Bisphosphonate Use in Breast Cancer

Lucy R. Langer, MD MSHS
January 2014
Our Bones are Dynamic
Bisphosphonates and Bone Health

Osteoporosis:
- First-line therapy for postmenopausal women with osteoporosis or fragility fracture
- Weekly PO (alendronate, risedronate) preferred (5yr)
- Annual IV if contraindications to PO or not tolerated (3yr)

The role of estrogen and androgen receptors in bone health and disease

Stavros C. Manolagas, Charles A. O’Brien, & Maria Almeida
doi:10.1038/nrendo.2013.179
The Pac-Man Theory of Cancer Mets
Bisphosphonates and Denosumab Interact with the Bone MicroEnvironment

1. XGEVA® Targets and Binds to RANK Ligand, Preventing Activation of Its Receptor, RANK, on Osteoclasts
2. By Binding to RANK Ligand, XGEVA® Inhibits Osteoclast Formation, Function, and Survival
3. XGEVA® Prevents the Maturation of Osteoclasts, Decreasing Bone Resorption and Breaking the Vicious Cycle of Bone Destruction

Bisphosphonates in Breast Cancer

1. Prevent SRE
   - Breast cancer
   - Myeloma
   - Lung Cancer with bone mets
   - Prostate cancer on ADT

2. Prevention of CTIBL

3. Adjuvant Treatment of Breast Cancer

4. Prevention of Breast Cancer
(Chemo)Therapy Induced Bone Loss

San Antonio Breast Cancer Symposium - Cancer Therapy and Research Center at UT Health Science Center - December 10-14, 2013

Bone loss with cancer therapies

Naturally occurring bone loss
- Normal men
- Postmenopausal women
- Menopausal women

CTIBL
- AI therapy in postmenopausal women
- ADT
- AI therapy plus GnRH agonist in premenopausal women
- Premature menopause secondary to chemotherapy

References:
Kanis JA. Osteoporosis 1997;22:55
Gnant M. Presented at: SABCS 2002

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Clodronate and Bone Mineral Density

![Graph showing change in bone density over time for Clodronate and Placebo treatments.](image)

*P < .001; †P < .01; ‡P < .05 between treatments.

**References:**

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Bisphosphonates in Breast Cancer

1. Prevent SRE
   - Breast cancer
   - Myeloma
   - Lung Cancer with bone mets
   - Prostate cancer on ADT

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Adjuvant Bisphosphonates

Bone Specific Disease-Free Survival
Non-Bone Disease-Free Survival
Overall Survival
Clodronate improves survival in patients with breast cancer

(N=1069)

**Bone metastasis-free survival**

- HR: 0.546
  - (95% CI: 0.312–0.954)
  - P = 0.031

- HR: 0.692
  - (95% CI: 0.484–0.990)
  - P = 0.043

**Overall survival**

- HR: 0.768
  - (95% CI: 0.591–0.999)
  - P = 0.048

*Powles, et al. Breast Cancer Res 2006; 8:R13*

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# Breast Cancer: Adjuvant Clodronate Trials

<table>
<thead>
<tr>
<th></th>
<th>Diel/Jaschke</th>
<th>Powles</th>
<th>Saarto</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>290</td>
<td>1,069</td>
<td>299</td>
</tr>
<tr>
<td>Selection</td>
<td>BM+ (DTC+)*</td>
<td>Stage I-III</td>
<td>LN+</td>
</tr>
<tr>
<td>Treatment length (yr)</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Follow-up time (yr)</td>
<td>8.5</td>
<td>5/10</td>
<td>10</td>
</tr>
<tr>
<td>Skeletal effect</td>
<td>NS</td>
<td>+</td>
<td>NS</td>
</tr>
<tr>
<td>Extraskeletal effect</td>
<td>NS</td>
<td>NS</td>
<td>-</td>
</tr>
<tr>
<td>Disease-free survival</td>
<td>NS</td>
<td>NS</td>
<td>- (ER-)</td>
</tr>
<tr>
<td>Overall survival</td>
<td>+</td>
<td>+</td>
<td>NS</td>
</tr>
</tbody>
</table>

BM = Bone marrow; LN = Lymph node; NS = Not significant; ER = estrogen receptor; + = Better than competitor; - = Worse than competitor; \* Primary breast cancer patients (T1 to T4 and N0 to N2) with micrometastases in the bone marrow.

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Potency of Bisphosphonates

Relative inhibitory potency in vitro, bone cultures

Relative inhibitory potency in vivo, TPTX animal model of bone loss

Zoledronic acid
Ibandronate
Risedronate
Olpadronate
Alendronate
Pamidronate
Neridronate
Clodronate
Etidronate

R = 0.97


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ABCSDG-12 Trial Design

- Recruitment 1999-2006
- 1,803 premenopausal patients
- Stage I&II, <10 pos nodes, ER+ and/or PgR+
- Duration of treatment: 3 years
- Pre-operative Chemo allowed
- Bone study until Juni 2003

Primary End Point: Disease-Free Survival

Zoledronic Acid Significantly Improves DFS Compared With Endocrine Therapy Alone

- ZOL 54/904 vs No ZOL 83/899
  - Hazard ratio (95% CI) 0.643 (0.46 to 0.91)
  - P value .011

Patients at risk
  - No ZOL 904
  - ZOL 899


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First DFS Events (ITT Population)

No ZOL vs ZOL

First event per patient, n

Death without prior recurrence
- Secondary malignancy
- Contralateral breast cancer
- Distant recurrence
- Locorogional recurrence

No ZOL (n = 904)

- 2
- 10
- 10
- 41
- 20

ZOL (n = 899)

- 0
- 9
- 6
- 29
- 10

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Adjuvant Treatment With Zoledronic Acid in Stage II/III Breast Cancer. The AZURE Trial (BIG 01/04)

AZURE: Study Design
Accrual September 2003 - February 2006

3,360 Breast Cancer Patients
Stage II/III

<table>
<thead>
<tr>
<th>Countries</th>
<th>Centres</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK</td>
<td>123</td>
<td>2710</td>
</tr>
<tr>
<td>Eire</td>
<td>10</td>
<td>247</td>
</tr>
<tr>
<td>Australia</td>
<td>28</td>
<td>226</td>
</tr>
<tr>
<td>Spain</td>
<td>8</td>
<td>107</td>
</tr>
<tr>
<td>Portugal</td>
<td>1</td>
<td>32</td>
</tr>
<tr>
<td>Thailand</td>
<td>2</td>
<td>25</td>
</tr>
<tr>
<td>Taiwan</td>
<td>2</td>
<td>13</td>
</tr>
</tbody>
</table>

Standard therapy

Standard therapy + Zoledronic acid 4 mg

6 doses Q3-4 weeks
8 doses Q 3 months
5 doses Q 6 months

Zoledronic acid treatment duration 5 years

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AZURE: Disease (DFS) and Invasive Disease Free Survival (IDFS)

**DFS**

Adjusted HR = 0.98  
95% CI [0.85, 1.13] p=0.79

**IDFS**

Adjusted HR = 0.98  
95% CI [0.85, 1.12] p=0.73


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Why is ABCSG-12 different from AZURE?

- Minimal overlap in patient selection and treatment
  - ABCSG-12: no adjuvant chemo – AZURE: 96% chemo
  - ABCSG-12: 70% stage I – AZURE: 0% stage I
  - ABCSG-12: 100% OFS – AZURE: no OFS
  - ABCSG-12: 7 doses in 3 years – AZURE: 19 doses in 5 years

- Both in AZURE and ABCSG-12: Perfect suppression or lack of estrogen in combination with adjuvant Zoledronic Acid leads to significant DFS and OS benefits.

- To optimize an adjuvant Bisphosphonate treatment strategy directed at dormant tumor (stem) cells („Seed and Soil“), adjuvant Zoledronic Acid should be used together with estrogen reducing treatments.

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AZURE: DFS by Menopausal Status

Pre, peri and unknown menopausal status

>5 years post-menopausal

Menopausal Interaction: $\chi^2_1 = 4.71; P=0.030$

Adjusted HR 1.03
95% CI: 0.89-1.20

N = 2318
702 events

Adjusted HR 0.77
95% CI: 0.63-0.96

N = 1041
347 events

Coleman R., presented at ECCO 2013
SABCS 2013

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Z/ZO-FAST Trial Design:

Eligibility:
ER+/PgR+ early breast cancer
Postmenopausal
T score ≥ −2

Stratification:
Adjuvant CT (yes vs no)
T score (> −1 vs between −1 and −2)


* Plus daily calcium (1000-1200 mg) and vitamin D (400-800 IU).
† Initiation determined by a postbaseline T score below −2, any clinical fracture, or an asymptomatic fracture at 36 months.
**ZO-FAST—Disease-free Survival**

- **Delayed ZOL**: -13%
- **Immediate ZOL**: -35%

<table>
<thead>
<tr>
<th>Time</th>
<th>Delayed ZOL</th>
<th>Immediate ZOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 months</td>
<td>2.8</td>
<td>3.2</td>
</tr>
<tr>
<td>24 months</td>
<td>3.9</td>
<td>6</td>
</tr>
<tr>
<td>36 months</td>
<td>4.9</td>
<td>8.1</td>
</tr>
<tr>
<td>48 months</td>
<td>5.5</td>
<td>9.2</td>
</tr>
</tbody>
</table>

-40% $P = .0314$

-41% $P = .0175$

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ZO-FAST: Disease Recurrence (ITT Population)

Disease Recurrence

Key Sites of Distant Recurrence

Abbreviations: DFS, disease-free survival; D-ZOL, delayed zoledronic acid; IM-ZOL, immediate zoledronic acid.

de Boer et al, SABCS 2011
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# Variable Efficacy in Unselected Population

<table>
<thead>
<tr>
<th>Study</th>
<th>Overall DFS Result (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZURE (n = 3359)</td>
<td>0.98 (0.85-1.13)</td>
<td>.79</td>
</tr>
<tr>
<td>ABCSG XII (n = 1803)</td>
<td>0.71 (0.55-0.92)</td>
<td>.011</td>
</tr>
<tr>
<td>ZO-FAST (n = 1065)</td>
<td>0.66 (0.44-0.97)</td>
<td>.04</td>
</tr>
<tr>
<td>NSABP-B34 (n = 3323)</td>
<td>0.91 (0.78-1.07)</td>
<td>.27</td>
</tr>
<tr>
<td>CLODROPLAC (n = 1069)*</td>
<td>0.69 (0.48-0.99)</td>
<td>.043</td>
</tr>
<tr>
<td>GAIN (n = 2994)</td>
<td>0.95 (0.77-1.16)</td>
<td>.59</td>
</tr>
</tbody>
</table>

*Analysis relates to bone metastasis-free survival.

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### Consistent Efficacy in “Postmenopausal”

<table>
<thead>
<tr>
<th>Study</th>
<th>“Postmenopausal” DFS (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZURE (n = 1041)</td>
<td>0.75 (0.59-0.96)</td>
<td>.02</td>
</tr>
<tr>
<td>ABCSG XII (n = 1390)</td>
<td>0.66 (0.48-0.92)*</td>
<td>.013</td>
</tr>
<tr>
<td>ZO-FAST (n = 1065)</td>
<td>0.66 (0.44-0.97)</td>
<td>.04</td>
</tr>
<tr>
<td>NSABP-B34 (n = 2139)</td>
<td>0.68 (0.5-0.92)</td>
<td>.013</td>
</tr>
<tr>
<td>CLODROPLAC† (n = 539)</td>
<td>0.66 (0.49-0.93)</td>
<td>.007</td>
</tr>
<tr>
<td>GAIN (n = 1557)</td>
<td>0.75 (0.49-1.14)‡</td>
<td>.17</td>
</tr>
</tbody>
</table>

*Includes patients > 40 yrs on goserelin; no significant effect for patients < 40 yrs.
†Analysis relates to OS.
‡≥ 60 yrs at study entry.

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Estimation of the Number Needed to Treat

- Number of patients needed to treat for 1 patient to gain disease-free survival (DFS) clinical benefit
  - NNT = 1 / Absolute risk reduction

- Zoledronic acid has similar DFS efficacy to other paradigm-changing cancer therapies (i.e., taxanes)

# The Magnitude of the ZA Effect

<table>
<thead>
<tr>
<th>Adjuvant Treatment</th>
<th>compared to</th>
<th>Absolute % DFS difference at 5 years</th>
<th>HR (95% CI)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMF</td>
<td>no CMF</td>
<td>NR</td>
<td>0.76</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Anthracycline</td>
<td>CMF</td>
<td>6</td>
<td>0.69 (0.58 to 0.82)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Docetaxel (TAC)</td>
<td>FAC</td>
<td>7</td>
<td>0.72 (0.59 to 0.88)</td>
<td>.001</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>no Tamoxifen</td>
<td>14.2 (10yrs)</td>
<td>0.61 (0.57 to 0.65)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Anastrozole</td>
<td>Tamoxifen</td>
<td>2.4</td>
<td>0.87 (0.78 to 0.97)</td>
<td>.01</td>
</tr>
<tr>
<td>Letrozole</td>
<td>Tamoxifen</td>
<td>1.9</td>
<td>0.81 (0.70 to 0.93)</td>
<td>.003</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>no Trastuzumab</td>
<td>6.4</td>
<td>0.76 (0.66 to 0.87)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>no ZA</td>
<td>4.5</td>
<td>0.71 (0.55 to 0.92)</td>
<td>.011</td>
</tr>
</tbody>
</table>


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Effects Of Bisphosphonate Treatment On Recurrence And Cause-specific Mortality In Women With Early Breast Cancer: A Meta-analysis Of Individual Patient Data From Randomised Trials


Early Breast Cancer Trialists’ Collaborative Group (EBCTCG)’s Bisphosphonate Working Group.
## Data Received And Included In Analyses

<table>
<thead>
<tr>
<th></th>
<th>Number trials</th>
<th>Number patients</th>
<th>Trials received</th>
<th>Patients received</th>
<th>Percent received</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trials of oral clodronate</td>
<td>7</td>
<td>5174</td>
<td>5</td>
<td>5053</td>
<td>98%</td>
</tr>
<tr>
<td>Trials of aminobisphosphonates*</td>
<td>29</td>
<td>17808</td>
<td>17</td>
<td>12738</td>
<td>72%</td>
</tr>
<tr>
<td><strong>All trials</strong></td>
<td><strong>36</strong></td>
<td><strong>22982</strong></td>
<td><strong>22</strong></td>
<td><strong>17791</strong></td>
<td><strong>77%</strong></td>
</tr>
</tbody>
</table>

**Aminobisphosphonates include:**
- Zoledronic acid (65% of patient data received),
- Oral ibandronate (24%),
- Oral pamidronate (8%),
- Oral res verdronate (2%)
- Oral alendronate (1%)

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Breast Cancer Recurrence: All Women

All Recurrences

17709 women  3408 events

Distant recurrences

17709 women  2835 events

Recurrent rates (% / year) and logrank analyses

<table>
<thead>
<tr>
<th>Allocation</th>
<th>Years 0 - 4</th>
<th>Years 5 - 9</th>
<th>Year 10+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisph</td>
<td>3.68 (1382 / 37591)</td>
<td>2.43 (319 / 13112)</td>
<td>1.04 (18 / 1730)</td>
</tr>
<tr>
<td>Not</td>
<td>3.69 (1344 / 34519)</td>
<td>2.43 (322 / 13268)</td>
<td>1.28 (23 / 1793)</td>
</tr>
<tr>
<td>Rate ratio, from (O-E) / V</td>
<td>0.93 ± 0.04</td>
<td>0.97 ± 0.08</td>
<td>0.66 ± 0.33</td>
</tr>
</tbody>
</table>

Distant recurrence rates (% / year) and logrank analyses

<table>
<thead>
<tr>
<th>Allocation</th>
<th>Years 0 - 4</th>
<th>Years 5 - 9</th>
<th>Year 10+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisph</td>
<td>2.07 (1135 / 38174)</td>
<td>1.90 (264 / 13669)</td>
<td>1.00 (264 / 13669)</td>
</tr>
<tr>
<td>Not</td>
<td>2.21 (1127 / 35109)</td>
<td>1.90 (264 / 13669)</td>
<td>1.44 (28 / 1944)</td>
</tr>
<tr>
<td>Rate ratio, from (O-E) / V</td>
<td>0.91 ± 0.04</td>
<td>0.98 ± 0.09</td>
<td>0.47 ± 0.06</td>
</tr>
</tbody>
</table>

Logrank 2p = 0.08

Logrank 2p = 0.03

10-y gain 1.1% (SE 0.9)

10-y gain 1.4% (SE 0.9)
Distant Recurrence: All Patients

**Bone Recurrence**

17709 women, 888 events

10-y gain 1.5% (SE 0.6)
Logrank 2p = 0.0009

**Non-bone Recurrence**

17709 women, 1947 events

10-y gain 0.1% (SE 0.8)
Logrank 2p = 0.71

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Breast Cancer Recurrence: Postmenopausal Women

**Distant Recurrence**
- 11,036 women, 1,564 events
- 10-y gain 3.5% (SE 1.2)
- Logrank 2p = 0.0003

**Bone Recurrence**
- 11,036 women, 508 events
- 10-y gain 2.9% (SE 0.8)
- Logrank 2p < 0.00001

**Non Bone Recurrence**
- 11,036 women, 1,056 events
- 10-y gain 0.9% (SE 1.0)
- Logrank 2p = 0.24

Significantly Greater Effect on Bone than Other Distant Recurrence

*Includes induced menopause and women aged >55 if unknown*
Mortality – All Women

Breast cancer mortality

17709 women  2097 events

10-y gain 1.7% (SE 0.9)
Logrank 2p = 0.04

Non-breast cancer mortality

17709 women  493 events

10-y loss 0.1% (SE 0.6)
Logrank 2p = 0.96

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Mortality In Post-menopausal Women

Breast cancer mortality

11036 women  
1146 events

10-y gain 3.1% (SE 1.3)
Logrank 2p = 0.004

All cause mortality

11036 women  
1524 events

10-y gain 2.3% (SE 1.5)
Logrank 2p = 0.007

Death rates (% / year: total rate – rate in women without recurrence) & logrank analyses

Allocation
Bisph  
Not
Rate ratio, from (O-E)/V

Year 0 – 4  
1.04 ± 0.08  
1.32 ± 0.09
-0.68 ± 0.07  
-0.78 ± 0.11  
0.92 ± 0.30

Year 5 – 9  
1.60 ± 0.14  
2.32 ± 0.16
-2.04 ± 0.16  
-0.78 ± 0.11  
-1.52 ± 0.30

Year 10+  
1.30 ± 0.49  
2.73 ± 0.73
-2.73 ± 0.73  
-0.52 ± 0.30  
-2.4 ± 0.36

Not
Bisph

23.8%
21.5%

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Conclusions

• Adjuvant bisphosphonates reduce bone metastases and improve survival in post-menopausal women.
  - 34% reduction in risk of bone recurrence (p=0.00001).
  - 17% reduction in risk of breast cancer death (p=0.004).
  - No significant reduction in first distant recurrence outside bone.
  - Risk reductions similar irrespective of ER, node status, use/non use of chemotherapy.
  - Benefits similar for aminobisphosphonates and clodronate.

• No effects apparent on disease outcomes in pre-menopausal women.

• No significant effects on non breast cancer deaths, contralateral breast cancer or loco-regional recurrence.
Conclusion and Perspectives

- Bone-targeted treatments modify the bone (marrow) microenvironment.
- In several large clinical trials, adjuvant bisphosphonates reduce the risk of metastases and prevent breast cancer deaths.
- A “low-estrogen” environment may be a prerequisite for clinically relevant benefits.
- If this is confirmed, adjuvant bisphosphonates should be considered a standard treatment in postmenopausal (natural/induced) breast cancer.
Cancer Cell Metastasis – New View

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Bisphosphonates in Breast Cancer

1. Prevent SRE
   - Breast cancer
   - Myeloma
   - Lung Cancer with bone mets
   - Prostate cancer on ADT

2. Prevention of CTIBL

3. Adjuvant Treatment of Breast Cancer

4. Prevention of Breast Cancer
# Cancer Prevention

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Comparator</th>
<th>Effect Size 95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wisconsin study</td>
<td>BP vs no BP</td>
<td>Breast cancer incidence</td>
<td>0.67 (0.51–0.89)</td>
<td>NR</td>
</tr>
<tr>
<td>(N = 5,911)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHI-OS</td>
<td>BP vs no BP</td>
<td>Breast cancer incidence</td>
<td>0.68 (0.52–0.88)</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>(N = 154,768)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCINIS</td>
<td>BP vs no BP</td>
<td>Breast cancer incidence</td>
<td>0.72 (0.57–0.90)</td>
<td>NR</td>
</tr>
<tr>
<td>(N = 4,039)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MECC study</td>
<td>BP vs no BP</td>
<td>Colorectal cancer incidence</td>
<td>0.41 (0.25–0.67)</td>
<td>NR</td>
</tr>
<tr>
<td>(N = 1,866)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Women’s Health Initiative (WHI): Oral bisphosphonates and breast cancer

Observational study (N=154,768)

Cumulative incidence of invasive breast cancer

- Bisphosphonate use
- No bisphosphonate use

HR, 0.68 (95% CI, 0.52 to 0.89); P<0.01

Hip fracture risk score used to compensate for potential BMD difference between patients on vs. not on bisphosphonate therapy

Side Effects of Adjuvant Bisphosphonates

American Association of Oral and Maxillofacial Surgeons
Position Paper on Bisphosphonate-Related Osteonecrosis of the Jaw—2009 Update
Approved by the Board of Trustees January 2009

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Osteonecrosis of the Jaw and Oral Health–Related Quality of Life After Adjuvant Zoledronic Acid: An Adjuvant Zoledronic Acid to Reduce Recurrence Trial Subprotocol (BIG01/04)

Emma J. Rathbone, Janet E. Brown, Helen C. Marshall, Michelle Collinson, Vikas Deshpande, Geraldine A. Murden, David Cameron, Richard Bell, Satya Srivastava, Prabin Chakraborti, Frances Yuille, and Robert N. Stockton

See accompanying editorial at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2013.50.0916
Thank You