

Diet and Breast Cancer: A Review on Prolon Fast Mimicking Diet in the Treatment of Breast Cancer

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ABSTRACT

Breast cancer (BC) was and continues to be one of the most widespread and growing malignant disease among women, and ranked as the most common cancer in women. Each year, more or less one million women are newly diagnosed with BC. It affects physical, social as well as mental aspects of women's life. BC can be controlled by lifestyle and dietary factors. Higher consumption of flaxseed, fruits, and vegetables especially cruciferous vegetables have found to be beneficial in lowering the risk of BC. Diet comprising of folic acid, selenium, vitamins, and antioxidants such as carotenoids have shown benefits as well. A very low calorie fast-mimicking diet "ProLon" considered to be the most effective anti-cancer diet plan to treat BC patients. It is a 5-day diet low in calories, proteins, carbohydrates, and rich in healthy fats, rejuvenate the body, improve health, and can ameliorate the incidence of BC.

KEY WORDS

Breast cancer; Diet; Fast mimicking diet; Omega-3 fatty acids; ProLon; Phytoestrogen

Introduction

Breast cancer (BC) is defined as a type of cancer develops from breast tissue, mainly from the milk ducts or lobules. BC is considered the most common cause of developing carcinoma in women. The repeatedly quoted statistics of BC is that one in eight women will develop BC in their lifetime. The classic symptom for BC is the formation of a lump in the breast or armpit. Nipple discharge, pain in the nipple, breast tenderness are the other major symptoms included (Koo et al., 2017). The major risk factors associated with BC are endocrine factors, genetic factors, environmental, and lifestyle factors. Early menarche, late age of natural menopause (≥ 55 years), nulliparous, and a late age at first birth (≥ 30 years) induce the lifelong possibility for developing BC. The risk for developing BC increases in women for those having any first-degree relative with BC. 13% of BC is due to germ-line mutations in either BRCA1 or BRCA2 (tumor suppressor genes) (Sun et al., 2017). The American Institute for Cancer Research and The World Cancer Research Fund estimated 30-40% of BC can be controlled by lifestyle and dietary measures. Diet, physical activity, and weight control are the modifiable risk factors that reduce the long-term side effects of the treatment protocol and promote health by decreasing BC comorbidities (Hypertension, Dyslipidemia, Obesity, Diabetes mellitus). To overcome the risk associated with the diet in BC a

Fast-Mimicking Diet (FMD)- “ProLon” is followed by patients. It is a 5-day diet low in calories, proteins, carbohydrates, and high in healthy fats designed to lose fat, rejuvenate the body, and improve health (Akhila et al., 2018).

Diet and breast cancer

Dietary fat: The epidemiological examinations have reported conflicting outcomes in regard to the relation of dietary fat with BC risk. There is a correlation between the type of dietary fat consumed and the menopausal status of women. The consumption of diets high in total fat and polyunsaturated fats increases the chance for developing BC in postmenopausal women than in pre-menopausal women. High fat intake resulting in the build-up of adipose tissue, which is considered as a site responsible for the transformation of androstane to estrone. The metabolic product of polyunsaturated fatty acids (PUFA): Arachidonic acid increases the conversion of androstenedione to estrone by activating P450 aromatase. The reduction in binding of estrogen to albumin and sex hormone-binding globulin (SHBG) by PUFA increases the transmitting levels of biologically potent estrogens results in the activation of a cell responsible for carcinoma (Cao et al., 2016). The n-3PUFA eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) hinder the production of arachidonic acid-derived eicosanoids tumors. The n-3PUFA binds and activates peroxisome proliferator-activated receptor- γ , results in stimulation of the proteoglycan syndecan-1 in human BC cell leading to inhibiting cell growth by promoting apoptosis. The n-6PUFA linoleic acid increases epidermal growth factor (EGF) and insulin by generating 13-hydroxy linoleic acid results in the growth of cancer cells. A low intake of n-3PUFA with a higher intake of n-6PUFA increases BC risk (Eliseo and Velotti, 2016).

Meat consumption: The consumption of red meat, considered the risk factor for developing BC. Postmenopausal women consuming a high amount of red meat are more prone to the development of BC than premenopausal women. The link between meat consumption and BC risk depends on the type of meat used, method of cooking, and temperature of cooking. The consumption of processed red meat develops 3 times higher BC risk than unprocessed red meat (Farvid et al., 2018). The amount of formation of potential pro-carcinogenic compounds, such as heterocyclic amines (HCA), polycyclic aromatic hydrocarbons (PAHs), and N-nitroso compounds depends on the cooking method, cooking temperature, and cooking time. The metabolic activation of heterocyclic amines (HCAs) by N-acetyl transferase (a major enzyme in the human breast tissue) contributes to an elevated BC risk. The highly reactive HCA metabolites bind to DNA leads to the generation of DNA adducts resulting in ductal or lobular carcinogenesis (Anderson et al., 2018).

Alcohol consumption: Higher alcohol intake increases the development of BC. Women who take 3 drinks of alcohol a day develop a 15% higher risk of BC than women who don't drink at all. The alcohol plays a major role in the pathogenesis of BC. The alcohol gets metabolized into acetaldehyde (AA) and other reactive oxygen species (ROS) by alcohol dehydrogenase (ADH) in the liver. They can bind proteins and DNA results in the induction of DNA modifications, chromosomal alterations, and DNA point mutations. Higher consumption of alcohol results in the inhibition of folate absorption and impede the DNA repair mechanism. Alcohol plays a direct role in BC tumorigenesis by down-regulating BRCA1 (a tumor suppressor gene), results in an increase in transcriptional activity of ER α leading to cell proliferation and genetic damage. Higher intake of alcohol results in an increased number of intracellular estrogens that promote the growth of mammary tumors (Zeinomar et al., 2019).

Tobacco consumption: In women, breast tissue has the ability to take in a variety of substances that cause tobacco cancer, including aromatic amines, polycyclic aromatic hydrocarbons, and N-nitrosamines. Mammary epithelial cells can then metabolise and turn on these compounds becoming electrophilic intermediates that can damage DNA and form adducts. Compared with non-smokers, smokers have a higher incidence of tobacco-related DNA adducts and p53 gene mutations (Jones et al., 2017).

Dietary Iron: Higher consumption of meat, fortification of iron-containing foods, and repeated use of iron supplements associates to increased tumor development in human and animal models. The iron has pro-oxidant properties. Higher dietary iron concentrations in the human body can cause oxidative stress, DNA damage, and peroxidation of lipid, which in turn leads to an increased risk of BC. The pathway mediated by ferroportin and hepcidin mediates iron efflux during tumor growth and metastasis. Ferroportin is a transmembrane protein that transports iron from the inside of the cell to the outside (Iron exporter) and hepcidin is a regulator of iron metabolism, inhibits iron transport by binding to the ferroportin and actuates its degradation, resulting to decreased export of cellular iron (Toklu and Nogay, 2018).

Carbohydrate and Glycemic index: The association between consumption of total carbohydrates, or specific types of carbohydrates (total sugar or specific sugars), glycemic index (GI), glycemic load (GL), and risk of BC are non-conclusive. Neither the carbohydrate intake nor GL results in increased BC risk in pre or post-menopausal women. There is a positive correlation between GL and ER⁺ BC risk in postmenopausal women. This might be due to increased insulin serum levels resulting from carbohydrate consumption. Insulin is responsible for the increased levels of growth hormone (GH), results in the production of IGF-1, that exhibit mitogenic and antiapoptotic effect on BC cells. Although, if there is no relationship between carbohydrate intake, GI or GL, and BC risk, glycemic control is preferable (Schlesinger Jones et al., 2017).

Dietary fiber: The food items rich in dietary fiber have a protective effect on BC. The dietary fiber consists of monomers responsible for producing a polymer of carbohydrates, which cannot be digested and absorbed by the small intestine in the body. The main polymers included are cellulose, hemicellulose, pectin, lignin from the cell wall of plants, hydrophilic colloid substances, etc. These components combine with carcinogenic substances present in the gut and promote their discharge and decomposition. The dietary fiber encourage the growth of the probiotic and hinder the growth of pathogenic bacteria that results in the inhibition of carcinogen production and promotes their putrefaction in the intestine (Mana, 2016). It also makes improvements in the phagocytosis of macrophages, block the synthesis of nitrosamine, and decreases the levels of estrogen in the human body. Absorption of ions, organic compounds, and estrogen formed by human intestinal microbial enzymes are the important physiological functions of dietary fiber results in the reduction of risk of BC. Furthermore, the dietary fiber may reduce the plasma levels of estrogen by blocking colonic β -D-glucuronidase activity, resulting in a reduction of deconjugation and reabsorption of estrogen and enhancement of the fecal excretion (Bradbury et al., 2014).

Phytoestrogens: Phytoestrogens are natural plant substances comprised of 3 main classes such as isoflavones, coumestans, and lignans. Between 3 isoflavones are considered to be the most important ones. Isoflavones are a type of polyphenol mainly found in soybean and soy products that reduces the risk of BC in both premenopausal and postmenopausal women, and also reduces the chance of recurrence among postmenopausal patients with BC and patients on endocrine therapy (Gonzalez-Vallinas et al., 2013). They are the powerful inhibitors of aromatase, the enzyme responsible for the conversion of androgens to estrogens. Phytoestrogens are selective estrogen receptor modulators (SERMs), and its activity is based upon genomic and non-genomic action. By genomic mechanism, phytoestrogens go through the cell membrane and interrelate with enzymes and receptors and inhibit estrogen from binding to their receptors. The opposite mechanism instigates estrogen-responsive gene products that can invigorate ER⁺ BC cell growth. In non-genomic mechanisms, phytoestrogen induces cancer cell differentiation, inhibition of tyrosine kinase, and activities DNA topoisomerase and halt angiogenesis (Kunheri et al., 2020).

Fruits and vegetables: Fruits and vegetables are rich in nutrients such as fibers, vitamin C and E, carotenoids, and other bioactive substances that exhibit anti-carcinogenic property and the higher intake results in a reduction of BC risk. Higher consumption of yellow/orange vegetables, cruciferous vegetables, and fruits and vegetables rich in vitamin C, α -carotene, and β -carotene lower the incidence of breast cancer. Higher intake of winter squash, broccoli, cabbage, spinach, and cauliflower were associated with a lower occurrence of BC (Steinmetz and Potter, 2016).

Dietary folate: Dietary folate intake decreases the occurrence of BC. Lower dietary folate intake results in the development of preneoplastic lesions, expression of breast stem cell population, or prevent terminal differentiation in mammary cells. The occurrence of these situations is prominent to women with large breast size, non-cancerous breast disease, family history of BC, or mutation of tumor suppressor genes (Shapira, 2017). Diet correlates with both increase or decrease in the BC risk, which may depend on the quantity and food type consumed. The overconsumption of food items leads to obesity which is considered as the major risk factor for cancer. It may be beneficial to start a diet rich in fibers, phytoestrogen, n-3PUFA, folate, vitamins, fruits and vegetables. The most suitable diet plan consisting of the above food items for BC patients is ProLon (Palazhy et al., 2018).

Fast mimicking diet- PROLON

ProLon is a 5-day diet program, belongs to the fifth generation of fast mimicking diets (FMDs) to lose fat in the body while promoting regenerative and rejuvenating changes through scientifically developed plant-based foods to improve the overall health. ProLon diet is the first and only clinically tested, scientific breakthrough in fasting-mimicking technology. ProLon FMD puts the body into a fasting state that triggers the body's mechanisms to recycle at the cellular level for rejuvenation from within. The ProLon diet is low in protein, calories, and sugars and high in healthy fats. ProLon FMD was developed by L-Nutra, a nutrition technology company based in Los Angeles. Dr. Longo is the inventor of the ProLon diet concept, after completing 2 decades of research on the outcome of fasting. The meal plan for this diet is emerged from the University of Southern California. The clinical trials are conducted at University of Berlin, Leiden University, and the University of Genoa. Simultaneously, a large number of doctors and dietitians have accepted it as a magnificent weight loss and body rejuvenation solution that can generate highly positive, even life-changing (Venetsanopoulou et al., 2019). It is responsible for the reduction of visceral belly fat while maintaining lean body mass. ProLon provides essential nutrients designed to keep the body nourished while going through the rejuvenating process of the fasting state. The meals include plant-derived nutrition bars, soups, crackers, energy drinks, and supplements. They will be gluten-free and uses healthy, mostly plant-based ingredients including olives, vegetables, fruits, nuts, seeds, dark chocolate, and herbal teas (Groot et al., 2019). The 5-day fast mimicking diet program shown in **Table 1** is safe and effective in reducing the development of breast cancer. No severe adverse effects reported for ProLon. This diet plan is unsuitable for women who are pregnant or breastfeeding, persons with underweight, or allergic to ingredients present in the food items. If a person is having any kind of infection the use of ProLon products should be postponed until the infection gets cured. The period for the use of the ProLon diet will depend on each patient's disease condition and the recommendations from the health care professionals. The goal is to use ProLon once a month (Valter, 2020).

Table 1: Diet chart of ProLon

Day 1	Day 2	Day 3	Day 4	Day 5
A cup of tea, nut-based bar, and algal oil for breakfast.	A cup of tea and a nut-based bar for breakfast.	A cup of tea and a nut-based bar for breakfast.	A cup of tea and a nut-based bar for breakfast.	A cup of tea, nut-based bar, and algal oil for breakfast.
A small serving of soup, olives, crackers, and 1 capsule of NR-1 supplement for lunch.	A small serving of soup, olives, and 1 capsule of NR-1 supplement for lunch.	A small serving of soup, crackers, and 1 capsule of NR-1 supplement for lunch.	A small serving of soup, olives, and 1 capsule of NR-1 supplement for lunch.	A small serving of soup, crackers, and 1 capsule of NR-1 supplement for lunch.
A cup of tea and a nut-based bar for afternoon snack.	A cup of tea and a nut-based bar for afternoon snack.	A cup of tea for afternoon snack.	A cup of tea and a nut-based bar for afternoon snack.	A cup of tea for afternoon snack.
A small serving of soup, a nut-based bar, and 1 capsule of NR-1 supplement for dinner.	A small serving of soup, a nut-based bar, and 1 capsule of NR-1 supplement plus the specially formulated glycerol concentrate called L-Drink for dinner.	A small serving of soup, and 1 capsule of NR-1 supplement plus L-Drink for dinner.	A small serving of soup, a nut-based bar, and 1 capsule of NR-1 supplement plus L-Drink for dinner.	A small serving of soup, and 1 capsule of NR-1 supplement plus L-Drink for dinner.

ProLon diet in the treatment of BC

Herbal tea: Hibiscus, Oolong, spearmint, lemon-spearmint, and green tea are the most used ones with anti-cancer properties. Green tea, made from the leaves of the plant *Camellia sinensis* which exhibits antitumor and anti-mutagenic activity. In *Camellia sinensis* a small amount of a polyphenol called Epigallocatechin (EGGG) is present that protects the cells from DNA damage produced by oxygen reactive species. Green tea reduces the harmful effects of radiation (Fujiki et al., 2018). Another most commonly used herbal tea is hibiscus tea formed from crimson or roselle flower. The anticancer properties of hibiscus are due to its antioxidant and hypolipidemic effects. The hibiscus can induce apoptosis in triple-negative and ER⁺ BC cells. Moreover, it

enhances the induction of apoptosis of chemotherapy treatments (Taxol and cisplatin) in triple-negative BC cells. The addition of hibiscus extract in chemotherapy treatment increases oxidative stress and reduces mitochondrial membrane potential. Oolong tea made from the leaves of the plant *Camellia sinensis* (same plant used to make green tea) can promote DNA damage and cleavage, play an inhibitory role in the growth of BC cell, multiplication, and tumorigenesis, and also a great concept as a chemo-preventive agent against BC (Christopher et al., 2019).

Nutrition bar: Also known as Fast bars or Nut -based bars. Fast bars are clinically tested as part of the ProLon FMD. They are filled with flavor and packed with healthy nutrients to satisfy hunger. They are available in flavors such as nuts and honey, cocoa nuts, nuts, and nibs, etc. They are non-GMO, gluten-free, and soy-free. The main ingredients used in the nut-based bars include nuts, honey, nibs, cocoa, pecans, almond, almond butter, coconut, inulin, flaxseed, coconut oil, sea salt, natural flavor, mixed tocopherols (preservative), citric acid, and ascorbic acid. They nourish the body to fasting goals for weight reduction and a healthy lifestyle (Khadakban et al., 2013).

Algal oil: Algal oil is used as a source of omega-3 PUFA. The 2 major omega-3 fatty acids present in algal oil are DHA and EPA, which inhibit cell growth by promoting apoptosis. Omega-3 PUFAs, especially DHA, can control the effectiveness of chemotherapy and radiotherapy for cancer patients by enhancing the sensitivity of malignant tumour cells. Dietary supplementation with DHA (algal oil) is capable of improving the efficacy of systemic chemotherapy and local breast irradiation. The intake of algal oil reduces the incidence of BC and increases the levels of BRCA1 and BRCA2 proteins (Shareef et al., 2016).

Soup: Available in varieties of flavors such as mushroom, minestrone, minestrone with quinoa, butternut squash, butternut squash with quinoa, spinach with white bean and black bean, and are rich with nutritious vegetables. Mushroom consists of therapeutic agents such as lectin, arginine, and ergosterol. They inhibit tumor growth thereby increase immune cell counts (especially in patients on chemotherapy and radiation treatment). Mushroom inhibit aromatase enzyme present in the body involved in estrogen synthesis. Another therapeutic compound present in mushroom is polysaccharide K (PSK). PSK can improve the effectiveness of monoclonal antibody therapy in BC patients. They are useful in preventing relapse too (Catsburg et al., 2015). Butternut squash is a good source of fiber, vitamins, folate, pantothenic acid, and manganese. They are also rich in micronutrients such as α -carotene, β -carotene, cucurbitacins, and lignan. These bioactive compounds decrease the risk of obesity, and cancer. Quinoa is whole grains with the anti-cancer property. They are gluten-free, rich in fibers, vitamin-B, vitamin-E, magnesium, potassium, zinc, and iron. Quinoa contains plant antioxidants called flavonoids; quercetin and kaempferol. Spinach is packed with a variety of bioactive compounds such as vitamin-A, C, K and folate, the minerals potassium and magnesium, and phytonutrients such as carotenoids (β -carotene, lutein, zeaxanthin) and flavonoids (kaempferol, myricetin, quercetin) with the cancer-fighting property. They prevent and repair DNA damage in cells and keep cells healthy and protect from cancer development. White beans are a nutritional powerhouse, rich in fiber and proteins, and also a good source of micronutrients including vitamin-B6, folate, and magnesium. They are high in polyphenol antioxidants that protect from carcinoma. The black beans are rich in selenium that decreases tumor growth rates (Levitsky and Dembitsky, 2015).

Crackers: It is a mix of ingredients including main seeds such as flaxseed, sesame seed, sunflower seed, chia seed, pumpkin seed, and hemp seed. Other ingredients present are kale, cashews, nutritional yeast, onion powder, black powder, etc. Flaxseed also termed as linseed is rich in omega-3 fatty acids, with a main component called lignans. The main lignan in flaxseed is 95% secoisolariciresinol diglucoside (SDG). After the SDG ingestion, bacteria present in the colon convert lignan into mammalian lignan, enterolactone, and enterodiol. They are structurally similar to estrogen with antioxidant activity. It acts as an antiestrogenic which permits its binding to receptors of cells, results in inhibition of growth of cancer cells. Moreover, flaxseed can increase the effectiveness of tamoxifen, a drug most commonly used to control BC recurrence (Calado et al., 2018). Pumpkin seeds carry antioxidants such as carotenoids and vitamin-E that can lower the inflammation and safeguard the cells from dangerous free radicals. The sesame seeds are rich in oil-soluble lignans with the anti-oxidative property. The sunflower seeds contain nutrients such as vitamin-E and selenium and are beneficial to prevent BC because selenium has been shown to induce DNA repair and synthesis in damaged cells to prevent cancer cell proliferation thereby promote their apoptosis. The chia seeds and hemp seeds are also powerful anti-cancer foods rich in alpha-linolenic acid (ALA) that limits the growth of BC cells. Kale, a vegetable belonging to cruciferous family, is rich in vitamin-C and vitamin-K exhibit antioxidant property.

Copper contents in cashew fight against cancer. Peanuts also consists of an antioxidant called resveratrol (a type of natural phenol, and a phytoalexin produced by plants) that can help to treat cancer. The omega-3 fatty acid, polyphenols, and antioxidant property of walnuts help to prevent the growth of BC cells (Nair et al., 2018).

Olives:Olives are abundant with antioxidants that may contribute to decrease the risk of cancer development. The presence of oleic acid alone is not responsible for anti-cancer effects. In its pure form, oleic acid induces the migration and multiplication of both hormone receptor-positive (ER⁺/PR⁺) and triple-negative BC cells. A proper intake of olives reduces the aggressiveness of mammary tumors. As a result of its intake, many molecular changes in cancer cells and tumors occurred. It includes changes in the configuration of cell membranes, signaling proteins, and gene expression. These changes result in reduced proliferation, increased apoptosis of BC cells, and protection against DNA damage (Escrich et al., 2014).

Olives maximise the treatment effects of aromatase inhibitors, Adriamycin, taxol (paclitaxel), and Herceptin. Extra-virgin olive oil (developed from the first pressings of olives) enhances the outcome of aromatase inhibitors in ER⁺/PR⁺ breast cancer cells by enhancing programmed cell death. Oleuropein (present in green olives) exhibit synergistic treatment effects in combination with Adriamycin for triple-negative BC. Olive oil also improves the efficacy of treating HER2 positive BC, and many prevent resistance to Herceptin (Brandt and Schulpen, 2017).

NR-1 capsule supplement:A vegetarian capsule, which is lightweight and easy to swallow. Nicotinamide Riboside is a form of vitamin-B3 that increases the levels of nicotinamide adenine dinucleotide (NAD⁺) which helps to bypass nicotinamide phosphoribosyltransferase (NAMPT) which is a rate-limiting enzyme for producing NAD⁺. The NAD⁺ is present in every living cell in the human body and it promotes metabolism, DNA repair, and cell signaling. High levels of NAD⁺ can prevent DNA damage and oxidative stress associated with cancer development (Nikaset al., 2020).

L-Drink:It is a glycerol-based flavored energy drink that helps protect amino acids in fasting mode to maintain lean body mass and promote hydration (Valter, 2020).

CONCLUSION

In short, in the evolution of BC and dietary factors, there is a clear or opposite relationship. Obesity is linked to higher rates of BC recurrence and mortality. Diet, physical exercise, and weight management are variable risk factors that reduce the long-term side effects of treatment options and promote health by reducing BC comorbidities. ProLon FMD is the best choice to overcome diet-related BC. The 5-day diet plan rich in fruits and cruciferous vegetables, adequate calories, and fiber, no refined sugar, no red meat, low in total fat but containing necessary essential fatty acids, flaxseed as a source of phytoestrogen, rich in selenium and folic acid, rich in antioxidants and phytochemicals from fruits and vegetables, and also boosted with beneficial probiotics and oral enzymes enhances the therapeutic efficacy and lower the rates of BC recurrence and mortality.

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CONFLICT OF INTEREST

The author(s) reported no potential conflict of interest.

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