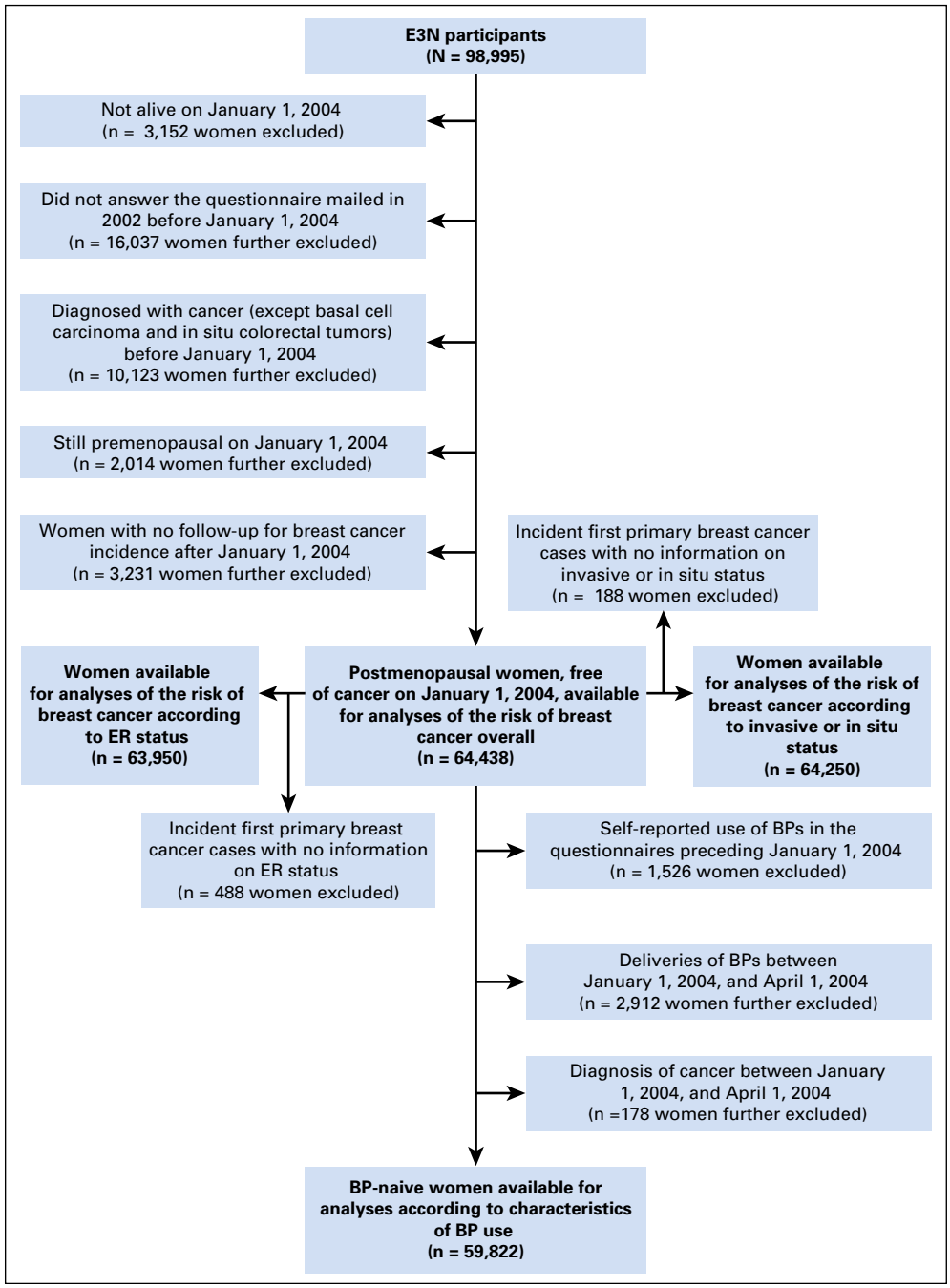

Fig 1. Flow chart. BP, bisphosphonate; E3N, Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale; ER, estrogen receptor.

RESULTS

Table 1 presents the characteristics of the included women. Over an average 7.2 (SD, 1.7) years of follow-up (462,145 person-years), 2,407 first primary breast cancer cases were identified.

At the end of follow-up, of the 64,438 included women, 12,935 had ever been exposed to BPs, of whom 1,526 self-reported BP use in the questionnaires sent before January 1, 2004. The most frequently reimbursed BPs were oral alendronic acid and oral risedronic acid (Table 2). Among women who initiated BP treatment during follow-up, the duration of use was $<$ 6 months for 29.8%, 6 to 12 months for 11.5%, 12 to 36 months for 30.3% and $\geq$ 36 months for 28.4%; 52.1% used alendronic acid; 42.1%, risedronic acid; 25.1%, ibandronic acid; and 7.7%, other BP molecules.

The age-adjusted HR of breast cancer associated with ever having been exposed to BPs, compared with never having been exposed, was 0.89 (95% CI, 0.78 to 1.00). The multivariable HR was 0.98 (95% CI, 0.85 to 1.12; Table 3 and Data Supplement). We found no significant effect modification by attained age ($P_{interaction}$ = .70), body mass index ($P_{interaction}$ = .16), time since menopause ($P_{interaction}$ = .50), use of hormone replacement therapy (HRT; $P_{interaction}$ = .61), use of calcium supplements ($P_{interaction}$ = .43), or use of vitamin D supplements ($P_{interaction}$ = .74).

Table 1. Characteristics of Participants Overall and According to Use of BPs at the End of Follow-Up (2004 to 2011; E3N Cohort [n = 64,438])

Characteristic	Never Exposed to BPs (n = 51,503)	Ever Exposed to BPs (n = 12,935)	All Participants (n = 64,438)	*P* for Difference Between Never and Ever Exposed
Sociodemographic factors				< .001
Age, years, mean (SD)	62.3 (6.3)	64.8 (6.6)	62.8 (6.4)	
Years of schooling				< .001
< 12	6,415 (12.5)	1,430 (11.1)	7,845 (12.2)	
12 to ≤ 14	26,832 (52.1)	7,342 (56.8)	34,174 (53.0)	
> 14	18,256 (35.4)	4,163 (32.2)	22,419 (34.8)	
Clinical risk factors for osteoporotic fractures[19] and BMD surveillance				
Smoking status				< .001
Never smoker	27,373 (53.1)	7,294 (56.4)	34,667 (53.8)	
Current smoker	5,267 (10.2)	1,114 (8.6)	6,381 (9.9)	
Past smoker	18,863 (36.6)	4,527 (35.0)	23,390 (36.3)	
Alcohol intake, g/d, mean (SD)	11.6 (14.1)	10. 6 (13.5)	11.4 (14.0)	< .001
Body mass index, kg/m^2, mean (SD)	24.1 (3.8)	22.8 (3.3)	23.8 (3.8)	< .001
Oral glucocorticoids[a] (at the end of follow-up)				< .001
No	50,874 (98.8)	12,133 (93.8)	63,007 (97.8)	
Yes	629 (1.2)	802 (6.2)	1,431 (2.2)	
History of hip fracture in the mother or father				< .001
No	46,791 (90.9)	11,267 (87.1)	58,058 (90.1)	
Yes	3,796 (7.4)	1,396 (10.8)	5,192 (8.1)	
Do not know	916 (1.8)	272 (2.1)	1,188 (1.8)	
Personal history of fractures,[b] osteoporosis, and bone densitometries				< .001
Fracture	5,559 (10.8)	2,416 (18.7)	7,975 (12.4)	
Osteoporosis without fracture	3,485 (6.8)	3,544 (27.4)	7,029 (10.9)	
No osteoporosis or fracture, and recent[c] bone densitometry	8,384 (16.3)	1,587 (12.3)	9,971 (15.5)	
No osteoporosis or fracture, but no recent[c] bone densitometry	34,075 (66.2)	5,388 (41.7)	39,463 (61.2)	
Secondary osteoporosis[d]				< .001
No	47,471 (92.2)	11,649 (90.1)	59,120 (91.7)	
Yes	4,032 (7.8)	1,286 (9.9)	5,318 (8.3)	
FRAX score				< .001
< 3.6	16,270 (31.6)	2,316 (17.9)	18,586 (28.8)	
3.6 to < 6.0	19,371 (37.6)	4,486 (34.7)	23,857 (37.0)	
≥ 6.0	15,862 (30.8)	6,133 (47.4)	21,995 (34.1)	
Other breast cancer risk factors				
Physical activity, Met-h/wk[e] mean (SD)	68.2 (48.3)	67.9 (49.9)	68.1 (48.6)	.57
Parity and age at first birth				< .001
Nulliparous	5,713 (11.1)	1,648 (12.7)	7,361 (11.4)	
First child before age 30 years, one or two children	25,855 (50.2)	6,503 (50.3)	32,358 (50.2)	
First child before age 30 years, three or more children	14,636 (28.4)	3,401 (26.3)	18,037 (28.0)	
First child after age 30 years	5,299 (10.3)	1,383 (10.7)	6,682 (10.4)	

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Table 1. Characteristics of Participants Overall and According to Use of BPs at the End of Follow-Up (2004 to 2011; E3N Cohort [n = 64,438]) (continued)

Characteristic	Never Exposed to BPs (n = 51,503)	Ever Exposed to BPs (n = 12,935)	All Participants (n = 64,438)	*P* for Difference Between Never and Ever Exposed
Use of oral contraceptives				< .001
Never	19,428 (37.7)	6,039 (46.7)	25,467 (39.5)	
Ever	32,075 (62.3)	6,896 (53.3)	38,971 (60.5)	
Age at menarche, years				< .001
< 13	23,318 (45.3)	5,389 (41.7)	28,707 (44.5)	
≥ 13	28,185 (54.7)	7,546 (58.3)	35,731 (55.5)	
Time since menopause, years, mean (SD)	11.8 (7.3)	14.7 (7.8)	12.3 (7.5)	< .001
History of breast cancer in first-degree relatives				.31
No	45,595 (88.5)	11,410 (88.2)	57,005 (88.5)	
Yes	5,908 (11.5)	1,525 (11.8)	7,433 (11.5)	
Personal history of benign breast disease				< .001
No	33,665 (65.4)	7,880 (60.9)	41,545 (64.5)	
Yes	17,838 (34.6)	5,055 (39.1)	22,893 (35.5)	
HRT use[f]				< .001
Never use	14,542 (28.2)	3,653 (28.2)	18,195 (28.2)	
Recent use	5,670 (11.0)	712 (5.5)	6,382 (9.9)	
Past use	31,291 (60.8)	8,570 (66.3)	39,861 (61.9)	
Gail risk, %				< .001
< 1.4	18,011 (35.0)	3,253 (25.1)	21,264 (33.0)	
1.4 to < 1.8	16,795 (32.6)	4,469 (34.5)	21,261 (33.0)	
≥ 1.8	16,697 (32.4)	5,213 (40.3)	21,910 (34.0)	
Medical follow-up				
Self-report of a mammogram performed during the previous follow-up cycle				.51
No	8,570 (16.6)	2,121 (16.4)	10,691 (16.6)	
Yes	42,933 (83.4)	10,814 (83.6)	53,747 (83.4)	
Number of medical consultations (GP or specialist) during the preceding year[g] (at the end of follow-up), mean (SD)	4.0 (3.6)	4.9 (3.9)	4.2 (3.7)	< .001
Reimbursements for osteoporosis treatments[h]				
Calcium (at the end of follow-up)				< .001
Never use	39,780 (77.2)	2,943 (22.8)	42,723 (66.3)	
Recent use	5,616 (10.9)	5,691 (44.0)	11,307 (17.5)	
Past use	6,107 (11.9)	4,301 (33.3)	10,408 (16.2)	
Calcitonin (at the end of follow-up)				< .001
Never use	51,056 (99.1)	12,581 (97.3)	63,637 (98.8)	
Recent use	46 (0.1)	24 (0.2)	70 (0.1)	
Past use	401 (0.8)	330 (2.6)	731 (1.1)	
Raloxifene (at the end of follow-up)				< .001
Never use	48,874 (94.9)	10,864 (84.0)	59,738 (92.7)	
Ever use	2,629 (5.1)	2,071 (16.0)	4,700 (7.3)	
Strontium ranelate (at the end of follow-up)				< .001
Never use	50,612 (98.3)	10,818 (83.6)	61,430 (95.3)	
Recent use	510 (1.0)	1,078 (8.3)	1,588 (2.5)	
Past use	381 (0.7)	1,039 (8.0)	1,420 (2.2)	

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Table 1. Characteristics of Participants Overall and According to Use of BPs at the End of Follow-Up (2004 to 2011; E3N Cohort [n = 64,438]) (continued)

Characteristic	Never Exposed to BPs (n = 51,503)	Ever Exposed to BPs (n = 12,935)	All Participants (n = 64,438)	*P* for Difference Between Never and Ever Exposed
Teriparatide (at the end of follow-up)				< .001
Never use	51,494 (99.98)	12,846 (99.3)	64,340 (99.8)	
Recent use	6 (0.01)	38 (0.3)	44 (0.1)	
Past use	3 (0.01)	51 (0.4)	54 (0.1)	
Vitamin D (at the end of follow-up)				< .001
Never use	32,009 (62.1)	1,438 (11.1)	33,447 (51.9)	
Recent use	13,184 (25.6)	8,970 (69.3)	22,154 (34.4)	
Past use	6,310 (12.3)	2,527 (19.5)	8,837 (13.7)	

NOTE. Data are presented as No. (%) unless indicated otherwise. Characteristics are at start of follow-up unless specified otherwise.
Abbreviations: BMD, bone mineral density; BPs, bisphosphonates; E3N, Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale; GP, general practitioner; HRT, hormone replacement therapy; Met-h, metabolic equivalent task-hour; SD, standard deviation.
[a]Exposure to oral glucocorticoids since January 1, 2004, for at least 3 consecutive months at a prednisolone daily dose of 5 mg or more (or equivalent doses of other glucocorticoids).
[b]Except for fractures of the nose, face, skull, foot, toes, hand, fingers, sternum, clavicle, or coccyx, and fractures occurring after high trauma, an accident, or falling from a height, or those caused by disease.
[c]Performed during the previous follow-up cycle.
[d]History of chronic liver disease or premature menopause (younger than 45 years of age).
[e]On the basis of walking, cycling, sports, do-it-yourself activities, gardening, and household activities.
[f]HRT includes any nonvaginal use of estrogens (with the exception of estriol) or tibolone. "Never use" corresponds to no reimbursement since January 1, 2004, and no self-reported use before; "Recent use" corresponds to at least one reimbursement during the previous year; and "Past use" corresponds to no recent use and either reimbursements or self-reported use > 1 year ago.
[g]Not considering the past 6-month period so as to avoid taking into account consultations linked to cancer diagnosis.
[h]"Never use" corresponds to no reimbursement since January 1, 2004, plus, for calcium, calcitonin, and raloxifene, no self-reported use in the 1993, 1995, and 1997 questionnaires; "Recent use" corresponds to reimbursements during the previous year; and "Past use" corresponds to no recent use and either reimbursements or, for calcium, calcitonin and raloxifene, self-reported use in the 1993, 1995, or 1997 questionnaires. Isolated reimbursements (ie, those occurring only once in a 12-month period) were ignored.

The potential for confounding by osteoporosis treatments other than BPs (HRT, calcium, calcitonin, raloxifene, strontium ranelate, teriparatide, and vitamin D) was weak: their inclusion in the model modified the HR associated with ever having been exposed to BPs by < 0.1 point. The same was observed for clinical risk factors for osteoporotic fractures (listed in Table 1) and BMD surveillance. The HR associated with BPs ever use was 1.04 (95% CI, 0.79 to 1.38; 88 exposed cases), and 1.22 (95% CI, 0.98 to 1.53; 160 exposed cases) in women with a personal history of fracture and in those with a personal history of osteoporosis without fracture, respectively.

Analyses according to characteristics of use, conducted among women who were BP-naive at baseline, yielded no statistically significant heterogeneity across different BPs and no statistically significant trend according to number of DDDs, duration of use, or time since last use (Table 4). We observed a decrease in breast cancer risk during the year after treatment initiation (HR, 0.56; 95% CI, 0.36 to 0.87; Table 4).

Because we suspected that screening bias could contribute to the latter result, we explored the following hypothesis: BP initiation could be preceded by a postmenopausal check-up, including a bone densitometry and, when appropriate, breast cancer screening. As a consequence, the probability of a breast cancer being diagnosed during the first months after BP initiation would be relatively low. We could only explore that hypothesis with reimbursement data from the year 2013 onward, because we had no detailed information on the type of medical examinations reimbursed before that year. We identified 1,686 women who initiated BPs between 2013 and 2015. Among these women, as suspected, we observed a peak of mammograms during the month preceding BP initiation (Fig 2).

We found no significant variation in HRs of breast cancer associated with BP exposure across breast carcinomas defined by their ER or invasive or in situ status (Table 3). The cumulative breast cancer incidence over time in BP ever- versus never-users is depicted in the Data Supplement, overall and according to ER and invasive or in situ status.

We conducted several sensitivity analyses that confirmed the robustness of our results. The HR associated with BP ever use was 1.00 (95% CI, 0.86 to 1.16) when analyses were restricted to women who ever underwent a bone densitometry (n = 52,751), 0.97 (95% CI, 0.84 to 1.13) when analyses were restricted to women who self-reported having had a mammogram performed in the previous follow-up cycle (n = 54,718), 0.99 (95% CI, 0.86 to 1.15) when follow-up started on January 1, 2005, instead of January 1, 2004, so as to have at least a 1-year history of reimbursement data (n = 63,721), and 0.96 (95% CI, 0.83 to 1.11) when cases for whom no pathology report was available were excluded (n = 64,250).

DISCUSSION

Overall, we found no decreased risk of breast cancer among postmenopausal women of the E3N cohort exposed to BPs. We found no duration- or dose-response relationship or differential effect across breast carcinomas defined by their ER or invasive or in situ status. The transient decrease in risk we observed in the year after BP initiation may have been the result of mammography screening bias.

Our results differ from those of previous observational studies, which showed decreased risks of breast cancer associated

Table 2. Exposure to Bisphosphonates During Follow-Up (2004 to 2011; E3N Cohort [n = 64,438])

Molecule	Route of Administration	Dose	No. Person-Years of Use
Risedronic acid	Oral	35 mg per tablet	9,935
Alendronic acid	Oral	70 mg per tablet	7,782
Alendronic acid	Oral	70 mg per tablet, associated with cholecalciferol	6,183
Ibandronic acid	Oral	150 mg per tablet	4,119
Etidronic acid	Oral	400 mg per tablet	1,461
Risedronic acid	Oral	75 mg per tablet	703
Zoledronic acid	Intravenous	5 mg per 100 mL	693
Risedronic acid	Oral	35 mg per tablet, associated with calcium and cholecalciferol	322
Risedronic acid	Oral	5 mg per tablet	130
Ibandronic acid	Intravenous	3 mg per 3 mL	127
Alendronic acid	Oral	10 mg per tablet	106
Risedronic acid	Oral	30 mg per tablet	7
Tiludronic acid	Oral	200 mg per tablet	2

Abbreviation: E3N, Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale.

with BP use (with odds ratios and HRs ranging from 0.7 to 0.9 in both case-control and cohort studies)[7-12] but agree with a recent post hoc analysis using data from two randomized trials of BPs for fracture prevention, which found that 3 to 4 years of oral alendronate or intravenous infusions of zoledronic acid did not decrease the risk of incident postmenopausal breast cancer (HR, 1.20; 95% CI, 0.89 to 1.63).[15] The existing literature is confusing regarding the estimated effect of BPs according to the timing of use: some authors found that the risk reduction associated with BP use existed only after at least 1 year of treatment,[8,10] others that it was present only among women with $<$ 2 years of use[9]; some found that the decrease in risk was not duration dependent,[12] others that it was more marked with increasing duration of use,[7] or that it tended to attenuate over time.[11]

Consistent with previous observational studies[10,12] and a post hoc analysis of randomized trials,[15] no heterogeneity across different BP molecules was observed in this study.

Our result of no differential association of BPs with ER+ and ER− breast cancers is consistent with the results of the Women's Health Initiative (WHI) observational cohort.[9] That cohort is also, to our knowledge, the only study evaluating separately the association between BPs and in situ and invasive breast cancers. Whereas there was no association of BP use with either in situ or invasive breast tumors in our study, the WHI investigators found a lower incidence of invasive breast cancers (HR, 0.69; 95% CI, 0.52 to 0.88) and a higher incidence of ductal carcinoma in situ (HR, 1.58; 95% CI, 1.08 to 2.31) in BP users.[9] The authors hypothesized that BPs could prevent in situ cancers from progressing to the invasive stage.

We found no effect modifier, which is in line with results from previous studies that evaluated interactions of BPs with age,[7,10,15] HRT,[7,10] and body mass index,[9,11,15] with the exception of a case-control study that reported that the risk reduction associated with BP use was restricted to nonobese women.[7]

Because a history of low BMD is not only an indication for the use of BPs but also has been associated with a decrease in breast cancer risk,[14] we assessed the extent to which adjustment for clinical risk factors for osteoporotic fractures or BMD-related

Table 3. HRs for Different Types of Breast Cancer Associated With Exposure to BPs (ever *v* never; E3N Cohort, 2004 to 2011)

Breast Cancer Characteristic (No. women included)	Never Exposed to BPs		Ever Exposed to BPs		
	No. Cases	HR* (95% CI)	No. Cases	HR* (95% CI)	*P*
All breast cancers (n = 64,438)	2,099	1 (reference)	308	0.98 (0.85 to 1.12)	.76
According to ER status (n = 63,950†)					
ER+	1,429	1 (reference)	199	0.95 (0.80 to 1.12)	.52
ER−	255	1 (reference)	36	0.98 (0.65 to 1.46)	.90
$P_{homogeneity}$					.89
According to invasive or in situ status (n = 64,250‡)					
Invasive	1,700	1 (reference)	245	0.97 (0.83 to 1.14)	.72
In situ	242	1 (reference)	32	0.87 (0.57 to 1.33)	.52
$P_{homogeneity}$					.64

Abbreviations: BPs, bisphosphonates; E3N, Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale; ER, estrogen receptor; HR, hazard ratio.

*From a Cox proportional hazard model, with age as the time scale, adjusted for years of schooling, alcohol intake, body mass index, personal history of fractures, osteoporosis and bone densitometries, parity and age at first birth, use of oral contraceptives, time since menopause, history of breast cancer in first-degree relatives, personal history of benign breast disease, hormone replacement therapy use, self-report of a mammogram performed during the previous follow-up cycle, raloxifene, and vitamin D. Categories used are those displayed in Table 1.

†Of the 64,438 women in the analytic cohort, 488 incident first primary breast cancer cases were excluded because of missing information on ER status.

‡Of the 64,438 women in the analytic cohort, 188 incident first primary breast cancer cases were excluded because of missing information on invasive or in situ status.

Table 4. HRs for Breast Cancer Associated With Exposure to BPs, According to Characteristics of Use (E3N Cohort; 2004 to 2011 [n = 59,822 BP-naive women])

Characteristic of Exposure	No. Cases	HR* (95% CI)	*P*
Molecule†			
Alendronic acid	76	0.94 (0.74 to 1.20)	.61
Ibandronic acid	22	0.80 (0.52 to 1.22)	.30
Risedronic acid	64	0.93 (0.72 to 1.21)	.61
Other	12	1.03 (0.58 to 1.82)	.93
$P_{homogeneity}$			.90
No. DDDs			
Never exposed to BPs	2,004	1 (Reference)	
≤ 112	44	0.87 (0.64 to 1.18)	.38
113 to ≤ 540	49	0.95 (0.70 to 1.27)	.71
541 to ≤ 1,246	39	0.97 (0.70 to 1.36)	.88
> 1,246	22	1.21 (0.78 to 1.86)	.39
P_{trend}‡			.39
Cumulative duration of use, months§			
Never exposed to BPs	2,004	1 (Reference)	
< 6	47	0.77 (0.57 to 1.04)	.08
6 to < 12	28	1.14 (0.78 to 1.66)	.51
12 to < 36	56	1.07 (0.81 to 1.41)	.65
≥ 36	23	1.04 (0.68 to 1.59)	.85
P_{trend}‡			.44
Time since first delivery, years			
Never exposed to BPs	2,004	1 (Reference)	
< 1	21	0.56 (0.36 to 0.87)	.009
1 to < 2	35	1.08 (0.77 to 1.52)	.66
2 to < 4	47	0.91 (0.68 to 1.23)	.56
≥ 4	51	1.31 (0.98 to 1.75)	.07
P_{trend}‡			.06
Time since last use, months‖			
Never exposed to BPs	2,004	1 (Reference)	
≤ 1	78	0.86 (0.67 to 1.09)	.21
> 1 to ≤ 12	29	1.07 (0.74 to 1.55)	.72
> 12 to ≤ 36	23	0.86 (0.56 to 1.30)	.47
> 36	24	1.44 (0.96 to 2.17)	.08
P_{trend}‡			.13

Abbreviations: BPs, bisphosphonates; DDD, defined daily dose; E3N, Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale; HR, hazard ratio.

*From a Cox proportional hazard model, with age as the time scale, adjusted for years of schooling, alcohol intake, body mass index, personal history of fractures, osteoporosis and bone densitometries, parity and age at first birth, use of oral contraceptives, time since menopause, history of breast cancer in first-degree relatives, personal history of benign breast disease, hormone replacement therapy use, self-report of a mammogram performed during the previous follow-up cycle, raloxifene, and vitamin D. Categories used are those displayed in Table 1. HRs were obtained from separate models, including one characteristic of exposure at a time.

†Variables corresponding to ever use (*v* never use) of each molecule displayed in the table were introduced simultaneously in the model.

‡Tests for linear trends were performed among exposed women and used the duration, dose, time since last use, and time since first use as continuous variables.

§The duration of use corresponding to a delivery was calculated as the shortest length of time between the standard duration of treatment contained in the box delivered and the time until the next BP delivery. The cumulative duration of use was calculated as the sum of durations of use corresponding to each delivery since January 1, 2004.

‖The date of last use was calculated as the date of last delivery plus the standard duration of treatment contained in the last delivered box.

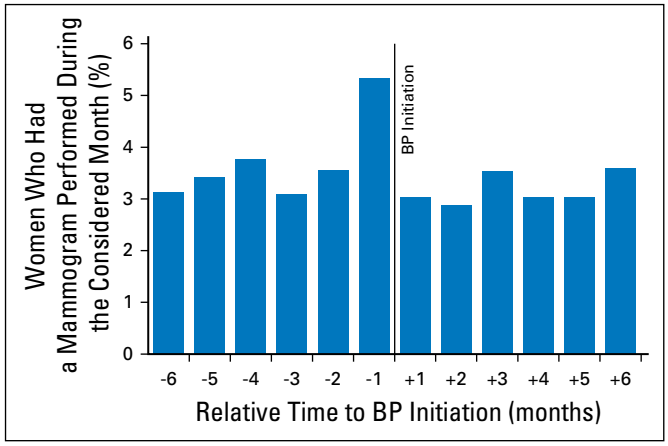

Fig 2. Mammography screening among women who initiated bisphosphonates (BPs) between 2013 and 2015 (n = 1,686).

parameters had an impact on estimates. Consistent with other studies,[7,9] our findings indicated that it had little effect, which implies that in our and some other settings, there is no strong association between a history of osteoporosis and the risk of breast cancer.

Because HRT is an effective treatment of osteoporosis, its consumption is unlikely among BP users (as in our cohort; Table 1). Consequently, because the current use of HRT is associated with increased breast cancer risk,[21-23] the higher the frequency of HRT current use among BP nonusers, the more pronounced the bias toward an overestimation of the protective role of BPs regarding breast cancer risk. In our analysis, this bias was weak, probably because of a relatively low level of HRT use in the post-WHI period (Table 1).[24] However, insufficient adjustment for current HRT use in previous observational studies, especially those including periods of time when HRT was largely prescribed, may have biased results toward an artificial protective effect of BPs.

The post hoc complementary analysis of the frequency of mammography before or after BP initiation that we conducted in our population showed a peak of mammography during the month preceding BP initiation (using data pertaining to the years 2013 to 2015). This suggests that the transient decrease in breast cancer risk we observed in the year after BP initiation could be at least partially the effect of healthy screenee bias, because BPs may have been preferentially prescribed to women with a recent negative mammogram.

The limitations of our study include potential misclassification of BP use, because exposure was based on deliveries rather than intake. Some women may therefore have been wrongly considered exposed to BPs, but this is unlikely for women with long-term apparent exposures. Although we adjusted for many potential confounders, we cannot exclude residual confounding. For example, we could not take into account the severity of osteoporosis, and we considered that a bone densitometry with an abnormal result corresponded to osteoporosis, whereas it may have corresponded to osteopenia. A few covariates, such as physical activity, that could have changed value were not updated during follow-up. It is likely that information on the exact time that had elapsed since the last mammography would have been necessary for minimizing any mammography screening bias. Finally, because of a lack of adequate information or a limited number of exposed cases, we could not provide results on specific issues; these issues (eg, the BP–breast cancer association among *BRCA* carriers, the association of BP use with de novo stage 4 breast cancer incidence, and the association of BPs administered in an intravenous form with breast cancer incidence) could be considered areas for future research.

The strengths of our study include its prospective design and the use of detailed information from a drug reimbursement

database to identify BP exposure, which excludes differential recall bias between cases and noncases. The relatively elevated number of exposed cases (n = 308), combined with the use of detailed information on both tumor characteristics and BP exposure (including duration, molecules, time since last and time since first use), allowed us to conduct an observational investigation with fine granularity of the assessment of associations between BP use and breast cancer incidence. In addition, we were able to take into consideration a priori important potential confounders, in particular, clinical risk factors for osteoporotic fractures and the use of HRT. Additional detailed information on mammograms for which E3N participants were reimbursed between 2013 and 2015 allowed us to explore the hypothesis that the BP–breast cancer relationship could be influenced by differential mammography screening between BP users and nonusers. We were hence able to evaluate the potential impact of confounding by HRT use, screening bias, or confounding by indication. These biases could have affected previous observational studies assessing the BP–breast cancer risk association. Their potential impact would be stronger in studies covering periods when HRT use was more common; it would also depend on the relationship between BP prescribing and mammography screening. Our study was conducted in France, among postmenopausal women observed from 2004 to 2011.

In conclusion, in our observational cohort of postmenopausal women, BP use, mostly oral, and likely prescribed for the management of osteoporosis, was not associated with decreased breast cancer risk. Our results therefore do not support the hypothesis that BPs could be effective for breast cancer prevention in postmenopausal women.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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