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Osteoporosis After Breast Cancer Chemotherapy: A Case Report

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ABSTRACT

We describe therapeutic challenges in a patient with breast cancer during follow-up after quadrantectomy. The patient had used hormone therapy for 5 years and then tamoxifen citrate, a selective estrogen receptor modulator, for 3 years. When seen by us, she was taking Arimidex, an aromatase inhibitor. In accord with recommendations in the literature, bisphosphonate therapy was prescribed by clinicians at the Menopause Center in cooperation with the Oncology Center. We suggest that cooperation between menopause centers and oncology centers should continue in the follow-up of such patients.

INTRODUCTION

Estrogens have important roles in the homeostatic maintenance of several target tissues, including mammary gland, uterus, bone, cardiovascular system, and brain.[1] Most of the activity of estrogen is thought to be mediated by its nuclear estrogen receptors, ERα and ERβ, which are members of the nuclear receptor superfamily that act as ligand-induced transcription factors.

Acting via its receptors, estrogen is also involved in the pathogenesis and progression of human breast cancer. In mammary tissue, estrogens promote proliferation, sometimes uncontrolled, that can ultimately lead to breast cancer. Malignant breast tumors are composed of a number of biologic subtypes displaying various pathologic and clinical features.[2,3] About 70% to 75% of breast cancers are ER positive, and one half express the progesterone receptor.[4,5] The ER and the progesterone receptor (regulated by estrogen via the ER) are used as prognostic markers in the clinical management of patients with breast cancer. Immunohistochemical ER assessment is part of the standard clinical work-up of patients with newly diagnosed breast carcinomas. However, the prognosis of a patient with ER-positive/progesterone receptor–positive breast cancer can be highly variable, and many hormone receptor–positive breast cancers do not respond to endocrine therapy.

Estrogen receptor status predicts response to hormonal therapies such as tamoxifen citrate and aromatase inhibitors[6] (AIs) but is a weak prognostic biomarker because it is related to tumor histology and grade.[7] Problems have been reported in clinical implementation of ER testing, including false-negative results, which have led to major difficulties in patient care.[8]

Estrogens also act on bone tissue, preventing osteoporosis. It is well established that the sex-specific loss of bone with age is related to estrogen withdrawal at menopause and that this loss can be prevented by estrogen therapy.[9] Estrogens suppress bone remodeling (initially resorption and subsequently formation). They seem to act by partially inhibiting the parathyroid-mediated first steps in the cellular resorption cycle.

CASE REPORT

A 57-year-old woman came to our Menopause Center for prevention of osteoporosis. She had entered menopause in 2000 at the age of 49 years, when she began continuous combined hormone therapy. After 5 years of hormone therapy, she was diagnosed as having an adenomatous breast cancer. She underwent superior right quadrantectomy in 2005 and subsequent adjuvant chemoradiotherapy. The tumor was ER positive. From 2005 to 2008, she took tamoxifen. In September 2008, her medical consultants prescribed Arimidex, an AI, for better protection.

After menopause, the patient's bone mineral density (BMD) was preserved by the use of hormone therapy for the first several years. She then took tamoxifen, a selective estrogen receptor modulator with positive estrogen effects on bone. From 1998 to 2008, the patient's dual-energy x-ray absorptiometry scan T score in the lumbar spine decreased by only 0.39 point (from −1.81 to −2.20 [Figures 1, 2, and 3]), without occurrence of any fracture.

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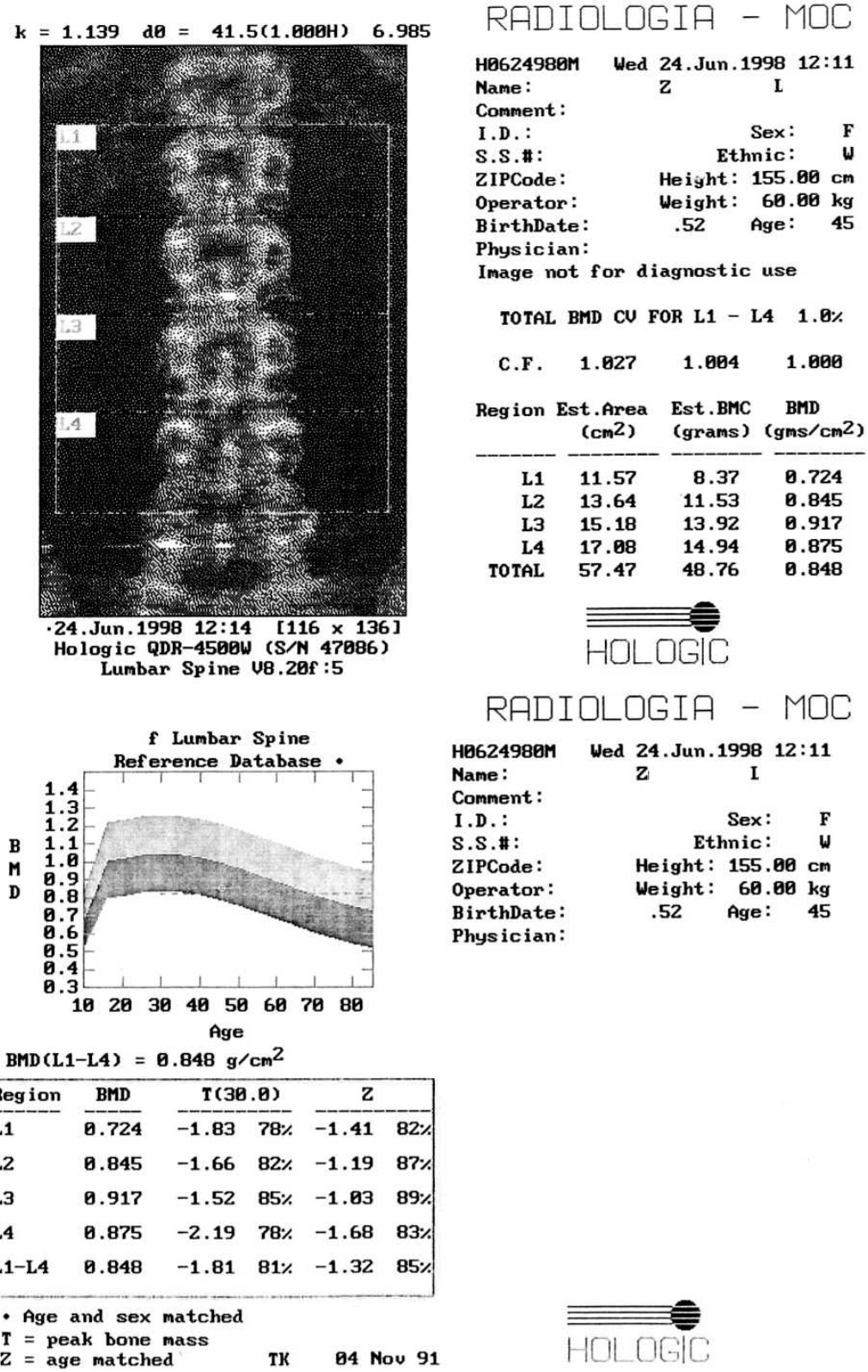

Figure 1. The patient's dual-energy x-ray absorptiometry scan in 1998.

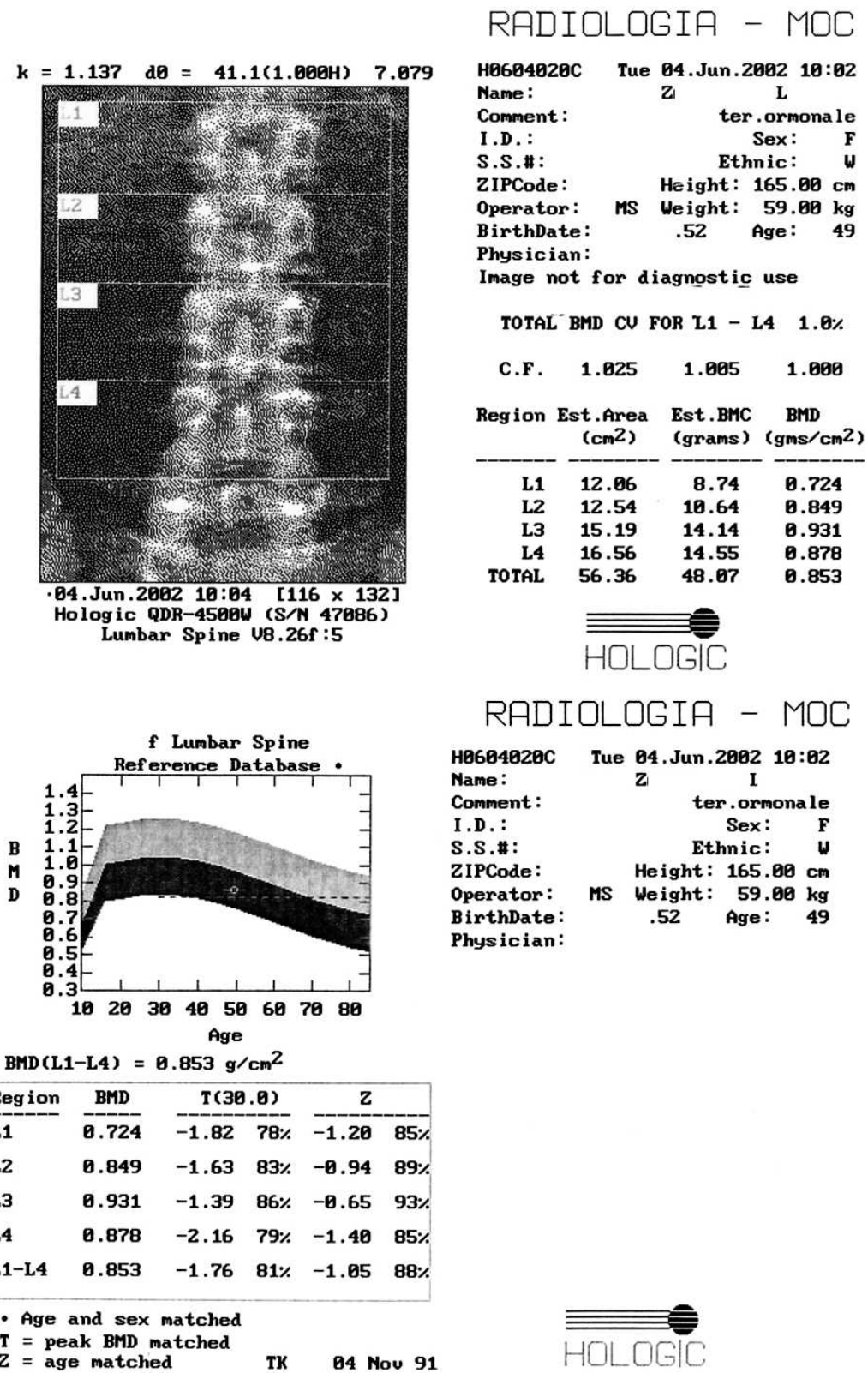

Figure 2. The patient's dual-energy x-ray absorptiometry scan in 2002.

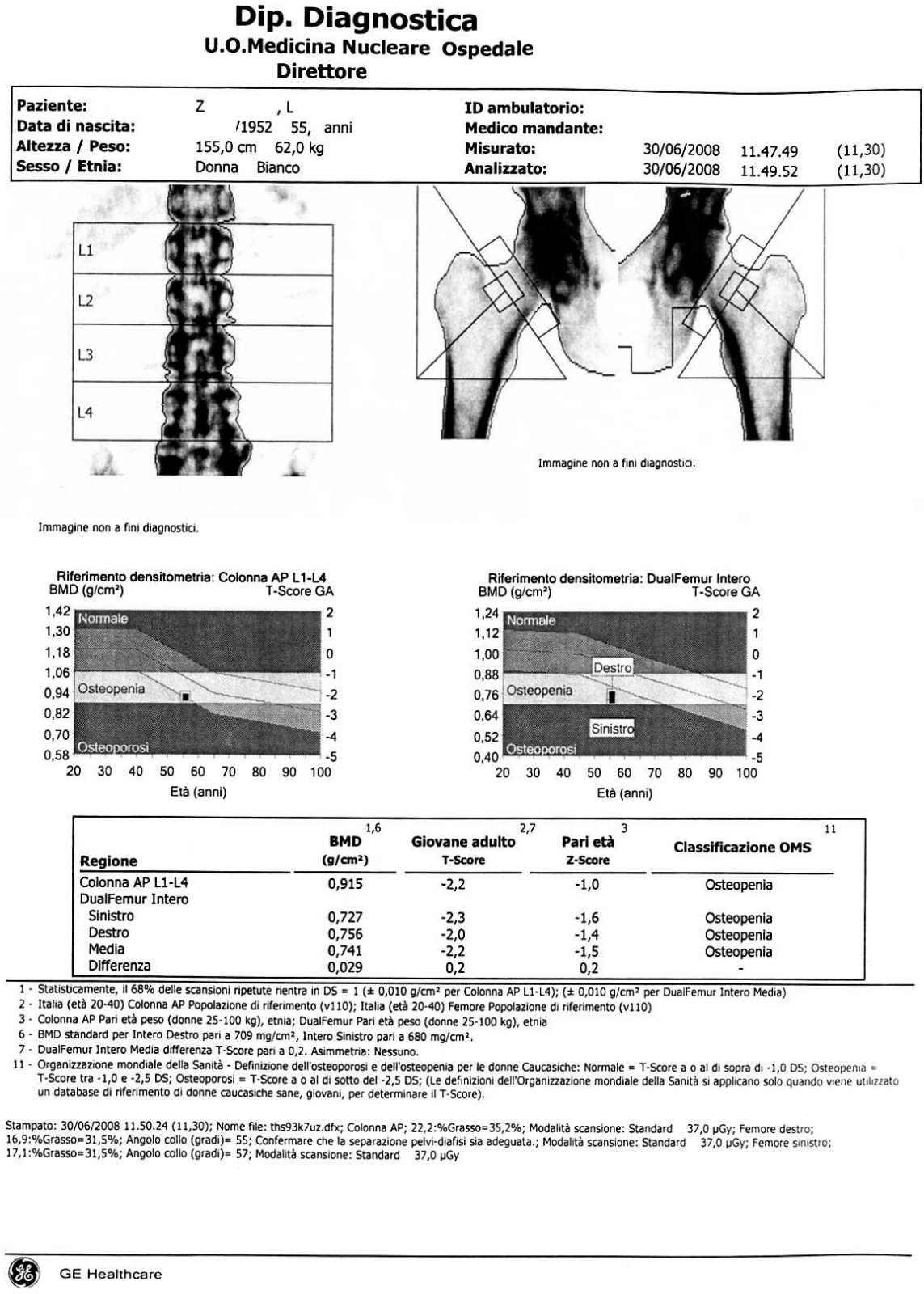

Figure 3. The patient's dual-energy x-ray absorptiometry scan in 2008.

Her current Arimidex regimen lacks estrogen action on bone. She is at high risk for osteoporosis with the combined natural hypoestrogen condition of menopause and the pharmacologic antiestrogen effect of AIs on bone. Therefore, we prescribed bisphosphonate therapy for bone protection in the patient.

DISCUSSION

Tamoxifen is in a class of medications known as antiestrogens. As a selective estrogen receptor modulator, it blocks the activity of estrogen in the breast and has been the standard adjuvant endocrine therapy for hormone receptor–positive early breast cancer for the past 30 years. However, there is definitive evidence that long-term use of tamoxifen is associated with serious adverse effects.[10] Because of their superior efficacy over tamoxifen, newer agents such as the third-generation AIs letrozole, anastrozole, and exemestane are established therapies for the treatment of advanced breast cancer.[11] The AIs act on aromatase; this is a cytochrome P450 enzyme complex that catalyzes the conversion of androgens to estrogens. These properties cause significantly increased bone loss; indeed, AIs inhibit endogenous production of estrogen by 50% to 90%.[12]

In addition to antiestrogenic effects, tamoxifen acts as an estrogen agonist in some tissues, which can lead to serious adverse effects unassociated with the AIs that prevent estrogen biosynthesis.[13] In particular, adverse events that are more frequent with adjuvant AI therapy compared with tamoxifen include arthralgia and myalgia, bone loss, and effects on the cardiovascular system and blood lipids. The effects of AIs on bone are predictable and may be easily managed, where necessary, with bisphosphonates. The AIs are now recommended as the preferred therapy by national and international guidelines.[14]

A randomized controlled study[15] compared a switch to exemestane vs continuation of tamoxifen in the adjuvant treatment of postmenopausal breast cancer. Results showed that tamoxifen preserves bone in postmenopausal women but that AIs accelerate bone loss and increase fracture risk.

A recent study[16] evaluated the effects of exemestane on bone turnover markers and on BMD. The data suggested that switching postmenopausal women from tamoxifen to exemestane causes a marked increase in bone turnover markers, with a consequent reduction in BMD.

A retrospective longitudinal study[17] of a large cohort of patients with breast cancer assessed the association between AIs and treatment-related bone loss in a large managed care population of women with breast cancer. Results demonstrated that AI therapies carry an increased risk of bone loss and that monitoring and treatment management strategies to reduce bone loss risk are warranted in women receiving an AI for breast cancer.

Most fractures occur in osteopenic women who are prescribed AIs. Current guidelines advocate BMD measurement in all patients receiving AIs, with selective use of antiresorptive therapy in osteoporotic women (T score exceeding -2.5), as AIs block estrogen production in peripheral tissues and the third-generation AIs anastrozole, letrozole, and exemestane reduce circulating estrogen levels, leading to accelerated bone loss and increased risk of fracture.[18] Indeed, the use of AIs increases bone turnover and induces bone loss at sites rich in trabecular bone at an average rate of 1% to 3% per year, increasing the incidence of fracture compared with that seen during tamoxifen use.[19] Therefore, emerging evidence supports concomitant use of bisphosphonates in all women taking AIs to prevent fracture and breast cancer recurrence.

The rate of bone loss in women who experience premature menopause before the age of 45 years or who are receiving ovarian suppression therapy is accelerated by the concomitant use of AIs. These patients are considered to be at high risk of clinically important bone loss and should have a baseline dual-energy x-ray absorptiometry assessment of BMD. The treatment initiation recommendations are based on a combination of risk factors for osteoporotic fracture and BMD levels and suggest the use of bisphosphonates in combination with a healthy lifestyle and an adequate intake of calcium and vitamin D[20] to prevent cancer treatment–induced bone loss in patients receiving long-term adjuvant breast cancer therapy.

Bisphosphonates act by inhibiting osteoclastic bone resorption. They have been shown to increase BMD and to reduce fracture risk in postmenopausal women with established osteoporosis.[21]

The Zometa/Femara Adjuvant Synergy Trial[22] found that the potent bisphosphonate zoledronic acid is efficacious in reducing bone loss in premenopausal women receiving combination adjuvant hormone therapy (goserelin [a gonadotropin-releasing hormone agonist] plus an AI or tamoxifen). In that study, postmenopausal women with stages I to IIIa ER-positive and/or progesterone receptor–positive breast cancer starting letrozole therapy were randomized to receive upfront zoledronic acid or delayed zoledronic acid. At 6 months, the first group showed a mean increase of 1.55% in lumbar spine (L1-L4) BMD compared with a mean decrease of 1.78% among women in the second group, resulting in a difference of 3.33% between the groups. Indeed, combining the anticancer efficacy of letrozole with the bone-protec-

tive effects of zoledronic acid may be a successful treatment in this setting.

Breast cancer survival is inversely related to body mass index, but previous investigations have not included large numbers of older women, to our knowledge. For example, a recent US study investigated the association between body mass index and mortality after breast cancer diagnosis in a cohort of older women of white race/ethnicity enrolled in the Study of Osteoporotic Fractures.[23] Results showed that the effect of increased body mass index on risk of mortality after breast cancer varied by age. These results differ from those observed among populations of younger postmenopausal breast cancer survivors.[24]

The Marburg Breast Cancer and Osteoporosis Trial[25] case-control study of 2492 women (mean ± SD age, 54.4 ± 10.3 years) elucidated the relationship between breast cancer and bone mass as ascertained by ultrasonometric measurements and investigated endogenous and exogenous exposure to estrogen. Estrogen is important in the pathophysiology of breast and bone, and cumulative exposure to estrogen may explain the link between breast cancer and bone mass. This study showed that T scores and Z scores were significantly higher in women with breast cancer and that they had a higher body mass index, were older at menopause, and had been exposed to estrogen longer than control women. In addition, the ultrasonometric variables speed of sound and stiffness index were higher in women with incident breast cancer than in healthy control subjects. Women with speed of sound and T scores in the higher quartiles generally have greater risk of breast cancer than women in the lowest quartile, but this study found no association between higher ultrasonometric variables and cancer-specific characteristics in patients.

Another US retrospective study[26] confirmed these findings in male breast cancer. Among the medical conditions examined in that study, increased male breast cancer risk was associated with a history of a bone fracture (relative risk, 2.20). The study demonstrated the commonalities with female breast cancer and affirmed the importance of hormonal mechanisms.

Another study[27] found that bone mass was a predictor of invasive ER-positive breast cancer. The Multiple Outcomes of Raloxifene Evaluation trial evaluated the relationship between bone mass and risk of breast cancer and determined the effect of raloxifene hydrochloride therapy on breast cancer incidence in women categorized as having low bone mass or osteoporosis. The investigators concluded that raloxifene treatment reduced the risk of invasive and ER-positive breast cancers in women with low bone mass and in women with osteoporosis.

The overall therapeutic index of AIs seems superior to that of tamoxifen, with improved efficacy and a better toxicity profile.[28] The use of AIs improves survival in breast cancer patients, despite adversely affected bone health. Indeed, adjuvant hormonal therapy for patients with endocrine-sensitive breast cancer has been dominated for several decades by the ''gold standard'' of tamoxifen.

In conclusion, it is important to prescribe bisphosphonates when switching patients' adjuvant therapy from tamoxifen to Arimidex. Menopause centers should work together in collaboration with oncology centers to integrate competencies for maximally effective follow-up of their patients.

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