Factors released during osteoclastic bone resorption enhance disseminated breast cancer cell progression by stimulating invasiveness, growth, and a bone-resorptive phenotype in cancer cells. Postmenopausal bone loss may accelerate progression of breast cancer growth in bone, explaining the anticancer benefit of the bone-specific antiresorptive agent zoledronic acid in the postmenopausal setting. 

In this issue of *Clinical Cancer Research*, Ottewell and colleagues (1) report that progression of metastatic breast cancer in bone was mediated by osteoclastic bone resorption in a preclinical model of surgical menopause (ovariectomy, O VX). In these studies, antitumor activity of the antiresorptive agent zoledronic acid (ZOL) was detected only in a postmenopausal estrogen-deficient setting when osteoclastic bone resorption was increased.

Bone has long been recognized as a unique metastatic microenvironment due to growth factors stored in mineralized bone matrix, vascularity, and an enrichment of cytokines capable of stimulating tumor cell invasiveness, growth, and a bone-resorptive phenotype in cancer cells (2). The bone microenvironment is further complicated by the fact that its cells are acutely sensitive to changes in endocrine status. Pre- and postmenopausal bone niches may differ greatly as host environments for disseminated cancer cells due to increased osteoclastic bone resorption that occurs in the setting of estrogen deficiency and ovarian failure as women reach menopause. This postulate is supported by recent clinical reports demonstrating differential anticancer effects of bone-targeted antiresorptive bisphosphonate therapy in patients with breast cancer depending on their menopausal status. In the AZURE, ZO-FAST, and ABCSG-12 trials, ZOL consistently improved disease-free survival in patients with breast cancer; however, this effect was limited to postmenopausal women (3–5). Direct anticancer effects of ZOL have been pursued with little evidence that physiologically relevant doses can directly elicit cancer cell apoptosis (6). Although direct antitumor effects of bisphosphonates have been shown in vitro (7), the anticancer activity of ZOL has been attributed to indirect effects via inhibition of osteoclastic bone resorption. Ottewell and colleagues provide the first preclinical data to explain the antitumor effect of ZOL in an estrogen-deficient postmenopausal state characterized by significant bone loss. These data are analogous to the clinical setting, in which ZOL shows anticancer benefit (3–5), and align with established concepts that tumor progression in the bone compartment is largely driven by cues from the microenvironment, and, specifically, by osteoclastic bone resorption.

Declining ovarian sex steroid production and a concomitant increase in inflammatory tone associated with menopause alter the bone microenvironment in ways that may promote cancer cell homing, tumor growth, and an osteolytic phenotype in cancer cells (Fig. 1). Under normal physiologic conditions, estrogen (i) acts directly on bone cells to regulate the lifespan of both osteoclasts and osteoblast and (ii) inhibits T-cell production of inflammatory cytokines, which can drive osteoclast activation and bone resorption (8). In the absence of estrogen, osteoclastic bone resorption outpaces formation via increased osteoblast expression of RANKL (receptor activator of nuclear factor-kappa B ligand), which binds to its cognate receptor RANK on the osteoclast and stimulates osteoclastogenesis (8). Reduced expression of the soluble decoy receptor for RANKL, osteoprotegerin (OPG), is also associated with estrogen deprivation and contributes to excessive bone resorption (8). Women can lose up to a quarter of their trabecular bone mass in a mere 5 to 7 years following menopause (9); this acute phase of bone loss is followed by a gradual and continued decline in bone mass for the remainder of postmenopausal life (9).

Increased bone resorption has been demonstrated in preclinical models to fuel cancer progression in bone (10) presumably via release of growth factors from the mineralized bone matrix, including TGF-β, insulin-like growth factor (IGF), fibroblast growth factors, and platelet-derived growth factor, which stimulate tumor growth and expression of osteolytic factors that perpetuate a feedforward bone destructive cycle (2). Furthermore, osteoclast-derived proteolytic enzymes can promote angiogenesis, cancer cell invasiveness, and engraftment at metastatic sites.
(11), further contributing to the potential pathways by which osteoclastic bone resorption may promote tumor progression in bone and colonization of dormant disseminated tumor cells. As predicted, Ottewell and colleagues report that gene expression of factors associated with osteoclastic bone resorption, including RANKL, Cathepsin-K, and MMP9, was increased in OVX bone, but not in ZOL-treated OVX bone. Blockade of bone destruction by ZOL thus prevents numerous downstream events that are triggered by a heightened state of bone resorption (Fig. 1). In this way, antiresorptives have the potential to drastically curb cancer cell progression in the postmenopausal setting. Premenopausal patients with breast cancer undergoing antiestrogen therapy that leads to artificial menopause and increased bone resorption using aromatase inhibitors or luteinizing hormone–releasing hormone agonists also stand to benefit from ZOL therapy, as reported clinically in the ZO-FAST and ABCSG-12 trials, respectively (4, 5).

Effects of ZOL on pre- and postmenopausal estrogen receptor (ER)-positive breast cancer progression were not addressed in these studies due to poor engraftment of the ER-positive breast cancer cell line, MCF-7. Despite this caveat, use of the ER-negative human MDA-MB-231 breast cancer line is advantageous because changes in tumor growth can be attributed exclusively to alterations in the bone microenvironment independent of the confounding effect of estrogen-mediated tumor growth.

The study by Ottewell and colleagues is important because it addresses the long-standing query of whether alterations in the bone microenvironment can alter tumor growth in bone. Such studies are difficult to perform in mice and in humans. Menopausal status in clinical trials is often self-reported, and definitions of premenopause and postmenopause can vary across studies. Preclinical modeling of ovarian failure by OVX eliminates that variability as cessation of ovarian hormone production can be precisely timed and the subsequent osteoclast-driven bone loss can be measured prospectively. However, this model lacks a perimenopausal phase characterized by increased follicle-stimulating hormone and decreased inhibin concentrations in a
state of relative estrogen sufficiency (12). As such, events in the mouse model may not reflect the window of the perimenopausal state and would require further study. In addition, estrogenic activity is not completely blocked with surgical menopause or OVX due to peripheral aromatization of androgens. Total estrogen depletion would require administration of an aromatase inhibitor in the setting of OVX and will likely lead to more profound bone loss and tumor progression relative to OVX alone in cancer-bearing mice. Nonetheless, despite these caveats, the message from this study is clear: The microenvironment matters and can influence tumor growth in bone. Changes to the microenvironment due to estrogen deficiency can be reversed by blockade of osteoclastic bone resorption and this strategy could have important therapeutic and preventive implications for our postmenopausal women with breast cancer.

These important findings raise further questions: (i) Could other clinical entities or cancer treatments that increase osteoclastic bone resorption, such as radiation, glucocorticoids, or aromatase inhibitors, influence cancer progression in bone? Can these effects be prevented? (ii) What are the mediators released from actively resorbed bone that contribute to tumor progression in bone? IGFs and TGF-β are candidates as both are released as a consequence of osteoclastic bone resorption and can promote tumor growth and invasion. Further preclinical studies such as those performed by Ottewell and colleagues can address the growing importance of the microenvironment and the clinical implications for our patients with breast cancer.

Disclosure of Potential Conflicts of Interest

T.A. Guise is a consultant/advisory board member and has provided expert testimony for Novartis. No potential conflicts of interest were disclosed by the other author.

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): L.E. Wright, T.A. Guise
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): L.E. Wright, T.A. Guise
Writing, review, and/or revision of the manuscript: L.E. Wright, T.A. Guise
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The Microenvironment Matters: Estrogen Deficiency Fuels Cancer Bone Metastases

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