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Bone mass and the risk of breast cancer: The influence of cumulative exposure to oestrogen and reproductive correlates. Results of the Marburg breast cancer and osteoporosis trial (MABOT)

P. Hadji *, M. Gottschalk, V. Ziller, M. Kalder, C. Jackisch, U. Wagner

Philipps University of Marburg, Department of Gynaecology, Gynaecological Oncology and Endocrinology, Pilgrimstein 3, D-35037 Marburg, Germany

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Abstract

Background: Recent studies suggest an inverse relation between breast cancer and osteoporosis. Oestrogen is important in the pathophysiology of both breast and bone, and although cumulative exposure to oestrogen may explain the link between breast cancer and bone mass, this has never been proved. The Marburg breast cancer and osteoporosis trial (MABOT) aimed to elucidate the relation between breast cancer and bone mass ascertained by ultrasonometry measurement and to investigate whether endogenous and exogenous exposure to oestrogen and reproductive correlates has a role in this association.
Methods: We performed a case–control study including 2492 women (mean age ± S.D., 54.4 ± 10.3 years) in whom diseases and drug treatments known to affect bone metabolism, except for HT, had been excluded. All women underwent ultrasonometry measurement at the heel; 242 of the women had an incident breast cancer without a prior, specific pharmacological breast cancer treatment. The ultrasonometry variables – speed of sound (SOS), broadband ultrasound attenuation (BUA) and the stiffness index (SI) – were calculated and compared in women with and without breast cancer. Because of significant intergroup differences in factors such as age, body mass index and exposure to oestrogen, a multiple linear regression analysis as well as a second analysis of ultrasonometry variables was undertaken using a randomly selected sample of 242 healthy women post-matched with the breast cancer group for possible confounding variables. Odds ratios were used to compare the relation between breast cancer risk and ultrasonometry heel measurements.
Results: Women with breast cancer were significantly older, weighed more, had a higher body mass index, were more likely to be parous and to have breast fed, were older at the menopause and had been exposed to oestrogen for longer than control women. In addition, the ultrasonometry variables speed of sound and the stiffness index *T*- and *Z*-score were significantly higher in women with breast cancer even after a matched pair analysis was performed ($p < 0.001$). Additionally, results of a multiple linear regression showed that women with breast cancer had a significantly higher SOS ($p < 0.001$), body weight ($p < 0.05$) and

* Corresponding author. Tel.: +49 6421 28 66486; fax: +49 6421 28 67070.
E-mail address: hadji@med.uni-marburg.de (P. Hadji).

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duration of breast feeding ($p < 0.05$) while osteoporotic fracture were reduced ($p < 0.001$). When women with breast cancer and their matched controls were finally grouped according to SOS and *T*-score quartiles, the odds ratios (95% confidence intervals) for breast cancer risk in the second, third and fourth quartiles compared with the lowest quartile were 2.5 (1.4–4.3), 3.1 (1.8–5.3) and 4.7 (2.7–8.2) as well as 1.9 (1.1–3.2), 2.3 (1.3–3.9) and 2.9 (1.7–5.0), respectively.
Conclusions: The ultrasonometry variables speed of sound, stiffness index, *T*- and *Z*-score are higher in women with an incident breast cancer than in healthy controls, even after post-matching for possible confounding variables. This association was confirmed in a multiple linear regression model. Women with SOS and *T*-score values in the higher quartiles have a greater risk of breast cancer than women in the lowest quartile. We found no association between the higher ultrasonometry variables and cancer specific characteristics or reproductive correlates such as age at menarche and menopause or cumulative oestrogen exposure. Although the biological mechanisms linking bone mass and the risk of breast cancer are not fully understood, factors other than reproductive correlates, endogenous and exogenous exposure to oestrogen must play a part.

Keywords: Breast cancer; Bone mass; Osteoporosis; Oestrogen; Risk factor

1. Introduction

Breast cancer and osteoporosis, two of the most common diseases in postmenopausal women, have a major impact on the life expectancy and quality of life of this group. Several risk factors for breast cancer have been identified, including a history of breast cancer in first degree relatives, obesity, nulliparity, late age at first full-term pregnancy, early menarche and late menopause [1,2]. Some of these factors are related to prolonged cumulative exposure to oestrogen.

Oestrogen may be the link between bone and the risk of breast cancer because of its potent effects on the mitotic activity of breast epithelium and on bone turnover [3,4]. The mechanism of action of oestrogen on breast epithelium is still not fully understood. However, the importance of oestrogen in the regulation of bone turnover is shown by the presence of oestrogen receptors in the cells responsible for bone formation (osteoblasts) and bone resorption (osteoclasts) [5,6]. Furthermore, oestrogen influences the production of mediators such as cytokines, and growth factors including insulin-like growth factor, interleukin-6, osteoprotegerin, RANKL and transforming growth factor β, which are involved in bone turnover and in breast cancer [7,8]. Consequently, prolonged amenorrhoea and menopausal loss of ovarian oestrogen are associated with increased bone loss that eventually leads to an increased risk of fractures [9–11]. Several investigators have suggested that bone mass or bone mineral density may reflect the cumulative exposure to oestrogen [12,13].

The possibility that bone mass may be related to the risk of breast cancer has been supported by a several published reports [14–20]. However, other workers have failed to show this association [21–23]. Yet, none of these studies could show that in women with breast cancer compared with control women, a higher bone mineral density was associated significantly with prolonged exposure to oestrogen simply because they did not accumulate all the data needed to examine this relation. Most studies used single-photon-absorptiometry or dual energy X-ray absorptiometry, which are considered the best non-invasive methods of measuring bone mineral density [24].

Ultrasonomerty measurement of bone has recently been introduced. It has been reported that ultrasonometry variables at the heel correlate highly (r 0.8–0.9) with bone mineral density at the same site [25], and even more highly with biomechanical properties of bone [26]. Cross-sectional and prospective studies have shown that ultrasound measurements are as reliable as bone mineral density determined by dual X-ray absorptiometry in predicting hip and vertebral fracture, and provide additional, predictive information that is independent of bone mineral density [27–30]. Additionally, recent reports indicate, that ultrasonometry variables are influenced by prolonged amenorrhoea, menopausal loss of ovarian oestrogen and by postmenopausal hormone replacement therapy [28,30].

The Marburg breast cancer and osteoporosis trial (MABOT) aimed to evaluate the association between breast cancer and bone mass in a large sample of women using bone ultrasonometry for the first time.