Vital Link

The journal of the Canadian Association of Naturopathic Doctors

Feature Articles

Empowering Patients Through Naturopathic Cancer Prevention

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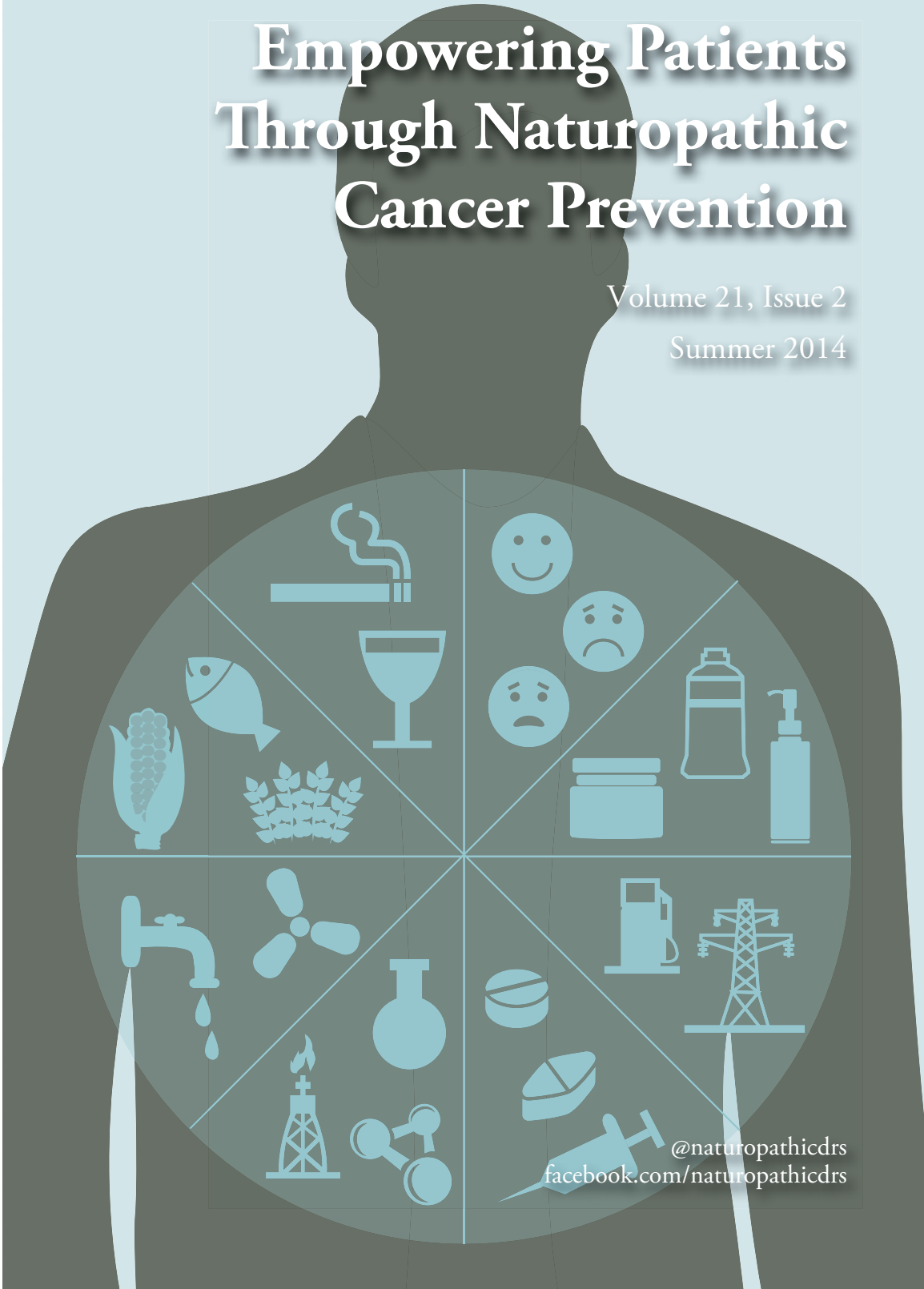
Summer 2014



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Vital Link
The journal of the Canadian Association of Naturopathic Doctors

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Empowering Patients Through Naturopathic Cancer Prevention

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The *Vital Link* is the professional journal of the Canadian Association of Naturopathic Doctors (CAND). It is published primarily for CAND members and features detailed reviews of specific causal factors: philosophical and research-based papers, clinical practice articles and case reviews, as well as international updates on the profession. The *Vital Link* has an outreach to other health care professions and promotes qualified naturopathic doctors to corporations, insurance companies and the Canadian government.

Forthcoming Themes

Fall/Winter 2014 Naturopathic Cancer Management
Winter/Spring 2015 Family Medicine

Submissions
When writing for the *Vital Link*, keep in mind its broad readership and outreach to other professions. Your contribution to the *Vital Link* will benefit the naturopathic profession as a whole and provide you with personal professional exposure. Previously unpublished material is preferred. Please contact the managing editor for submission guidelines.

Circulation
The *Vital Link* is published three times per year and is distributed to over 2000 qualified Canadian NDs and students of CNME-accredited naturopathic programs in Canada and the U.S. The *Vital Link* is also distributed to the CAND's corporate members and in our media kit. The journal is available in print and e-formats, by paid subscription.

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Naturopathic Notes

Dr. Iva Lloyd, BScH, BCPP, ND

With so much focus put on the treatment of cancer, in both the naturopathic and conventional medicine fields, the powerful concept of cancer prevention is often lost. Naturopathic medicine has proven it has a valuable role to play in cancer treatment and integrative cancer care, but I believe that the greatest impact that naturopathic medicine offers is with respect to cancer prevention. The breadth of the naturopathic assessment is well suited to addressing individual susceptibility and the numerous factors that increase a person's risk of cancer.

In this issue, Dr. Chris Spooner explores connections between environmental toxins and cancer. He reviews the research on the disruption of mitochondrial function, the increase of reactive-oxygen-species (ROS) and the depletion of glutathione and other antioxidants due to environmental toxins. It is valuable to understand the cellular tolerance of environmental toxins, exactly which toxins accumulate in the mitochondria, and how these toxins disrupt cellular function and trigger tumor formation and increase cancer progression; this knowledge helps NDs to provide the most effective treatment strategies to both decrease cancer risk and to eliminate the toxins associated with cancer.

Dr. Sat Dharam Kaur looks at the research between nutrition, diet and cancer. Food is no longer a simple matter and choosing healthy food requires individuals to be educated on the health risks of food additives, herbicides and pesticides and genetically modified foods. Dr. Kaur provides an overview of those foods and food contaminants that are associated with increased cancer risk. She also advises us about foods that are associated with decreasing cancer risk as well as those that may be beneficial when healing from cancer.

A growing concern is the increased incidence of cancer in the pediatric population and the high mortality rate of childhood cancers. Naturopathic doctors Jennifer Macdonald, Keshia Kamphuis and Jessica Sangiuliano consider in their paper the association of exposure to toxins in utero and the development of cancer in childhood. Research is reviewed linking diethylstilbesterol, ionizing radiation, chemotherapeutic agents and the heavy metals arsenic, cadmium and lead. The increased susceptibility of a growing fetus to these toxins and how naturopathic doctors can provide proactive preconception care to prevent childhood cancer is also discussed.

Across all age groups, there has been a tremendous increase in the use of prescription medications. Dr. Christopher Knee, ND, MSc and CCNM naturopathic Canadidates, Kaeli Sweigard, Robin Urekar, Ayesha Qureshi, Neha Aggarwal and Andrea Hession, BN, provide a detailed systematic review of the link between some of the most common prescription medications and cancer. Their review includes proton-pump inhibitor, statin, sulfonylurea, hormone-replacement (therapy), calcium-channel blocker, and immunosuppressant medications.

To complete this edition I have written an article on the link between the mind and cancer. Specific psychological states, such as hopelessness, are associated with increased cancer risk and/or increased cancer mortality and progression of the disease. Understanding the role in cancer played by an individual's mental-emotional status allows naturopathic doctors to ensure they are treating the whole person.

There is growing consensus that to reduce the rates of cancer the primary focus of research and funding will have to shift from treatment to prevention. We trust that the articles in this edition will initiate a renewed interest and insight into cancer prevention and as always we welcome your comments.

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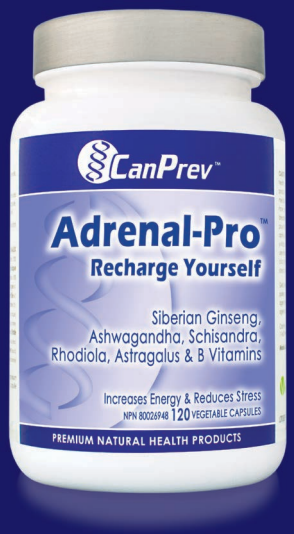

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Dietary and Nutritional Guidelines for Cancer Prevention and Recovery

Dr. Sat Dharam Kaur, ND

"Let food be thy medicine and medicine be thy food" wrote Hippocrates in 400 BC. This is advice that we as naturopathic doctors strive to share with our patients. Today's food culture, however, requires educated choice in the types of foods we ingest, as many of our foods have been contaminated with pesticides, herbicides, food additives and/or have been genetically modified.

In this article we'll explore the dietary choices that may expose us to greater risk of, help to protect us from, or recover from many forms of cancer.

We'll start by examining food practices that increase our susceptibility to cancer.

Pesticides and Cancer

Certain pesticides have a clearly demonstrated link to specific cancers in children and adults.

Non-Hodgkin Lymphoma (NHL) is more common in farmers, pesticide applicators, pesticide factory workers, landscapers, lumberjacks and golf course superintendents[1] (lumberjacks may apply phenoxy herbicides such as 2,4-D for weed control before taking down trees).[2] A study of 155,000 farmers found an increased susceptibility to Non-Hodgkin lymphoma after exposure to pesticides, proportional to the number of acres sprayed.[3] A Canadian study demonstrated a link between exposure to the weed-killers dicamba and methoprop, the insecticide carbamate, and NHL.[4]

Two studies have found a link between elevated leukemia rates and livestock farmers.[5] Increased rates of all types of leukemia were found in children whose parents used insecticides in the garden and on indoor plants, and whose mothers had been exposed while pregnant.[6] Indeed, the most critical exposure period for later development of leukemia is when the fetus is exposed *in utero*.[7]

Several studies have shown an association between pesticide exposure and brain cancer.[8] Children growing up with parents who were exposed to pesticides at work experience an increased risk.[9]

Exposure to the pesticides hexachlorobenzene,[10] chlordane, malathion, 2,4-D[11] and atrazine[12] has been shown to increase breast cancer risk.[13] A higher incidence of stomach cancer was also found in areas with elevated atrazine contamination in the water.[14]

In one U.S. study of 55,000 male pesticide applicators, an increased rate of prostate cancer was prevalent, especially in those with a family history of prostate cancer, and those who were exposed to methyl bromide, a common pesticide.[15] An association has been found between occupational exposure to pesticides and increased risk of both kidney and pancreatic cancer.[16,17]

Given the numerous studies linking pesticide exposure to a variety of cancers, and that exposure *in utero* can increase risk later in life, it is advisable that we reduce or eliminate exposure across all age groups. Many individuals find it challenging to afford the higher cost of organically grown food. One way to decrease exposure is to grow more of our own food in backyard or community gardens, or participate in a local food co-op.

The Environmental Working Group in the U.S. analyzed pesticide residues of 48 different fruits and vegetables and ranked them as most or least contaminated. The following chart is a guideline to understanding which foods are most contaminated and would be safer if purchased organically grown, and which have fewer pesticides and are safer to consume when not organically grown.[18]

Food Tip: Eat organically grown food as much as possible.

MOST CONTAMINATED FOODS	LEAST CONTAMINATED FOODS
1. apples	1. avocado
2. strawberries	2. sweet corn
3. grapes	3. pineapple
4. celery	4. cabbage
5. peaches	5. frozen sweet peas
6. spinach	6. onions
7. sweet bell peppers	7. asparagus
8. imported nectarines	8. mango
9. cucumbers	9. papaya
10. cherry tomatoes	10. kiwi
11. snap peas	11. eggplant
12. potatoes	12. grapefruit
13. hot peppers	13. cantaloupe
14. domestic blueberries	14. cauliflower
15. lettuce	15. sweet potato

Genetically Modified Food and Cancer

The health risks of consuming genetically modified (GM) foods are largely unknown, and they have not been proven safe for human consumption. Potential health risks that may occur from eating GM food include increased allergies from ingesting foreign proteins, neurological effects and hormone disruption from increased pesticide exposure,[19] reproductive effects, liver and kidney toxicity, and cancer. Many years of research are needed to confirm or disprove these health risks.

Several studies in mice have shown no harmful effects when GM corn was consumed for 90 days. One controversial study, in contrast, found that rats fed Roundup-tolerant genetically modified corn over a 2-year period developed more cancers than rats that were not fed the GM foods. The female rats in the study died 2-3 times more quickly than controls, and were more likely to develop large mammary tumors, with accompanying changes in sex hormone levels. Liver congestion and necrosis was up to 5.5 times higher and kidney disease was more common in the rats that consumed GM food.[20]

Until proven safe, we would be wise to avoid genetically modified foods, and encourage organically grown or Non-GMO Project-verified food instead. Foods that are commonly GM in Canada include corn, soy, beets, and canola. While trace amounts of pesticides and GMOs have been documented in some organic foods, certified organic food is by definition both pesticide-free and non-GMO.

Food Tip: Avoid genetically modified foods until proven safe.

Food Additives and Cancer

Another area of concern in food safety is the presence of food additives, some of which may increase cancer risk. Carrageenan, used as a thickener, has been demonstrated to increase the risk of colon cancer if consumed over a long period of time.[21] Sodium nitrite, added as a preservative in prepared meats, such as hot dogs, can also increase colon cancer risk.[22] Food dyes in general exhibit toxicity and can be carcinogenic, specifically Red 3, Red 40, Yellow 5 and Yellow 6.[23] Read labels to avoid these additives.

Food Tip: Avoid carrageenan, food dyes and sodium nitrite.

Food Packaging and Cancer

Food packaging containing plastics can increase our susceptibility to hormone-driven cancers, such as breast and prostate cancer.

Parabens are used as a preservative, in packaging material and are commonly found in our foods. They mimic the hormone estrogen and are implicated in breast cancer. One study examined eight food groups – beverages, dairy products, fats and oils, fish and shellfish, grains, meats, fruits and vegetables, and analyzed them for traces of parabens. All of these food groups contained parabens. Infants and toddlers consumed the most parabens in their foods when tallied as a percentage of their body weight.[24] The accumulation of parabens in our tissues over our lifetime may make us more susceptible to breast cancer later in life.[25,26]

Phthalates are added to plastics to make them soft and flexible and are found in food containers (often plasticized PVC), as well as being ubiquitous in the environment. Phthalates have been detected in all types of food, and levels are higher when the food has been in contact with plastic materials. Cheese and cream have high phthalate levels, and food is contaminated during processing when exposed to PVC from tubes, conveyor belts or disposable gloves. Paper and cardboard packaging made from recycled fibers also contains phthalates.[27]

Bisphenol A (BPA) is added to plastic to make it hard and durable, and is found in the lining of most canned food. Exposure to BPA has been demonstrated to increase the risk of both breast and prostate cancers.[28,29]

Food Tip: To minimize our exposure to hormone-disrupting chemicals found in food packaging, we can avoid canned and plastic-wrapped food as much as possible, and look for products packaged in glass, stainless steel or paper. Water and juice should also be stored in glass or stainless steel, rather than plastic containers.

Now we'll look at what foods to limit or avoid in our diets in order to deter cancer growth.

Minimize or Avoid Meat

The cooking of meat generates a class of chemicals called heterocyclic amines, which are both carcinogenic and estrogenic, and are implicated in the initiation and progression of breast cancer,[30] as well as cancer of the colon, prostate, pancreas, lung, stomach and esophagus.[31] Meat also contains polycyclic aromatic hydrocarbons, N-nitroso compounds and heme iron, all of which may increase risk of colon cancer.[32] These harmful compounds are increased when meat is grilled or barbecued.

Being higher on the food chain, meat accumulates toxins such as PCBs and dioxin, which are known carcinogens and hormone disruptors linked with breast cancer.[33] Approximately 90-98% of human exposure to dioxins and PCBs comes from our diet, with meat, fish and dairy being the predominant sources.[34] Even organic meat will contain PCBs and dioxin.

A high meat diet causes greater reabsorption of estrogen through the intestinal wall. Meat eaters will therefore have higher estrogen levels than vegetarians, which can make them more susceptible to breast cancer.[35]

Food Tip: Avoid or minimize meat intake.

Minimize or Avoid Fish

Although purified fish oils have anti-inflammatory and anti-cancer benefits, fish themselves may contain mercury, arsenic, cadmium, PCBs, dioxins and PBDEs, potentially increasing cancer risk.[36] Dried fish increase the risk of stomach cancer,[37] and preliminary studies suggest that high fish intake may increase endometrial cancer.[38] Pregnant or nursing women who consume fish may be transferring a higher level of hormone disrupting chemicals to their children,

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making them more susceptible to hormonally based cancers later in life.

In contrast, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) inhibit a variety of cancers by increasing apoptosis[39] and modulating the activity of the pro-inflammatory TNF family cytokines.[40] Purified fish oils, therefore, can be taken to inhibit cancer growth.

Food Tip: Avoid fish, but do use purified fish oil as a supplement.

Avoid or Minimize Dairy Fat

Studies on dairy and cancer are mixed, with many studies showing no relationship between dairy intake and cancer risk. However, some studies suggest increased breast, prostate, pancreatic[41] and hepatocellular[42] cancer risk with consumption of dairy fat.

One of the mechanisms that may link dairy fat to cancer is that high fat dairy can increase insulin growth factor 1 (IGF-1) levels.[43,44] IGF-1, a hormone produced in the liver, increases risk of both breast cancer and prostate cancer.[45] One study showed that premenopausal women with high levels of IGF-1 in their blood were seven times more likely to develop breast cancer than women with low levels,[46] while men with the highest levels of IGF-1 were four times as likely to develop prostate cancer as men with the lowest levels.[47] A 1995 study in rats published in the *Journal of Endocrinology* found that casein, a protein found in milk, slows down the breakdown of IGF-1, allowing it to circulate in blood at higher levels for longer periods of time.[48]

A large, case-control study in France in 1986 found that women who ate cheese regularly had 50% more risk of breast cancer than women who didn't eat cheese and those who drank milk regularly had 80% higher risk of breast cancer.[49]

Food Tip: Avoid or minimize dairy, especially dairy fat.

Avoid Sweets – Sugar, Honey, Maple Syrup, Fruit Juice, Soft Drinks etc.

Cancer cells derive their energy from glucose. Glucose increases insulin and IGF-1 levels, which stimulate cancer growth when receptors for these hormones are present. Esophageal cancer is associated with higher glycemic load in dietary patterns.[50] There is also a correlation between high intake of sweets and localized breast cancer in young women.[51] A low sugar diet and avoidance of refined carbohydrates with a high glycemic index may be protective.

Sugars and refined carbohydrates may also promote an overgrowth of unwanted organisms in the intestinal tract, such as *Candida* spp and parasites. Cancer patients are prone to candidiasis when their immune systems have been suppressed during and after chemotherapy and radiation,[52] or after antibiotic use. Care should be taken to identify patients with Candida overgrowth and recommend a diet that discourages fungal growth.

Food Tip: Avoid refined carbohydrates, sugars and high glycemic sweeteners. Choose carbohydrates that have a low glycemic index, such as most legumes, pearl barley, quinoa and green vegetables.

Avoid Alcohol

Alcohol consumption causes individuals to be more susceptible to cancer of the liver, colon, oral cavity, esophagus, rectum, pancreas and breast.[53,54] A weekly intake of up to one drink a day will increase risk. Women who have even one drink a day have an 11% higher risk of breast cancer.[55] In one study, the breast cancer risk was increased 250% in women who drank two or more alcoholic beverages per day.[55] Alcohol may interfere with the liver's ability to detoxify both chemicals and excess estrogen in the body. It is believed that chronic alcohol intake can induce cancer through several mechanisms: 1) induces DNA damage from acetaldehyde, the primary metabolite of alcohol; 2) contributes to oxidative stress and; 3) interference with DNA methylation, leading to chromosome instability.[56]

Use Plant-Based Sources of Protein

A vegetarian diet includes more fibre (which lowers estrogen, insulin and IGF-1), is more alkaline, and keeps estrogen and IGF-l levels lower. It also decreases inflammation.

Although there is little published research on the effects of a more alkaline milieu and cancer suppression, one study suggests that the external pH of solid tumors is acidic because of increased metabolism of glucose. In a mouse model experiment, an acid pH surrounding a tumor was shown to stimulate tumor cell invasion and metastasis, while oral NaHCO(3) selectively increased the pH of tumors and reduced the formation of spontaneous breast cancer metastases. The treatment significantly increased the extracellular pH, but not the intracellular pH, of the tumors.[57]

Another study confirms that increased intake of fruits and vegetables and decreased consumption of meat, creates a more alkaline urine.[58]

A 2014 study showed that individuals between 50-65 years of age who had a high animal protein intake had a 75% increase in overall mortality and a 4-fold increase in cancer death risk during the 18 years of the study, in comparison to those with either a low protein intake or those whose protein was plant based. [59] Another study on mice found that a diet containing 20% plant protein inhibited tumor weight by 37% as compared to a 20% animal protein diet.[60] An intake of 0.8 grams of vegetarian protein per kg of body weight (or approximately 35-60 grams) is adequate to meet adult protein needs.[59]

Food Tip: Adequate plant-based protein could include the following daily combination: 1 cup of cooked legumes, 1/2 cup firm tofu, ½ cup quinoa and 2 tbsp. of nuts or seeds. Legumes include kidney beans, soybeans, chickpeas, split peas and lentils. Include 10-20 grams of organic soy protein as part of total protein intake to reduce risk of breast[61] and prostate[62] cancers.

FOOD	PROTEIN CONTENT (GRAMS)	QUANTITY REQUIRED
Miso	5.9	½ cup
Tofu, silken	8.1	½ cup
Tofu, firm	15.6	½ cup
Soybeans, boiled	16.6	½ cup
Soybeans, dry-roasted	39.6	½ cup
Soy milk	5.6	1 cup
Tempeh	19.0	½ cup
Soy protein powder	58.1	1 ounce
Kidney beans	15	1 cup, cooked
Lentils	16	1 cup, cooked
Split peas	17	1 cup, cooked
Chick peas	14.5	1 cup, cooked
Almond butter	5	2 tbsp
Almonds	2.8	12
Sunflower seeds	6.5	1 oz
Pumpkin seeds	7	1 oz (142 seeds)
Sesame seed butter	2.6	1 tbsp
Hemp seed	5	1 tbsp
Flaxseed	2.5	1 tbsp
Quinoa	8.1	1 cup

Use Soy (Organic), Which Contains Genistein.

Genistein influences enzymes that regulate cell growth and division, and has anti-oxidant properties. It induces apoptosis, or programmed cell death, in damaged or cancerous cells of the breast,[63] ovary[64] and prostate.[65] Genistein inhibits the formation of blood vessels that feed cancerous tumors (angiogenesis) helping to starve tumors of their blood supply.[66] A genistein-supplemented diet in studies with mice with breast tumors was found to reduce lung metastases 10-fold.[67]

Soy isoflavones decrease the invasiveness (adhesion and motility) of breast cancer cells[68] and regulate genes and cellular signaling involved with tumor initiation, promotion and progression.[69] A diet high in soy may also reduce IGF-1 levels,[70] inhibiting cancer growth.

Food Tip: Use 10-15 grams of organic soy protein in food form (tofu, tempeh, soy milk) daily or several times a week.

Consume at Least 8 Servings of Fruits and Vegetables Daily

The following chart outlines protective phytochemicals, their mechanism of action, and in which foods they are found.

Cancer Fighting Phytochemicals Found in Fruits and Vegetables

PHYTO-CHEMICAL	MECHANISM OF ACTION	FOOD SOURCES
ALLYL SULFIDES	Increases liver enzymes to detoxify carcinogens.[71]	garlic, onions, leeks
CAPSAICIN	Induces apoptosis in cancer cells.[72]	chili peppers
CAROTENOIDS	Neutralize free radicals, enhances immunity, induce apoptosis,[73] promotes cell differentiation.[74]	parsley, carrots, spinach, kale, winter squash, apricots, cantaloupe, sweet potatoes, seaweed
POLYPHENOLS	Neutralize free radicals reduce damaging effects of nitrosamines. Down-regulates tumor necrosis factor, inflammatory cytokines and NfkB.[75]	broccoli, carrots, green tea, cucumbers, squash, mint, basil, citrus
FLAVONOIDS	Block hormone receptor sites, preventing attachment of cancer-promoting hormones. Activate BRM, an anti-cancer gene.[76]	most fruits and vegetables, including parsley, carrots, citrus, broccoli, cabbage, cucumbers, squash, yams, eggplant, peppers, berries
CURCUMIN	Assists liver in detoxifying carcinogens. Anti-inflammatory; inhibits proliferation and induces apoptosis in cancer cells.[77]	turmeric
ELLAGIC ACID	Neutralizes carcinogens in the liver, antioxidant, inhibits cancer cell division, induces apoptosis in cancer cells.	red raspberries, walnut skin
PUNICIC ACID	Inhibits growth and induces apoptosis in breast and prostate cancer[78] cells.	pomegranate seed and oil
URSOLIC ACID	Induces apoptosis in breast, colon, bladder, and prostate[79] cancer cells.	loquat leaf, Greek sage, rosemary
EUCALYPTOL	Induces apoptosis in cancer cells.[80]	rosemary, cardamom, eucalyptis essential oil
ISOFLAVONES (GENISTEIN AND DAIDZEN)	Binds to estrogen receptors, preventing harmful estrogens from binding; blocks formation of blood vessels to tumors, inhibits enzymes associated with tumorogenesis; inhibits activation of breast cancer genes.	soybeans, tofu, miso, lentils, dried beans, split peas, garbanzo beans, green beans, green peas, mung bean sprouts, red clover sprouts
INDOLES	Induce protective liver enzymes, stimulate healthy C2 estrogen production; decrease C4 estrogen that initiates breast cancer.	raw cabbage, broccoli, Brussels sprouts, kale, cauliflower, bok choy, kohlrabi, mustard, turnips
ISOTHIOCYANATES	Prevents DNA damage; blocks production of tumors induced by environmental chemicals, assists liver detoxification.	mustard, horseradish, radishes, turnips, cabbage, broccoli, cauliflower, Brussels sprouts, kale, bok choy, watercress, garden sorrel
LIMONOIDS	Induces protective enzymes in liver and intestines.	citrus fruit rind, essential oils of lemon, orange, celery, lemongrass
LINOLENIC ACID	Regulates production of beneficial prostaglandins.	flaxseeds and flaxseed oil
LYCOPENE	Neutralizes free radicals. Causes cell cycle arrest and induces apoptosis.[81]	tomatoes, red grapefruit, guava
LUTEIN	Neutralizes free radicals.	spinach, kiwi, tomato, grapes
MONOTERPENES	Induces protective enzymes, inhibits cholesterol production in tumors, stimulates destruction of breast cancer cells, inhibits growth of cancer cells.[82]	cherries, lavender, parsley, yams, carrots, broccoli, cabbage, basil cucumbers, peppers, squash, eggplant, mint, tomatoes, grapefruit
PHENOLIC ACIDS	Blocks effects of free radicals; inhibits formation of nitrosamine.	berries, broccoli, grapes, citrus, parsley, peppers, soy, squash, tomatoes, grains
PLANT STEROLS (BETA-SITOSTEROL)	Causes cell cycle arrest in breast cancer cells[83] and lowers fat levels in the body.	broccoli, cabbage, soy, peppers, whole grains
PROTEASE INHIBITORS	Blocks activity of enzymes involved in the growth of cancer.[84]	beans and soy products
QUERCETIN	Slows down cancer cell division.	onions, apples, green cabbage
QUINONES	Neutralizes carcinogens.[85]	rosemary, pau d'arco tea
SULFORAPHANE	Increases ability of the liver's detoxifying enzymes to remove carcinogens.	broccoli sprouts, broccoli, cauliflower, Brussels sprouts

Fresh Vegetable Juices

The cancer-protective phytochemicals listed in the chart above are found primarily in vegetables and fruits. One of the ways to ensure a high intake of these nutrients is through juicing vegetables. Many cancer therapies, such as Gerson therapy, recommend several glasses a day of vegetable juice. A vegetable base to begin with can be carrot, celery, kale and beet.

Food Tip: Consume one or more glasses of fresh vegetable juice daily, and add freshly ground flaxseeds to juice before drinking to decrease the glycemic load. Save the pulp to use in veggie burgers or soup broth.

Consume Brassicas Daily

The brassica family includes cabbage, kale, broccoli, cauliflower, Brussels sprouts, kohlrabi, turnip, rutabaga, garden sorrel, radish, watercress and collards. All of the brassicas contain the phytochemical, indole-3-carbinol, which at 300 mg. daily, doubles C2 hydroxyestrone (a protective estrogen metabolite) and decreases C16 hydroxyestrone (a harmful estrogen metabolite), reducing risk of hormonally driven cancers. This amount would be found in 1/3 of a head of raw cabbage. Indole-3-carbinol decreases the likelihood of metastases in prostate, endometrial and breast cancer[86] cells.

Brassicas also contain thiols, which improve liver detoxification, and isothiocyanates, which help to prevent DNA damage. Cruciferous vegetables may reduce risk of gastric and lung cancers.[87]

Broccoli sprouts and watercress are high in sulforaphane, which improves liver detoxification and protects from environmental chemicals. Sulforaphane inhibits growth of various cancer stem cells.[88]

A word of caution with the raw brassicas - they may interfere with thyroid function and cause a rise in TSH unless a source of iodine, such as sea vegetables is used as well. Check TSH levels every few months to assess thyroid function.

Food Tip: Consume at least 1/2 cup daily of brassicas. Include coleslaw 3x a week.

Watercress

Watercress contains sulforaphane and helps to suppress the invasiveness of breast cancer cells[89] and causes apoptosis (cell death) in breast cancer cells.[90]

Food Tip: Use watercress in soups and salads.

Seeds, Sprouts and Cereal Grasses

Seeds, sprouts and cereal grasses are rich in protective phytoestrogens, vitamins, minerals and enzymes. The sprouts highest in phytoestrogens include clover, mung bean, soybean, yellow pea, green lentil, chick pea, fenugreek and adzuki bean.

Seeds high in phytoestrogens include flax, pumpkin and sunflower. Phytoestrogens offer a protective effect by binding to estrogen receptors, displacing the body's stronger estrogens, estradiol and estrone.[91]

Barley greens decrease proliferation and increase apoptosis of leukemia and lymphoma cells while wheat grass[92] has been shown to induce apoptosis and arrest cell division in human breast and cervical cancer cells.[93]

Food Tip: Include seeds, sprouts and cereal grasses in the daily diet.

Consume Flaxseed Daily

Flaxseeds contain lignans, which have anti-viral, anti-bacterial and anti-fungal properties. Flaxseeds inhibit the growth of breast[94] and prostate[95] cancer. In studies with mice, a diet containing 10% flaxseed reduced breast cancer tumor cell proliferation and increased apoptosis, causing decreased tumor size by 74% in the presence of high estradiol levels and 22% when estradiol levels were low. It increased the inhibitory ability of Tamoxifen at both low and high estradiol levels.[96]

Food Tip: Eat at least 2 tbsp of freshly ground flaxseeds daily, added to cereal, smoothies, juice, soups, or salads.

Fiber

We need both soluble and insoluble fiber in our diets. Dietary fiber improves elimination, decreases a tendency to constipation, helps to eliminate toxins through the bowel, maintains the health of the intestinal flora and decreases cancer risk. Wheat bran and psyllium, when used together, confer protection from breast cancer.[97] A high fiber diet also offers protection from prostate and colon cancer.[98]

Food Tip: Consume a combination of bran, psyllium, ground flaxseeds, chia seeds and legumes regularly, for an optimal 45 grams of fiber daily.

Consume Garlic, Onions and Leeks

Garlic helps prevent the initiation, promotion and recurrence of many cancers, including breast cancer.[99] Garlic is high in the trace mineral selenium, which can inhibit cancer growth.[100] Garlic's antibacterial, antifungal and anti-viral properties may deter cancers related to infectious organisms (*H. pylori* in stomach cancer; HPV in cervical cancer). The garlic family contains sulphur-bearing amino acids and allyl sulfides, which help with liver detoxification.

Food Tip: Consume 3 cloves of raw garlic daily, added to salads, stir-fries and green smoothies.

Sea Vegetables

Sea vegetables include arame, nori, hijiki, kelp, dulse, wakame, kombu and mekabu. They are rich in minerals and confer increased alkalinity to the body. Sea vegetables are high in iodine, which

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suppresses the development and size of both benign and malignant tumors.[101] The high consumption of seaweed in Japan has been associated with their low breast cancer incidence. Studies on rats show that kelp inhibits the binding of estradiol to alpha and beta estrogen receptors and reduces serum estradiol levels.[102] Mekabu causes apoptosis in breast cancer cells.[103] Brown seaweeds have anti-inflammatory, anti-microbial, anti-viral and anti-tumoral properties.[104]

In addition, brown seaweeds can help to protect us from radiation toxicity, as they contain sodium alginate, which binds to radioactive molecules so they can be excreted.[105]

Food Tip: Consume sea vegetables daily in soups or salads, unless there is hyperthyroidism or autoimmune thyroid disease.

Consume Lycopene, Found in Tomatoes, Guava, Watermelon, Grapefruit, Rosehips

Lycopene is a form of carotene and antioxidant, reducing susceptibility to ovarian,[106] prostate,[107] breast,[108] cervical, oral and esophageal cancer. It gives the red color to fruits and vegetables. Tomatoes are its highest source, comprising 80% of dietary lycopene. Lycopene is 5x more bioavailable when tomatoes are cooked, and olive oil improves its absorption.

Food Tip: Use tomato sauce or stewed tomatoes weekly in your cooking. Limit tomatoes and use guava instead if you experience joint pain.

Flaxseed Oil Inhibits Breast and Colon Cancer

Flaxseed oil improved the effectiveness of Herceptin on breast cancer cells when used with it in a mouse study.[109] Flaxseed oil reduced breast cancer tumor size by 33%, tumor cell proliferation by 38%, and increased cell death by 110% when added to the diet in studies on mice.[110] Flaxseed oil makes Tamoxifen more effective in reducing the growth of ER+ breast tumors.[111] In studies on rats, colon cancer is inhibited by flaxseed oil.[112]

Food Tip: Use 2 tbsp of unheated flaxseed oil daily as part of your diet. Keep refrigerated.

Olive Oil is Protective

Olive oil has anti-inflammatory and anti-cancer effects.[113] Olive oil contains oleic acid (omega 9), which is anti-HER2, and slows growth of HER2 driven breast cancer.[114] When cooking with olive oil, add a small amount of water to the pan first, then add the olive oil, so that its temperature is not higher than that of boiling water.

Food Tip: Use olive oil and garlic liberally in salad dressing.

Use Foods to Aid Glycemic Control

Elevated blood sugar and insulin resistance encourage the growth of many forms of cancer, including breast and prostate. Along with maintaining a low sugar, low glycemic diet, foods that can be added to the diet to regulate blood sugar are listed below.

Food Tip: Add cinnamon, berries, chamomile tea, garlic, onions, leeks, chives, parsley, avocado, olive oil, flaxseed, oat bran, psyllium, lemon and prickly pear cactus[115] to your diet to regulate blood sugar levels.

Include Shiitake and Oyster Mushrooms

Shitake mushrooms have traditionally been used to treat cancer, rheumatoid arthritis, poor circulation, parasites, lack of stamina, and cerebral hemorrhage. Lentinan, from shitake mushrooms, increases the number of macrophages, T-killer cells and T-helper cells and prolongs the life of some cancer patients.[116] Oyster mushrooms inhibit breast cancer cell growth.[117]

Food Tip: consume 3-4 shiitake or oyster mushrooms a day for a month at a time, taking a break for a week and then include them in your diet again.

Use Turmeric Liberally

Turmeric has antioxidant, anti-tumor and anti-inflammatory activity. Curcumin, the main active ingredient in turmeric, is thought to prevent the formation of a blood supply to cancerous tumors, so they are less able to proliferate. It actively targets stem cells of various cancer lines (brain, head, neck, breast, lung, colorectal, pancreatic) that may be resistant to chemotherapy.[118]

Curcumin reduces the growth of both hormone-dependent and hormone-independent breast cancer cells.

Food Tip: Have one tbsp or more of turmeric powder daily. Absorption is best when heated with oil and taken with black pepper, so consider adding it to stir-fries and soups.

Grow and use Greek Sage (*Salvia triloba*) as tea or add to food

Greek sage contains the highest amount of ursolic acid (as do rosemary, lavender, winter savory, thyme), which is antimicrobial, anti-tumor and anti-inflammatory. It inhibits the growth of *Candida*, *staphylococci*, and Epstein-Barr virus and is active against many forms of cancer.[119]

Food Tip: Consider growing your own Greek sage and using it in tea.

Use Rosemary in Tea and Cooking

Rosemary contains the essential oil eucalyptol, which helps to kill *Candida albicans*, bacteria and parasites. It also contains ursolic acid, which helps to kill breast cancer cells. Rosemary contains a phytochemical called a quinone that acts to neutralize carcinogens. An extract of rosemary leaves increased the 2-hydroxylation of estradiol and estrone by 150% in mice to form more of the "good" C-2 estrogen and decreased the formation of the "bad" C-16 estrogen by 50%. It also increased the linking of estradiol and estrone to form the glucuronide complex in the liver, allowing estrogen to be eliminated more effectively. Thus rosemary can reduce the risk of estrogen related cancers.

Food Tip: Grow rosemary indoors and pour boiling water over a sprig to make tea.

Add Goji Berries to Salads, Cereals, Snacks

Goji berries are one of the highest food sources of antioxidants. They also regulate estrogen metabolism and inhibit growth of breast cancer cells dependent on estrogen[120] by increasing the formation of the protective C2 hydroxyestrone.[120]

Food Tip: Add goji berries to cereals, salads and snacks.

Use Spices that Inhibit NF-kB, a Switch that Activates Cancer Genes

NF-kB is cancer's master switch, which activates more than 400 genes involved in tumour proliferation, survival, angiogenesis and invasiveness. The triggers to activate NF-kB are carcinogens, oxidation, viral infection, inflammation, radiation, chemotherapy and stress.[121]

The spices listed below inhibit NF-kB and can be included in our daily diets.

Food Tip: Use anise, basil, black pepper, caraway, cardamom, chili pepper, cinnamon, clove, coriander, cumin, fennel, fenugreek, flaxseed, garlic, ginger, Holy basil, lemongrass, licorice, mint, mustard seeds, nutmeg, oregano, parsley, rosemary, saffron, tamarind, turmeric[122] to deter cancer.

Use Antioxidant Rich Foods and Spices

Antioxidant containing foods can be divided into 4 primary categories:

Legumes: small red bean, kidney bean, pinto bean, black bean, navy bean

Berries: goji, blueberry, raspberry, strawberry, cranberry, blackberry, amla (Indian gooseberry)

Tree Fruit: apple, cherry, plum, pear, orange

Nuts: pecan, macadamia, walnut

Other foods rich in antioxidants include raw cacao powder, white tea, green tea and dark chocolate (unsweetened of course).

Spices and herbs also contain high amounts of anti-oxidants. The richest in amount of antioxidants of these, in descending order are: cloves, peppermint, allspice, cinnamon, oregano, thyme, sage, rosemary and saffron.[123]

Food Tip: Include at least one serving of food from each of the antioxidant food categories in your daily diet. Use herbal teas such as chai, rosemary, peppermint, sage and green or white tea.

Pomegranate

Pomegranate extracts have been shown to prevent proliferation of stem cells and can cause apoptosis (cell death) in breast cancer cells, as well as reducing angiogenesis (blood supply). Pomegranate extracts contain ellagic acid, ursolic acid and luteolin, all of which reduce cell proliferation and can act as aromatase inhibitors[124] Pomegranate extracts are strongest when fermented and have a synergistic effect with soy in cancer prevention.[125] Pomegranate seed oil contains punicic acid, which inhibited ER+ and ER- breast cancer cells in a laboratory setting by more than 90%[126]

Food Tip: Use pomegranate in salads, cereals, juices and snacks.

Rotate Your Foods

Consuming the same foods day after day can lead to the development of sensitivities to those foods, which may result in weakened immunity. Brewer's and baker's yeast, wheat, gluten, eggs, sugar, peanuts, citrus, corn, dairy and tomatoes are common allergies. Tofu and soy products can also provoke sensitivities in some people.

Food Tip: Prepare a diet plan that rotates foods frequently.

Practice Fasting Once Weekly, Consuming Less than 500 Calories During that One Day

Intermittent fasting helps to reset IGF-1 and insulin to normal levels. Studies demonstrate intermittent fasting and chronic caloric reduction to be equivalent in causing weight loss, which will deter many forms of cancer. Intermittent fasting can reduce visceral fat stores, insulin-like growth factor 1 (IGF-1) levels and cell proliferation, and increase insulin sensitivity and adiponectin levels.[127]

With the dietary guidelines suggested in this paper, you can reduce your risk of developing various forms of cancer and can help patients recover from existing cancers.

About the Author

Sat Dharam Kaur has been practicing as a naturopathic physician since 1989. She is the author of The Complete Natural Medicine Guide to Breast Cancer and the Complete Natural Medicine Guide to Women's Health and specializes in treating cancer and women's health issues at Trillium Healing Arts in Owen Sound, Ontario. She travels extensively facilitating the Healthy Breast Program, creating an international network of Healthy Breast Educators to help reduce the global burden of breast cancer through education in prevention. Sat Dharam co-produces a monthly ezine related to breast health and is co-founder of the MammAlive Foundation for Women's Health and Education. When at home, Sat Dharam enjoys living on an off-the-grid organic farm with her husband and family.
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Mitochondrial Dysfunction: A Crossroads of Environmental Toxins and Cancer

Dr. Chris Spooner, ND

Mitochondria are increasingly found to play a central role in many human illnesses. These cytoplasmic organelles are supposedly derived from symbionts that evolved from ancient bacteria. Their DNA is quite unique as it is non-nuclear in nature, replicates independently of cell in which they reside and is exclusively maternally derived.

Mitochondria compartmentalize the metabolic pathways and physiological states of the cell, generating much of the cellular energy, regulating the cellular oxidation–reduction (redox) state, producing most of the cellular reactive oxygen species (ROS), buffering cellular Ca^{2+} and initiating cellular apoptosis. They are responsible for generating over 90% of cellular energy and 90% of free radicals and are essential for steroid synthesis and β-oxidation of fatty acids, but with regards to cancer they have been found to be gatekeepers of cell death (apoptosis & necrosis). The manner in which these functions operate has a direct role in whether a cell enters into programmed cell death or whether it activates survival signals that have the potential to lead to cellular transformation and carcinogenesis. At the heart of this process is the generation of ROS (also named free radicals) that have long been assumed to initiate and perpetuate cellular damage leading to aging and cellular dysfunction. Recent studies suggest an important role for the mitochondria, especially mitochondrial ROS production, as an upstream regulator of cancer-related signalling pathways that promote where mitochondrial ROS form crucial intermediary signal that can result in inflammation-associated cancer.[1]

Mitochondria were first proposed to be involved in cancer by Otto Warburg who reported that cancer cells exhibited "aerobic glycolysis".[2] This was originally interpreted as an indication that the function of the mitochondria was defective. However, it is now understood that cancer cells are in an altered metabolic state rather than a defective state, characterized by increased glycolytic metabolism and the continued use of oxygen. Cancer cells show various degrees of increased glycolysis, depending on the cell types and growth conditions. Generally, in the presence of oxygen, cancer cells produce about 60% of their ATP through glycolysis whereas normal cells seem to generate most of their ATP through mitochondrial oxidative phosphorylation (OXPHOS) using glucose, fatty acids, and other metabolic intermediates as energy sources. This increased dependency of cancer cells on the glycolytic pathway represents an important metabolic difference between normal and malignant cells.[3]

Given this increased metabolic activity, cancer cells actually require functional mitochondria; however mutations in mitochondrial genes alter the mitochondrial bioenergetic and biosynthetic state instead of inactivating mitochondrial energy metabolism as was once thought. It has been suggested that switching to glycolysis could represent an advantageous adaptation for cancer cells for several reasons. First, glycolysis alone generates ATP more rapidly than glycolysis coupled to OXPHOS, although with a low efficiency. Second, glycolysis also generates carbon intermediates that are used for various pathways, such as fatty acid synthesis, maintenance of the non-essential amino acid pool during cell growth, and synthesis of nucleotide precursors for RNA and DNA. Third, more rapid glycolysis coupled to lowered OXPHOS efficiency triggers the accumulation of pyruvate and formation of lactate, which results in cellular acidification, and seems to favour cancer cell invasion. As an added benefit, some of the accumulated pyruvate can be also redirected for lipid synthesis. Similarly, the decreased OXPHOS leads to citrate accumulation and export from the matrix, where it is converted to cytosolic acetyl-CoA and can be utilized for fatty acid and cholesterol synthesis. In summary, this altered metabolic state is considered to be the result of adaptation of cancer cells to the new, potentially anoxic environment of the neoplastic lesion via Hypoxia-inducible factor (HIF) and/or Akt, implicating a reduction/damage of mitochondrial metabolism.[4]

It is possible that aerobic glycolysis in cancer cells is a phenomenon that results from a more complex metabolic rearrangement in which mitochondria play an active role. Thus, glycolysis and the Krebs cycle, beta oxidation, and anabolic metabolism in general adapt to respond to the new primary function of this cell (i.e., uncontrolled proliferation) by providing energy and building blocks for the synthesis of nucleotides and amino and fatty acids.

These adaptive changes in bioenergetic and biosynthetic states send signals to the nucleus through mitochondrial 'retrograde signalling' to change signal transduction pathways, transcriptional circuits and chromatin structure. These changes occur so as to meet the perceived mitochondrial and nuclear requirements of the cancer cell. Cancer cells then reprogram adjacent stromal cells, activating inappropriate and out-of-context programmes that are important in cellular development, stress response, wound healing and nutritional status. The end result is to optimize the cancer cell environment.

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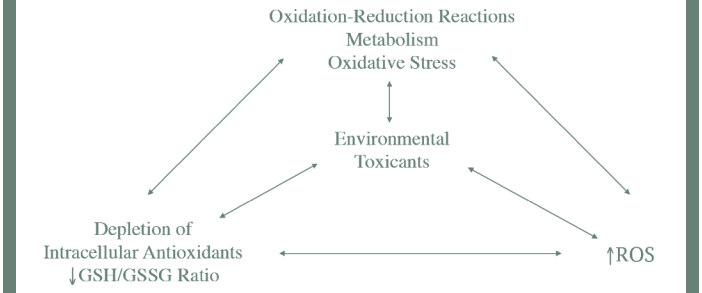
With respect to environmental toxins, effects of chemicals on mitochondrial functioning are mediated through reactive oxygen species. Much of this damage occurs to mitochondrial DNA, which is uniquely susceptible to the damaging effects of ROS. Exposure to environmental toxicants can result in direct attack of the mitochondria via the generation of ROS, which then create further damage by depletion of antioxidant defenses promoting further oxidative stress.[5] For example, depletion of intracellular glutathione (GSH) has been shown to occur by the direct conjugation/reaction of environmental agents to GSH, or indirectly by the activity of GSH-transferases. Depletion of these antioxidant defenses facilitate the accumulation of ROS and other reactions by environmental toxicants.[6]

The concept of excessive ROS as mediators of cellular damage and triggers for programmed cell death (apoptosis) has been long established, however, in the 1990s, researchers made a groundbreaking discovery when it was found that mitochondria played a pivotal role in the regulation of apoptosis and activation of adaptive cellular responses as opposed to simply being a mechanism of initiating cellular death. Before that time it was assumed that cell death from mitochondrial dysfunction resulted mainly from failures in ATP production where the release of several proteins including cytochrome C and apoptosis-inducing factors actively triggered cell death. (Fig.1)

FIGURE 1



The connection to environmental mitochondrial toxicity has not been easy to establish. It took years to recognize the mitochondrial toxicity of many drugs even though drugs are, in general, much better studied for toxicity than most environmental contaminants. This suggests that many environmental pollutants may be undiscovered mitochondrial toxicants[7] and it is becoming clear that there are several factors that are unique to mitochondria that make them vulnerable to environmental toxins.

Mitochondria have not been considered obvious targets for drug toxicity and consequently it has taken some time for them to be considered potential targets of drug-induced toxicity. Understanding how drugs might damage mitochondria eventually lead to better understanding of environmental toxin mediated mitochondrial damage. A screen of 550 drugs revealed that 34% have mitochondria damaging effects. Drugs have now been identified that inhibit and uncouple the electron transport chain (ETC); inhibit mitochondrial transport pathways, fatty acid oxidation or uptake, the citric acid cycle, mtDNA replication, and mitochondrial protein synthesis; and generate (or exacerbate generation of) ROS.[8]

One well-studied example is adriamycin (doxorubicin), a chemotherapeutic whose clinical use is limited by the fact that it also causes irreversible and cumulative cardiomyopathy. It appears to act largely by poisoning mitochondria, both via redox cycling to generate ROS and by inhibiting ATP production via uncoupling of oxidative phosphorylation.[9]

The physical structure of mitochondria is one factor that can lead to targeted damage. Specifically, the high lipid content of mitochondrial membranes facilitates accumulation of lipophilic compounds such as polycyclic aromatic hydrocarbons (PAHs)[10] and some alkylating agents.[11] Cationic metals, such as lead, cadmium, mercury, and manganese, also have been shown to accumulate in mitochondria.[12-16] As the inner mitochondrial matrix is negatively charged and mildly alkaline due to the actions of the proton pump and oxidative phosphorylation, positively charged cations can enter via calcium transporters along a charge gradient that is established by the pH differential between outer and inner membranes. This also results in accumulation of certain organic chemicals, particularly amphiphilic xenobiotics[17,18] that contain polar water-soluble terminal groups attached to a water-insoluble hydrocarbon chain.

Another factor contributing to the mitochondrial susceptibility is the presence of cytochrome P450s in mitochondria, which can activate chemicals that are relatively nonreactive prior to metabolism, such as PAHs and mycotoxins.[19-21] In these cases, the induction of P450 in conjunction with decreased phase 2 conjugation reactions leads to the accumulation of ROS. Environmental toxicants have effects in both phases. For example, PAHs can up regulate CYP1A2 and are responsible for the bio activation of benzo-a-pyrene. Furthermore, mercury is as an excellent example of an inhibitor of the phase 2 associated enzyme, glutathione synthetase.

Mutations in the DNA are another important factor in cellular de-differentiation. Mitochondrial DNA (mtDNA) is more vulnerable than nuclear DNA (nDNA) to environmental toxin-induced mutations. Several suggested reasons include mtDNA's physical location outside of the nucleus, in the cytosol, its reduced protein packaging compared with nDNA, and its reduced repair capacity. Physically, mtDNA is anchored to the matrix side of the inner membrane, in close proximity to the electron transport chain (ETC) and many proteins that contain transition metal ions. The ETC normally generates a significant amount of ROS by electron loss. A very large difference between nDNA and mtDNA is the relative lack of repair pathways present in mitochondria. Many types of damage are either irreparable or only very slowly repaired. In addition, mitochondrial damage can lead to greater mitochondrial dysfunction, in turn leading to greater release of ROS and damage.[22]

Mutations that occur in nuclear-DNA-encoded mitochondrial proteins and mitochondrial-DNA-encoded proteins can shift cellular metabolism towards glycolysis, glutaminolysis, macromolecular

synthesis and the conversion of $NADP^+$ to NADPH. Both types of mitochondrial DNA mutations have been associated with many types of cancers. The mutations of mtDNA in cancer cells may alter cancer cell metabolism and/or proliferation and allow cancer cells to survive by increasing their capacity to adapt to a changing environment.[23]

It is important to note that different tissues and cell types will have unique environments and will create tissue specific conditions. Evidence from mitochondrial disease and mitochondrial drug toxicity indicate that different cell types will display different susceptibilities to mitochondrial toxicants.[24, 25] There are many factors that may sensitize specific cell types to mitochondrial toxicity. For example, high reliance on mitochondrial function may mean that dysfunction more easily causes cell death (e.g., as often seen in mitochondrial diseases that target high energy-use cells) because the increased function may result in higher ROS production in some circumstances. The case of adriamycin, previously noted, causes principally mitochondrial toxicity in the heart, where much electron flow occurs in mitochondria, whereas in the liver it causes endoplasmic reticulum damage because this is where electron flow is localized in that tissue.

Another factor that will influence mitochondrial susceptibility to toxins is age and developmental stage.

Some developmental stages are likely more sensitive to mitochondrial toxicants due to age-dependent differences in mitochondrial content, mitochondrial metabolism, and mitochondrial defence/repair mechanisms. Mitochondrial count and volume and mtDNA copy number vary dramatically with age in humans and other species. Although most cells thus far examined have 103–104 copies of mtDNA, somatic and germ cells in the early embryo may contain as few as 10 copies, constituting a "bottleneck" in mtDNA copy number.[26-28] mtDNA transfer into daughter cells at mitosis appease to be random and, therefore, it is possible for there to be low copy number at least in some cell types. It is also possible for some cells to end up with a high percentage of damaged or mutant mtDNA after multiple cycles of cell division. This means high levels of damaged mtDNA would then be inherited by all of the cells derived from the progenitor cell.[29-32]

Age-related changes in mitochondrial metabolism are also well documented. Early life stages often display more anaerobic metabolism and spherical morphologies, and older individuals typically show signs of mitochondrial dysfunction. In old age, there is also a lower copy number and reduced capacity to generate energy. This might inhibit repair processes and stress responses and magnify the effects, thereby increasing vulnerability with age.[33-35]

As demonstrated above, many of the physical, chemical, and biological characteristics of mitochondria make them vulnerable to toxicant exposure. At the same time, mitochondria are generally robust[36] and are protected in a number of ways, including greater redundancy of mtDNA, and the ability to replace defective components.[37] Furthermore, in an interesting twist, it appears that ROS are an important factor in this resiliency. It would seem that, with respect to ROS, the mitochondria's greatest weakness is also its greatest strength.

More recent research suggests that ROS consisting of super-oxide, hydrogen peroxide, and multiple others, do not only cause oxidative stress, but also participate in cell signalling and communication, particularly between nuclear and mitochondrial genes. ROS appear to function as signalling molecules that promote health by preventing or delaying a number of chronic diseases, and ultimately extend lifespan. While high levels of ROS are generally accepted to cause cellular damage and to promote aging, lower levels of these appear to induce adaptive responses and actually improve systemic defence mechanisms and function under adverse conditions.

Although ROS are best known as damaging agents in pathology, a more nuanced view has developed and it is not as black and white as previously proposed. On the one hand, ROS have been implicated in cellular damage, contributing to the aging and disease process. On the other hand, the emerging view requires a re-evaluation of the roles of mitochondrial ROS (mtROS) generation and suggests that the improvement of mitochondrial capacity is associated with increased lifespan and health. It would appear that mtROS serve as important signalling molecules that initiate both cellular and systemic physiological changes. The important concept is to recognize that there may exist a biphasic action where environmental or toxin generated ROS at high doses unquestionably exert detrimental effects on cellular integrity while under different conditions they may serve as an important stimulus for adaptive and regenerative processes. This kind of biphasic or non-linear response to potentially harmful substances was named "hormesis" or mitohormesis.[38]

Environmental stressors such as calorie restriction, hypoxia, temperature stress, and physical activity, can stimulate ROS-mediated signals, that set off a series of adaptive responses that can lead either to DNA damage culminating in cell cycle arrest and cellular apoptosis or conversely, survival signalling. It is during the repair cycles whereby DNA repair and antioxidant defenses can lead to immortalization of partially damaged cells which then have the potential to transform into tumour cells, thereby establishing a link to the development of cancer with mitochondrial function and ROS mediated signalling and damage.

An interesting example of this is arsenite. Arsenite is extremely toxic and causes a transient increase in reactive oxygen species (ROS) and is assumed to exert detrimental effects even at lowest concentrations. However it has been observed that exposure to low-dose arsenite promotes growth of cultured mammalian cells. In the nematode C. elegans, low-dose arsenate promotes resistance against thermal and chemical stressors and extends lifespan of this metazoan, whereas higher concentrations reduce longevity. When considering these results in the context of Fig. 2 a possible explanation would be the low level of ROS generation is sufficient to induce DNA repair mechanism sufficient to a point that is actually health promoting.[39]

Some ROS, such as hydrogen peroxide (H_2O_2), can act as

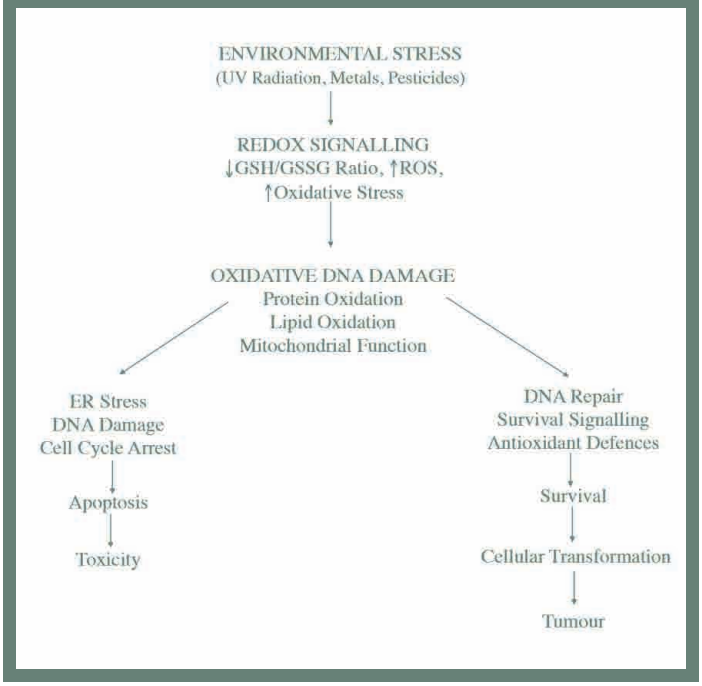
messengers both in the extracellular environment and within cells.[40-44] This suggests that mitochondria are an important redox signalling node, partly because of the flux of the ROS superoxide (O_2·–) generated by the respiratory chain and other core metabolic machineries within mitochondria.[45-47]

Redox signalling induced by environmental toxicants involves changes in antioxidant defenses such as decreases in the GSH/GSSG ratio and oxidative stress via accumulation of ROS. The consequences of the depletion of antioxidant defenses and increased ROS result in changes to proteins, DNA damage, lipid oxidation leading to alterations in mitochondrial function and ultimately, cellular growth and differentiation

With regards to the development of malignancy, this signalling system plays an important role in both the activation of pathways for removal of unwanted, damaged cells and survival signals in response to environmental exposures. It is at this point where mitochondrial ROS production results in either sufficient damage to initiate apoptosis or else initiates DNA repair and survival. This occurs through the activity of oncoproteins and tumour suppressors that then modulate mitochondrial function to "promote" malignant cell transformation.

Generation of oxidative stress is regarded as oncogenic risk factor because of two major effects. First, occurrence of hydroxyl-radicals may lead to oxidative DNA damage. Second, a continuous disturbance of redox homeostasis via increased ROS generation can be associated with chronic pro-inflammatory signalling, leading to induction of proto-oncogenes and/or anti-apoptotic factors as well as an adaptive increase in cellular anti-oxidant response potentially affording cellular protection against stressful environments that would not otherwise support cell growth.[48-49]

FIGURE 2



Xenobiotic compounds have numerous effects, including but not limited to toxic mitochondrial damage. Exogenous ROS and/or ROS generated by metals and xenobiotics may excessively increase endogenous ROS levels, thereby disturbing physiological signalling. This may explain the impact of low levels of chronic exposures that are insufficient to trigger acute toxicities, including apoptosis yet contribute to tumour development and carcinogenesis.[50] In many instances, both apoptotic and survival signalling pathways have been observed to be activated in parallel in response to environmental toxicity. It appears that tumour development may depend on whether or not survival mechanisms are activated which, in turn is highly dependent on the intensity, length and type of exposure.

Environmental toxicity-induced apoptosis and its dysregulation can be major factors in the pathophysiology of distinct diseases such as neurodegeneration, whereas deregulated activation of survival signals promotes cellular transformation and uncontrolled cellular division. The connection between changes in mitochondrial function and the resulting production of ROS is crucial for all cells**.** Cells in the body that retain normal growth control**s** will eventually undergo normal cellular senescence leading to appropriate turnover by their death and replacement, normal apoptosis. In contrast, cells undergoing the process of oncogenic transformation continue to survive as immortalized cells leading to uncontrolled proliferation and the formation of tumours.[51]

Cancer cell transformation is critically dependent on the interactions of key oncogenes and tumour suppressor genes and their encoded products. It is the progressive changes in mitochondrial function and ROS production that enable cells escape from the apoptotic cycle and permit them to survive the normal process of senescence and induction of oxidative damage-mediated cell death and develop into tumour-initiating cells.

Furthermore, as mitochondrial metabolism changes with elevated and sustained ROS production, respiratory pathways become partially uncoupled from ATP synthesis (Oxidative Phosphorylations). leading to increased mtDNA mutation and protein damage and eventually the promotion of malignancy through suppression of DNA repair. This then permits the perpetuation of mutations that facilitate the inactivation of mechanisms associated with senescence and programmed cell death.

Scatena (2012) cites many studies that show that mitochondria play a fundamental role in cell death by apoptosis or necrosis. Moreover, metabolic enzymes of the Krebs cycle also have been recently recognized as oncosuppressors. Recently, studies have re-evaluated the role of oxidative mitochondrial metabolism in cancer cell growth and progression. Some of these data indicate that modulation of mitochondrial respiration may induce an arrest of cancer cell proliferation and differentiation (pseudodifferentiation) and/or death, suggesting that manipulation of some mitochondrial activities may induce anticancer effects.[52] Ironically, it appears that activating cellular survival pathways in response to numerous stressors, including environmental toxins can potentially lead to malignant cellular transformation. It is this deregulated activation

of survival signals stimulated by the alteration or impairment of apoptotic signalling that promotes cellular transformation. The challenge that arises for naturopathic physicians working with patients in an integrated model is how to best assess and utilize this knowledge and work with the body to restore homeostasis.

About the Author

Dr. Chris Spooner practices in Vernon, BC. He received a B.Sc. in Biology from the University of Victoria in 1991 and his ND from the Canadian College of Naturopathic Medicine in 1998. In 2006 he completed a post doctoral fellowship at the Southwest College of Naturopathic Medicine in Tempe, Arizona.

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While At SCNM Dr. Spooner developed a wellness center in the Phoenix Fire Department Medical center. The goal of this center was to provide naturopathic health care the 3000 firefighters of the greater Phoenix area.

Dr. Spooner has been an advisor on CAM therapies to the board of directors of the American Association of Occupational Health Nurses. In 2003 he was Vice President of the British Columbia Naturopathic Association and has been a member of the board of Directors of the College of Naturopathic Physicians of BC where he acted as chair of the Finance committee, member of the Pharmaceutical and Diagnostic Referral committee and the Scope of Practice committee.

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Psychological States Associated with Cancer

Dr. Iva Lloyd, BScH, BCPP, ND

> "Your beliefs become your thoughts,
> Your thoughts become your words,
> Your words become your actions,
> Your actions become your habits,
> Your habits become your values,
> Your values become your destiny."
> ~ *Mahatma Gandhi*

For those of us that see an individual as an integrated whole, with the psychological, functional and structural aspects interacting as one with the personal essence, the question as to whether mental or emotional states can result in disease seems naïve. Of course they can. Specific psychological states have been linked to virtually every disease. Why then does western medicine find it so hard to believe that thoughts and emotions can cause cancer? There is an acceptance that the emotional states such as depression and hopelessness can impact survival and recovery, but still there is a reluctance to accept that thoughts and emotions can be causal factors.[1] In exploring this topic we will look at how the eastern systems of medicine that have been around for thousands of years such as traditional Chinese medicine and ayurvedic medicine link the mind and cancer. We will then explore some of the current views and ways to incorporate the psychological aspects of health in the pursuit of cancer prevention.

Traditional Chinese Medicine

Chinese medicine texts, as far back as 200 B.C. list specific psychological states as one of the known causes of cancer. They recognized that specific emotions, especially those that were suppressed or extreme, could result directly in cancer or alter the physiology of the individual and indirectly contribute to cancer. Some references taken from the book, *Management of Cancer with Chinese Medicine* include:[2]

- The Nei Jing mentions that tumor formation is due to the inhibited movement of Ying Qi (Nutritive Qi) and Wei Qi (Defensive Qi), inappropriate joy or anger, and unseasonable cold or warmth.
- In Confucians' Duties to Their Parents, Zhang states that the formation of cancerous tumors is due to accumulations, or to violent changes brought about by anger, joy, sorrow, pensiveness and fear.
- Ge Zhi Yu Lun [On Inquiring into the Properties of Things], published in 1347, indicates that tumors form when Spleen Qi is dispersed and Liver Qi is forced into transverse counterflow due to the accumulation of sorrow, anger and depression.

The internal damage caused by emotions can contribute to the formation of cancerous tumors[2] as follows:

- Sorrow, anxiety and excessive thought and preoccupation damage the spleen and stomach, consume the blood and body fluids and cause Qi to stagnate, thus generating phlegm. Once phlegm is formed, it obstructs the passages.
- Depression and anger deplete and damage the Qi and blood in the liver and spleen.
- Sorrow and depression damage the liver.
- Unfulfilled wishes or desires accumulate in the heart and disrupt the movement of Qi.

Ayurvedic Medicine

Ayurvedic medicine, similar to naturopathic medicine understands that most diseases are a result of many factors in varying degrees of influence (one of the key factors being a person's psychological state); there is the understanding that psychological experiences are somatised or experienced within the body.[3] The emotions that are considered to be the most troublesome are extreme passion, hopelessness and lethargy.[3,4] Any emotion that blocks the flow of energy, is experienced in extremes, or is suppressed causes a blockage in one of the doshas (Vatta, Pitta or Kapha) and can contribute to disease. Excesses in Pitta (fire and water) and Kapha (water and earth) are generally associated with the formation of tumors. Kapha is responsible for the increase in cell mass and stagnation, whereas Pitta in nutrient imbalances.[4] An excess in Vatta (which often manifests as worry or anxiety) is associated with disrupting the natural flow of energy throughout the body and is associated with increased proliferation of cancer cells.[3,4]

According to ayurvedic writings, the power of hopelessness is extreme. Brief periods of hopelessness in a weakened system may be sufficient to initiate cancer forming cells. Long-standing hopelessness or an intense shock or loss in a well-integrated individual may be

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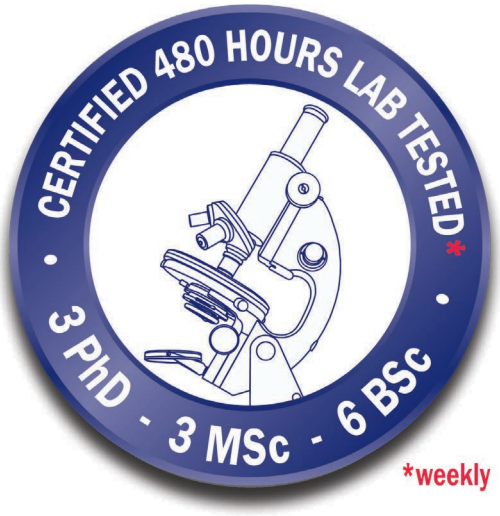

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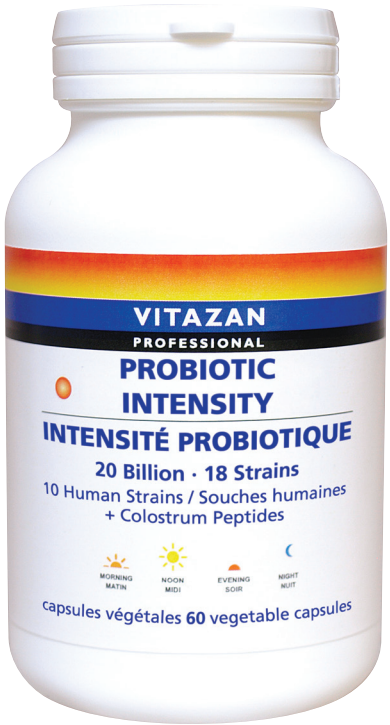

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sufficient to cause cancer, especially if the emotions are not dealt with and resolved.[4] Hopelessness is considered to be a form of mental encouragement for cancer cells, regardless of the physical or environmental carcinogen that initiated the cancer.[4] In ayurvedic medicine the health of emotions is linked to the health of blood. Red blood cells are needed to nourish the seven body tissues and to provide the individual with prana (life force). An increase in white blood cells indicates that the body has shifted from supporting health to eliminating toxins and protecting itself from external pathogens. Low red blood cell counts and high white blood cell counts weaken the body and provide a breeding ground for cancer cells. High white blood cell counts are also associated with a sense of hopelessness at a cellular level.[4]

Other ayurvedic links between psychological states and cancer formation include:[4]

- Physical or mental experiences which a person cannot "digest". The experience will find a host cell that matches emotionally.
- Strong relationships and bonds with others are viewed to be protective against cancer.
- Loneliness and a sense of separation from others tends to be associated with increased cancer risk.
- Giving too much and receiving too little generally results in disappointment. Extreme or chronic disappointment often leads to anger or envy, which causes an imbalance that permeates all aspects of an individual.
- Any powerful dissatisfaction can affect a person's desire for life.

Western Thinking

The great philosopher Galen was one of the first to link cancer and mental state. In his dissertation over 2,000 years ago he noted that women were more susceptible to cancer if they were melancholic.[5] The ancient Greeks believed that the mind and body were one and that disease was often due to emotional distress. In the 1700s British physicians noted the link between psychological states and the onset of cancer. Gendron emphasized that causations of cancer included "disasters of life and grief" and Burrows associated the link to "the uneasy passions of the mind with which the patient is strongly affected for a long time."[5] Yet, as beliefs about cancer causes shifted to physiological mechanisms and physical assaults on the body, the idea of psychology contributing to cancer was largely discounted (until recent times, that is).

Hans Selye, a Canadian researcher, coined the term "stress" in the 1930s. His research proved that both noxious emotional stimuli and physical stimuli produced dramatic physiological changes including gastric ulcerations and renal enlargement. These physiological changes were associated with increased cortisone-like secretions. Selye believed that cancer was an adaptive response to stress over a prolonged period of time and that positive emotional relationships and mental states could retard or reverse cancer growth.[5] As a follow up to Selye's adaptation theory, cancer has often been proposed to be a disease of civilization. This idea was first proposed in 1843 by a physician and one of Napoleon's surgeons, Stanislas Tanchou, who was of the opinion that "cancer, like insanity, increases in direction ratio to the civilization of the country and of the people."[5] In 1957 Dr. Alexander Berglas wrote a paper, entitled, "Cancer: Its Nature, Cause and Cure". This paper states that primitive people are relatively free of cancer and that those that are unable to adapt to present daily living conditions will be at increased risk of death from cancer.[5]

In the 1970s and 1980s the physicist Fritz-Albert Popp was doing experiments looking at the electromagnetic radiation or light that was emitted off human beings and individual cells. He found that the light that healthy individuals emitted, demonstrated a strong degree of coherence and seemed to follow the natural biorhythms. When the same study was conducted on individuals with cancer it was found that cancer patients had lost these natural periodic rhythms and also their coherence. They "had lost their connection with the world. Their internal communications were scrambled and their light was going out."[6] In the realm of energetic medicine (polarity therapy for example), a consistent belief is that cancer is associated with of an aspect of a person's life being out-of-sync. The aim of polarity therapy is to find the factor(s) that are causing a person to shut-down, i.e., turn out their own light.[7]

Although there is a tremendous amount of research linking diseases to emotional states, Western medicine is reluctant to acknowledge a causal link between thoughts, emotions and the onset of cancer.[1] As a result, much of the research has involved epidemiological studies linking psychosocial factors to disease progression and recovery. Stress, chronic depression and lack of social support or social isolation are seen as risk factors[8] and depression and hopelessness are considered more predictive of cancer progression than stressful events. Strong social support has been shown to be buffer psychological and biological stress and is linked to increased survival rates.[8] Psycho-spiritual well-being is negatively affected by emotional distress, anxiety, helplessness, hopelessness and fear of death. The emotional states that improve psycho-spiritual well-being and hence, quality of life and ability to handle a terminal illness such as cancer, include prognostic awareness, family and social support, autonomy, hope and meaning in life.[9] Understanding the direct physiological link between stress and cancer is getting closer as current research finds that stress may actually fuel cancer by activating transcription factor 3 (ATF3), a member of the cyclic AMP response. The activation of this adaptive-response gene may affect apoptosis, resulting in increased susceptibility and progression of cancer.[10]

I find it curious that the majority of Western thinking makes a distinction between the emotional states that cause cancer and the emotions that are associated with recovery from cancer. No such distinction exists in Eastern thinking; from an Eastern perspective feelings of hopelessness, sorrow or anger and fear are considered contributing factors to both the initiation of cancer and to the progression of cancer. From a naturopathic perspective

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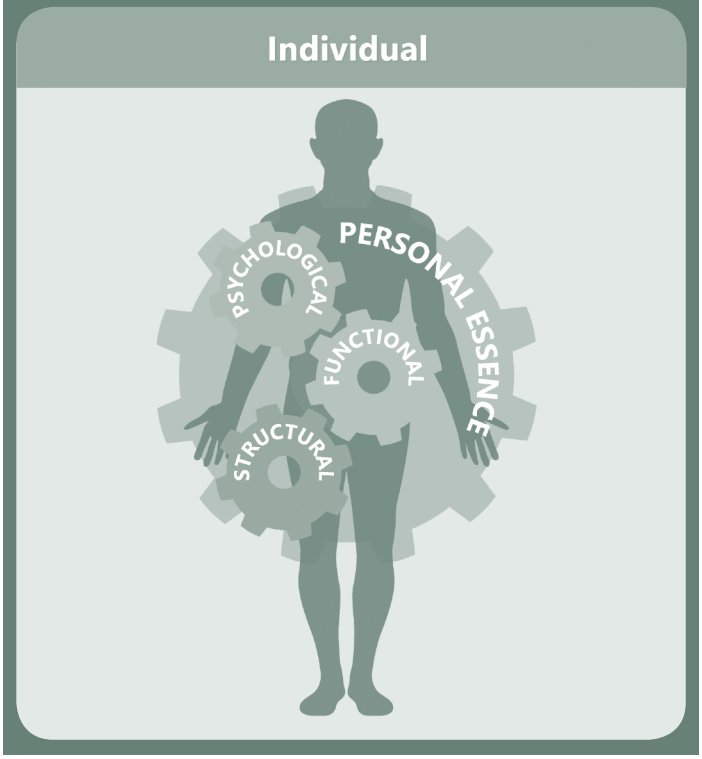
the integration of all aspects of the individual is more in line with Eastern thinking (see Figure 1).

FIGURE 1



There are many myths and stigmas to a cancer diagnosis. Table 1 illustrates the primary myths and perceptions that people generally hold with respect to cancer. These myths and perceptions have been shown to impede every aspect of early cancer-detection, treatment, recovery and survival. It is interesting to consider that while these perceptions are merely thoughts, they have been shown to have a direct physiological impact and contribute to symptoms and conditions.

TABLE 1: The myths and perceptions of cancer.[11]

• **Death**	• **Loss of control and independence**
• **Fear**	• **Helplessness**
• **Pain and suffering**	• **Isolation**

Two emotional states that are commonly studied with respect to cancer are depression and hopelessness. A PubMed research search yields 15,730 articles relating to depression and cancer and 354 relating to hopelessness and cancer. Research shows that both depression and hopelessness are associated with decreased quality-of-life, decreased recovery and an increased desire to end life.[12,13] High levels of emotional distress, depression, anxiety, uncertainty and hopelessness are associated with increased levels of cancer pain.[14] Psychological and cognitive behavioural treatments have been linked to decreasing cancer pain.[14] Dr. Jeremy Geffen, the well-respected medical oncologist and author of the book, entitled, *The Journey through Cancer: Healing and Transforming the Whole Person* puts forward the seven levels of healing:[15]

1. Education and Information
2. Connection with Others
3. The Body as a Garden
4. Emotional Healing
5. The Nature of the Mind
6. Life Assessment
7. The Nature of Spirit

Through his experience in working with those with cancer he strongly connects a positive psychological state with decreased mortality, faster recovery and overall better quality of life. The main emotional states linked to increased recovery and survival include feeling supported, letting go of fear and anger, finding meaning, purpose and love in your life.[15]

Some of the challenges that I see with addressing the link between psychological states and the onset of cancer include avoiding blame and having compensatory health beliefs (see section, below).

Avoiding Blame

For some reason western medicine is quite okay with blaming the onset of cancer with smoking, drinking too much alcohol, a poor diet, and environmental toxins that we may or may not choose to expose ourselves to. However, it is felt that associating cancer on the mind or on unresolved emotions is cruel and will result in undue suffering and blame. I have too often seen patients die of cancer and other diseases after spending countless hours and dollars addressing factors that are socially acceptable, but avoiding the emotional factors which may have contributed significantly to their disease. Cancer, like most diseases, is multi-factorial and mental/emotional states are highly relevant factors. I have also found that patients are generally aware of their internal turmoil, of their feelings of isolation or hopelessness and they are able to recognize when they have unresolved emotions and unfulfilled desires. My experience is that patients are looking for guidance on how to work through their emotion struggles or sense of hopelessness. When patients are told that their thoughts and emotions are not a relevant part of the disease process, it is dishonoring and can be destructive and add to the progression of the disease itself.

Compensatory Health Beliefs

The hedonic principle explains the search for ideal balance between maximum pleasure and minimal disadvantage. The search for this elusive balance often results in motivational conflict and cognitive dissonance. In an attempt to resolve these issues, individuals often

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employ compensatory health beliefs (CHBs). CHBs are beliefs that healthy behaviours can neutralize or compensate for the negative effects of an unhealthy (but pleasurable) behaviour .[16] For example, individuals convince themselves that having that forbidden food or dessert today will be balanced out by the exercise they are planning tomorrow.

In some ways CHBs can be beneficial as individuals recognize the need to balance out harmful behaviours, such as putting a greater emphasis on healthy nutrition or by taking herbs to compensate for heavy alcohol consumption. CHBs are used and actually encouraged by many people, physicians and self-help organizations some of whom seem to believe that a person can safely avoid addressing something that is "disease forming" by putting a greater emphasis on something else that is "health enhancing". The research indicates that CHBs undermine a person's intentions and their ability to change or address unwanted behaviours.[16] Although most of the research focus on CHBs has been on behaviours such as quitting smoking or food avoidance, it offers a valid model for how individuals handle emotional states and for the belief that they hold with respect to the need to address them.

I often convey to patients that "addressing any factor will only affect the outcome to the degree that it is part of the problem." That statement follows the naturopathic principle, "treat the cause". If a person has been diagnosed with cancer and through the assessment it is deduced that the causal factors include a sense of hopelessness in one's life and environmental toxins, it is unlikely that they will achieve health by putting the emphasis of treatment on improving diet and taking supplements to enhance immune health. A health-promoting treatment plan will often improve quality of life and may decrease mortality, but only by addressing the causal factors will a full recovery be possible.

Assessment Considerations

How a naturopathic doctor screens a patient for cancer risk or treats a patient with cancer is strongly dependant on their beliefs about the causes of cancer. If a functional approach to health and disease is taken it is likely that the assessment will be pared down and will omit many potential causes, including the psychological factors. For those NDs that truly include "treating the whole person" as part of their approach it would involve an in-depth look at a person's psychological state and the impact that their emotions are having on their state of health and quality of life.

The Intake

In your intake or as part of your intake questionnaire ask questions about a person's psychological state, their level of satisfaction with their life, the impact of traumatic events, how they handle stress, what gives them pleasure and what regrets they have.[7]

- Listen for the key emotions that are linked to cancer – hopelessness, isolation, depression, indecision and suppressed anger or fear. The type of situations that I find have a tremendous impact on health and that I listen for include: being on the fence, feeling trapped, not feeling supported and emotionally charged secrets. Explore in detail feelings of hopelessness and depression or others that are relevant for the patient to understand if the feelings are acute or chronic, and how those feelings have affected a person's life.
- Listen for the "energy" that a person conveys. How easily are they triggered when they discuss significant events in their life?
- Is a person existing or are they living? Is there a balance between what they do for others and what they receive from others? Does a person seem to make decisions for their own life or are they taking direction from others?
- To what degree is their focus on the past, on the present or the future? If too much of their focus or story is on the past it is likely that a person is hanging onto charged emotions.
- Listen for the somatic metaphors and the way that the physical symptoms match the language of the patient.

The only way to assess the psychological aspect of a person is by listening to them. By letting them tell their story. By asking relevant, open-ended questions and then truly listening to what they say, how they say it and how it links to their symptoms and state of health. There are many different tools to assist individuals in addressing and shifting their mindset, such as: mindfulness, meditation, gentle yoga, Tai Chi, Qi Gong and other forms of exercise that encourage stillness. Sat Dharam Kaur explores a number of options in her book, *The Complete Natural Medicine Guide to Breast Cancer.*[17] The following are strategies that I find are helpful in treating patients.

Beliefs

As part of any assessment I encourage you to ask a patient about their beliefs about health and disease. What emphasis do they put on the impact of emotions? What a person believes will strongly impact the outcome. As all disappointment in life comes from unfulfilled expectations and expectations are set by our beliefs, helping patients uncover their true beliefs, both the rational and irrational, is important. Bruce Lipton in his book, *Biology and Belief* tells the story of a retired shoe salesman who was told that he had an incurable cancer of the esophagus. Within two weeks of the diagnosis he died. The autopsy found very little cancer in his body, definitely not enough to kill him, and there was no sign of esophageal cancer. It is believed that the man died because he believed that he was going to die, not from cancer.[18] The longer a naturopathic doctor is in practice the more they come across similar stories. The notion that beliefs shape a person's reality has been shown repeatedly in research.[19] There are a number of books written on exploring and changing beliefs. I encourage you to incorporate addressing beliefs as part of your work with patients.

Free-Form Writing and Journaling

We generally associate emotions with being stored in the right side of the brain. Everyday mind-chatter and anxiety are often viewed as being part of the left-side of the brain. The purpose of journaling and free-form writing is to get past the "noise" of the mind-chatter and the logical thoughts and understand the deeper emotions. Free-form writing and journaling are effective tools for helping people detox old emotions and to release current habits and expressions. The general rules for journaling and free-form writing include:

- If the goal is to dissipate emotions or to detox emotionally you want to journal and shred (or burn). Do not keep the writings nor share them with others.
- Most people need to write without stopping for at least 1 to 2 hours. When initially writing what will come up are logical thoughts. You need to continue to write until you get past the logical thoughts to truly uncover the deeper emotions.
- Keep in mind that stored emotions don't age with a person. If an emotional trauma was stored at the age of eight, when you write, the emotion the eight year-old felt will come up. People are often taken aback by a "childish" emotion they may experience unless they know to expect it.
- Emotional traumas are stored because at the time of the situation a person was overwhelmed. When writing it is helpful to imagine the situation as a movie with the emotional trauma as the climax. It is important to write past the point of being triggered in order for the nervous system to reset and for the body to release the charge. Stopping at the point of the emotional charge could re-traumatize a person.

Avoid "Icing on the Cake" Strategies

We have all heard that it is more healthy to be positive than negative. I would like to challenge that idea. It is true that being positive is associated with better outcomes, but that is true long-term only if the "positive" words are true. Saying the "right thing", but thinking something else is a form of suppression. It is like icing on a cake; many current books on health focus on the top layer (what a person says and how they project themselves), but true psychological health is achieved when the spoken word matches the conscious thought and matches a person's unconscious beliefs.[7] Using positive thoughts and words as a form of affirmation as you work on specific goals and behaviours can be very effective. However, when the positive words become a mask for deeper troubling waters underneath they can impede expression, be a form of suppression and can contribute to disease itself. It is contentment and stillness at the core that breeds health.

Dissipate Before You Distract

In polarity therapy the health of an emotion is linked to its "truth". Emotions are not positive or negative, they are either truthful or false. They either reflect what a person is truly feeling or they don't. For example, the expression of anger is much healthier than the false expression of acceptance with an underlying feeling of anger.[7] In our society it is more acceptable to be positive, loving, accepting of everything and everyone, but that is neither realistic nor truthful.

The goal is to feel the emotion that you have and find acceptable ways to dissipate those emotions that you don't want to feel or hold. Some use short bursts of activity, breathing exercises, journaling, while others prefer to yell or talk it out. It doesn't matter, as long as the emotion that is on the surface is truly felt and expressed. Once you have released the emotion then you can distract yourself. An important question to ask a patient is what they do when they are triggered or upset. What you are looking for is whether or not they know how to release unwanted emotions. Moving to distraction without dissipation is a form of suppression. The second phase is to make the necessary changes in your life so that you experience more of the emotions that you desire.

Conclusion

A person's state of mind is as integral to their health as their nutritional status or their ability to breathe. Giving the same level of credence to the psychological aspect of a person as you do their functional and structural aspects is the basis of treating whole person. Emotions can create a susceptibility to cancer that is fed by other carcinogenic factors and conversely, the cancer can feed an underlying susceptibility. Emotions may be the primary cause of disease or one of many; each individual is unique and for some people addressing psychological factors is their way to good health.

Naturopathic medicine is unique in that, at its core, it acknowledges the profound effect a person's psychological state can have on their health. This link has always been integral to naturopathic medicine and in the last few decades has been consistently proven through systems theory and disease network research. Naturopathic doctors who provide a safe space for patients to address their underlying thoughts and emotions, and assist patients in working through these issues, can have a tremendous impact on their patients' state of health and quality of life.

About the Author

Dr. Lloyd is the founder of Naturopathic Foundations Health Clinic, a multi-disciplinary clinic in Markham, Ontario that focuses on the naturopathic and energetic aspects of assessment and treatment. She is also founder and Editor in Chief of the website www.ndhealthfacts.org which is designed as a hub for naturopathic information. She is part-time professor at the Canadian College of Naturopathic Medicine and past-Chair of the Canadian Association of Naturopathic Doctors (CAND).

Dr. Lloyd is the Naturopathic Editor in Chief of the *Vital Link*, the journal of the CAND and sits on various other editorial boards. She has written many articles on health related topics for *Energy Currents*, *International Energy*, for the *Healthy Living* magazine and

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She has done various seminars both nationally and internationally that focus on the energetic of health and naturopathic medicine. Dr. Lloyd is a consultant on preventive medicine, causal factors of disease and on promoting health strategies.

She is the author of four books: *Building a Successful Naturopathic Practice*, *Messages From The Body – a Guide to the Energetics of Health*, *The Energetics of Health, a Naturopathic Assessment* and *The History of Naturopathic Medicine, a Canadian perspective*.

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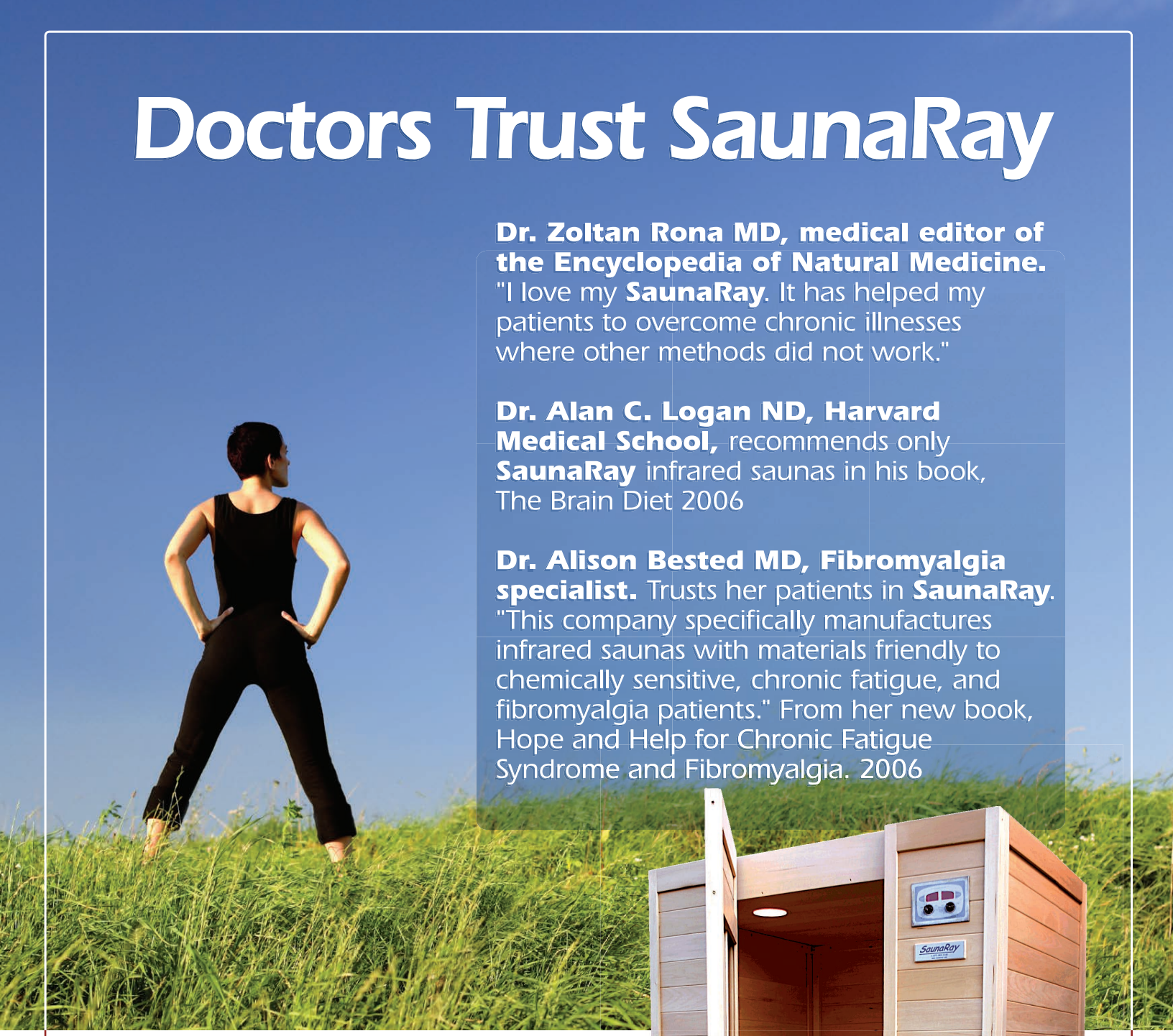

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Exposure of Toxins *in Utero* and Childhood Cancer Development

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Childhood cancer remains the second leading cause of death between the ages of 0 to 15 in Canada,[1] with a mortality rate of 25%. Approximately 10,000 children are living with cancer in Canada today[2] with the most prevalent cancers being leukemia (32%), tumours of the brain and nervous system (19%), the lymphatic system (11%), kidneys, bones and muscles (13%).[3]

Some causes of cancer can be attributed to genetic predisposition (20%),[6] however, the well-established link between environmental toxin exposure *in utero* and the development of childhood cancers cannot be ignored. Well-researched causes include the pharmaceutical diethylstilbesterol (DES), ionizing radiation, and chemotherapeutic agents.[6] Evidence increasingly indicates that parental exposures to certain toxic chemicals including pesticides, solvents, and certain industrial by-products [dioxins and polycyclic aromatic hydrocarbons (PAHs)], can result in childhood cancer development as well.[4, 5] With known toxins linked to the development of childhood cancers, we are able to conclude that a potentially large percentage of childhood cancers may be preventable.[6]

In this article we examine the relationship between toxic substance exposures *in utero* and certain childhood cancers. We review the evidence for certain chemical exposures for which there are increasing evidence of potential carcinogenicity in children. This paper identifies clinical management techniques a naturopathic doctor can employ focusing on prevention, proper assessment and screening, and effective detoxification.

Childhood Cancers linked to Toxins

The connections between *in utero* exposure to DES and ionizing radiation and the subsequent development of cancer are well established. Diethylstilbestrol is a synthetic form of estrogen that was prescribed to prevent miscarriage and premature labour between 1940 and 1971.[7] The use of DES started to decline after the 1950s because it was not found to be useful in preventing these pregnancy complications.[8] Diethylstilbestrol use essentially stopped after 1971 when studies identified a link between prenatal exposure to DES and adenocarcinoma of the vagina or cervix in young women.[7,9] DES has also demonstrated teratogenic activity causing limb malformations and structural changes in the genital tract. [9] Daughters of women exposed to DES have experienced premature birth, neonatal death, infertility, and ectopic pregnancy.[10] The genital tract abnormalities observed include hypoplasticity of the uterine tissue, short and narrow fallopian tubes, and absent fimbria. [9] These structural abnormalities may account for the fertility and pregnancy concerns that have been associated with DES. [10] Women with prenatal exposure to DES have also been found to have increased risk of breast cancer.[11] Exposure to DES *in utero* is connected to the development of adenocarcinoma of the vagina or cervix in young women, limb and genital tract malformations, fertility complications, as well as breast cancer.

Prenatal exposure to ionizing radiation is associated with the development of childhood cancer.[12] Ionizing radiation includes exposure to nuclear radiation as well as the use of x-rays and radiopharmaceuticals in various diagnostic and therapeutic procedures.[13] Animal models demonstrate an association between prenatal exposure to ionizing radiation and the development of lung, liver, and ovarian tumours in offspring.[12] An increased incidence of cancer was seen with exposure to a combination of toxins such as urethane, an acetone solvent and prenatal radiation exposure.[12] Human studies also demonstrate a similar connection between *in utero* exposure to ionizing radiation and the development of childhood cancer.[13] Epidemiological studies link exposure to ionizing radiation *in utero* with the development of leukemia[14] and lymphomas in childhood.[15] The exposure linking cancer can be as little as 1 or 2 RAD.[16] (A RAD is a unit of measurement that represents the absorbed radiation dose, and 1 to 2 RAD can occur with exposure of a diagnostic radiographic series).[16]

Pregnant workers also need to consider their occupational exposure. Occupational exposure to ionizing radiation occurs for individuals working in the production of nuclear power, naval offices on submarines, and radiologists.[12] The International Commission on Radiological Protection (ICRP) states that pregnant medical radiation workers may work as long as the fetal dose can be kept below 0.1 RAD or less of ionizing radiation.[17] The same dose is quoted for pregnant patients undergoing necessary x-ray exposure for diagnostic purposes, with greater doses being weighed considering a risk-benefit ratio.[17]

Exposure to a variety of toxins has been examined to determine the causal link between *in utero* exposure and childhood cancer. Causal links to childhood cancers exist between exposure to air pollution,

pesticides, industrial solvents, heavy metals, and cigarette smoke.[6] Air pollution consists of combustion by-products including petroleum, polycyclic aromatic hydrocarbons (PAHs), and dioxins,[6] all of which are known carcinogens.[18] PAHs are carcinogenic pollutants, resulting from incomplete combustion, that are found in tobacco smoke, air pollution, and charbroiled foods.[19] Prenatal exposure to air pollution is associated with an increased risk of developing numerous cancers such as lymphoma, retinoblastoma, and leukemia.[6] The odds of developing acute lymphoblastic leukemia (ALL) and retinoblastoma increase by 9%, 15%, and 23% with exposure to each 25 ppb increase in the concentrations of pollution.[20] While the odds of developing ALL increased over the course of an entire pregnancy, the risk of developing retinoblastoma is greater for exposure during the second and third trimester.[20]

Numerous childhood cancers, most commonly brain cancer, leukemia, and lymphoma, are associated with prenatal exposure to household pesticides.[18,21-23] Even a single use of professional exterminators during pregnancy is associated with an increased risk of childhood lymphoma and leukemia.[24] The carcinogenic pesticides most likely to be used for home extermination include chlordane, heptachlor, diazinon, and chlorpyrifos.[25] Prenatal exposure to flea collars, containing tetrachlorvinphos, carbaryl, and propoxur, are linked with the development of childhood leukemia, as well as brain cancer.[23,26] A single exposure to flea collars is linked with an increased risk of childhood leukemia and brain cancer.[26]

Whether a pesticide is carcinogenic depends on both the active and inert ingredients it contains. Some of the chemical families associated with the development of childhood cancer include organochlorines, organophosphates, pyrethroids, carbamates, and triazine. Chemicals from these families make up the active ingredients in pesticides. The active ingredients in pesticides are not the only chemicals that need to be examined when considering toxicity. For example, the inert ingredient xylene is used in almost 900 pesticides and has been associated with increased risk of brain tumors, rectal cancer, and leukemia.[13] A single pesticide can be composed of over 600 chemicals, including solvents and other fillers, complicating analysis.[13]

Parental exposure to solvents in the water, home, or workplace have been shown to be correlated with childhood development of cancer.[28] Solvents from manufacturing include substances such as trichloroethylene, carbon tetrachloride, benzene, and chlorinated solvents.[6] Environmental exposure of mothers to trichloroethylene during pregnancy is associated with the development of leukemia.[29,30] Trichloroethylene is an environmental contaminant that results from leakage from industrial settings.[13] It was previously used in the dry cleaning industry, and is currently used for metal degreasing and for the manufacture of adhesives, paint removers, varnishes, paints, lacquers, typewriter correction fluids, printing inks, and spot removers.[13]

Benzene is a known carcinogenic solvent.[6] Benzene is found in cigarette smoke, automobile exhaust, crude oil, and is used to make rubbers, dyes, detergents, and lubricants.[13] Prenatal exposure to benzene has been linked to childhood cancers such as leukemia.[6]

Exposure of pregnant mothers to carbon tetrachloride is associated with the development of neuroblastoma in their offspring.[31] A greater risk of cancer development is correlated to higher concentrations of carbon tetrachloride in the air.[31] Carbon tetrachloride has been banned in consumer products in developed countries, however, it is still used in the production of refrigeration fluid and propellants for aerosol cans, and as a pesticide.[13] Pregnant women should be aware of their exposure to these solvents.

Occupational exposure to pesticides and solvents has also been linked to the development of childhood cancer. Farmers have a high occupational exposure to pesticides. Greater cancer rates have been found in the children of farmers.[13] Maternal and paternal occupational exposure to pesticides are associated with a significantly increased risk of developing childhood acute myeloid leukemia (AML).[32,33] Exposure of both parents to solvents in preconception is associated with the development of brain tumours in offspring.[34,35] Higher leukemia rates have been associated with paternal occupational exposure to solvents as well, and in particular chlorinated solvents.[30]

For more information of the various types of environmental exposures, exposure sources, cancer type, and exposure timing, refer to Table 1.

Childhood Cancers linked to Heavy Metals

Childhood cancers have been linked to arsenic, cadmium and lead exposure *in utero*. Inorganic arsenic, for example, is a potent human carcinogen. Numerous animal studies and an epidemiological study indicated that exposure to arsenic in drinking water *in utero* was associated with increased childhood mortality due to malignant lung disease.[36] Both inorganic arsenic and its methylated metabolites cross the placental barrier, causing epigenetic effects, mainly via DNA hypomethylation, immune suppression, neurotoxicity, and interaction with enzymes critical for fetal development and programming.[36] DNA damage has been shown to occur at cumulative urinary concentrations of 4.4ug/L of arsenic, with household tap water levels at 0.36ug/L (less than the current drinking water standard of 10ug/L).[37]

Lead is tightly bound to red blood cells and is readily transferred from maternal circulation through the placenta to the fetus.[38] Placental transfer begins as early as the 12th week of gestation, and has been linked to childhood development of AML.[38,39] The level of concern for pregnant women would be a blood lead level of 10g/dL or more.[39]

Cadmium is an endocrine disrupting chemical that binds to the estrogen receptor (ER)-α and the androgen receptor (AR).[40] In animal studies, cadmium exposure has been shown to increase circulating testosterone levels, reduce the expression of androgen receptor in the mammary gland, and mimic the effect of estrogens on the mammary and uterine tissues. *In utero* exposure at a dose of 75ug/kg of feed results in pre-malignant hyperplastic alveolar nodules (HANs) in rats.[40] Multiple human studies have also concluded that cadmium is a human carcinogen, and that it readily crosses the

TABLE 1: Links between Toxic Chemical Exposures *in utero* and Childhood Cancers

**Please note that this refers to exposure during adulthood/in utero*

TOXIC EXPOSURE	SOURCE OF EXPOSURE	CANCER OR TUMOUR TYPE	TIMING OR DURATION
Ionizing Radiation	Environmental, Occupational and Medical Intervention Exposure to parents X-ray machines, CT scans, fallout of testing of nuclear weapons in atmosphere, industrial gamma rays, radioactive waste, consumer products, soil **Route of transmission:** Dermal, oral, act directly on fetus	Leukemia Lymphoma	Before and during pregnancy (not provided)
Diethylstilbestrol (DES) ***Estrogen pharmaceutical prescribed from the late 1940s to the early 1970s to prevent miscarriage***	Maternal Medical intervention. Prescription medication. **Route of transmission:** oral, trans -placental	Adenocarcinoma (vaginal and cervical)	During pregnancy
Pesticides ***(insecticides, fungisides, rodenticides, herbicides)***	Occupational and Environmental exposure to parents. Fruits and vegetables, drinking water, lawns, occupational, soil, agricultural, home, garden, pest strips **Route of transmission:** Dermal (skin or eyes), Oral, Inhalation	Leukemia Acute Lymphocytic Leukemia (ALL) Acute Non-Lymphocytic Leukemia (ANLL) Nervous System Tumour Brain Tumour Neuroblastoma Non-Hodgkin's Lymphoma (NHL) Wilms' Tumour	3 months before conception and during pregnancy During pregnancy During Pregnancy Near conception (exact time not provided) During pregnancy (not provided) (not provided) (not provided)
Solvent Mixtures ***ethylenes, benzene, alcohols, chlorine/ chlorides, methyl ethyl ketone (MEK), Turpentine***	Occupational and Environmental exposure to parents. Manufacturing, industrial discharge, paint, drinking water, adhesives, cigarette smoking **Route of transmission:** Inhalation, Dermal, Oral	Leukemia ALL ANLL Nervous System Tumour Neuroblastoma	Prior to and during pregnancy Before and during pregnancy During pregnancy Near conception (exact time not provided) (not provided)
Petrochemicals, Dioxins & Polycyclic Aromatic Hydrocarbons, Diesel/motor vehicle Exhaust (nitrogen dioxide), Petroleum	Occupational and Environmental Exposure to parents. Vehicle exhaust, gasoline, distillation of coal tar, heating petroleum, manufacturing / industrial, drinking water, soil, non-prescription dermatological products **Routes of transmission:** Oral, inhalation, dermal, crosses placental barrier	Leukemia ALL ANLL Neuroblastoma Hepatoblastoma Wilms' Tumour Urinary Tract Cancer	Before and during pregnancy Before and during pregnancy During pregnancy (not provided) (not provided) (not provided) (not provided)

Sources: Gouveia-Vigeant;[6] World Health Organization;[12] Giusti,[7] Meinert[21]

placental barrier.[41] The results of these studies study suggests that similar effects would occur in a human species and could lead to early mammary tumourigenesis (ATSDR).

Fetal Susceptibility and Etiology

The fetus is subjected to the environment their mother creates for them, with the placenta offering little protection from known toxins. Prenatal exposures to toxins, therefore, is a direct result of maternal exposures. In order to reduce cancer risk for their children, mothers need to be cognizant of their toxin exposure. Mothers can become exposed to various toxins through ingestion, inhalation, and skin absorption. Fetal exposure occurs through mobilization of toxins in the mother's blood through the placenta and into fetal circulation.[42] Over 200 chemicals and toxins have been isolated from the umbilical cord blood of newborns.[43] Some of the substances found include mercury, organochlorine pesticides such as DDT, dioxins, industrial toxic chemicals such as polychlorinated biphenyls (PCBs), and pollutants such as polyaromatic hydrocarbons.[43] Clinicians need to educate their perinatal patients to the fact that their fetus is subjected to virtually the same toxins that they are, emphasizing that there are hundreds of potential toxins that can cross the placenta.

Transportation of toxins across the placenta seems to occur readily as most toxic compounds are found to be at relatively the same concentrations in the maternal circulation as in the fetal circulation.[44]

Though the levels are comparable, some toxins are found in higher concentrations in the newborns than would be expected given the maternal serum.[45] The lower capacity of the fetal metabolism may lead to the accumulation of toxins that usually are found in minor concentrations in mothers.[45] DDT is an example of a toxin that accumulates more in newborns.[45] Pregnant mothers should be vigilant with their efforts to reduce toxin exposure because their fetus is more susceptible to the accumulation of certain toxins.

Prenatal toxin exposure should be avoided because fetuses are more vulnerable than their mothers to the effects of toxins due to their rapid growth and underdeveloped toxin defense. Depending on the window of exposure, a chemical may be affecting a pluripotent stem cell that can go on to affect major systems in the developing body. The fetus is also more vulnerable to toxins than their mother because their immature, porous blood brain barrier allows for increased exposure of sensitive neural tissue to chemicals. Fetuses have lower levels of chemical binding proteins and underdeveloped detoxification mechanisms.[46] As a result, a fetus lacks the same ability to detoxify in comparison to their mothers.[47] An underdeveloped detoxification system may account for why higher levels of certain compounds such as bisphenol A and DDT[45] are found in the fetus and amniotic fluid compared to the maternal serum.[48] Fetal immune systems are also undeveloped and they demonstrate reduced DNA repair capacity.[47] Reduced DNA repair can lead to the accumulation of undesirable DNA changes and can increase the likelihood of cancer development. The rapid growth, increased exposure, and reduced repair ability increase fetal susceptibility to the effects of carcinogens. Therefore, exposure to toxins and carcinogens *in utero* is more influential than exposure that occurs later in life.

Transplacental toxins cause cancer through immune system dysregulation, endocrine disruption, decreasing placental function, and causing DNA changes. Several pesticides such as DDT, pyrethroids, and chlorinated pesticides can dysregulate the immune system.[49] The function of the placenta can also be affected by chemical exposure. Substances such as cadmium can accumulate in the placenta and interfere with micronutrient transfer.[46, 42] In particular, zinc transfer to the fetus is impaired.[50] Zinc is important for DNA repair, and may be important to protect against the initiation and progression of cancer.[51] Reduced nutrient levels further weakens the fetus, increasing susceptibility to carcinogens. Direct damage to DNA can be caused by several toxins. Prenatal tobacco smoke, PAH exposure, and pesticides such as propuxur can cause chromosomal aberrations such as DNA mutations.[49] Exposure to air pollution, in particular PAHs, is found to alter DNA function and expression by altering DNA methylation.[18] This disrupted expression can lead to the development of cancer.[18]

Endocrine disruptors also have the ability to alter the DNA methylation patterns of key genes that produce changes to how the DNA is copied.[52] Endocrine disruptors are chemicals that affect the

function of the endocrine system by mimicking or blocking the actions of hormones, altering signalling or disrupting production.[52] Pesticides, cadmium, and DES are some example of endocrine disruptors. There are varied mechanisms by which toxins cause cancer, with some of the mechanism considered additive such as a disrupted placental barrier, reduce micronutrient transfer, and impaired immune system.

Epigenetics and Transgenerational Inheritance

The inheritance of environmentally induced phenotype changes is referred to as transgenerational inheritance.[52] Exposure to toxins *in utero* has been associated with the inheritance of breast and prostate cancers. Changes to non-coding DNA are likely to account for these types of cancers.[53] For example, known toxins such as dioxins have been shown to alter DNA methylation.[52] The concept of transgenerational cancers is significant because it demonstrates how toxin exposure during the preconception period can potentially cause cancer in the offspring. Additionally, cases of cancer inheritance have been seen in grandchildren of the exposed individual.[52] Therefore, carcinogens have the potential to have multigenerational effects.

Environmental exposure to toxins such as endocrine disruptors can also induce epigenetic changes. Several animal studies demonstrate that exposure to certain chemicals can cause cancer in the trial animals by altering DNA methylation and modifying histones.[54] It has been suggested that the disruption of the stem cells can lead to cancer.[39,48] Exposure to air pollution, in particular PAHs, is found to alter DNA methylation.[18] Both hypermethylation and hypomethylation are associated with the development of cancer.[18] Epigenetic changes demonstrate the importance of avoiding chemicals that cause these alterations because multiple generations can potentially be affected. The epigenetic progenitor model of cancer also explains the late onset of adult cancer. Toxins *in utero* are connected with childhood cancer, but potentially could also be contributing to the development of cancer in adulthood. Epigenetic changes are important because it helps to explain the mechanism by which toxins are carcinogenic and how multiple generations can be affected.

Proactive Preconception Care

With the growing environmental links to childhood cancer, naturopathic doctors have a unique opportunity to provide the proactive preconception care that is critical in preventing or reducing environmental toxin exposure. Preconception care should include a screening tool to assess risk (such as a screening questionnaire), toxin testing where indicated, exposure reduction and implementation of a detoxification protocol that targets specific organs and toxins according to risk.

Maternal and paternal environmental toxin exposure can be assessed through a screening questionnaire (Table 2).[56] Most screening questionnaires assess exposure through three main areas: home, occupation, and lifestyle. Environmental toxin exposures common in the home include household insecticides, garden herbicides and pesticides, as well as paint and lead pipes in older homes. Occupational exposure to solvents and petrochemicals are important contributors to total body burden. These exposures are common in manufacturing, construction and the oil/gas industry. Solvents are also present in detergents and cleaners, such as those used in dry cleaning. Screening questionnaires commonly include lifestyle exposures such as consumption of non-organic produce, contaminated water, pollution, and cigarette smoke.

TABLE 2: Prenatal Environmental Screening Questionnaire for Clinical Assessment

ASSESSMENT	YES	NO
Have you or anyone living in your house ever been treated for lead poisoning?		
Do you live in a house built before 1978?		
Are there any plans to remodel your home?		
Have you ever lived outside the United States?		
Does your family use imported pottery or ceramics for cooking, eating, or drinking?		
Have you used any home remedies such as azarcon, greta, pay-loo-ah?		
Have you ever eaten any of the following: Clay, Soil or Dirt, Pottery, Paint chips?		
Is there a mercury thermometer in your home?		
Do you eat any of the following types of fish: Shark, King Mackerel, Swordfish, Tilefish, Albacore Tuna ("white" tuna)?		
If so, do you eat more than one meal per week of the selected fish?		
Does your home have a:		
Smoke detector?		
Carbon monoxide detector?		
Does anyone who lives in your home smoke?		
Do any people who will be taking care of the baby smoke?		
Do you use pesticides (insecticides, herbicides, rodenticides) such as Raid, 'Weed & Feed' or OFF:		
Inside your home?		
Outside your home?		
On your pets?		
What do you do for work?		
Are you exposed to any of the following at work:		
Metals		
Solvents		
Chemicals		
Radiation		
Fumes		

Source: Consortium for Reproductive Health in Minority Communities[56]

Nutrient-Environmental Toxin Interactions

Deficiencies of certain nutrients can increase individual susceptibility to the negative effects of carcinogens and reduce the ability to eliminate them. Selenium and iodine deficiency, for example, can reduce the detoxification efficiency of environmental chemicals,[57] whereas deficiencies in folate and vitamin B12 can enhance the activity of various carcinogens.[58] Numerous nutrients are required for optimal functioning of liver detoxification pathways including riboflavin, niacin and pyroxidine.[59] If these nutrients are deficient, detoxification of carcinogens via the liver will be impaired. Low dietary intake of protein can increase absorption of heavy metals such as cadmium,[60] which is commonly found in cigarette smoke. Repletion of the essential mineral zinc when deficient can reduce the negative consequences of heavy metals such as cadmium.[61] Some nutrients, such as vitamin E, have demonstrated an ability to reduce oxidative stress from carcinogens.[62]

These few examples of nutrient-environmental toxin interactions are not exhaustive. It is prudent to assess the individual nutrient status of each patient through applicable laboratory investigations and clinical assessment, and replete where necessary. Special attention should be given to patients on low calorie, vegan or vegetarian diets as they are at particular risk for nutrient deficiencies.

Environmental Toxin Testing

The accuracy of testing for environmental toxin exposure has been debated. Urine and blood testing provides some indication of current or ongoing exposure, but are considered poor indicators of bioaccumulation or total body burden.[63] The use of chelating agents in heavy metal testing may provide more insight into total body burden as metals are mobilized from tissue stores. It is worth adding that the number of environmental toxins and chemicals far exceed the scope of available testing. Interpretation of test results should be done on an individual basis by the attending physician, with consideration of the clinical context and exposure history. Testing may be particularly useful for patients who have complex or unknown exposure histories.

Comprehensive toxicant panel testing are available through many integrative laboratory companies. Chlorinated pesticides, volatile solvents, polychorlinated biphenyl (PCBs), volatile organic compounds (VOCs) as well as heavy metals are some of the available toxicant panels. Testing tap water for contamination is available through local public health offices or through private companies, but is limited to heavy metal contaminants.

Reducing Risk

Once a practitioner has identified risk and avenues of exposure, it is imperative to guide a patient to avoid ongoing exposure. Avoidance becomes the single most important preventative measure for long-term reduction of total body burden of toxins and exposure in children. Refer to Table 3 for alternative suggestions to reduce exposure.

TABLE 3: Reducing Risk of Toxin Exposure

AVOID	ALTERNATE SOLUTION
Conventional fruits and vegetables	Buy organic and local produce when possible. Avoid the Dirty Dozen. Shop for the Clean 15. (See www.ewg.org)
Pesticides	If you must use: Wear protective clothing when handling/ near pesticides and wash hands after handling. Store in closed, labeled bottles. Do not spray if wind is strong, or temperature is above 30 degrees Celsius. (See http://www.agf.gov.bc.ca/pesticides/b_2.htm). Practice Integrated Pest Management Read labels: Caution indicates low level of harm and Danger indicates high level of harm. For more information go to the National Pesticide Information website, http://npic.orst.edu/
Plastics: numbered 3 or 7, plastic lined canned foods	Stainless Steel, Glassware, Plastics other than number 3 or 7. Never heat plastic.
Reduce consumption of meat, fish, dairy products	Eat a balanced diet containing abundant amounts of fruits, vegetables, legumes and grains. Consume low-moderate amounts of meat and dairy products.
Conventional personal care products containing the word "phthalate" including soaps, shampoo, lotions, perfumes, hair spray and nail polish	Vegetable-based glycerine soaps, castile soap, natural-based products
Cigarette Smoke	Find help to quit! Smoke and carbon monoxide detectors should be installed on all floors and near bedrooms. Avoid public places where smoking is allowed Make your home smoke-free
Pest-strips, and home and garden use of insecticides	Seal entryways, ensure your house is clean and dry, spray a dilution of neem oil extract; oranges diluted in water for house ants; lay traps. Plant marigold and feverfew around garden. (See www.beyondpesticides.org)
Engine exhaust	Wear a mask if walking or biking outside during heavy traffic times.
Tap water if you live in a home that was built before 1975	Drink water filtered through a reverse osmosis and alkalizing system.
Commercial Household Cleaners	Use a vinegar and water solution (1:3 ratio), Castile Soap
Lead-containing home remedies, paints and toys. Avoid eating/ drinking from pottery and painted pots, or bowls.	Get home tested for lead if home was built before 1978. Hire a contractor if renovations need to be done to an older home. Purchase lead-free products and use lead-free eating and drinking utensils. Eat foods enriched with iron (lean red meats, chicken), calcium (dairy products and green leafy vegetables), and vitamin C (oranges, grapefruits, tomatoes, and green peppers)
Eating large amount of salt-water fish, including shellfish, and larger sized fish.	Eat fresh, cold-water fish, the smaller the better.
Avoid mercury thermometers.	Use digital or mercury-free thermometer.

Source: Consortium for Reproductive Health in Minority Communities[56]

Detoxification

Once environmental exposures have been eliminated or reduced, the practitioner can focus their efforts on guiding their patients through detoxification of the stored and accumulated toxins. Elimination strategies should be low risk and be mindful of the individual patient, their exposure history and environmental toxin test results.[63] Studies are lacking on the optimal timing of detoxification vis-à-vis the anticipated conception date. It is reasonable to minimize gamete exposure to the offending environmental toxins by implementing detoxification strategies well in advance of conception. The duration of sperm development is longer than that of the ovum and takes approximately ninety days. At a minimum, it is sensible to complete detoxification and implement avoidance measures more than ninety days prior to conception. Avoidance practices however are beneficial at any time and should be maintained on a long-term basis.

One main route of detoxification of carcinogens is through the activation of Phase I and Phase II enzymes present in liver. Phase I enzymes typically add a reactive group to the parent carcinogen, often creating a more toxic molecule. This more reactive intermediate molecule must pass through Phase II enzymes to be transformed into a water soluble compound that is readily excreted through the bile, feces and urine.[59] Supporting the function of Phase I and II enzymes, as well as the end elimination organs such as the kidneys and colon is an important way to support parental elimination of toxins in the preconception period.

Phase I enzymes require nutrient cofactors for optimal function which must be replenished from dietary or supplement sources. These nutrients include riboflavin, pyroxidine, niacin, folic acid and vitamin B12. Important Phase II reactions include sulfation, glucoronidation and glutathione conjugation.[59] Sulfation reactions require sulphur groups which can be commonly found in onions, *brassica* family vegetables, and eggs.[63] Cysteine-containing compounds, such as N-acetyl cysteine, enhance Phase II detoxification by supporting glutathione conjugation. [59]

A number of botanicals have been shown to increase the function of Phase I and Phase II enzymes. These include *silymarin,*[64] curcuminoids,[65] rosemarinic acid,[66] dandelion root,[67] nettle,[68] fenugreek[69] and hibiscus.[70] Other herbs and nutrients have demonstrated ability to upregulate carcinogen detoxifying activities of Phase II enzymes in the liver including aloe vera,[71] red beetroot[72] and clarified butter.[73] Incorporating any of these nutrients and botanicals into a preconception detoxification program may enhance deactivation and elimination of carcinogens.

Supporting end elimination organs such as kidney and colon is important to complete the elimination of metabolites of carcinogenic substances. Adequate hydration and dietary fibre intake are critical for the final excretion of carcinogens and other toxins through urine and stool.

The skin is the largest excretory organ in the human body and also becomes an important route of elimination for carcinogens. Sweat inducing therapies have been shown to reduce total body burden of many environmental chemicals and heavy metals.[74-76] Significant improvements in symptoms after solvent intoxication has been reported following sauna therapy.[77] While further research investigating the effects of sweating on the carcinogens mentioned in this article is lacking, it remains a practical component of a detoxification program. Dry, wet or infrared sauna and exercise as sweat inducing therapies have not shown significant differences in their toxin excretion rate when compared to eachother.[75]

Chelating medications may be required in patients who have heavy metal toxicity. Dimercaptosuccinic acid (DMSA) is one chelation agent that effectively binds to heavy metals that have links to childhood cancers including arsenic, lead and cadmium. Chelation is generally well tolerated[77] but judicious selection of chelation agent based on laboratory testing is important as agents have differing affinities. It is important to replete essential and non-toxic minerals that are also excreted during chelation to minimize adverse effects.

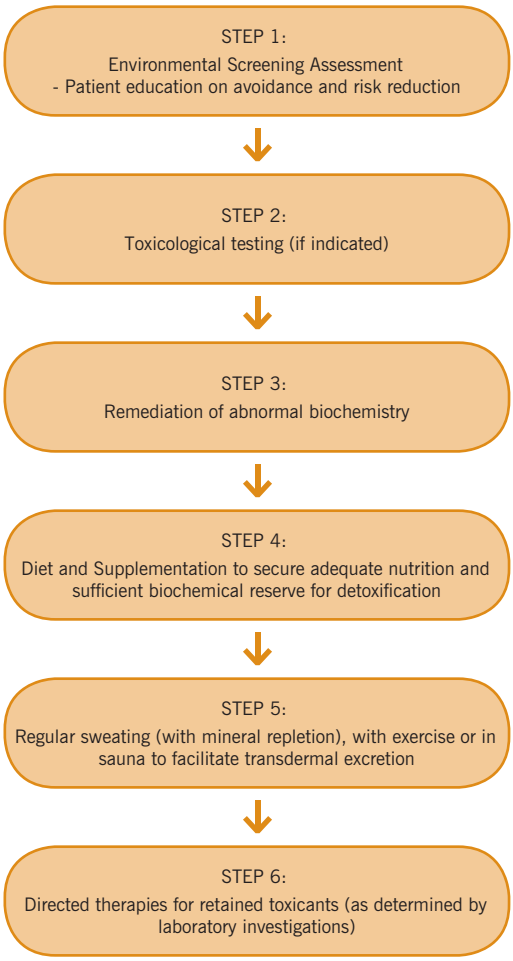
We have provided a summary chart and general, evidence-based detoxification protocol for NDs guiding patients through preconception detoxification (refer to Figure 1). Initial steps are to identify the suspected toxins through a risk assessment questionnaire and environmental toxin testing. Patient education around toxin avoidance is a critical step in ensuring long term prevention of toxin exposure to both parents and fetus. Detoxification protocols should involve repletion of nutrients found to be deficient on clinical assessment and lab testing, saunas or sweating therapies, and the judicious selection of therapeutic agents that target specific toxins and desired excretory pathways.

Conclusion

There is a plethora of evidence linking toxin exposure *in utero* to childhood cancers. Maternal toxin exposure should be limited during the prenatal period due to increased fetal susceptibility to the carcinogenic effects of these toxins. Many parents may seek naturopathic care in an effort to identify their risk, reduce exposure, and eliminate toxicities to minimize the risk of cancer development in their future offspring.

To ensure clinical competency, healthcare providers should remain up-to-date on current research linking toxins to childhood cancers and utilize best practices when it comes to reducing risk, appropriate testing, and effective elimination. With proactive preconception care, naturopathic doctors contribute to the generation of healthy families with a better quality of life, and the creation of healthy foundations for future generations.

FIGURE 1:
Six Step General Clinical Approach to Detoxification



*Examples for step 5 include: (1) glutathione and sulfur-containing foods, N-acetyl cysteine, or taurine to support glutathione synthesis, (2) folate and related nutrients for arsenic metabolism and excretion, (3) lipoic acid therapy for detoxification of mold, (4) adequate minerals such as calcium, iron and zinc to reduce absorption of heavy metals, (5) Chlorella to decrease absorption and enhance excretion of toxicants, (6) Fiber to reduce absorption and facilitate elimination

Source: Sears M, Genius S[63]

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Commonly Prescribed Medications and Their Associated Cancer Risks

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Introduction

Associations between various medications and cancer risk have been well documented. However, factors such as underlying indications, diagnostic screening, and lifestyle remain challenges that must be controlled for in further studies. It is likely that there are multiple confounding factors in the etiology of the development of cancer and these are crucial for any practitioner to take into account.

Clinical recommendations for the prevention of cancer must consider not only observational studies, but the results of long-term clinical trials and post-market surveillance as well.

Some of the conditions we encounter on a daily basis in practice, such as GERD, atopic dermatitis, diabetes, hypercholesterolemia, hypertension, or menopause are being treated through regular pharmaceutical intervention, potentially putting patients at increased risk of developing various types of cancer. This review outlines the potential for altered risk of various cancer types in association with regular use of proton-pump inhibitor, statin, sulfonylurea, hormone-replacement (therapy), calcium-channel blocker, and immunosuppressant medications.

Statins and Cancer Risk

HMG-CoA reductase inhibitors ('statins') are among the world's most commonly prescribed medications, often for decades of use.[1] Increasing evidence indicates that the effects of statin medications may extend beyond reducing plasma cholesterol levels, to include potential anti-inflammatory as well as chemo-preventive and therapeutic effects.[2] HMG-CoA reductase is the major rate-limiting step of the mevalonate pathway, which ultimately produces many products crucial to cell function, membrane integrity, cell signalling, protein synthesis, and cell cycle progression.[1] It may be possible that disrupting this pathway may affect the ability of cancer cells to function properly. Additionally, a reduction in the availability of cholesterol may limit cellular proliferation required for cancer growth, metastasis, and angiogenesis.[3]

A search for statins and cancer risk on PubMed reveals over 5000 journal articles, yet most are observational (case control or cohort) studies and lack rigorous design or long-term follow-up. Two recent and extensive reviews by Boudreau et al.[1] and Gazzerro et al.[2] explore the evidence by cancer type, and potential physiological and biochemical mechanisms at length, but highlight the lack of consistent findings among trials.

Breast Cancer

Preclinical studies have suggested that lipophilic statin medications may have anticancer properties for hormone-receptor negative breast cancer. One study found a slightly increased risk of breast cancer among pravastatin users of over five years,[4] however a large case control study of over 22,000 cases published in 2010 failed to demonstrate increased or decreased risk in statin users.[5] More recently, a 2014 review by Advani et al. confirmed that most observational trials to date are conflicting; however, more appropriate clinical trials are ongoing, specifically in patients who may be at increased risk, such as those with a positive family history of breast cancer.[6]

Prostate Cancer

Overall, there has been some early evidence of statins inhibiting prostate cancer growth in both preclinical and animal models, potentially through impaired glucose transport and uptake by tumor cells.[7] A recent meta-analysis of 27 observational (15 cohort and 12 case control) studies did find a reduction in the risk of both total and clinically advanced prostate cancers by about 7% and 20%, respectively, among statin users.[8] There appears to be consistent evidence that statin use is associated with reduced risk of advanced or aggressive prostate cancers,[1] however this may also be due to increased frequency of clinical follow-up compared to otherwise healthy, non-statin users. Overall, the effects of long-term statin use on overall prostate cancer risk, or potential therapeutic effects of statin use among prostate cancer patients, have yet to be elucidated.

Colorectal Cancer

A recent matched cohort study of 33,625 adults who were starting orlistat were matched with up to 5 non-statin controls. After a median follow-up period of 2.86 to 2.96 years, there was no evidence of increased risk.[9] An updated meta-analysis in 2014 combined results from 40 RCTs and observational studies, involving more than 8-million subjects, and found a statistically significant reduced risk (RR 0.92) for only the case control studies, with substantial overall heterogeneity.[10] Overall, there remains potential for numerous confounding variables such as competing risk (non-statin users

succumbing to cardiovascular events before cancer incidence can occur), socioeconomic status, aspirin and NSAID use, multivitamin use, and frequency of health screening.[11]

Conclusion

There are few strong or consistent associations regarding statin use and cancer risk. Differences in type of statin use and dosage may influence risk, depending on the cancer type.[1] While clinical trials related to statin use are plentiful, most do not measure cancer incidence as a primary outcome or do not follow-up beyond five to ten years.[11] Most potentially positive data to date stem from observational trials, which should not be used in making any immediate clinical recommendations for statins in the primary prevention of cancer.

Proton-Pump Inhibitors (PPI) and Gastric Cancer Risk

Proton pump inhibitors (PPIs) are a widespread treatment indicated for several acid-related conditions including gastroesophageal reflux disease (GERD) and the healing of peptic ulcers.[12] However, it is of concern that certain mechanisms underlying the action of PPIs have a theoretical basis in gastric cancer pathology.[12-17]

PPIs such as omeprazole irreversibly inhibit hydrogen ATPase in gastric parietal cells, reducing acid secretion.[12] Decreased gastric acidity may result in the production of nitrosamine and the associated risk of adenocarcinoma.[13] Gastric suppression may also lead to hypergastrinemia, which may have trophic effects on the stomach mucosa such as hyperplasia of enterochromaffin-like (ECL) cells.[14]

Current evidence indicates that PPI inhibition of lysosomal enzyme activities may compromise immune function, leading to tumorigenesis.[15] Investigations of these theoretical associations have been performed in animal models, e.g. in Mongolian gerbils, long-time PPI dosing can worsen atrophic gastritis in those infected with *H. pylori* and promote adenocarcinoma development.[16,17] The association, however, between gastric cancer risk and PPI use in humans is unclear.

In a multicenter study of 554 patients taking 5 years of the PPI esomeprazole, of those patients receiving PPI therapy, there was a significant increase of ECL hyperplasia, however neoplastic ECL growth was not observed ($P < 0.001$). It is important to note that *H. pylori* negative patients taking esomeprazole did not demonstrate significant changes in morphology of gastric mucosa, and mucosal inflammation was reduced in the antrum of 29 *H. pylori* positive patients ($P < 0.001$).[18]

Excess risk of gastric cancer has been associated with an increasing number of PPI prescriptions [(IRR=2.1, 95%CI:1.0-4.7) >=15 prescriptions] and lengthy follow-up [(IRR=2.3, 95%CI:1.2-4.3) >=5 years of follow-up] when compared with the non-use of acid-suppressing drugs. However, in this prospective population-based cohort study among 15,065 Danish PPI users, specifics regarding dosages and length of PPI use were not given, and it is possible that results were due to confounding by indication, (i.e., *H. pylori* infection).[19]

A recent meta-analysis of 11 observational studies indicated with statistical significance that acid-suppressive drugs may act as a stimulator for gastric cancer (OR=1.42, 95%CI:1.29-1.56).[13] Three of these investigations dealt specifically with PPIs, and while the overall risk of gastric cancer increased when adjusting for PPI users, statistical significance disappeared. (OR=1.39, 95%CI:1.19-1.64). The effect of underlying conditions such as *H. pylori* infection was not taken into account. It has been recently postulated that in gerbil models PPIs alone don't cause cancer, but promote the incidence of cancer caused by *H. pylori*.[5,16] Acid suppression can alter the pattern of *H. pylori* colonization in the stomach.[14] Indeed, current European guidelines recommend *H. pylori* eradication in patients requiring long-term PPI therapy, while Canadian and American guidelines do not.[12,20,21]

Use of PPIs has been associated with an increased incidence of gastric cancer, however current evidence on the topic does not establish a clear link. It is possible that current associations between PPI use and gastric cancer are a result of confounding by indication, i.e., an inability to separate the effect of PPIs on gastric cancer risk from the effect of an underlying condition. Future multi-center trials that control for indications, use gastric cancer as an end-point and focus on long-term PPI users are necessary, before implications for clinical practice can be established.

Anti-Diabetic Medication, Sulfonylurea and Pancreatic Cancer Risk

Pancreatic cancer is the fourth leading cause of cancer in the United States with a five year survival rate of about 5%.[22] The poor prognosis of pancreatic cancer merits the importance of identifying high risk patients and minimizing the burden of potential causes.[22] Smoking, alcohol consumption, obesity and family history of cancer are all risk factors associated with increased pancreatic cancer risk.[23] Research suggests that non-insulin-dependent diabetes mellitus (NIDDM) and hyperinsulinemia may have an increased risk of developing malignancies such as gastric, hepatocellular, pancreatic, endometrial and colorectal cancers.[24,25] It is estimated by the International Diabetes Federation that 8.3% of the world's population has diabetes, with a prevalence of 10.5% in North America.[25] NIDDM is associated with increased mortality risk from solid tumors including colon cancer, breast cancer and pancreatic cancer.[26] While the association between NIDDM and pancreatic cancer is complex, it is important to explore if there is an influence of glucose lowering medications on increased pancreatic cancer risk.[22,26,27] A case control study performed at MD Anderson Cancer Center found that those with diabetes had a 2.37 fold increase risk of pancreatic cancer.[23] The importance of identifying safe therapies for diabetes is crucial to negate complications. Furthermore with the rise in cancer mortality, it is of growing interest and concern to identify whether anti-diabetic therapeutic agents influence tumor progression.[26,28]

Anti-diabetic therapies include drugs that increase circulating insulin levels such as sulfonylureas and exogenous insulin, as well as drugs that act through the mechanism of reducing insulin resistance, such as metformin and glitazones.[29,30] In Canada, patients with NIDDM mostly manage hyperglycemia with metformin monotherapy and sulfonylureas (SU) use is the most common additional therapy.[28] It is postulated that SU promote insulin secretion which can stimulate cell proliferation and possibly have carcinogenic effects.[22,23,25,26,30] It has been hypothesized that tumors have an altered expression and function of insulin IGF-1 receptors and therefore a possible mechanism of increased cancer risk may be due to insulin's trophic action on these IGF-1 receptors.[26,31] Insulin can act directly on cancer cells via insulin receptor-A, a subtype of the insulin receptor which is a mitogenic receptor.[25] Insulin levels may also directly promote growth and resistance to apoptosis of cancer cells *in vitro*.[26] Currie et al. found that in a retrospective cohort study of 62,809 subjects, SU monotherapy noted an increased risk of colorectal cancer by 70-80% while increased risk of progression to pancreatic cancer was 400%.[26]

A population based cohort study by Bowker et al[30] looked at 10,309 subjects and found that NIDDM patients on SU or exogenous insulin had a statistically significantly increased risk of cancer-related mortality compared to patients who received metformin therapy. A retrospective cohort study of 62,809 subjects found that of the 12% of subjects on SU monotherapy, the adjusted hazard ratio of a solid tumor was 1.36.[26] A meta-analysis by Thakkar et al.[24] explored metformin and SU use on cancer risk. Data revealed that among 18 sulfonylurea studies, there was an increase in all-cancer risk, however randomized controlled trials and case-control studies did not show statistically significant results. Large clinical trials need to be explored to determine true association.

Another study found a non-significant increased risk of pancreatic cancer among patients taking insulin secretagogues such as SU.[23] Comparing an analysis among medication users compared to non-medication users, it was found that individuals using insulin secretagogues had the highest risk of pancreatic cancer, with a 2.52 fold increased risk, compared to patients taking insulin and metformin.[23] In particular, short term use of equal to or less than 2 years of insulin secretagogue use was shown to be associated with increased risk of pancreatic cancer.[23] This observation however could be attributed by chance alone due to the small number of insulin secretagogue users in the study.[23] Therefore, more research with a greater sample size is needed to explore this association between pancreatic cancer and SU. It is also worthwhile to study and compare other anti-diabetic therapies to determine which pharmacological agents confer protective effects and which promote carcinogenesis.

Hormone-Replacement Therapy and Breast Cancer Risk

The link between hormone-replacement therapy (HRT) and breast cancer has been well documented, particularly receptor-positive carcinoma,[32-34] though the precise mechanism as to how exogenous estrogen, with or without progestogen, influences the development of cancer remains unclear. In theory, the influence of estrogen on the proliferation of cancerous cells is logical since more than two-thirds of breast tumours express high levels of posttranslationally modified estrogen receptors (ER).[35,36] There exists no evidence that estrogen actually initiates cancer *de novo*, but instead it is likely that HRT promotes the development of small, pre-existing tumours.[33,37-39] It has been suggested that the increased proliferation of cells due to estrogen stimulation results in an increased rate of replication errors,[40-42] as well as free radical damage;[40] amplification of a coactivator of ER;[42] repression of the expression of a corepressor;[42] and mutations in the ER itself, permitting activation at a lower estrogenic concentration.[42] Owing to epigenetic factors, breast cancer risk may be increased in daughters who were exposed to high levels of estrogen *in utero*.[43] Risk of breast carcinoma has also been suggested to be a result of the fact that HRT can increase breast density and therefore decreases the sensitivity and specificity of mammography,[33,36,44,45] augmenting the likelihood of an abnormal mammogram.[44,46]

The Women's Health Initiative (WHI) was a randomized, placebo-controlled trial terminated ahead of schedule in 2002 due to early results showing a significant increase in the risk of breast cancer in women taking estrogen plus progestin vs nonusers (0.60% vs 0.42%, annualized rate, respectively; HR = 1.55, 95%CI = 1.41 to 1.70, P<.001).[34,47] The association between HRT and increased risk of breast cancer has been confirmed in other studies as well, particularly for current users.[46,48,49] Risk of developing breast cancer due to HRT has not been reported to be dose-dependent,[50] nor does it appear to be dependent on route of intake or derivative.[37] Whether or not combination hormonal therapy or estrogen alone confers less of a risk has also been debated, though the addition of progestogen may add to risk of breast cancer as it increases mitotic activity in the breast throughout a normal luteal phase.[39] Various studies have conferred conflicting results in this regard.[33,37,51-54] In fact, physiologic concentrations of estradiol alone have been shown to induce apoptosis in breast cancer cells in culture and animal models deprived of estrogen. This apoptotic effect long-term estrogen deprivation may account for observed decrease in breast cancer risk with increasing time from menopause.[37,55-57]

Whether or not HRT use influences breast carcinoma histology (notably towards lobular carcinoma, which is harder to diagnose clinically than ductal), has not been definitively established, with several opposing reports.[58-61]

An increase in mortality resulting from breast cancer in HRT users vs nonusers has been suggested in some studies, though considering an increased frequency of breast cancer diagnosis in HRT users, a subsequent increase in deaths on a population basis is logical.[34,48] However, numerous reports conclude that HRT may confer a positive prognostic effect vs nonusers in terms of stage at diagnosis, differentiation, and size.[33,45,54,59,62-64]

There is debate surrounding the extent to which chronology of HRT use affects carcinogenesis.[45] Many studies have found that risk is highest at the onset of menopause, with emphasis on a

five-year postmenopausal window conferring highest risk.[34,48,61,65] Some have proposed that risk may diminish, even to baseline, with discontinued use.[50,52,54,61,66] On the contrary, certain studies have determined that ever use remains a significant factor increasing the risk of breast cancer,[61] with some suggesting that longer duration of ever use results in higher risk.[38,47,51,67] It has been postulated that elucidating the precise nature of the interaction between HRT and time of use could render it feasible to develop a protocol whereby relief can be conferred for the treatment of menopausal symptoms while minimizing breast cancer risk. Currently the North American Menopause Society Position Statement regarding hormone therapy does not recommend use of combined hormone therapy beyond 3 to 5 years.[68]

Calcium-Channel Blockers and Cancer Risk

Hypertension is one of the most common chronic conditions affecting North Americans, with greater than 65 million people affected in the United States alone.[69] As a drug class, antihypertensive medications are among the most frequently prescribed pharmaceuticals in the United States.[70] More than 678.2 million prescriptions for antihypertensives were filled in the United States just in 2010.[70] Each antihypertensive medication can be classified into one of four broad classes: ACE inhibitors, β-blockers, calcium channel blockers (CCBs), and diuretics.[71] Calcium channel blockers are the ninth most commonly prescribed drug class in the United States, with over 97.9 million prescriptions filled in 2010.[70,72] Considering that antihypertensive medications are often taken for the duration of an individual's life once prescribed, it is of increasing interest that the long term effects and possible associations with the use of these pharmaceutical drug classes are further researched and explored.[70]

Interest in a potential link between pharmaceutical use and a rising incidence of cancer led to a surge of research in the 1990s focused on this area. Concern and controversy with calcium channel blocker use was first raised in 1996 through a retrospective analysis gathered by Pahor et al., which linked the intervention to an increased incidence, risk, and susceptibility of cancer in the study population.[73] The study, reported that CCB use in an elderly cohort increased the risk of cancer by 72%.[72,73] While the authors acknowledged the methodological limitations of their study, including the limited number of cancer cases (N=61 total), these results raised significant concern for public health.[73,74] In response to the work done by Pahor et al., and to several other studies correlating CCB use and cancer incidence, the World Health Organization (WHO), in conjunction with the International Society of Hypertension, examined evidence available at the time,[73,75-77] concluding that available evidence does not provide adequate evidence of increased cancer risk.[77] More recent, larger studies have revived the hypothesis, however, that long-term CCB use is linked to an increased incidence of cancer, with breast cancer in particular, and may be considered a public health concern.[70,72] A 2013 study including 2763 women aged 55 to 74 found that long term use of CCBs over 10 years "was associated with higher risks of ductal breast cancer (OR, 2.4; 95%CI, 1.2-

4.9)(*P*=.01 for trend) and lobular breast cancer (OR, 2.6; 95%CI, 1.3-5.3)(*P*=.01 for trend)."[70] In notable contrast to these results, no increased risk of breast cancer was discovered with the use of the remaining three antihypertensive classes, the ACE inhibitors, β-blockers, and diuretics.[70]

The mechanism behind the biologic hypothesis connecting CCB use and increased carcinogenicity has been deduced because the blockage of calcium channels can impede apoptosis, thereby enabling the replication of damaged cells with malignant potential.[71,78] However, other research indicates that the mechanism of CCBs on apoptosis is highly complex and multifaceted, as both increases and decreases of intracellular calcium have been associated with increased apoptosis.[74]

To date, many studies have shown a positive association between calcium channel blocker use and increased cancer risk.[70,71,73,75,76] However, due to small sample sizes and other methodological limitations, only a handful of these studies can be considered in influencing clinical recommendations.[70,71] Further research needs to be conducted to clearly delineate the correlation between CCB use and cancer incidence. Long term use over 10 years, as well as variations in CCB type such as immediate vs sustained release need to be further assessed.[70,71] The use of CCBs as a potential modifiable risk factor for cancer has implications in the field of public health, with clinical and epidemiological ramifications with widespread long-term use of CCBs.

Immunosuppressants and Cancer Risk

Generally considered the most common chronic inflammatory skin disease in the industrialized world, atopic dermatitis (also known as eczema), with its pruritic and relapsing nature has an estimated lifetime prevalence of 2-10% and 15-30% in adult and pediatric populations respectively.[79] Allergic rhinitis and/or asthma have been reported in up to 73% of children with atopic dermatitis (AD)[80], and AD itself has also been associated with malignancies, such as cutaneous T-cell lymphoma.[81]

The mainstay treatment for atopic dermatitis prior to the year 2000 involved topical corticosteroids. While they act as anti-inflammatories and help reduce *S. aureus* colonization,[79] they are also known to carry the risk of local adverse effects, such as skin atrophy, striae, and acne rosacea, and systemic complications from long-term use, such as adrenal suppression and growth retardation.[82] Corticosteroid application to genital, facial, and intertriginous structures, has increased potential for adverse events, such as contact sensitization, skin atrophy, and glaucoma formation due to increased absorption rates up to 300-fold, and is to be avoided.[83]

The two topical calcineurin inhibitors (TCI) used to treat AD include Pimecrolimus 1% cream (*Elidel*, launched 2001) and Tacrolimus 0.1% or 0.3% ointment (*Protopic*, launched 2000) were the first and only topical medications approved for chronic treatment of AD in pediatric patients over age 2.[84] These medications help to prevent activation of the immune and inflammatory responses by binding to macrophilin-12 (FKBP-12) and inhibiting the calcium-dependent phosphatase, calcineurin. As a result, T-cell activation is inhibited by blocking the transcription of cytokines IL-2 and interferon gamma (TH-1 type) and cytokine synthesis of IL-4 and IL-10 (TH2-type) in human T cells. The release of inflammatory cytokines and mast cells mediators is also prevented after IgE stimulation.[85] As the production of pro-inflammatory cytokines by mast cells, B cells, CD4 TH-1 and CD4 TH-2 cells are linked to tumor-promoting inflammation, the inhibition of these immune responses combined with the synthesis of tumour-suppressive cytokine IL-10 result in a cancer-risk reduction benefit to the TCI-medicated patient.[86]

Widespread off-label use of TCIs quickly became first-line therapy in children under two years of age diagnosed with AD. Postmarketing reports of malignancies and a nonhuman primate study demonstrating an occurrence of lymphoma in monkeys exposed to thirty times the maximum recommended human dose,[81] resulted in a reconsideration of the risk/benefit profile of these agents by the FDA in 2005, with identification of a causal link between internal use of these agents and the development of both types of lymphoma and skin cancers.[87] The FDA's black box warning states a lack of established causal relationship but emphasizes use of these products as second-line therapy.[85] It is suggested that current data no longer seem to support the use of a black box label on these TCIs for numerous reasons, of note the rate of lymphoma formation from TCI use reported to date is lower than that predicted in the general population.[84]

Lymphoma

A nested case-controlled study within the PharMetrics database evaluated the association between topical immunosuppressants and lymphoma in an AD patient cohort.[88] Four random controls, matched by length of follow-up, were allocated per case. On review, 294 cases of lymphoma occurred within 293,253 patients of all ages, with 81 patients under age 20. Lymphoma type could not be specifically determined in 66% of the cases; however, no association was found between TCI use and lymphoma of any type (adjusted odds ratio [95%CI]; 0.82 [0.42-1.61] and 0.79 [0.37-1.71]), respectively. In adjusted analysis, severity of atopic dermatitis was the main factor associated with increased lymphoma risk.[88]

A retrospective cohort observational study of 953,064 subjects diagnosed with AD or eczema between 2001-2004 analyzed data using the Cox proportional hazards model, assessing for onset of cancer diagnosis.[89] A significantly increased risk for T-cell lymphoma was initially found among subjects exposed to tacrolimus. However, a subsequent chart review found record of early T-cell lymphoma lesions prior to TCI exposure in 4 cases, which, once excluded, resulted in the age and sex hazard ratio for T-cell lymphoma to be 5.44 (95%CI 2.51 to 11.79; p > 0.001) for tacrolimus and 2.32 (95%CI 0.89 to 6.07; p = 0.086) for pimecrolimus. While the use of topical tacrolimus may be associated with an increased risk of T-cell lymphoma, no statistically significant increased risk was found for the other cancer subgroups, including melanoma.[89] Cutaneous T-cell lymphoma also has the potential of being misdiagnosed as atopic dermatitis, with its insidious onset and chronic nature,

thus complicating the proper assessment of TCI use and resultant lymphoma risk.[84]

A case-controlled study of 3,500,194 individuals under the age of 80 using the UK-based database The Health Improvement Network, was completed to assess the risk of lymphoma associated with AD, with the use of topical corticosteroid or topical calcineurin inhibitor use.[90] Patients with established risk factors for lymphoma were excluded from the study, and no cases of lymphoma were found in TCI users. It was deemed that the number of TCI-exposed patients was insufficient to identify any possible association between lymphoma and TCI drug use. Topical corticosteroid (TCS) use was associated with an increased lymphoma risk (OR, 1.46; 95%CI, 1.33-1.61), with risk relevant to TCS potency strength.[90]

Skin Cancer

A nested case-controlled study[91] employed the use of mailed questionnaires to adults over age 30 with dermatitis to investigate the association between TCI exposure and nonmelanoma skin cancer (NMSC). Receiving 3,535 responses of which 25.7% reported exposure to TCI (14.4% for the cases, 30.7% for the controls), odds ratios were calculated to quantify presence of NMSC with presence of TCI exposure within the group. The unadjusted odds ratio was 0.38 (0.31-0.47) and the adjusted [age, gender, previous nonmelanoma skin cancer (NMSC), atopic dermatitis history] was 0.54 (0.41-0.69). Based on the odds ratio of association, the study found decreased incidence of NMSC with increased TCI exposure, therefore TCI use was not found to be associated with an increased risk of NMSC in adults.[91]

A review conducted by Tennis et al.[92] used deductive meta-analysis to ascertain if either AD or TCI use led to the development of malignancies (cutaneous T-cell lymphoma, basal cell carcinoma, squamous cell carcinoma, melanoma and noncutaneous lymphomas). Upon review of relevant and available literature, including 268 abstracts and 27 papers, they found the relative risk of all lymphoma associated with general AD/eczema ranged from 0.7-1.8, while the relative risk ranged from 2.0-3.7 in those with severe AD/eczema.[92] It is therefore hypothesized that the risk of lymphoma may be associated with the AD disease process. No evidence was found to support an association between melanoma or nonmelanoma skin cancer and TCI use.[92]

In line with The Canadian Society of Allergy and Clinical Immunology's current guidelines, it appears that the research supports the use of TCIs in common practice, for the treatment of AD unresponsive to high-potency corticosteroids or AD localized to the face, eyelids or skin folds, in patients greater than 2 years of age. Benefits and theoretical risks should be compared and considered when advising patients.[80] Further controlled studies on the use of topical calcineurin inhibitors in patients less than 2 years as well as epidemiological studies for a minimum of 4 years in duration are required for proper assessment of risks associated with specific populations and long-term use of TCIs.[81]

Conclusion

Naturopathic doctors can continue to provide exceptional care while maintaining a realistic perspective on current research as it becomes available. Studies with larger sample sizes and clear end-points will be helpful in the continued exploration of associations between medication use and cancer risk, as well as consistent follow-up studies in order to ascertain long-term effect. Clarifying risks vs benefits is vital in providing evidence-based recommendations, recognizing that certain medications have actually been shown to confer protective effects above and beyond potential carcinogenic risk.

As the ability to prescribe pharmaceutical drugs has come to the forefront of discussion regarding naturopathic scope of practice in Ontario, the importance of education on medication and associated health risks is paramount. As primary health care practitioners who vow to "do no harm" and focus on preventative medicine whenever possible, it is our responsibility to be well versed on commonly prescribed medications and any links to cancer risk. Reading and reflecting on relevant, current research allows us to help educate our patients, and in turn helps us better prepare for any potential changes to naturopathic scope of practice in the province.

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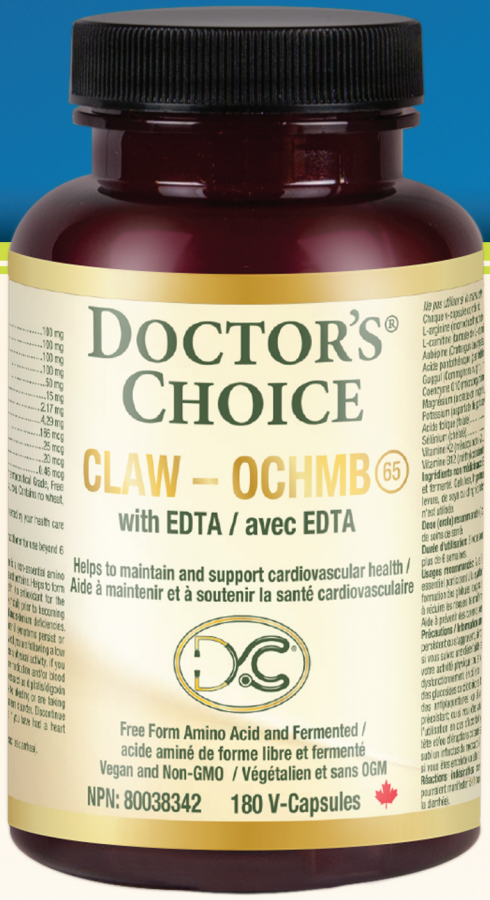

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