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Bone resorption and bone metastasis risk

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ABSTRACT

Breast cancer tumors have a tendency to metastasize to the bone. After development of a bone metastasis, the median survival time is 40 months. Currently, little is known about the modifiable risk factors for developing bone metastases in women diagnosed with breast cancer. One possible modifiable risk factor is increased bone resorption. Increased bone resorption is caused by an imbalance between osteoblasts and osteoclasts favoring osteoclast-driven bone resorption. Osteoclast activity results in the release of growth factors from the bony matrix that are requirement for successful breast cancer tumor cell proliferation within the bone. Mice studies have shown that mice that have been genetically engineered to have higher bone mineral density, and thus lower bone resorption, have a decreased incidence of bone metastases. Alternatively, mice genetically engineered to have lower bone mineral density or increased bone resorption have a higher incidence of bone metastases. In human studies, antiosteoporotic drugs have been shown to decrease osteoclast activity and prevent bone metastases. These studies suggest that increased osteoclast activity, which results in low bone mineral density, may be a modifiable risk factor for developing bone metastases in women with breast cancer. Women undergoing chemotherapy for breast cancer develop low bone mineral density in response to the direct effects of chemotherapeutic drugs on bone cells—including osteoclasts, osteoblasts, and osteocytes—and through the decrease in circulating estrogen as a result of chemotherapy-induced ovarian dysfunction. Therefore, it is important for future studies to determine the risk of developing bone metastases associated with increasing bone resorption as measured by low or decreasing bone mineral density in women diagnosed with breast cancer, as well as to determine the best intervention(s) to promote a balance between osteoclasts and osteoblasts to favor osteoblast activity during chemotherapy treatment.

Introduction

Breast cancer is the most commonly diagnosed cancer in women in the U.S, with an estimated 246,660 newly diagnosed cases each year [1]. Breast tumors have a tendency to metastasize to bone, with up to 20–30% of women diagnosed with early breast cancer developing bone metastases (BM) [2–4]. The median survival time after developing bone metastases is 40 months [5]. In order to prevent bone metastases in and increase the life expectancy of women with breast cancer, factors that increase the risk for developing BM must be identified.

To date, several risk factors for developing bone metastases in women with breast cancer have been studied. These risk factors include: age, menopausal status, BMI, and tumor characteristics [6,7]. In some, but not all studies, women who were older, postmenopausal, had a higher BMI at time of breast cancer diagnosis and those who had luminal A or B breast cancer subtypes or tumor grades 1–3 had a significantly greater incidence of bone metastasis [6,7]. Serum markers of bone resorption, such as cross-linked telopeptides of collagen type I (CTx) and bone sialoprotein (BSP), are associated with increased risk for developing BM and a shorter time to development of BM in women with breast cancer [7–9]. In fact, a greater percentage of women with breast cancer characterized as osteoporotic—a disease state in which osteoclast activity exceeds osteoblast activity, resulting in decreasing BMD—had disseminated tumor cells within their bone marrow compared to women with breast cancer who were characterized as having normal BMD or osteopenic [10]. Bone resorption results in the release of growth factors from the bone matrix that promote tumor cell survival and proliferation within the bone microenvironment, suggesting that increased osteoclast activity as measured by decreasing BMD or serum markers of osteoclast activity may be a significant risk factor for developing BM [11,12]. Taken together, the use of serum markers of bone resorption and the different prevalence of disseminated tumor cells between women with breast cancer with different BMD suggest that increased osteoclast activity that results in decreased BMD may be

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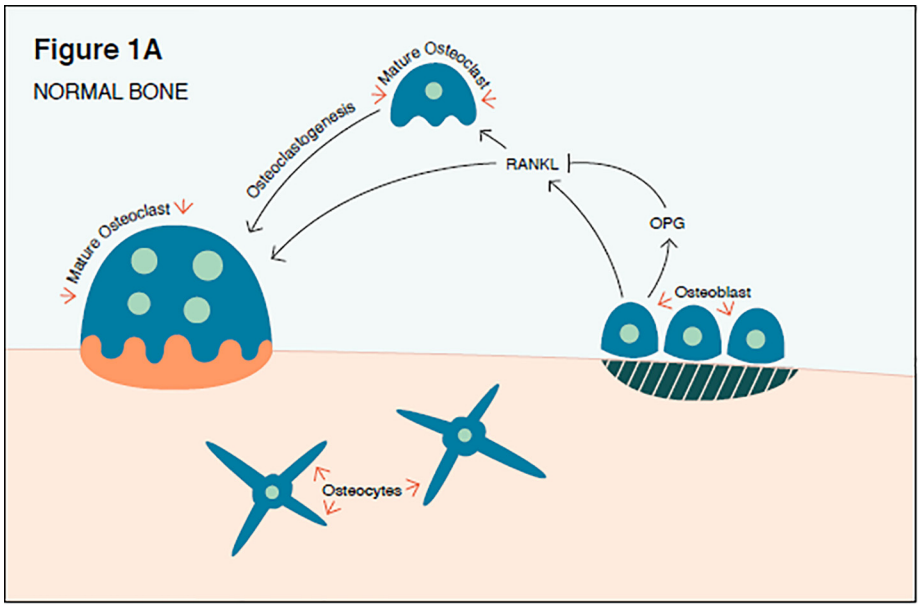

Fig. 1A. Osteoblasts secrete both OPG and RANKL. RANKL binds to RANK receptors on premature osteoclasts to stimulate osteoclastogenesis and on mature osteoclasts to increase osteoclast activity. OPG is a decoy receptor for RANKL—it will bind to RANKL and prevent it from binding to RANK receptors on premature and mature osteoclasts. The ratio of RANKL:OPG determines the activity of osteoclasts and rate of bone resorption.

associated with an increased risk for developing BM.

The purpose of this paper is to summarize evidence to support a mechanistic hypothesis that increased osteoclast activity associated with decreasing BMD increases the risk for developing BMs in women with breast cancer due to the release of growth factors from the bone matrix that are required for tumor cell proliferation. This paper will present an overview of the bone microenvironment in a healthy individual, followed by the effects of vitamin D deficiency found in women with breast cancer and chemotherapy drugs on the bone microenvironment. Following, human and murine studies that associate altered osteoclast activity with incidence of BM development will be presented in support of the hypothesis that increased osteoclast activity associated with low BMD is a risk factor for developing BM in women diagnosed with breast cancer.

Normal bone microenvironment

Osteoclasts and osteoblasts are the bone cells that are directly responsible for bone resorption and deposition, respectively, and maintain the bone microenvironment [13]. As shown in Fig. 1A, osteoblasts secrete two factors: osteoprotegrin (OPG) and receptor activator of NF-κB ligand (RANKL) [14]. RANKL binds to RANK receptors that are present on immature osteoclast precursors to initiate osteoclastogenesis, or the development of mature osteoclasts, and to RANK receptors that are present on mature, multinucleate osteoclasts to initiate bone resorption [12,24]. OPG is a decoy receptor for RANKL [14]. The OPG to RANKL ratio will therefore affect osteoclast activity, with higher ratio suppressing osteoclastogenesis and a lower ratio initiating osteoclastogenesis [14]. Estrogen plays a vital role in maintaining a homeostatic balance between osteoclast and osteoblast activity by promoting a higher OPG to RANKL ratio and thus inhibiting osteoclast activity [15]. In women with breast cancer, this microenvironment is affected by vitamin D deficiency and chemotherapy drugs, as will be discussed below.

Vitamin D deficiency and bone resorption

Women diagnosed with breast cancer have significantly vitamin D levels than healthy age-matched women, with many women with breast cancer being classified as vitamin D deficient [13,14]. Vitamin D deficiency stimulates a continuous, elevated level of parathyroid hormone secretion [18]. Continuous, elevated secretion of parathyroid hormone results in catabolic effects on bone. Parathyroid hormone binds to parathyroid hormone receptor 1 (PTH-R1) on osteoblasts and results in an increased RANKL:OPG ratio [19]. As previously mentioned, this increased RANKL production results in the promotion of osteoclastogenesis and bone resorption.

Chemotherapy and bone resorption

Women with breast cancer undergoing chemotherapy experience a decrease in BMD and are at increased risk for developing osteopenia or osteoporosis [13–17]. This relationship is independent of BMD at time of diagnosis [22]. Chemotherapy may directly affect the cellular components controlling bone remodeling or may affect BMD indirectly through a decrease in circulating estrogen, as effected by chemotherapy-induced amenorrhea [16–22]. The following sections will describe in further detail how chemotherapy and the hypoestrogenemia associated with chemotherapy-induced amenorrhea independently promote decreased BMD.

Direct effects: chemotherapy and bone

BMD in women treated with chemotherapy has been shown to decrease independently from chemotherapy-induced ovarian dysfunction and subsequent decrease in estrogen [24]. Chemotherapy has direct cytotoxic effects on bone cells, specifically increasing osteoclast activity, inhibiting osteoblast activity, and inducing osteocyte apoptosis (Fig. 1B). Two standard breast cancer chemotherapy regimens (1. combination cyclophosphamide, epirubicin, and 5-flourouracil (CEF) and 2. doxorubicin) administered in therapeutic doses in a murine model resulted in significant reduction in trabecular bone volume [18,19]. Micro-CT analysis of rat tibias revealed a significant decrease in trabecular number at 3 weeks and trabecular BMD at 6 weeks in mice treated with CEF [25]. Similarly, rats treated with anthracyclines also demonstrated a significant decrease in trabecular bone volume and number at the end of treatment [26]. The decreased trabecular bone volume and number in these studies were associated with an uncoupling between osteoclast and osteoblast activity [18,19]. In mice treated with anthracyclines, there was a significant decrease in osteocytes and bone lining cells of the tibia compared to controls [26]. While there was no change in osteoblast number in mice treated with CEF or anthracyclines, there was a significant decrease in serum concentrations of ALP, a marker of bone formation, and ex vivo mineralization