Biomedicine & Pharmacotherapy 107 (2018) 571–582

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

# Postmenopausal osteoporosis and breast cancer: The biochemical links and beneficial effects of functional foods

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ARTICLE INFO

*Keywords:*
Breast cancer
Postmenopausal
Osteoporosis
Links
Functional foods
Effects

ABSTRACT

Breast cancer as a multifactorial disease has been classified among the major causes of morbidity and mortality in women across the world, with a higher prevalence among post-menopausal women. Osteoporosis, a condition characterized by altered bone mineralization is also commonly found among post-menopausal women. Consequently, post-menopausal women are at risk of morbidity and mortality associated with breast cancer and postmenopausal osteoporosis. This may not be unconnected to the fact that, there may be existent biochemical links between the two mayhems, which might rally round between the cellular and molecular connectivity based on the actions and inactions of RANKL, estrogen, free radicals-induced oxidative stress and metabolic implications of age related obesity among others. Cells and tissues including breast and bone are more prone to oxidative stress with age, and oxidative stress could alter the activity of key proteins and pathways required for protection against breast cancer and osteoporosis. As a result, the potentials of antioxidant rich functional foods in preventing, managing and possibly treating breast cancer and postmenopausal osteoporosis cannot be overemphasised. This review mainly uses ISI, SCOPUS and PubMed indexed journals and books containing various experimental reports vacillating from humans, animals and in vitro studies in relation to breast cancer and postmenopausal osteoporosis, biochemical links and possible beneficial effects of functional foods. One distinct feature of the review is that it categorically intends to provide a critical appraisal on the said available experimental data within the variables of breast cancer and osteoporosis among females vis-à-vis the potentials of functional foods.

## 1. Introduction

Breast cancer as a multifactorial disease has been classified among the major causes of morbidity and mortality in pre and post-menopausal women in many countries of the World [1]. Menopause is a form of generative aging characterized by ovarian follicular dysfunction and estrogen inadequacy leading to dramatic upsurge in bone resorption and eventual loss [2]. From the same disposition, postmenopausal osteoporosis could be seen as a biochemical phenomenon characterized by stumpy bone mass and microarchitectural weakening due to loss of the direct effect of estrogens on osteoclasts [3]. Therefore, biochemical link between breast cancer and postmenopausal osteoporosis is of great concern and interest especially among ageing women, owing to the compromise on the part of their normal body's physiological processes. This may as well be due to a growing incidence of breast cancer and osteoporosis among postmenopausal women [4,5].

*Abbreviations:* AP, activator protein-1; APC, adenomatous polyposis coli; ATM, ataxia-telangiectasia; BDNF-AS, brain-derived neurotrophic factor antisense; BIN1, bridging integrator 1; BMP6, bone morphogenetic protein 6; BRCA, breast cancer associated gene; CpG, cytosine located 5′ to guanosine; DMBA, dimethylbenzene anthracene; ER, estrogen receptor; GSTP1, glutathione S transferase P1; HER2, human epidermal growth factor receptor 2; HOTAIR, HOX transcript antisense intergenic RNA; MALAT1, metastasis associated lung adenocarcinoma transcript 1; PTEN, phosphatase and tensin homolog; PR, progesterone receptor; PVT1, plasmacytoma variant translocation 1; RANKL, receptor activator of nuclear factor kappa beta ligand; SP-1, stimulating protein-1 (SP-1); TNFSF11, tumor necrosis factor ligand super family member 11; TP53, tumor protein 53; UCA1, urothelial carcinoma-associated 1

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https://doi.org/10.1016/j.biopha.2018.08.018
Received 2 July 2018; Received in revised form 2 August 2018; Accepted 6 August 2018

These biochemical links rally round the up and down regulation of receptor activator of nuclear factor-κB ligand (RANKL) and estrogen, vis-à-vis the metabolically-induced oxidative stress relative to gene ontology. Indeed, it has been reported that when up regulated, RANKL encourages osteoclast differentiation with a consequential induction of excessive bone resorption instigating loss of bone integrity [4]. Interestingly, the RANKL/RANK pathway has been implicated in breast development and breast carcinogenesis [6].

Bone and breast tissues are both reliant on estrogen [7], a key hormone that regulates bone density [8], thereby maintaining an equilibrium between bone formation and bone resorption by either downregulating osteoclast levels or enhancing osteoblast proliferation [9]. In breast carcinogenesis, increased exposure to estrogen is linked with early menarche, late menopause, estrogen replacement therapy, obesity and high blood levels of estrogen increase the menace, incidence and severity of breast malignancy in pre- and postmenopausal women [10].

Irresistible levels of ROS generation resulting in oxidative stress have been implicated in postmenopausal osteoporosis and carcinogenesis [11]. On the contrary, superfluous ROS generation resulting in oxidative stress causes osteocyte apoptosis, implicated in augmented turnover of bone restoration and bone loss [12,13]. Hydrogen peroxide to be precise, has been found to improve osteoclasts activity, further supporting the notion that oxidative stress is connected with increased bone resorption and low bone mass [14]. However, altered redox state in favor of pro-oxidants in the tumor microenvironment, induces the generation of activated fibroblasts resulting in modifications on epithelial cells that promote tumorigenesis [15].

Being one of the anomalies of lipid metabolism, obesity has been reported to confer protection on bone by increasing mineral density, thereby lessening osteoporotic fracture risk [16]. This observation has been designated “obesity paradox” [17]. Nevertheless, obesity has been linked to poor response outcomes among ER-positive breast cancer patients [18]. A combination of breast cancer and obesity is seen in postmenopausal women, which poses a contest in the treatment of postmenopausal breast cancer patients suffering from osteoporosis [19].

Functional foods are those classes of food with health-promoting and disease preventing effects in addition to their natural nutritional values [20–22]. Prevention of osteoporosis and cancer is among the several beneficial effects of functional foods to humans. It is therefore, not surprising that such kind of diets could harbor cancer chemopreventive and therapeutics potentials [23] in addition to ameliorative effects on some of the cancer’s secondary or otherwise effects. This is evident as in the case of breast cancer and postmenopausal osteoporosis. Some of the functional foods that have been reported with ameliorative, preventive and curative properties in relation to breast cancer and postmenopausal osteoporosis are isoflavones-rich food [24], fixed oils [25], omega-3 fatty acids [26,27], honey [28], fruits [29,30] and dietary phytochemicals [31,32] to mention but a few. Recently, the knowledge and applications of nanotechnology [33–35] in delivery of most bioactive compounds from functional in combating breast cancer [36] and osteoporosis [37], are currently being explored (Fig. 1).

At present, there are various experimental reports vacillating from humans, animals and in vitro studies in relation to breast cancer and postmenopausal osteoporosis, biochemical links and possible beneficial effects of functional foods in that regard. However, a clear and focus wide-ranging review that collates all these research evidences, critically appraise the accomplishments documented so far as well as provide future research insights in prevention, treatment and management of breast cancer and postmenopausal osteoporosis vis-à-vis the potentials of functional foods have not been adequately explored in the current literature. Therefore, this review deems it fit to provide a critical appraisal on the said available experimental data within the variables of breast cancer and osteoporosis among females as little or no attention has been accorded this case study (Table 1).

## 2. Molecular basis of postmenopausal osteoporosis

Menopause, a form of reproductive aging, is characterized by ovarian follicular dysfunction and estrogen insufficiency which could lead to dramatic increase bone resorption and subsequent bone loss [2]. Normally, menopause which is a physiological phenomenon is strongly associated with postmenopausal osteoporosis [38]. Bone is a metabolically active and high energy consuming tissue, which is continuously remodeled, shaped and repaired through its lifetime by osteoblasts and osteoclasts [39,40]. Osteoblast cells, derived from mesenchymal stem cells are responsible for bone formation while osteoclast cells are derived from hematopoietic progenitor cells embedded in bone marrow and participate in bone resorption [41].

Postmenopausal osteoporosis is characterized by low bone mass and microarchitectural deterioration due to loss of the direct effect of estrogens on osteoclasts [3].Specifically, the decline of estrogen production has been shown to cause decrease in bone mass during the onset of menopause [41–43]. During menopause, the osteoprotective effect of estrogen is compromised leading to increased expression of bone-resorbing cytokines which promote osteoclastogenesis and osteoclastic activity [44–47]. Estrogen receptors in differentiated osteoclasts are functional and cause decreased bone-resorbing activity and enhanced apoptosis [48,49]. Loss of estrogen also affects osteoblast progenitor cells through decreased estrogen receptor-α (ER-α) expression and lower response to mechanical stimulation [3].

Receptor activator of nuclear factor-κB ligand (RANKL) is expressed by osteoblast cells, binding of RANKL to its receptor activator of nuclear factor-κB (RANK) expressed by osteoclast precursor results in the differentiation, prolong activity osteoclasts and increases bone resorption [9,50]. Estrogen suppresses RANKL, bone-resorbing cytokines such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) and macrophage-colony stimulating factor (M–CSF) expression by osteoblast cells and thus, preventing osteoclast formation [13,14,51].

Oxidative stress altered normal redox state and was implicated in reducing osteoblast cells formation and induces its apoptosis [3]. Presently, several studies have demonstrated a positive correlation between oxidative damage and postmenopausal osteoporosis. For instance, the decrease in bone mineral density (BMD) in postmenopausal osteoporotic women was linked to higher oxidation of plasma lipid [52] and lowered superoxide dismutase (SOD), catalase and glutathione peroxidase activity [50]. Ovariectomy has been shown to induce oxidative damage and decrease the efficacy of antioxidant defense mechanisms, thus leading to osteoporosis [53]. Altogether these findings suggest a paradigm shift from the ‘estrogen-centric’ account of the pathogenesis of postmenopausal osteoporosis to one in which age-related mechanisms intrinsic to bone and oxidative stress are protagonists [9].

## 3. Molecular basis of breast cancer

Breast cancer is a major cause of morbidity and mortality among pre and post-menopausal women in both developed and developing countries [1]. Understanding the mechanisms of breast cancer pathogenesis holds the key for unravelling a cure for this disease. Basically, the factors underlying carcinogenesis have been broadly divided into genetic and epigenetic factors [54].

### 3.1. Genetic basis for breast cancer

Heritable alterations to DNA sequence and composition among individuals, resulting in altered protein function has been observed among breast cancer patients [55]. Notably, Breast cancer associated gene 1 and 2 (*BRCA1* and *BRCA2*) are anti-oncogenes that code for tumor suppressor proteins [56]. Mutations in BRCA 1 and 2 are regarded as risk factors for susceptibility to breast cancer and other cancers including ovarian, colon and prostate cancers [57]. It has also been observed that individuals with mutations in BRCA 1 and 2 genes