RESEARCH COLLECTION ON

BREAST CANCER VOL. 2

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Chapters from books edited by: **Esra Gunduz** and **Mehmet Gunduz**

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Preface

This is the second in a major, two-volume set, 'Breast Cancer', that provides a comprehensive resource of current knowledge, clinical information and new research in the field, drawing on expert contributions. Some of the major thematic areas covered include: new advances in biology, imaging and therapeutics, such as implications of circulating tumour cells; diagnostic optical imaging and radiotracer molecular imaging; new knowledge on the tumour microenvironment, stem cells and metastasis, for example, on mesenchymal stem cells and the role of interleukin-6; new and established alternative therapeutic modalities, such as boron compounds and lunasin; and current understanding of carcinogenesis, cell grown and signalling pathways, including discussions of signal transduction pathways, cross-talk between breast cancer cells and the immune system, and trastuzumab-resistance. Breast cancer is the most commonly diagnosed form of cancer, and the leading cause of cancer-related deaths among women. These volumes benefit from the high-quality and leading edge work of researchers around the world to provide a rich variety of perspectives on this prevalent disease. They will benefit physicians in oncology as well as providing many stimuli for new research

BREAST CANCER – CURRENT AND ALTERNATIVE THERAPEUTIC MODALITIES

Edited by **Esra Gunduz** and **Mehmet Gunduz**

Boron Compounds in the Breast Cancer Cells Chemoprevention and Chemotherapy

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1. Introduction

Various biological functions of Boron (B) compounds are known (Blevins & Lukaszewski, 1994; Tariq & Mott, 2007; Nielsen, 2008). Boron is found in nuts, vegetables, dried/fresh fruits and red wine (Brown & Shelp, 1997). Boron is also present in bacterial antibiotics, such as tartrolon, borophycin, boromycin and aplasmomycin (Rezanka & Sigler, 2008); in the bacterial quorum sensing molecule *auto-inducer AI-2* (Bemd et al., 2002); and in vibrioferrin, a B-containing siderophore produced by particular marine bacteria (Shady et al., 2007). In plants, the rigidity of the cell wall depends on the rhamnogalacturonan II complex (RG-II) formation, a pectic polysaccharide covalently linked by cis-diol bonds to apiosil residues of borate-esters (Ishii & Matsunaga, 1996, 2001). Several articles have provided information about transporters responsible for efficient B uptake by roots, xylem loading and B distribution among leaves. The transporters are required under B limitation for efficient acquisition and utilisation of B. Two types of transporters are involved in these processes: NIPs (nodulin-26-like intrinsic proteins) for boric acid channels and boron exporters encoded by BOR1 (Miwa & Fujiwara, 2010). The expression of the genes encoding these transporters has been shown to be finely regulated in the B availability response to ensure tissue B homeostasis. Furthermore, the tolerance of plants to the stress produced by low B or high B in the environment can be generated by altering the expression of these transporters (Tanaka & Fujiwara, 2007). All of these transporters are involved in boron transport regulation in plants. B is an essential element not only for vascular plants but also for diatoms, cyanobacteria and a number of marine algal flagellate species (Rezanka & Sigler, 2008). Recently, ATR1 has been found to be responsible for the high B tolerance in *S. Cerevisiae*. ATR1 encodes a multidrug resistance transporter and it is widely distributed in bacteria, archaea and lower eukaryotes (Miwa & Fujiwara, 2010). Animals such as zebra, fish, trout and frogs also require boron (Rowe & Eckert, 1999; Fort et al., 1999). Borate ions activate the mitogen-activated protein kinases pathway and stimulate the growth and the proliferation of human embryonic kidney 293 cells (Park et al., 2005). The B-transporter, NaBCl, controls plasma borate levels in human kidney cells (Park at al., 2004). The fact that B has such a broad range of physiological functions is not surprising. The electron structure of B and its position in the periodic table (adjacent to carbon) make B-containing molecules electrophilic with the trigonal

planar structures that are isoelectronic neutral relative to carbocations. The additional bond with B allows the formation of anionic tetravalent compounds with tetrahedral structures, which behave as nucleophiles (Petasis, 2007). Various types of B-containing molecules already exist and have been investigated as therapeutic agents. These molecules include B-containing analogues of natural biomolecules (Morin, 1994), the antibacterial and antimalarial agent diazaborine (Baldock et al., 1998), antibacterial oxazaborolidines (Jabbour et al., 2004; Jabbour et al., 2006), antibacterial diphenyl borinic esters (Benkovic et al., 2005), the antifungal agent benzoxaborole AN2690 (Baker et al., 2006) and a B-N bond containing an estrogen receptor modulator (Zhou et al., 2007). Except for the drug Bortezomib, the majority of B compounds currently used in cancer treatment are in the Neutron Capture Therapy (BNCT) class (Beddoe, 1997; Endo et al., 2003). The discovery of many B-containing molecules is predicted, and these molecules will be useful in applications involving cell surface signalling (Bolanos et al. 2004; Redondo-Nieto et al., 2008). The main objective of this review is to reveal other promising research directions for B-based chemicals in chemoprevention and chemotherapy, particularly in breast cancer.

2. Boron compounds in cancer prevention

2.1 Dietary boron and cancer risk

A diet with low B has been found to lead to a number of general health problems and to increase cancer risk. The most common symptoms of B deficiency include arthritis, memory loss, osteoporosis, degenerative and soft cartilage diseases, hormonal disequilibria and a drop in libido (Scorei & Popa, 2010). The daily uptake of B varies as a function of food selection, the use of some specific personal products and the water B content. Reported values for the overall B uptake vary as follows: 0.8-1.9 mg/day in the European Union, 1.7-7 mg/day in the United States, ~0.93 mg/day in Korea, 2.16-2.28 mg/day in Australia, 1.75-2.12 mg/day in Mexico and 1.8-1.95 mg/day in Kenya (Rainey & Nyquist, 1998). These dissimilarities may be correlated with regional differences in the abundance of high-energy food and in food products rich in fibres and plant proteins. The actual B requirements for the human body remain unclear. Thus, more knowledge about the biological functions of B and the regulation of its exchange is required (Nielsen, 2009). The B Tolerable Upper Intake Level (UL) for adults of ~18 years is ~20 mg B per day (Scorei & Rotaru, 2011).

2.1.1 Lung cancer

The mortality due to lung cancer has reached higher values for men than for women (Espey et al., 2007). A negative correlation has been found between the amount of B intake and the incidence of lung cancer, although the underlying mechanism remains unclear (Meacham et al., 2007). Experimental evidence has shown that nutrition with some B-compounds (such as boric acid, borax and calcium fructoborate) has had anti-oxidant or/and anti-inflammatory consequences (Nielsen, 2000; Hunt, 1998; Scorei et al., 2005). Correlations exist between some lung cancers and 17-beta-estradiol, and the treatment includes 17-beta-estradiol-based Hormone Replacement Therapy (HRT) (Schabath et al., 2004). Dietary supplementation with B has been shown to increase the concentration of 17-beta-estradiol (Wang et al., 2008), mimic the HRT effect and, in the case of postmenopausal women, it may be used to decrease the cancer risks associated with low estrogen levels (Devirian & Volpe, 2003). Low dietary B

(alone or together with HRT) has been correlated with an increase in lung cancer risk for women (Mahabir et al., 2008). The reduction of lung cancer risk may involve estrogen receptor binding substrates, other than estrogen, including carcinogenic Polycyclic Aromatic Hydrocarbons (PAHs) from cigarette smoke condensate (Pike et al., 1999). Women with high dietary B intake and HRT users may present higher hormone levels that compete with cigarette smoke carcinogens for estrogen receptors. If this model is correct, increasing the B intake during HRT will also limit the carcinogenic potential of PAHs from cigarette smoke. Recently, the highest quartile of B intake has been confirmed to be associated with the lowest lung cancer risks for smokers, while the highest risk exists in smokers with low dietary B and no HRT (Mahabir et al., 2008).

2.1.2 Prostate cancer

Dietary B is inversely correlated with the occurrence of prostate cancer (Yan et al., 2004), even if the source of this correlation remains unclear. The prostate cancer risk was one third smaller for men ingesting more than 1.8 mg B per day from food, relative to only 0.9 mg B/day. A relatively high correlation (r = 0.63) was found between the B concentration from the subsurface water and the prostate cancer distribution in Texas (Barranco et al., 2007). A broader understanding of the cellular mechanisms that involve B have shown that boric acid (BA) inhibits prostate cancer cell growth by decreasing cyclin A-E expression, though B does not induce cell death (Barranco et al., 2009). Furthermore, cells treated with BA demonstrate diminished adhesion and migration, which indicates a low metastatic potential. B has been hypothesised to have effects on prostate cancers through its influence on steroid hormones (particularly androgens, which are involved in prostate carcinogenesis) (Gann et al., 1996). Three research directions have been followed to study the relationship between B and prostate cancer risk: steroid hormone regulation, anti-cancer metabolites and cell proliferation. Several potential BA binding sites may be involved in prostate cancer. For example, Prostate Serum Antigen (PSA), a serine protease, is a potential site for direct boration (Gallardo-Williams et al., 2003). Boric acid decreases the expression of five major cyclin proteins (A, B_1, C, D_1 and E), which have significant roles in the cell cycle (Barranco & Eckhert, 2006) and inhibit the release of Ca(II) stored by the NAD+cADPR system. This regulation of cyclins could explain the effects of B on prostate cancer cells. When B consumption was ~1.17 mg per day, no correlation with prostate cancer frequency was observed (Gonzalez et al., 2007).

2.1.3 Cervical cancer

Cervical cancer is the second most frequent cancer in women worldwide (Parkin et al., 1993). The cause of this discrepancy is still unclear and can involve a combination of environmental, genetic, social and infectious factors. For example, Human papillomavirus (HPV) is the primary cause of cervical cancer. HPV 16 and HPV 18 are responsible for ~95% of cervical cancers. Many other factors also correlate with the incidence of cervical cancer (Ursin et al., 1996; Ylitalo et al., 1999; Castellsague et al., 2002). According to one hypothesis, the low cervical cancer incidence in Turkey correlates with its B-enriched soil (Sayli et al., 2001; Simsek et al., 2003). Indeed, the ingestion of B via drinking water prevents cervical cancer risk (Korkmaz et al., 2007). This effect has been suggested to be due to the B interference chemistry in the life cycle of HPVs, but no correlation could be found regarding the incidence of oral cancers, which are also induced by HPVs. Serine protease inhibitors