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REPORT

Boron**Maintains Bones, Joints, Neurons and May Reduce Prostate Cancer Risk**

by Stephen B. Strum, M.D., FACP

Medical Oncologist Specializing in Prostate Cancer

As our knowledge of biological systems has increased over the past ten years, a greater understanding of the importance of cellular communication and balance has been reached. The integrative nature of medicine, so characteristic of biological orchestration, has now come to embrace the use of substances that a few decades ago were hardly recognized as important to human health.

Coenzyme Q10, acetyl L-carnitine, alpha lipoic acid, lycopene, selenium, and gamma tocopherol are a few examples of new players in the biologic symphony. Boron can now be added to our list of vital nutrients in the orchestration of health.

While boron has long been known to promote healthy bone density, new research shows that it can shrink prostate tumor size, lower PSA, and may help to prevent prostate cancer. Additional findings show that boron alleviates joint discomfort and preserves cognitive function. The good news is that this low-cost mineral has been added to the most popular supplements that Foundation members are already taking.

BORON'S EFFECT ON CANCER***Boron reduces prostate cancer incidence by up to 64%***

In a study by Zhang et al, men who ingested the greatest amount of boron were 64% less likely to develop prostate cancer (PC) compared to men who consumed the least amount of boron (see Figure 1). This information was presented at the annual Experimental Biology conference in Florida in 2001.¹ The study, from the Cancer Epidemiology Training Program at the UCLA School of Public Health, compared dietary patterns of 76 men with prostate cancer to that of 7,651 males without cancer. The greater the quantity of boron-rich foods consumed, the greater the reduction in risk of being diagnosed with prostate cancer. Those men consuming the most boron (i.e., in the upper quartile of boron consumption) had a 64% reduction in prostate cancer, while men in the second quartile had a 35% reduction in risk and those in the third quartile reduced their risk by 24%. Men in the lowest quartile of boron consumption ate roughly one slice of fruit per day, while those in the highest quartile consumed 3.5 servings of fruit per day plus one serving of nuts. Boron-rich foods include plums, grapes, prunes, avocados, and nuts such as almonds and peanuts. A serving of 100 grams of prunes (12 dried prunes) has 2-3 mg of boron and 6.1 grams of fiber.²

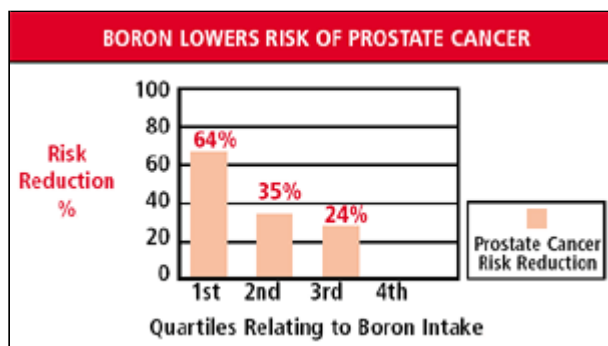


FIGURE 1. Lower Prostate Cancer Risk Associated with Boron Consumption.

Those men consuming the most boron had the greatest protective effect against the development of prostate cancer. Sources of boron include non-citrus fruits like dried prunes, plums, grapes, raisins, nuts such as almonds and peanuts, red wine, and coffee. No protective effect of boron was noted against breast, colorectal, uterine, cervical, or skin cancers.¹⁸

Boric acid acts to inhibit serine proteases—it decreases PSA by 87% and reduces tumor size in a prostate cancer mouse model

The mechanism of boron's effect on reducing prostate cancer incidence in the study by Zhang et al previously cited is not known. However, a preliminary report on the effect of boric acid (boron) solutions given to mice bearing the human prostate cancer cell-line called LNCaP may shed some light on this mechanism. In a study published in the 2002 Proceedings of the American Association of Cancer Research, Gallardo-Williams et al indicated that mice receiving 1.7 or 9.0 mg/kg/day of boric acid solution



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orally had decreases in tumor size by 38% and 25%, respectively.³ The same groups had drops in PSA (prostate-specific antigen) of 88.6% and 86.4%, respectively. The control group receiving only water had no drop in PSA or decrease in tumor size.

Additional findings of interest included a decreased amount of mitoses in the mice treated with boric acid compared to the control group. Mitoses reflect chromosomes or genetic material that are in the process of cell division. Mitotic figures can be seen using a conventional microscope; the greater the number of mitoses, the greater the intensity of cell division and tumor growth (see Figure 2). The authors also found that the histochemical expression of IGF-1 (insulin-like growth factor type 1) was markedly reduced by boron treatment. Circulating blood levels of IGF-1 were not reduced in the treated mice, however.

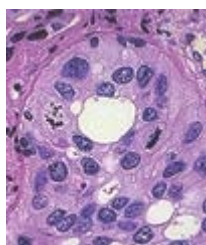


FIGURE 2: Mitoses in Prostate Cancer Biopsy. Mitoses (also called mitotic figures) may be easily found using the light microscope. If mitoses are abundant in number, it can be presumed that the proliferative rate of the tumor is high. High mitotic rates are seen with more aggressive histologic grades of prostate cancer.

This study by Gallardo-Williams is of potentially great significance and the rationale for such a study merits further discussion. The authors' evaluation of boric acid was based on a hypothesis that relates to the important finding that PSA is not only a biomarker of prostate cancer activity but also a functional enzyme produced by prostate cancer cells that acts to promote its very own tumor growth.¹⁰ My interpretation of their hypothesis is as follows:

- PSA is an enzyme (a serine protease) that frees IGF-1 from insulin-like growth factor binding protein.
- IGF-1 has been shown to promote the growth of prostate cancer.
- A reduction in PSA's enzymatic activity should decrease the amount of IGF-1. This in turn should decrease prostate cancer growth.
- Boric acid is a known inhibitor of several serine proteases.
- Blood boric acid levels as low as 8 mcg/ml can inhibit the proteolytic activity of PSA (authors' separate work).
- Boric acid administration should therefore reduce PSA.
- This reduction of PSA should be accompanied by decreased expression of IGF-1 and decreased tumor growth.

This report apparently has led to further clinical trials now in progress.

The anti-cancer effect of boron compounds has been the subject of prior studies that involved tumor cell lines of human malignancies grown in culture. These studies are summarized in Table 1.

Cancer Cell Type(s)	Effect on Tumor Cell	Boron Compound(s)	Reference
Acute lymphocytic leukemia Chronic lymphocytic leukemia	Growth inhibition after treatment with boron compounds	dihydroxy (oxybiguanido) boron (iii) hydrochloride monohydrate (HB) guanidine biboric acid adduct (GB) hydroxosalicyl hydroxomato boron (iii) (SHB)	4
Ehrlich ascites tumor	Significant anti-tumor action that was further increased by combining with ultrasound therapy	dihydroxy (oxybiguanido) boron (III) hydrochloride monohydrate	5
Ehrlich ascites tumor	Significantly increased survival time	guanidine biboric acid adduct (GB)	6
L1210 murine leukemia cells DU-145 prostate cancer cells A549 lung carcinoma cells MCF-7 breast cancer cells	Dose-dependently inhibited DNA synthesis	Borato-1,2-diaminocyclohexane platinum (II) (BDP)	7

LNCaP prostate cancer cells	Reduced PSA by 86-89% and reduced tumor volume by 25-38%; mitoses and IGF-1 decreased in tissue studies	Boric acid solution	3
Mouse and human leukemias Human uterine, colon, and lung adenocarcinomas Human gliomas	Inhibited growth	Amino-o-carborane-hydrochloride 7	8
Murine and human leukemia Uterine carcinoma tumor cell lines	Potent in vivo antineoplastic activity and in vitro cytotoxicity	Adenosine 5'[N,N-di-(gamma-o-carboranyl)propyl] phosphorodiamidate 1	9

TABLE 1. Anti-Cancer Activity of Boron. Studies of the anti-cancer efficacy of a number of boron compounds against a wide range of tumor cell lines (shown above) warrant clinical trials in humans.

BORON'S EFFECT ON BONE METABOLISM

Calcium-Magnesium <=> Boron Interactions

A large number of experiments conducted in humans involving boron supplementation or deprivation show that boron is vitally involved in bone metabolism. It is well accepted that calcium and magnesium are important constituents or building blocks of healthy bone. In situations of adequate calcium supply but deficient magnesium resources, boron appears to substitute or “pinch hit” for magnesium during the process of bone formation. Under such conditions, the concentration of boron within bone tissue increases.

Boron's effect on bone appears to be mediated by its ability to reduce the urinary excretion of calcium and also magnesium. In situations where adequate boron intake rather than boron depletion prevails, the net effect of boron is to raise ionized calcium levels. This effect of boron—to preserve calcium and decrease urinary losses of calcium—is caused by its actions on the kidney.



As stated above, this calcium-preserving effect of boron becomes pronounced in circumstances in which dietary magnesium is low. With this biologic effect, boron is acting as a backup system to preserve calcium in the blood and reduce urinary calcium loss. In effect, boron acts literally and figuratively as a “bodyguard” to preserve calcium and magnesium in situations of nutritional stress that would otherwise adversely affect metabolic processes involved with these substances.¹¹

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The effect of boron intake was analyzed in a human study involving 12 post-menopausal women not on estrogen replacement therapy. Patients were first given a boron-deficient diet consisting of 0.25 mg of boron daily for 119 days. This was followed by a 48-day period in which the same patients received boron supplementation at a dose of 3 mg per day. Patients were also studied during periods of adequate magnesium intake versus magnesium deficiency. Deprivation of boron and/or magnesium caused changes that are similar to those seen in women with post-menopausal osteoporosis, including increased loss of urinary calcium. However, in women receiving 3 mg of boron per day, urinary losses of both calcium and magnesium were significantly diminished, especially if dietary magnesium was low. Also noted were increased levels of plasma ionized calcium, beta estradiol, and testosterone.¹²

Vitamin D <=> Boron Interactions

Boron manifests additional integrative effects on bone metabolism in its actions relating to vitamin D (cholecalciferol). Vitamin D affects absorption and utilization of calcium and also has major anti-cancer effects relating to slowing tumor cell proliferation.¹³ Vitamin D enhances calcium absorption through the stomach and small intestine. The effect of boron on raising plasma calcium levels may, in part, be due to its enhancing effect on vitamin D.¹⁴ Again, boron is acting as a helper, backup agent, and/or facilitator to maintain bone integrity in its actions on vitamin D and calcium.

BORON'S EFFECT ON ARTHRITIS

The inhibition of enzymes such as serine proteases (e.g., PSA) was mentioned in relation to the anti-cancer effects of boron. In a review of the literature on boron's metabolic activities, Hunt et al also emphasized the down-regulation of other enzyme activities by boron.¹⁵ For example, boron has been shown to inhibit cyclooxygenase (COX) and lipoxygenase (LOX). These two enzymes mediate the inflammatory cascade and are pertinent to therapies directed against inflammatory conditions. Such anti-inflammatory capabilities of boron are clearly pertinent to its anti-cancer effect, because the reduction of COX II and LOX enzymes leads to a decrease in prostaglandin E2 (PGE2) and other unfavorable eicosanoids such as leukotrienes. These hormonal breakdown products of arachidonic acid were discussed and illustrated in an article on prostate cancer in the June 2003 Life Extension magazine. We now know that omega-6 fatty acid metabolism that is allowed to continue down this pathway represents a vital stimulus for angiogenesis and cancer growth.



The very same prostaglandins and leukotrienes are mediators of inflammatory conditions such as degenerative joint disease and osteoarthritis. PGE2 and leukotrienes have been implicated in causing problems with joint swelling, restricted joint motion, and other arthritic complaints. Anti-arthritic agents like glucosamine sulfate work through inhibition of COX II and PGE2 by suppressing nuclear factor kappa beta (NfκB)—a proinflammatory cytokine.^{18,19} There is also evidence that boron has similar modes of action in reducing arthritic conditions.²⁰⁻²² These findings are clinically supported by evidence showing that areas of the world with low levels of boron in the soil have a higher percentage of people suffering from arthritis in comparison to regions with higher soil levels of boron. There is also epidemiologic evidence that in areas of the world where boron intake is 1 mg or less per day, the estimated incidence of arthritis ranges from 20% to 70%, whereas in areas of the world where boron intake is usually 3-10 mg, the estimated incidence of arthritis ranges from 0 to 10%.²³ In a study of 20 patients with osteoarthritis, the 50% who received a daily supplement of 6 mg of boron noted subjective improvement (less pain on movement), while only 10% of those who had received placebo improved over the same time interval.²⁴

In another study, bone adjacent to joints with osteoarthritis tends to be less mineralized than control bone and bone from fracture patients. Interestingly, bone samples in such instances have significantly lower concentrations of boron.²⁵

Lastly, there have been studies that show the anti-arthritic effects of S-adenosylmethionine (SAME) are equivalent to those seen with non-steroidal anti-inflammatory agents (NSAIDs) but without the toxicity seen with NSAIDs.²⁷⁻²⁹ Also interesting is a report indicating a very high affinity of SAME for boron.³⁰ An interesting consideration would be to evaluate the efficacy of SAME in reducing arthritic symptoms in relationship to boron consumption and boron blood levels.



BORON'S EFFECT ON BRAIN FUNCTION

There are many parallels between the medical applications of NSAIDs and the biological properties of boron. These shared benefits may be due to the common mechanisms involved in the down-regulation of pro-inflammatory cytokines and the subsequent reduction in COX II and LOX enzymes. These mechanisms provide some explanation for the positive clinical benefits of boron such as those seen in patients with arthritis and boron's relation to the reduction in the incidence of prostate cancer, and hopefully in the use of boron in prostate cancer treatment. Since it is now commonly accepted that the routine use of NSAIDs significantly reduces the incidence of Alzheimer's disease,^{31,32} it is not surprising that papers have been published on boron's positive effect on cognitive function.³³

Penland et al conducted experiments in men and women to investigate the functional role of boron in relation to brain electrophysiology and cognitive performance (see Table 2). Findings were compared in healthy older men and women while on a diet deprived of boron versus a diet with ample boron (approximately 0.25 mg boron/2000 kcal/day versus approximately 3.25 mg boron/2000 kcal/day). The ability of patients to perform skills involving cognition and psychomotor tasks were assessed and showed significant impairment during the boron-deprived diet. Brain-wave patterns were evaluated using an electroencephalogram (EEG) and showed an increased proportion of low-frequency activity in patients on the boron-deprived diet. Similar findings are often observed in response to general malnutrition and heavy metal toxicity. The authors concluded from such data that boron appears to play a significant role in human brain function and cognitive performance, and that boron is an essential nutrient for humans.²⁶

BORON: OTHER FUNCTIONS

Boric acid solution (3%) dramatically improves wound healing through action on the extracellular matrix, a finding that has been obtained in vitro.³⁴

Sources of Boron

Boron is a trace mineral that is found in non-citrus fruits such as plums, red grapes, apples, pears, and avocados, as well as in legumes and nuts. It is also present in significant amounts in coffee and red wine. Dried fruits contain a much higher amount of boron than fresh fruit. For example, fresh plums contain 0.45 mg of boron per 100 grams (g), but the same weight of dried prunes (about 12 prunes) contains 2.15 mg of boron.¹ Although boron currently is not considered an essential element in the diet of humans, many scientists believe it merits the status as an essential "ultra-trace" element.³⁵ The usual dietary boron consumption in humans is 1-2 mg/day for adults. But boron requirements may be as high as 9-12 mg per day.

Function Studied	Boron-deprived Diet	Boron-ample Diet	p value
Manual dexterity Eye-hand coordination Attention Perception Encoding and short-term memory Long-term memory	Decreased	Normal	<0.5
Electroencephalogram (EEG) spectral analysis			
Low-frequency activity	Higher	Lower	<0.5
High-frequency activity	Lower	Higher	

TABLE 2: Effects of Boron Deprivation on Cognitive Performance and Brain Activity. In multiple studies, older men and women showed statistically significant impairment in cognitive function on a low-boron diet in comparison to a diet ample in boron. EEG activity was also abnormal in patients on the low-boron diet.²⁶

BORON TOXICITY

In the 1870s, it was determined that sodium borate (borax, a form of boron) had the ability to preserve foods. Over the next 50 years, borates were valued as preservatives and used to extend the palatability of fish, meat, cream, and butter.³⁵ The first evidence of the potential for toxicity associated with borate consumption occurred in 1904. Human volunteers, consuming over 500 mg per day of boric acid, had symptoms of decreased appetite, nausea, abdominal discomfort, and diarrhea. After this was reported, the use of boron as a food preservative and taste enhancer greatly declined, and by the mid-1950s boron was essentially banned worldwide in the food industry. Ironically, boron has been replaced with monosodium glutamate that has been shown to be neurotoxic³⁶ yet remain in widespread use.

Boron compounds are toxic to all species tested at high doses, but they are not carcinogenic or mutagenic.³⁷ A rat developmental toxicity study of boron determined a "no observed adverse effect level (NOAEL) of 9.6 mg of boron per kg per day. Toxicology studies of boron in humans have shown safety up to a maximal daily intake of 0.3 mg/kg of boron, which equates with a daily intake of 18 mg of boron for a 60-kg (132-pound) individual.³⁸

Four patients with elevated serum boric acid levels after single, acute ingestions of 10-297 grams were reported to the Rocky Mountain Poison and Drug Center (RMPDC) between January 1983 and August 1985. In these cases, systemic effects were absent. In 1983-4, 364 cases of boric acid exposure were reported to the RMPDC, with only one fatality from a probable chronic ingestion. In this case, vomiting, nausea, diarrhea, and abdominal cramps were present. These observations suggest that significant poisoning is unlikely to result from a single, acute ingestion of boric acid.³⁹

A report by Pinto et al showed that boric acid ingestion can induce urinary losses of vitamin B2 (riboflavin).⁴⁰ Patients taking boron supplements may wish to also consider B vitamin supplementation. Gordon et al reported a case of two infants using pacifiers dipped in a honey-borax solution over a period of several weeks in 1973. These infants had findings of hair loss, anemia, and seizures. All signs and symptoms disappeared after discontinuation of the borax and honey preparation.⁴¹

The critical effects of boron in several species involve male reproductive toxicity and developmental toxicity. Testicular effects occurred at approximately 26 milligrams of boron equivalents per kilogram of body weight per day. Data on endocrine toxicity include altered follicle stimulating hormone and testosterone levels within 14 days of treatment.³⁷ It is important to emphasize that the doses that cause these effects are far higher than the levels to which the human population could be exposed. Humans would need to consume daily approximately 3.3 grams of boric acid (or 5.0 grams of borax) to ingest the same dose level as the lowest animal NOAEL. No effects on fertility were seen in a population of workers exposed to borates or to a population exposed to high environmental borate levels.⁴² Therefore, the likelihood of boron toxicity caused by boric acid and inorganic borates is remote.

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CONCLUSIONS ON BORON'S ROLE IN HEALTH AND DISEASE

Boron, the fifth element in the periodic table of elements, has a number of important functions that are worthy of intense clinical attention. Boron is an integrative element supporting the functions of calcium, magnesium, and vitamin D. Boron enhances bone and joint integrity and brain function. The results of a recent study indicate that boron is the most significant element in the prevention of prostate cancer. This finding complements an exciting basic research study showing that boron, an inhibitor of serine proteases such as PSA, lowered PSA and prostate cancer volume significantly. This simple and relatively inexpensive element deserves a major focus of funding in the world of research and clinical medicine.

Stephen B. Strum, M.D. has been a board-certified medical oncologist since 1975. In 2000 he became the first medical director of the Prostate Cancer Research Institute in Los Angeles. Dr. Strum has published widely about prostate cancer as well as other areas to optimize outcomes for those with cancer.

Glossary

ACRONYM: A word formed from the initial letters of a name, such as BNCT for Boron Neutron Capture Therapy.

ADJUNCT: Something added to another for embellishment or completion.

ADJUVANT: An additional therapy that is added to a primary treatment to increase or aid its effect. Adjuvant therapy is usually given once the primary therapy is completed, e.g., radiation therapy after primary surgery. Neoadjuvant therapy indicates that the additive therapy is given prior to the so-called primary therapy. For example, neoadjuvant androgen deprivation therapy is often used prior to radiation therapy.

COCKEREL: A young rooster.

KILOGRAM (kg): A unit of mass equaling one thousand grams or 2.2 pounds.

MICROGRAM (mcg or mg): A unit of mass equaling one millionth of a gram.

MICRON: A unit of length equal to one millionth of a meter or approximately 1/25,000 of an inch.

MILLIGRAM (mg): A unit of mass equaling one thousandth of a gram.

NOAEL: No-Observed-Adverse-Effect Level. This is an acronym used to categorize toxicity of various drugs, vitamins, and supplements.

PROTEOLYTIC: Having the ability to break down proteins by enzyme actions.

QUARTILE: The value of the boundary at the 25th, 50th, or 75th percentiles of a frequency distribution; this is divided into four parts, each containing a quarter of the population. In a class of 100 students, those 25 students with the highest grades are in the upper quartile of the class, while the 25 with the lowest grades are in the lowest quartile.

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