HormoneSynergy Clinic, LLC
Kathryn Retzler, ND
4640 SW Macadam Ave., Suite 290
Portland, OR 97239
503.230.7990
www.hormonesynergy.com

Hormones & Breast Cancer Risk

The statistics about breast cancer are sobering. Understanding your risk and how to minimize it are best based on facts and your individual risk. This handout will summarize the research regarding hormones and breast cancer and will provide recommendations you can implement to lower your risk.

Currently, breast cancer is the most frequently diagnosed cancer in women and the second leading cause of cancer deaths—lung cancer is the first. A woman's risk for developing breast cancer increases with age. Women have approximately a 12% chance of developing breast cancer if they live to be 90 years old; this also means the risk of not getting breast cancer is approximately 88%. Incidence of breast cancer has decreased since 2000 and death rates have decreased since 1989. A woman's chance of dying from breast cancer is approximately 3% (1 in 36). There are expected to be 255,180 new cases of invasive breast cancer diagnosed in the US in 2017 along with 63,410 cases of non-invasive (in situ) breast cancer. Breast cancer is expected to claim 40,610 lives in 2017.[1]

Cancer occurs when cells divide and grow without restraint. The growth and death of cells is usually regulated; however, when normal cell regulators malfunction and cells don't die at the proper rate they continue to divide and cancer can develop. Breast cancer usually grows slowly. By the time a tumor is large enough to be felt as a lump, it may have been growing for 10 years and the spread of tumor cells (metastasis) may have already occurred. Therefore, screening methods such as mammography, ultrasound, or MRI may be useful tools in providing early detection. A blood test from ONCOblot that detects ENOX2, a protein found on all cancer cells, can detect breast cancer even at stage 0 (<2 million copies, compared to ≥ 1 trillion cells for a positive mammogram). Unfortunately, ONCOblot or ENOX2 testing may pick up ductal carcinoma in situ (DCIS), thought to be a precancerous condition, or other early cancers that may not progress to invasive cancer.

Knowing the risk factors for breast cancer can help you identify your specific risk. Breast cancer risk factors can be categorized as "modifiable" and "non-modifiable." Although non-modifiable risk factors cannot be altered, modifiable risk factors can be changed based on daily choices regarding diet, exercise, lifestyle habits, and stress management. **Reducing modifiable risk factors can help you prevent breast cancer.** In fact, meta-analysis has shown that simply by improving diet, maintaining ideal body weight, and getting regular physical activity, **30% to 40% of all instances of cancer could be prevented**. Increasing vegetable and fruit intake alone could prevent 20% or more of all cases of cancer and could prevent approximately 200,000 cancer-related deaths annually.[2]

Non-modifiable risk factors for breast cancer include:

- Being female
- Advancing age
- Family history (mother, sister, or daughter doubles the risk; however, 85% of cases have no family history)

HormoneSynergy Clinic, LLC
Kathryn Retzler, ND
4640 SW Macadam Ave., Suite 290
Portland, OR 97239
503.230.7990
www.hormonesynergy.com

- Genetics: BRCA1 (55-65% lifetime risk) or BRCA2 (45% lifetime risk) according to the National Cancer Institute
- Early menarche (first menstrual period)
- Late menopause
- Diethylstilbestrol (DES) use by mother

Modifiable risk factors for breast cancer include:

- Poor diet: high animal and trans fats, low fiber intake, deficient intake of fruits and vegetables
- Obesity (BMI > 30) and high insulin[3-6]
- Antibiotics used for more than 500 days in a lifetime, or more than 25 prescriptions over 17 years[7]
- Lack of exercise
- Hormone therapy: synthetic progestins and possibly estrogen replacement depending on duration of use (estrogen may promote the growth of existing cancers, but it is unclear whether estrogen plays a role in cancer development); birth control pills (some studies show this, some don't)
- Breast trauma
- Late age pregnancy, never having been pregnant, lack of breast feeding
- High alcohol intake (>1 drink per day)
- Cigarette smoking
- Working the "graveyard" shift (research is conflicting)
- Environmental toxin exposure (radiation, xenoestrogens, second hand smoke)
- Radiation to chest or face before age 30[8]

Breast Cancer & Hormones

Currently every 50-year-old woman has about a 2.8% chance of developing breast cancer by age 60. This translates to an absolute risk of 2.8 breast cancer cases out of 100 women.

Most large, observational and intervention studies show the overall risk of developing breast cancer is higher with the use of hormone replacement therapy (synthetic estrogens and synthetic progestins). This means out of 100 women age 50 using synthetic hormone replacement (according to the Women's Health Initiative data), the number who will develop breast cancer by age 60 is 3.5. Therefore, for every 100 women who use synthetic estrogen and synthetic progestin (Prempro®) slightly less than one extra woman will develop breast cancer. That increase, from 2.8 to 3.5 per 100 women, represents a 25% increase in risk.

When evaluating information regarding hormone use and breast cancer risk, it's necessary to determine what hormone is being discussed—especially synthetic progestins versus bioidentical (human) progesterone and synthetic estrogen, usually conjugated equine estrogens—since the risk varies across these variables. In addition, risk varies based on the number of years of

hormone use. Not enough studies have been performed using individualized dosages of compounded hormones (based on lab testing, clinical assessment, and risk factors) since most studies use uniform modes of delivery and dosages of hormones for all women. However, one published small, short-term study of 189 women reported no increased risk of breast cancer, blood clots, or strokes with bioidentical hormones that were prescribed based on individualized dosages (determined via blood testing and symptom control).[9] Women in this study were monitored for one to three years, and most had significant improvements in menopausal symptoms.

The following summary is meant to give you succinct information based on available research regarding estrogens, progestins and progesterone, and testosterone regarding breast cancer risk.

Estrogen & Breast Cancer

Estrogens, especially estradiol and estrone, stimulate proliferation of both breast tissue and breast cancer cells. There is a clear association between lifetime estradiol exposure and breast cancer risk (the longer a woman is exposed to estradiol, the higher her risk for breast cancer).

It's understandable that there is much confusion about the use of estrogen replacement therapy (ERT) and breast cancer risk; this is true for the use of bioidentical estrogens as well as synthetic forms such as Premarin. To clarify the relationship between ERT and breast cancer risk, it's helpful to review the results of large, well-conducted studies—the Women's Health Initiative (a randomized, controlled trial), the Million Women Study (observational study performed in the UK), and the Nurses' Health Study (observational study)—as well as trends seen in smaller studies.

The Women's Health Initiative, which was a randomized, placebo-controlled trial, found a 26% increased risk of breast cancer in women using synthetic Premarin combined with synthetic Provera, called Premro, but not in women using Premarin alone.[10,11] Note that the average age of women in the WHI was 63.2 yrs. In addition, 50% of women were current or former smokers, the average BMI was 28 (overweight), & 33% had high blood pressure.

The Million Women Study found a 30% increased risk with ERT (bioidentical oral, transdermal, and estradiol pellet implants as well as synthetic ERT) and double that risk with estrogen plus synthetic progestins.[12] Lastly, the Nurses' Health Study also found a 23% increased risk only in women using long-term (more than 15 years) estrogen replacement and a 67% increased risk with estrogen plus synthetic progestins.[13]

A few studies (one with 261 women, one with 508 women) have shown no increased risk of breast cancer,[14,15] or risk of recurrence in women who'd been treated for breast cancer (123 women)[16] with estradiol pellets, especially if used in combination with testosterone.[17]

Several studies evaluating hormone replacement in breast cancer survivors have been favorable. One study of 277 breast cancer survivors who used estrogen replacement did not show increased recurrence rates after more than three years of treatment; in fact, the women who used estrogen replacement had a lower chance of dying from all causes.[18] In a longer, 5-

year trial, 77 breast cancer survivors who used estrogen replacement were compared to 222 breast cancer survivors not on ERT. The women who did not use ERT were more likely to experience a recurrence of breast cancer (13.5%) versus women who used ERT (3.6%).[19]
A meta-analysis of nine observational studies found no risk of recurrence in breast cancer survivors who used hormone replacement.[20] This analysis included 11 trials with 669 breast cancer patients. Four trials had control groups that showed no increase recurrence rate—in fact, women who used hormone therapy had a lower recurrence rate than women who didn't (8% vs 11%). Taken together in 11 studies (7 uncontrolled trials) on 669 breast cancer patients with HT there was no significant increase in the recurrence of breast cancer with a relative risk of 0.82 (meaning an 18% lower risk of recurrence in women using ERT).

Although the above studies and meta-analysis did not show increased recurrence of breast cancer with ERT, the HABITS trial (Hormonal Replacement Therapy after Breast Cancer—is it Safe?) was stopped early due to increased risk of breast cancer recurrence. This open randomized clinical trial included 434 breast cancer survivors aged 40-75 years. After a median follow-up of 2.1 years, 26 women in the HRT group and 7 in the non-HRT group had a new breast-cancer event (3 times as many women had a recurrence in the ERT group).

ERT that is used vaginally, especially estriol, does not increase the risk for breast cancer.[21–25] Vaginal estriol also does not increase the risk for recurrence in breast cancer survivors.[26] There is no accumulation of hormones or metabolites with vaginal estrogen or progesterone therapy.[27–29]

Although the media and some uninformed physicians portray estrogen as the smoking gun regarding hormones and breast cancer, it's important to remember that most breast cancer occurs in women over age 50. Younger women have the highest estrogen production but the lowest risk for breast cancer. This may be related to the fact that younger women are more likely to have higher testosterone production and to ovulate, producing higher levels of progesterone. Lack of adequate progesterone and testosterone, and accumulating DNA damage that can initiate cancer, increase with age. Many breast cancers are estrogen-receptor positive despite women having low estrogen production and anti-estrogen drugs are used to treat breast cancer. One explanation for this "estrogen paradox" is that breast fat cells produce their own estrogen; in fact, fluid from breast duct contains 10-50 times more estrogen than that of the blood. High estrogen levels associated with breast cancer may reflect increased production by the breast itself.

Synthetic Progestins, Bioidentical Progesterone, & Breast Cancer

The data is irrefutable that synthetic progestins (such as Provera®) significantly increase the risk of breast cancer. However, bioidentical progesterone, the same hormone made by the human body, is a different molecule than synthetic progestins and has a different effect on breast cancer risk.

Progesterone deficiency (in women who don't ovulate or who don't make enough progesterone) has been shown to increase the risk of breast cancer. In one study, progesterone deficient women had a 5.4 times increased risk of premenopausal breast cancer and a 10 times increased risk of death from all malignant cancers.[30] Another study evaluated hormone levels in

women under age 45 who developed premenopausal breast cancer. There was no association between serum SHBG (sex hormone binding globulin), estradiol, testosterone or androstenedione and premenopausal breast cancer risk. The only link was an inverse relationship between risk and luteal phase progesterone levels—women with the highest progesterone levels had the lowest risk.[31] The risk of developing breast cancer seems to be decreased in women with high luteal phase progesterone levels.[32,33]

In a French study that followed 80,000 women for an average of 8 years, estradiol use alone increased breast cancer risk 29%, estradiol plus bioidentical progesterone did not increase risk; however, estradiol plus synthetic progestins increased the risk by 69%.[34] Looking at another cohort of the French study of more than 54,000 women, the synthetic progestin (medroxyprogesterone acetate or Provera®) used with estradiol increased breast cancer risk by 40%; however, women who used bioidentical progesterone actually had a 10% decreased risk.[35]

It appears that breast cancer risk does not increase with the use of bioidentical progesterone (oral micronized progesterone, such as Prometrium,® topical progesterone cream, or intravaginal progesterone).[36–38]

Testosterone and Breast Cancer

The role of testosterone in breast cancer is often confusing due to the use of synthetic, methyltestosterone versus bioidentical testosterone in many studies. In animal and human studies, testosterone supplementation does not increase breast cancer risk.[39–41]

Testosterone inhibits the growth of breast cancer cells via the androgen receptor.[42–46] Testosterone works by preventing breast cells from dividing and multiplying, and by inducing apoptosis (programmed cell death).[47–51] Adrenal androgens (DHEA and androstenedione) and testosterone counteract the way estrogen stimulates the growth of breast cancer cells.[52–54]

Some studies have found that if a woman has androgen-receptor positive breast cancer, her prognosis is better than a woman who doesn't.[55,56] In women with breast cancer treated with anti-estrogens (such as Tamoxifen®), those given androgens have better outcomes.[57,58] Interestingly, synthetic progestins may increase the risk of breast cancer by blocking the androgen receptor and negating the protective effects of testosterone on breast tissue.[59]

An excellent paper reviewing data from preclinical, clinical, and epidemiological studies evaluated the body of research regarding testosterone and breast cancer risk.[60] The authors suggest that several lines of evidence argue against increased breast cancer risk with testosterone (T). They include (1) breast tumor cells treated with androgens do not increase growth. Androgens actually appear to be protective since they inhibit tumor cell growth. (2) Many epidemiological studies claiming an association between T and breast cancer did not adjust for estrogen levels. Studies adjusted for estrogen levels report no association between T and breast cancer. (3) Data from clinical studies where women with endocrine and sexual disorders received androgen supplementation do not show any increase in incidence of breast cancer. (4) Women with polycystic ovary disease, who exhibit high levels of androgens, do not

show increased risk of breast cancer compared with the general population. (5) Female to male transsexuals, who receive supraphysiological doses of T for long time periods prior to surgical procedures do not report increased risk of breast cancer. (6) Finally, women with hormone responsive primary breast cancer are treated with aromatase inhibitors which block conversion of androgens to estrogens, therefore elevating androgen levels. These women do not experience increased tumor growth. The conclusion of the paper was that the evidence available strongly suggests that T does not increase breast cancer risk in women.

Clinical studies have shown that testosterone given as a patch or pellet can prevent breast proliferation and decrease estrogen receptors.[61,62] In addition, women who receive testosterone pellets have been shown to have no increased risk of breast cancer even though they were taking estrogen and synthetic progestins.[63] Breast cancer risk may be lower in women using testosterone alone or combined testosterone/anastrazole pellets.[64]

Lowering your risk for breast cancer

Benjamin Franklin's famous words—*an ounce of prevention is worth a pound of cure*—are certainly applicable to all areas of health. The following recommendations can lower your risk ofbreast cancer (these steps may actually lower your risk for nearly all chronic diseases).

Check the boxes next to the recommendations you will follow:

- ☐ **Focus on what you know you need to eat**, rather than just trying to avoid unhealthy foods. Ask yourself if you've met your body's nutritional needs—minimum of 5-7 servings of vegetables and fruit, good quality protein, healthy fats, and whole (not refined) grains—every day.

- ☐ **Restrict eating to a maximum 12-hour window.** Fasting for at least 12 hours decreases inflammation and blood sugar, and has been shown to decrease breast cancer recurrence.[65] Ideally, stop eating after dinner until breakfast. Give your body at least 12 hours to focus on repairing itself rather than on digestion.

- ☐ **Eat a healthy, Mediterranean-type diet.** This type of diet has been shown to significantly lower breast cancer risk.[66] A Mediterranean diet consists mainly of vegetables, fruit, whole grains (e.g., brown or wild rice, quinoa), beans, seafood, nuts, yogurt, feta cheese, and olive oil. The standard American diet (appropriately called the "SAD" diet) consists mainly of meat, cheese, fried food, potatoes, pizza, and white flour products—avoid or significantly limit eating a SAD diet.

HormoneSynergy Clinic, LLC
Kathryn Retzler, ND
4640 SW Macadam Ave., Suite 290
Portland, OR 97239
503.230.7990
www.hormonesynergy.com

- **Keep blood sugar and insulin low and prevent diabetes.** A meta-analysis of nearly 16,000 cases of breast cancer in more than 575,000 women showed increased breast cancer in women who ate a higher glycemic index diet.[67] Meta-analysis has shown the diabetic women have a 20% increased risk for breast cancer and 25% increased risk of dying from breast cancer.[68] In cell cultures, breast cancer cells take up glucose when insulin is added; these cells no longer grow or divide when insulin is removed from the growth medium.

- **Eat more produce.** Fruits and vegetables (and nuts, seeds, and legumes) contain healthy fiber that may lower breast cancer risk. In fact, meta-analysis has shown a significant reduction in breast cancer risk in women who eat a diet high in soluble fiber.[69] Your fiber intake goal should be >25 grams per day.

Consider making a smoothie once a day. Include colorful, low-glycemic berries (blueberries, cranberries, blackberries, raspberries, pomegranate seeds, or strawberries), protein powder, unsweetened Greek yogurt (if you're not dairy intolerant), nuts, and green leafy vegetables (e.g., kale or spinach). You can add unsweetened coconut or almond milk. Avoid bananas, mangoes, pineapple, and rice milk—they increase blood sugar too much.

A simple way to boost your vegetable intake is to order a vegetable platter every week from a natural foods market or cut vegetables in advance. Store them in Debbie Meyer Green Bags® or other containers that preserve freshness. Bring hummus or other high-protein dip (consider edamame pureed with avocado, lime, Greek yogurt and cilantro) to work, or serve with dinner. Convenience is key—if vegetables are washed and cut in advance, you're more likely to eat them for lunch or snacks.

You can also make **salad in a jar.** This is a simple way to make sure you eat several servings of vegetables per day:

1. Gather several wide-mouthed jars, such as a Mason jars.
2. Put salad dressing on bottom. Consider using 50% olive oil, 50% balsamic vinegar or olive or coconut oil mixed with lemon juice or mustard.
3. Add harder vegetables (such as radishes, carrots, onions, celery, broccoli, cabbage, cauliflower), nuts, beans (black, pinto, edamame, chick peas), and cherry tomatoes or blueberries next. These are least likely to become soggy over time. Avoid high water content fruits and vegetables (such as red peppers, strawberries, cut tomatoes, and cucumbers).
4. Add cheese if you'd like (if you don't have issues with dairy and if you've decided to eat animal products).
5. Put greens on top. Consider romaine, arugula, kale, or spinach. Tear leaves rather than cutting them with a knife to prevent browning of edges.

6. Sprinkle ground or whole flaxseeds on top for omega 3 oils and fiber or other raw seeds (such as chia or sunflower) and sprouts on top.
7. Top with lid. When ready to serve, shake jar and empty contents onto plate.

- **Choose healthy protein sources.** Protein needs vary based on gender, weight, age, and activity level. Most adults need 0.8 to 1.0 g per 2.2 lbs of body weight.[70] This translates to approximately 50-65 g for a 140-lb woman and 65-80 g for a 175-lb woman. Good quality protein includes vegetarian options such as whey, non-GMO soy, beans, quinoa, and nuts. Animal products such as dairy, eggs, poultry, and lean meat may also good protein options. Wild-caught fish is an excellent healthy protein source. To minimize your exposure to toxins, it's best to eat free-range meat and wild caught fish and to avoid fish high in heavy metals such as tuna and swordfish.

- **If you're hungry when you wake up, start your day with a healthy breakfast (not Cheerios!).** Avoid all cereals including instant oatmeal—they're usually high in refined carbohydrates and added sugar and low in fiber and they dramatically increase blood glucose. In addition, granola is not a health food. Consider substituting unsweetened, high-protein yogurt (such as Greek yogurt) for milk or start your day with a protein smoothie (with kale and berries). Whey or pea protein are excellent protein powders to use. If you're not hungry in the morning, don't force yourself to eat breakfast. The old advice of eating every 2 to 3 hours to "increase" metabolism, may actually lead to weight gain and certainly trains people to eat by their watch, not internal hunger cues. Rather than eating by the clock it's most important to plan healthy food for when you do get hungry.

- **Increase your intake of berries and pomegranate seeds** either in smoothies, or as dessert. Berries are high in proanthrocyanadins and antioxidants, and can help strengthen the inner walls and endothelial lining of blood vessels and protect against cancer through multiple mechanisms.[71] Aim for eating at least one-half cup of berries every day.

- **Eat healthy fat.** The total amount of fat you eat may not be as important as the type of fat. "Healthy fats" include monounsaturated and polyunsaturated fatty acids.

Monounsaturated fats are found in olive oil and nuts such as walnuts, almonds, pecans, cashews, and hazelnuts. Good sources of polyunsaturated fats include flaxseed, chia seeds, grapeseed, and fish oils. These healthy fats may reduce the risk for breast cancer.[72]

"Unhealthy fats" include too much saturated fat and all trans fats. Saturated fat is necessary for health; however, your body can create it so it isn't an essential fat, and most people eat too much of it. Trans fats are made by heating liquid vegetable oils in the presence of hydrogen (hence the name, "hydrogenated oil"). Trans fats significantly increase breast cancer risk.[73] It's easy to avoid eating trans fats—stay away from commercially packaged baked goods, snack foods, and fast food. Don't eat

any food with "partially hydrogenated oil" on the label, avoid margarine and shortening, and don't eat fried food in restaurants.

- **Avoid advanced glycation end products (AGEs).** These compounds are formed inside and outside the body from carbohydrate attaching to protein. AGEs promote free radical activity (oxidative stress) and inflammation and accumulate in tissues and organs. Besides contributing to cardiovascular disease and diabetes, AGEs increase cancer risk.[74] In addition, AGEs literally cause aging. AGEs form during frying, roasting, and baking (especially any "browning" of food). To reduce AGEs, cook foods at low temperatures and with lots of water-based moisture by steaming, stewing, poaching, and braising. Stay away from fried foods.

  Foods that you should avoid due to very high AGE levels include bacon, fast food hamburgers and hot dogs, cheese, pizza, fried food (especially meat, chicken, and potatoes).[75]

- **Eat lots of herbs and spices.** Many spices have high a polyphenol content and potent antioxidant, anti-inflammatory, and immune system modulating activity. One study using a high-antioxidant spice blend (including black pepper, cinnamon, cloves, garlic powder, ginger, oregano, paprika, rosemary, and turmeric) significantly decreased postprandial (after meal) insulin and triglyceride levels.[76] Adding these spices, and a daily dose of Cassia cinnamon (1-2 teaspoons or 1-6 grams) can lower blood sugar, LDL cholesterol, and triglyceride levels.[77,78]

- **Enjoy dark chocolate.** Eating dark chocolate high in flavonoids (at least 70%) may benefit breast cancer risk. One constituent of cocoa has been shown to arrest breast cancer cell cycles in vitro.[79] Dark chocolate has a high antioxidant content (1 oz. has an ORAC value of 4,000-5,900—more than berries, green tea, and red wine). Dark chocolate also enhances insulin sensitivity, lowers LDL and raises HDL, and improves blood flow to the heart and brain.[80-83]

- **Drink green tea.** Green tea is one of the healthiest beverages you can drink. Green tea and green tea extracts have been shown to reduce insulin and glucose, improve high blood pressure, decrease inflammation (hsCRP & TNF-α), and reduce oxidative stress.[84-87] Green tea contains EGCG (epigallocatechin gallate) which helps block vascular endothelial growth factor (VEGF), preventing formation of blood vessels that feed tumors. Green tea has also been shown to inhibit the growth of cancerous tumors and increase their death.[88,89] Suggested dosage is 300-1500 mg of green tea capsules per day. For breast cancer prevention, drinking three to five cups of green tea per day is recommended. Consider brewing a fresh pot of green tea (or a mixture of green tea and peppermint) each morning, pouring into a glass jar, and sipping on it throughout the day for a refreshing alternative to water, soda, or coffee.

HormoneSynergy Clinic, LLC
Kathryn Retzler, ND
4640 SW Macadam Ave., Suite 290
Portland, OR 97239
503.230.7990
www.hormonesynergy.com

- **Drink alcohol in moderation or not at all.** One alcoholic drink per day increases breast cancer risk by 10%, and two drinks increase the risk by 20 to 40%.[90] A recent Harvard study showed that 3 to 6 drinks per week increased risk by15%. Alcohol increase aromatase and ER-alpha receptors (making breast cells more sensitive to estrogens). Alcohol also depletes glutathione, necessary for detoxification and a potent antioxidant and cancer preventer.

- **Exercise!** Sustained physical activity for 30-45 minutes, 3 to 7 times per week, has been shown to decrease the risk of breast cancer between 20 and 60%[91,92]

- **If feasible, have children and breast feed at a younger age.** Giving birth before age 25 and having multiple children is known to be breast protective. Most research shows that, regardless of the mother's age, breastfeeding also lowers breast cancer risk.[93,94]

- **Maintain normal weight**—obesity can significantly increase your risk for breast cancer.[95–97]

- **Don't smoke.** Cigarettes are known carcinogens for many different types of cancer including breast cancer.[98] Smoking also dramatically increases free radicals, shortens telomeres, and accelerates aging.

- **Minimize inflammation.** Nuclear factor kappa beta (NFKβ) is a transcription factor that activates genes involved in inflammation and cancer formation, proliferation, and progression. NFKβ is also involved in survival of cancer stem cell, invasion of tissue, angiogenesis, and metastasis of cancer cells. Researchers believe that 95% of all cancers are associated with NFKβ activation.[99] Cigarettes, stress, poor diet choices, obesity, alcohol, infections, radiation, and environmental toxins all trigger NFKβ activation.

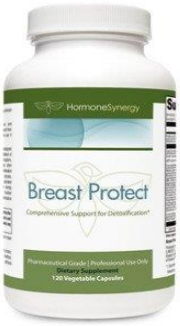
- **Empty your "stress bucket" daily.** Chronic, prolonged stress impairs your cell's ability to repair DNA damage, leading to an increased possibility of defective cell division and cancer formation.[100] Decreasing stress may be as simple as remembering to take several deep breaths. See the "Emptying Your Stress Bucket" handout for ideas on how to minimize the impact of stress.

- **Maintain a serum vitamin D level >30 ng/mL, possibly 40-70 ng/mL.** Vitamin D and sunlight exposure are breast cancer protective.[101] If you don't know your vitamin D level, consider supplementing with 1000 IU of vitamin D3 per day; this dosage has been shown to lower overall cancer risk by 60%.[102]

- **Go through a yearly detox program.** Many studies have linked environmental toxins to breast cancer.[103] Yearly detoxification can enable you to minimize exposure and enhance metabolism and excretion of stored toxins.

HormoneSynergy Clinic, LLC
Kathryn Retzler, ND
4640 SW Macadam Ave., Suite 290
Portland, OR 97239
503.230.7990
www.hormonesynergy.com

Some nutritional supplements may help lower your risk for breast cancer. They include the following:



- **HormoneSynergy Breast Protect,** designed to support phase I and phase II liver detoxification of environmental pollutants, endocrine disruptors, estrogen metabolites, xenoestrogens, and other toxins. Micronutrients, phytonutrients, and activated cofactors provide additional support for antioxidant activity and energy production. 2 capsules of Breast Protect contain:
  - ✓ **DIM (diindolmethane)—75 mg:** DIM is the active metabolite of indol-3-carbinol. DIM supplementation increases 2-hydroxylation of estrogen. Animal and human studies have shown that DIM increases the ratio of the protective "good" 2-hydroxyestrone to 16 alpha hydroxyestrone.[104,105] In a study of postmenopausal women, subjects who took DIM showed a 47% increase in this ratio, compared to women who took the placebo.[106] Other studies suggest that DIM plays a role in supporting normal cell proliferation in estrogen-sensitive tissues, and indol-3-carbinol has been shown to lower breast cancer risk.[107-109]
  - ✓ **Calcium D-glucarate—250 mg** has been shown to inhibit beta-glucuronidase, an enzyme produced by colonic microflora, involved in phase II liver detoxification. Elevated beta-glucuronidase activity is associated with increased breast cancer risk. Calcium D-glucarate supplementation prevents recycling of environmental toxins and hormones back into the liver, aiding in their elimination from the body and possibly lowering breast cancer risk.[110-114]
  - ✓ **Green tea—250 mg:** contains EGCG (epigallocatechin gallate), which helps block vascular endothelial growth factor (VEGF), preventing formation of blood vessels that feed tumors. Green tea has also been shown to inhibit the growth of cancerous tumors, and increase their death.[115,116]
  - ✓ **Milk thistle (100 mg), selenium (15 mcg), alpha-lipoic acid (100 mg), N-acetyl cysteine (100 mg)** increase glutathione production and block NFkB to lower inflammation. Glutathione is possibly the most important antioxidant and detoxifier of the human body.
  - ✓ **Curcumin or turmeric (50 mg)** is a natural polyphenol derived from the rhizome of *Curcuma longa* or turmeric. Curcumin is one of the most potent chemopreventive and anticancer agents ever studied. Its biological effects range from antioxidant, anti-inflammatory to inhibition of angiogenesis (blood vessel formation) and is also shown to possess specific antitumoral activity.[117-119]
  - ✓ **Resveratrol (18.5 mg), pterostilbene (15.5 mg), glucoraphanin (15 mg) or sulforaphane from broccoli seed extract, curcumin, and green tea** included in Breast Protect, increase Nrf2, a master regulator of antioxidant responses including glutathione production, utilization, and regeneration, catalase, and superoxide dismutase.

- **Antioxidants**—especially carotenoids (such as beta-carotene, lycopene, lutein, and zeaxanthin), C, E, selenium, and zinc may lower breast cancer risk (as well as improve telomere length to slow aging).[120,121]

- **Melatonin** is a potent antioxidant that inhibits breast cancer cell growth.[122–124] A high percentage of women with breast cancer have low melatonin levels.[125] Women who work the "graveyard" shift have a higher risk for breast cancer; therefore, avoid working through the night to prevent disruption of this powerful hormone. If you supplement with melatonin, the recommended dosage depends on prevention (3-5 mg before bed) or breast cancer treatment (beneficial dosage may be significantly higher).

- **Fish oil**—Higher omega-3 (fish oil) to omega-6 ratio may reduce the risk of breast cancer.[126,127] Fish oil has been shown to retard the growth of breast cancer in the laboratory, and inhibit breast cancer from developing and spreading in animal studies. Take 1,000 to 3,000 mg EPA and DHA per day.

Putting It All Together

Understandably, many women are afraid of breast cancer—it is much too common, and is too often fatal. It may be helpful to note that women are 10 times more likely to die of cardiovascular disease and twice as likely to die of stroke as breast cancer. In addition, the 3 most common chronic diseases in women are cardiovascular disease (heart attack and stroke), Alzheimer's and other forms of dementia, and osteoporosis. These conditions may be prevented or their impact may be reduced by maintaining optimal hormone levels. For example, decreased estrogen and testosterone are associated with metabolic changes that increase a woman's risk for cardiovascular disease (higher total and LDL cholesterol, higher triglycerides, and lower HDL cholesterol). Estrogen replacement can improve cholesterol levels and the health of blood vessels. Body composition changes that occur with menopause include increased total body fat, especially with accumulation around the waist, and decreased lean body mass. This increased fat to lean body mass and muscle ratio increases the risk for diabetes, cardiovascular disease, dementia, and some forms of cancer. This change in body composition may improve with bioidentical hormone (especially testosterone) supplementation.[128]

Because bone loss is usually asymptomatic, it's common to underestimate the consequences of osteoporosis. Currently, 20 to 30% of menopausal women have osteoporosis. One third of women over 50 will have an osteoporosis-related bone fracture; this risk increases to 50% of women over age 60. The risk for hip fracture is equal to the risk for breast, uterine, and ovarian cancers—combined. Not only is a hip fracture debilitating, but a woman has the same risk of dying from a hip fracture as she does from breast cancer.

Other long-term problems with menopause include cognitive impairment, thinning skin, urinary frequency, vaginal dryness, tooth and gum disease, weight gain, sleep problems, and sexual dysfunction. Considering the fact that bioidentical hormones can help with all of these symptoms and conditions, it's important to weigh your specific risks and benefits when deciding whether to use bioidentical hormones.

[1] BreastCancer.org: http://www.breastcancer.org/symptoms/understand_bc/statistics

[2] Amin A, et al. Perspectives for cancer prevention with natural compounds. *J Clin Oncol.* 2009; 27(16): 2712–2725.
[3] Morimoto LM, et al. Obesity, body size, and risk of postmenopausal breast cancer: The Women's Health Initiative. *Cancer Causes Control.* 2002; 13(8):741-51.
[4] Gunter MJ, et al. Insulin, insulin-like growth factor-1, and risk of breast cancer in postmenopausal women. *J Natl Cancer Inst.* 2009;101(14):1030-1.
[5] Morimoto LM, et al. Obesity, body size, and risk of postmenopausal breast cancer: The Women's Health Initiative. *Cancer Causes Control.* 2002; 13(8):741-51.
[6] Ahn J, et al. Adiposity, adult weight change, and postmenopausal breast cancer risk. *Arch Intern Med.* 2007;167(19):2091-102.
[7] Velicer CM, et al. Antibiotic use in relation to the risk of breast cancer. *JAMA*. 2004;29(7):827-35.
[8] Breastcancer.org: http://www.breastcancer.org/risk/factors/radiation
[9] Mahmud K. Natural hormone therapy for menopause. *Gynecol Endorcrinol.* 2010;26(2):81-5.
[10] Rossouw JE, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. *JAMA.* 2002;288(3):321-333.
[11] Anderson GL, et al. Conjugated equine oestrogen and breast cancer incidence and mortality in postmenopausal women with hysterectomy: extended follow-up of the Women's Health Initiative randomised placebo-controlled trial. *Lancet Oncol.* 2012;13(5):476-86.
[12] Beral V, Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet.* 2003;362(9382):419-27.
[13] Chen W, et al. Unopposed estrogen therapy and the risk of invasive breast cancer. *Arch Intern Med.* 2006;166:1027-1032.
[14] Davelaar EM, Gerretsen G, Relyveld J. [No increase in the incidence of breast carcinoma with subcutaneous administration of estradiol.] *Ned Tijdschr Geneeskd* 1991;135(14):613-5.
[15] Dimitrakakis C, et al. Breast cancer incidence in postmenopausal women using testosterone in addition to usual hormone therapy. *Menopause* 2004;11(5):531-5.
[16] Natrajan P, Gambrell D. Estrogen replacement therapy in patients with early breast cancer. *Obstet Gynecol.* 2002;187:289-95.
[17] Somboonporn W, Davis S. Postmenopausal testosterone therapy and breast cancer risk. *Maturitas.* 2004;49:267-275.
[18] Decker DA, et al. Estrogen replacement therapy in breast cancer survivors: a matched-controlled series. *Menopause*. 2003 Jul- Aug;10(4):277-85.
[19] Vassilopoulou-Sellin R, et al. Estrogen replacement therapy for menopausal women with a history of breast carcinoma: results of a 5-year, prospective study. *Cancer*. 2002;95(9):1817-26.
[20] Col N F, et al. Hormone replacement therapy after breast cancer: a systematic review and quantitative assessment of risk. *J Clin Oncol*. 2001;19:2357-2363.
Meurer LN, Lená S. Cancer recurrence and mortality in women using hormone replacement therapy after breast cancer: Meta-analysis. *J Fam Pract*. 2002 Dec;51(12):1056-62.
[21] Bergkvist L, et al. The risk of breast cancer after estrogen and estrogen-progestin replacement. *N Engl J Med.* 1989;321:293-7.
[22] Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet.* 2003;362:419-27.
[23] Fournier A, et al. Breast cancer risk in relation to different types of hormone replacement therapy in the E3N-EPIC cohort. *Int J Cancer*. 2004;114:448-454.
[24] Rosenberg L, et al. Menopausal hormone therapy and other breast cancer risk factors in relation to the risk of different histological subtypes of breast cancer: a case-control study. *Breast Ca Research*. 2006;8(1):1-13.
[25] Lyytinen H, et al. Breast cancer risk in postmenopausal women using estrogen-only therapy. *Obstet Gynecol*. 2006;108(6):1354-1360.)
[26] Dew J, et al. A cohort study of topical vaginal estrogen therapy in women previously treated for breast cancer. *Climacteric.* 2003;6:45-52.
[27] Keller PJ, et al. Oestrogens, gonadotropins and prolactin after intra-vaginal administration of oestriol in post-menopausal women. *Maturitas*. 1981;3:47-53.
[28] Nahoul K, et al. Profiles of plasma estrogens, progesterone, and their metabolites after oral or vaginal administration of estradiol or progesterone. *Maturitas.* 1993;16:185-202.
[29] Kuhl H. Pharmacology of estrogens and progestogens: influence of different routes of administration. *Climacteric.* 2005;8(suppl 1):3-63.
[30] Cowan LD, et al. Breast cancer incidence in women with a history of progesterone deficiency. *Am J Epidemiol* 1981;114(2):209-17.

[31] Sturgeon S, et al. Serum levels of sex hormones and breast cancer risk in premenopausal women: a case-control study. *Cancer Causes and Control.* 2004;15:45-53.
[32] Micheli A, et al. Endogenous sex hormones and subsequent breast cancer in premenopausal women. *Int J Cancer.* 2004;112:312-318.
[33] Kaaks R, et al. Serum sex steroids in premenopausal women and breast cancer risk within the European Prospective Investigation into Cancer and Nutrition (EPIC). *J Natl Cancer Inst.* 2005;97:755-765.
[34] Fournier A, et al. Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study. *Breast Cancer Res Treat*. 2008;107(1):103-11.
[35] Fournier A, et al. Breast cancer risk in relation to different types of hormone replacement therapy in the E3N-EPIC cohort. *Int J Cancer*. 2005;114(3):448-54.
[36] Plu-Bureau G, et al. Percutaneous progesterone use and risk of breast cancer: results from a French cohort study of premenopausal women with benign breast disease. *Cancer Detect Prev.* 1993;23(4):290-6.
[37] Fournier A, et al. Unequal risks for breast cancer associated with different hormone therapies: results for the E3N cohort study. *Breast Cancer Res Treat.* 2008;107(1):103-111.
[38] de Lignieres B, et al. Combined hormone replacement therapy and risk of breast cancer in a French cohort study of 3175 women. *Climacteric*. 2002;5:332–40.
[39] Somboonporn W, Davis S. Postmenopausal testosterone therapy and breast cancer risk. *Maturitas*. 2004;49:267-275.
[40] van Staa TP, Sprafka JM. Study of adverse outcomes in women using testosterone therapy. *Maturitas.* 2009;62(1):76-80.
[41] Dimitrakakis C, et al. Breast cancer incidence in postmenopausal women using testosterone in addition to usual hormone therapy. *Menopause* 2004;11(5):531-5.
[42] Hackenberg R, Schulz K. Androgen receptor mediated growth control of breast cancer and endometrial cancer modulated by antiandrogen and androgen-like steroids. *J Steroid Biochem Molec Biol.* 1996;56(1-6):113-117.
[43] Szelei J, et al. Androgen-induced inhibition of proliferation in human breast cancer MCF7 cells transfected with androgen receptor. *Endocrinology* 1997;138(4):1406-1412.
[44] Ortmann J, et al. Testosterone and 5-alpha-dihydrotestosteorne inhibit in vitro growth of human breast cancer cell lines. *Gynecol Endocrinol.* 2002;16:113-120.
[45] Ando S, et al. Breast cancer: from estrogen to androgen receptor. *Molecular and Cellular Endocrinol.* 2002;193:121-128.
[46] Boccuzzi G, et al. 5-En-androstne-3β, 17 β-diol inhibits the growth of MCF-7 breast cancer cells when oestrogen receptors are blocked by estradiol. *Br J Cancer*. 1994;70:1035-1039.
[47] Dimitrakakis C, Bondy C. Androgens and the breast. *Breast Cancer Res*. 2009;11(5):212.
[48] Szelei J, et al. Androgen-induced inhibition of proliferation in human breast cancer MCF7 cells transfected with androgen receptor. *Endocrinology* 1997;138(4):1406-1412.
[49] Kandouz M, et al. Proapoptotic effects of antiestrogens, progestins and androgen in breast cancer cells. *J Steroid Biochem Mol Biol.* 1999;69(1-6):463-71.
[50] Lapointe J, et al. Androgens down-regulate bcl-2 protooncogene expression in ZR-75-1 human breast cancer cells. *Endocrinology.* 1999;140(1):416-421.
[51] Ando S, et al. Breast cancer: from estrogen to androgen receptor. *Mol Cell Endocrinol.* 2002;193(1-2):121-8.
[52] Boccuzzi G, et al. 5-en-androstene-3beta,17beta-diol inhibits the growth of MCF-7 breast cancer cells when oestrogen receptors are blocked by oestradiol. *Br J Cancer.* 1994;70:1035-1039.
[53] Zhou J, et al. Testosterone inhibits estrogen-induced mammary epithelial proliferation and suppresses estrogen receptor expression. *FASEB J*. 2000;14:1725–1730
[54] Poulin R, et al. Androgens inhibit basal and estrogen-induced cell proliferation in the ZR-75-1 human breast cancer cell line. *Breast Cancer Res Treat* 1988;12:213–225
[55] Langer M, et al. Androgen receptors, serum androgen levels and survival of breast cancer patients. *Arch Gynecol Obstet*. 1990;247:203-209.
[56] Bryan R, et al. Androgen receptors in breast cancer. *Cancer.* 2006;54(11):2436-2440.
[57] Tormey DC, et al. Evaluation of tamoxifen doses with and without fluoxymesterone in advanced breast cancer. *Ann Intern Med*. 2003;98:139–144
[58] Ingle JN, et al. Combination hormonal therapy with tamoxifen plus fluoxymesterone *vs.* tamoxifen alone in postmenopausal women with metastatic breast cancer. A phase II study. *Cancer.* 1991;67:886–891
[59] Birrell S, et al. Disruption of androgen receptor signaling by synthetic progestins may increase risk of developing breast cancer. *FASEB Journal.* 2007;21:2285-2293.
[60] Traish A, et al. Testosterone and risk of breast cancer: appraisal of existing evidence. *Horm Mol Biol Clin Invest* 2010;2(1):177-190.

[61] Zhou J, Ng S, et al. Testosterone inhibits estrogen-induced mammary epithelial proliferation and suppresses estrogen receptor expression. *FASEB Journal.* 2000;14:1725-1730.
[62] Hoffling M, et al. Testosterone inhibits estrogen/progestogen-induced breast cell proliferation in postmenopausal women. *Menopause.* 2007;14(2):1-8.
[63] Dimitrakakis C, et al. A physiologic role for testosterone in limiting estrogenic stimulation of the breast. *Menopause.* 2003;10(4):292-298.
[64] Glaser R, Dimitrakakis C. Reduced breast cancer incidence in women treated withsubcutaneous testosterone, or testosterone with anastrozole: a prospective, observational study. *Maturitas*. 2013;76(4):342-9
[65] Marinac CR, et al. Frequency and circadian timing of eating may influence biomarkers of inflammation and insulin resistance associated with breast cancer risk. *PLoS ONE*;2015:10(8): e0136240. doi:10.1371/journal.pone.0136240
[66] Cottet V, et al. Postmenopausal breast cancer risk and dietary patterns in the E3N-EPIC prospective cohort study. *Am J Epidemiol.* 2009;170(10):1257-67.
[67] Dong JY, Qin LQ. Dietary glycemic index, glycemic load, and risk of breast cancer: meta-analysis of prospective cohort studies. *Breast Cancer Res Treat*. 2011;126(2):287-94.
[68] Larsson S, et al. Diabetes mellitus and risk of breast cancer: A meta-analysis. *Int. J. Cancer*. 2007;121: 856–862.
[69] Aune D, et al. Dietary fiber and breast cancer risk: a systematic review and meta-analysis of prospective studies. *Ann Oncol*. 2012;23(6):1394-402.
[70] Volkert D, Sieber CC. Protein requirements in the elderly Int J Vitam Nutr Res. 2011;81(2-3)109-119.
[71] Aiyer HS. Influence of berry polyphenols on receptor signaling and cell-death pathways: implications for breast cancer prevention. *J Agric Food Chem*. 2012;60(23):5693-708.
[72] Khodarahmi M, Azadbakht L. The association between different kinds of fat intake and breast cancer risk in women. Int J Prev Med. 2014; 5(1): 6–15.
[73] Chajès V. Association between serum trans-monounsaturated fatty acids and breast cancer risk in the E3N-EPIC Study. *Am J Epidemiol.* 2008; 167(11): 1312–1320.
[74] Turner D. Advanced glycation end-products: a biological consequence of lifestyle contributing to cancer disparity. *Cancer Res.* 2015; 75(10); 1925–9.
[75] Uribarri J, et al. Advanced glycation end products in foods and a practical guide to their reduction in the diet. *J Am Diet Assoc*. 2010;110(6):911-16.
[76] West S, Skulas-Ray A. Spices and herbs may improve cardiovascular risk factors. *Nutrition Today.* 2014;49(5):S8-S9.
[77] Davis PA, Yokoyama W. Cinnamon intake lowers fasting blood glucose: meta-analysis. *J Med Food*. 2011;14(9):884-9.
[78] Allen RW, et al. Cinnamon use in type 2 diabetes: an updated systematic review and meta-analysis. *Ann Fam Med*. 2013;11(5):452-9.
[79] Ramljak D. Pentameric procyaniddin from Theobroma cacao selectively inhibit growth or human breast cancer cells. *Mol Cancer Ther*. 2005;4(4):537-46.
[80] Mursu J, et al. Dark chocolate consumption increases HDL cholesterol concentration and chocolate fatty acids may inhibit lipid peroxidation in healthy humans. *FRBM.* 2004;37:1351-9.
[81] Taubert. Chocolate and blood pressure in elderly individuals with isolated systolic hypertension. *JAMA.* 2003;290:1029-1030.
[82] Grassi D, et al. Short-term administration of dark chocolate is followed by a significant increase in insulin sensitivity and a decrease in blood pressure in healthy persons. *Am J Clin Nutr.* 2005; 81:611-614.
[83] Grassi D, et al. Cocoa reduces blood pressure and insulin resistance and improves endothelium-dependent vasodilation in hypertensives. *Hypertension.* 2005;46:398-405.
[84] Liu K, et al Effect of green tea on glucose control and insulin sensitivity: a meta-analysis of 17 randomized controlled trials. *Am J Clin Nutr*.2013;98(2):340-8.
[85] Khalesi S, et al. Green tea catechins and blood pressure: a systematic review and meta-analysis of randomized controlled trials. *Eur J Nutr*. 2014;53(6):1299-311.
[86] Bogdanski P, et al. Green tea extract reduces blood pressure, inflammatory biomarkers, and oxidative stress and improves parameters associated with insulin resistance in obese, hypertensive patients. *Nutr Res.* 2012;32(6):421-7.
[87] Min-Jing Li, et al. Green tea compounds in breast cancer prevention and treatment. *World J Clin Oncol.* 2014; 5(3):520–528.
[88] Sun CL, et al. Green tea, black tea and breast cancer risk: a meta-analysis of epidemiological studies. *Carcinogenesis.* 2006;27(7):1310-5.
[89] Seely D, et al. The effects of green tea consumption on incidence of breast cancer and recurrence of breast cancer: s systematic review and meta-analysis. *Integr Cancer Ther.* 2005;4(2)144-55.

[90] Smith–Warner SA, et al. Alcohol and breast cancer in women: a pooled analysis of cohort studies. *JAMA* 1998; 279:535–40.
[91] Cummings SR, et al. Prevention of breast cancer in postmenopausal women: approaches to estimating and reducing risk. *J Natl Cancer Inst.* 2009;101(6):384-98.
[92] McTiernan A, Kooperberg C, White E, et al. Recreational physical activity and the risk of breast cancer in postmenopausal women: The Women's Health Initiative Cohort Study. *JAMA.* 2003; 290(10):1331–1336.
[93] Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. *Lancet.* 2002;360(9328):187-195.
[94] Yang L, Jacobsen KH. A systematic review of the association between breastfeeding and breast cancer. *J Womens Health (Larchmt).* 2008;17(10):1635-1645.
[95] Maehle BO, Tretli S. Pre-morbid body-mass-index in breast cancer: reversed effect on survival in hormone receptor negative patients. *Breast Cancer Res Treat*. 1996;41(2):123-30.
[96] Morimoto LM, et al. Obesity, body size, and risk of postmenopausal breast cancer: the Women's Health Initiative. *Cancer Causes Control.* 2002. 13(8):741-51.
[97] Gunter MJ, et al. Insulin, insulin-like growth factor-1, and risk of breast cancer in postmenopausal women. *J Natl Cancer Inst*. 2009;101(14):1030-1.
[98] Terry P, Rohan T. Cigarette smoking and the risk of breast cancer in women: a review of the literature. *Cancer Epidemiol Biomarkers Prev*. 2002;11:953-971.
[99] Prasad S, et al. NF-kappaB and cancer: how intimate is this relationship. *Mol Cell Biochem*. 2010;336(1-2):25-37.
[100] Antoni MH, et al. The influence of bio-behavioural factors on tumour biology: Pathways and mechanisms. *Nat Rev Cancer.* 2006; 6(3):240–248.
[101] John EM, et al. Vitamin D and breast cancer risk: the NHANES I epidemiologic follow-up study, 1971-1975 to 1992. National Health and Nutrition Examination Survey. *Cancer Epidemiol Biomarkers Prev*. 1999;8(5):399-406.
[102] Lappe JM, et al. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. *Am J Clin Nutr*. 2007;85(6):1586-91.
[103] Gray J, et al. State of the evidence: the connection between breast cancer and the environment. *Int J Occup Environ Health.* 2009;15(1):43-78.
[104] Rajoria S, et al. 3,3'-diindolylmethane modulates estrogen metabolism in patients with thyroid proliferative disease: a pilot study.*Thyroid*. 2011;21(3):299-304. [
[105] Sepkovic DW, et al. Diindolylmethane inhibits cervical dysplasia, alters estrogen metabolism, and enhances immune response in the K14-HPV16 transgenic mouse model. *Cancer Epidemiol Biomarkers Prev*. 2009;18(11):2957-64.
[106] Dalessandri KM, et al. Pilot study: effect of 3,3'-diindolylmethane supplements on urinary hormone metabolites in postmenopausal women with a history of early-stage breast cancer. *Nutr Cancer*. 2004;50(2):161-67.
[107] Del Priore, et al. Oral diindolylmethane (DIM):pilot e valuation of a nonsurgical treatment for cervical dysplasia. *Gynecol Oncol.* 2010;116(3):464-67.
[108] Fares F, et al. The potential efficacy of 3,3'-diindolylmethane in prevention of prostate cancer development. *Eur J Cancer Prev*. 2010;19(3):199-203.
[109] Wong GY, et al. Dose-ranging study of indole-3-carbinol for breast cancer prevention. *J Cell Biochem Suppl* 1997;28-29:111-6.
[110] Heerdt AS, et al. Calcium glucarate as a chemopreventive agent in breast cancer. *Isr J Med Sci*. 1995;31(2-3):101-5.
[111] Webb TE, et al. Mechanism of growth inhibition of mammary carcinomas by glucarate and the glucarate:retinoid combination. *Anticancer Res* 1993;13:2095-2100.
[112] Bhatnagar R, et al. Growth suppression of human breast carcinoma cells in culture by N-(4-hydroxyphenyl) retinamide and its glucuronide and through synergism with glucarate. *Biochem Pharmacol* 1991;41:1471-1477.
[113] Curley RW, et al. Activity of d-glucarate analogues: synergistic antiproliferative effect in cultured human mammary tumor cells appear to specifically require the d-glucarate structure. *Life Sci.* 1994;54:1299-1303.
[114] Abou-Issa Het al. Relative efficacy of glucarate on the initiation and promotion phases of rat mammary carcinogenesis. *Cancer Res.* 1995;15:805-810.
[115] Sun CL, et al. Green tea, black tea and breast cancer risk: a meta-analysis of epidemiological studies. *Carcinogenesis.* 2006;27(7):1310-5.
[116] Seely D, et al. The effects of green tea consumption on incidence of breast cancer and recurrence of breast cancer: s systematic review and meta-analysis. *Integr Cancer Ther.* 2005;4(2)144-55.
[117] Surh YJ, Chun KS. Cancer chemopreventive effects of curcumin. *Adv Exp Med Biol*.2007;595:149-72.

[118] Singh S, Khar A. Biological effects of curcumin and its role in cancer chemoprevention and therapy. *Anticancer Agents Med Chem*. 2006;6(3):259-70.
[119]Aggarwal BB, et al. Anticancer potential of curcumin: preclinical and clinical studies. *Anticancer Res*. 2003;23(1A):363-98.
[120] Tamimi RM, et al. Circulating carotenoids, mammographic density, and subsequent risk of breast cancer. *Cancer Res.* 2009;69(24):9323-9329.
[121] Shen J, et al. Telomere length, oxidative damage, antioxidants, and breast cancer risk. *Int J Cancer*. 2009;124(7):1637-1643.
[122] Cos S, et al. Melatonin inhibits DNA synthesis in MCF-7 human breast cancer cells in vitro. *Life Sci.* 1996;58(26):2447-53.
[123] Ram PT, et al. Differential responsiveness of MCF-7 human breast cancer cell line stocks to the pineal hormone, melatonin. *J Pineal Res.* 2000;28(4):210-8.
[124] Subramanian A, Kothari L. Suppressive effect by melatonin on different phases of 9,10-dimethyl-1,2-benzanthracene (DMBA)-induced rat mammary gland carcinogenesis. *Anticancer Drugs*. 1991;2(3):297-303.
[125] Schernhammer ES, Hankinson SE. Urinary melatonin levels and postmenopausal breast cancer risk in the Nurses' Health Study cohort. *Cancer Epidemiol Biomarkers Prev.* 2009;18(1):74-9.
[126] Goodstine Sh, et al. Dietary (Ω-3)/(Ω-6) fatty acid ratio: possible relationship to premenopausal but not postmenopausal breast cancer risk in US women. *J. Nutr.* 2003;133:1409-1414.
[127] KIim J, et al. Fatty fish and fish omega-3 fatty acid intakes decrease the breast cancer risk: a case-control study. *BMC Cancer*. 2009;9:216.
[128] Davis SR, et al. Effects of estradiol with and without testosterone on body composition and relationships with lipids in postmenopausal women. *Menopause*.2000;7(6):395-401.