Review

A review of the Mediterranean diet and nutritional genomics in relation to cancer in women

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Women's cancer • Nutritional genomics • Nutrigenetics • Nutrigenomics • Mediterranean diet

Summary

Cancer is the leading cause of death among women all over the world. Female tissue-specific cancers are the most commonly diagnosed among women and account for most cancer-related deaths. The main risk factors for women's cancer are hereditary factors, specific exposure to dangerous chemicals, disorders such as hormone imbalance, and lifestyle. High body mass index, low physical activity, low intake of fruit and vegetables, smoking, excessive alcohol consumption, lack of cancer screening and treatment are the most common risk factors. Nutrigenetics and nutrigenomics are both part of nutritional genomics. Nutrigenetics is how a person's body reacts to nutrients based on his/her genotype. It can be used to create a personalized diet, maintain a person's health, avoid disease, and if necessary to sustain therapy. Nutrigenomics studies the impact of nutrition on gene expression and the epigenomic, proteomic, transcriptomic and metabolomic effects of dietary intake. There is evidence that diet matters for different women's cancers, and is related to cancer progression, survival and treatment. The optimum combination for cancer prevention is a diet rich in vitamins and fibre, with low meat consumption, low milk intake and moderate use of alcohol. The Mediterranean diet looks to be an optimal diet with a good nutrition pattern, qualifying it as a therapy to prescribe.

A review of the Mediterranean diet in women's cancer and nutritional genomics

Cancer is a major cause of death among women, with a an incidence of 9.2 million new cases and 4.4 million deaths per year according to the International Agency for Research on Cancer (2020) in high- and middle-income countries [1]. Cancer is increasing in all countries, irrespective of income, due to population growth and aging. Females constitute 49.5% of the global population, and a larger proportion of the population over 60 years of age, where cancer is more common, irrespective of income, due to a change in average lifespan and factors that contribute to death rates [2]. Female tissue-specific cancers such as breast, ovarian, uterine and endometrial account annually for over 3,000,000 cancer-related incidents [3]. Breast, colorectal, cervical and lung cancer are the types most frequently diagnosed in women and the cause of most cancer-related deaths [4].

Many risk factors are linked to the incidence of cancer and are mainly personal and environmental. Genetic factors, exposure to chemical substances, disorders such as hormone imbalance and unhealthy lifestyle are the main risk factors. The five most common are high body mass index, low physical activity, low intake of fruit and vegetables, smoking and excessive intake of alcohol. Absence of cancer screening and treatment also play a role, especially in undeveloped countries, as well as chronic infections (Hepatitis B and C, *Helicobacter pylori*, human papillomavirus and Epstein-Barr virus) [5, 6].

Smoking is considered to be number one risk factor, causing 22% of deaths due to cancer. Individual genetic and hereditary factors contribute significantly to the transformation of healthy cells and precancerous lesions into malignancies [7]. Number two risk factor is unhealthy lifestyle: poor diet, obesity, sedentary lifestyle and physical inactivity. A change in dietary habits is estimated to improve avoidance of cancer by 30 to 50% [8].According to the World Health Organization, the five leading behavioral and dietary risks are responsible for approximately one-third of cancer deaths: high body mass index, low consumption of fruit and vegetables, smoking, low physical activity and excessive consumption of alcohol [9].

Ovarian, endometrial, vulvar, vaginal and cervical cancer are all tumors of the female reproductive system. The incidence of ovarian, vulvar and vaginal cancers is low (1.7%, 0.3%, and 0.1%, respectively in 2018). Risk factors unrelated to diet are early menarche, nulliparity, menopause after age 55, smoking and heredity, while diet may be significantly linked to cervical and endometrial cancer [5]. Cervical cancer, the fourth most common cancer and the fourth cause of death worldwide is closely linked to diet [10]. Regular consumption of fruit and vegetables, and thus nutrients such as vitamins

E, C and A, carotenoids, folates and minerals, may help reduce the risk of cervical cancer due to the role played by these nutrients in protecting against and inhibiting the proliferation of cancer cells and preventing DNA damage [11].

Endometrial cancer is primarily caused by unbalanced and/or prolonged exposure of the endometrium to estrogens. Unless counterbalanced by progestogens, this increases endometrial cell mitotic activity, resulting in increased DNA replication and an increase in the probability of somatic mutations. Women who enter menopause late, are nulliparous, have polycystic ovary syndrome, use estrogen replacement therapy (without progestogens) or are obese are at risk of the above unbalanced or prolonged exposure [12]. Hormonal regulation of the menstrual cycle is linked to endometrial inflammation. Chronic endometrial inflammation is linked to being overweight or obese [13].

Breast cancer is the most common malignant cancer in women and the second most frequent cancer worldwide [14]. It is a heterogeneous disease. The gene-expression profile is classified into two major groups according to estrogen receptor (ER) expression: ER-expressing positive (ER+) is significantly related to hormonal factors, unlike ER-expressing negative (ER-) [15].

Many risk factors are linked to cancer onset: menopause lowers the risk of breast cancer, while hormonal dysregulation and prolonged exposure to endogenous hormones, like estrogen and estrogen receptor positivity, are associated with increased risk. Aging and genomic mutations impact cancer progression. Heritable mutations in DNA repair genes *BRCA1* and *BRCA2*, apart from being associated with breast cancer development, are also indicators of endometrial and ovarian cancer. Tumor suppressor protein 53 (TP53) mutations, angiogenic factors and signaling molecules are other remarkable factors [3].

There is growing interest in the links between susceptibility to cancer, prognosis and exposure to risk factors like diet. Such research is motivated by the fact that bioactive agents found in everyday foods have enormous potential in oncology due to their ability to regulate coding or non-coding genes, and as adjuvants in cancer therapy [9, 16].

Nutritional genomics is the study of how diet may influence the expression of genetic information and how an individual's genetic makeup influences response to nutrients, metabolism, and the bioactive compounds in food. It aims to identify genetic variants associated with a genetic response to diet and with diet-related diseases, to develop disease treatment and prevention strategies, and to improve dietary guidelines [17]. Its principles are based on the concept that diet is a critical predisposing factor for certain diseases in certain people under certain conditions. Variations in individual genotype can help explain the balance between health and disease. Dietary ingredients alter gene expression and/or gene structure, and therefore the human genome. Genes regulated by dietary factors may play a role in the onset, severity, progression and development of chronic diseases [18].

Nutritional genomics includes nutrigenetics and nutrigenomics [17]. These two disciplines have acquired importance in clinical research and practice: they explore the two-way interaction between diet and the human genome.

Nutrigenetics seems to have its origins in classical genetics. It concerns the interaction of nutritional and genetic factors that may play a role in disease progression. Its primary goal is to investigate the effects of genetic variations, specifically single-nucleotide polymorphisms (SNPs), on the metabolic response to diet. It is therefore concerned with how the body responds to nutrients in relation to genotype [19].

The methylenetetrahydrofolate reductase gene (*MTHFR*), which is involved in folic acid metabolism and maintenance of normal homocysteine levels in the blood, is a well-known example of gene-nutrient interaction. A specific *MTHFR* SNP is related to elevated homocysteine levels in the blood, particularly in the presence of folic acid deficiency [20], which is linked to increased predisposition to colon cancer [21]. Nutrigenetics connects nutrition, human genes and environmental exposure, with the focus on genes. It can be used to personalize diet in order to maintain health, prevent onset of disease and aid treatment.

Nutrigenomics provides a more comprehensive view of how nutrients affect gene expression, and the transcribed characteristics associated with those genes and with direct effects manifested by metabolomic and proteomic activities [22]. Nutrigenomics originated from the Human Genome Project and is concerned with the impact of nutrition on gene expression and the epigenomic, proteomic, transcriptomic and metabolomic effects of dietary intake [17]. One example to illustrate nutrigenomics is the single nucleotide change that determines phenylketonuria. Carriers should avoid foods rich in phenylalanine. Many Asian populations lack the aldehyde dehydrogenase necessary to metabolize ethanol and develop skin irritation after consuming alcohol. Another example is galactosemia, a disease caused by an inherited genetic deficiency in one of the enzymes involved in metabolizing galactose [21].

Nutrients may affect many cell processes, some associated with tumorigenesis. One concern is therefore how specific nutrients influence the development and growth of cancer. Natural nutrients can disrupt tumor progression at many levels while also increasing chemotherapeutic effectiveness and reducing the side-effects associated with these treatments [16]. Proper nutrition is especially important for cancer patients because the illness and its treatments can impair appetite. Cancer and its treatments can also impair the body's capacity to endure and use dietary nutrients. Cancer treatment generally requires treating the tumor as well as the patient, and nutrition is an essential component of the treatment plan [23].

Several studies have documented the epigenetic impacts of nutrition on phenotype and predisposition to disease throughout life. Dietary nutrients interact with genes, the dietary and environmental factors have an impact on epi-

genetics. Certain bioactive food components or micronutrients are known to play a role in DNA methylation, histone modifications, gene expression, and biological and metabolic regulatory pathways [24]. Deficiency of any key nutrient, a lack of methyl donors, or inhibition of methyltransferases can result in gene mutations by activating promoter genes and DNA hyper or hypomethylation, which with age and cell proliferation silence tumor suppressor genes, allowing cancer to develop. Moreover, nutrients can either inhibit epigenetic enzymes like DNMT, HDAC and HAT or change the substrate accessibility required for such enzyme reactions. They can also alter the expression of specific genes, affecting health and longevity [24].

Since epigenetic marks can be altered, they provide an additional explanation for how external factors, such as diet, can impact biological processes and phenotypes. Many nutritional components, including folate, choline, methionine, selenium and retinoic acid, have been shown to affect DNA methylation patterns [25].

Nutrigenomic studies indicate that macronutrients and micronutrients like certain vitamins, minerals and dietary fibre are not only beneficial for cancer prevention but also in treatment, particularly regarding the major characteristics of cancer cells, such as uncontrolled proliferation possibly leading to metastasis [19]. Flaxseed diets, for example, have been shown to aid in the treatment of breast cancer. The mechanism includes a flaxseed lignan that is converted into a compound that binds to estrogen receptors and thus inhibits cell growth [26].

A recent study provided evidence that diet matters for breast cancer survival. While high blood glucose and circulating insulin levels are related to breast cancer prognosis, shreds of statistical of evidence show that women with increased glycemic load have a 31% higher risk of death from breast cancer and a 26% higher risk of all-cause mortality [27]. Chronic hyperinsulinemia can be caused by a high glucose intake, which reduces the production of insulin-like growth factor-binding proteins while increasing insulin-like growth factor 1 [28]. This increase causes a reduction in sex hormone-binding globulin production and inhibits apoptosis, stimulating synthesis of sex hormones and proliferation of ovarian cells. All of these alterations can promote development of ovarian cancer [28, 29].

Another study showed a strong relationship between risks of ovarian cancer and dietary glycemic index in overweight women, non-diabetics, non-users of oral contraceptives and alcohol consumers, and in women without a family history of ovarian or breast cancer, demonstrating a significant increase in the risk of ovarian cancer in all women with a high glycemic diet [30].

According to some pre-clinical studies, nutrients such as carbohydrates, saturated fat, red and processed meat, increase endogenous estrogen levels and could be risk factors for breast cancer [14]. Cholesterol is the precursor of the steroid hormones estrogen and progesterone. A high-fat diet leads to over-synthesis of estrogen, which stimulates cell proliferation in the female genital tract [31]. The polyphenols found in vegetables and fruit and are known as polyhydroxy phenols. They are common in items such as green tea, cinnamon and curcumin, and they number more than 8000 in the human diet. Polyphenols have an epigenetic role in the prevention of cancer through gene silencing and chromatin remodeling [32]. This may be due to their ability to modify histones and to inhibit DNA methyltransferase.

Research into the effects of curcumin, a known antiproliferative and apoptotic, in the experimental breast cancer alpha-model, showed that curcumin inhibits cell proliferation and invasion, metastasis and angiogenesis in various cancers through interaction with many cell signaling proteins [33].

Manganese superoxide dismutase (MnSOD) is a mitochondrial enzyme involved in the detoxification of reactive oxygen species. Since MnSOD contains manganese in its active site, factors that affect manganese availability can also have a marked effect on lipid peroxidation. This emphasizes the importance of fruits and vegetables including pineapple, acai and spinach as well as nuts and legumes, which are rich manganese sources. Increased risk of breast cancer has been linked to a polymorphism (valine to alanine substitution) in the mitochondrial targeting sequence of the MnSOD gene, which is thought to alter transport of the enzyme into the mitochondria. Women who eat less fruit and vegetables have a stronger correlation between breast cancer indidence and reduced fruit and vegetable intake [34, 35].

The World Cancer Research Fund/American Institute for Cancer Research, the American Society for Clinical Oncology and the American Cancer Society have published collective dietary guidelines for breast cancer survivors which recommend increased intake of fruit, vegetables, legumes and whole grains and reduced intake of sugar, sugary drinks and calorie-dense foods [36].

Various studies indicate that a diet rich in vitamins and fibre, low in meat and milk, and with moderate intake of wine is the best combination for cancer prevention. Putting these pieces of evidence together, the Mediterranean diet seems to be qualified for use as a prescribed medication [5]. It reflects the traditional eating habits of people from Mediterranean countries. In general, it is high in fruit, beans, nuts, fish, green vegetables, legumes, cereals, grains and virgin olive oil. Although its main feature is considered to be low meat and dairy intake, the eating habits of Mediterraneans vary by country and region. Being low in saturated fats and high in minimally processed plant-based foods, the Mediterranean diet is considered an ideal nutritional model. Observational and epidemiological studies suggest that it may have protective effects against cardiovascular disease and cancer, because Mediterranean countries show lower rates of these diseases than other countries [37, 38]. Olive oil contains about 30 phenol compounds, including hydroxytyrosol and oleuropein, and is the principal source of fat in the Mediterranean region. These compounds are powerful antioxidants that have been shown to protect cells from free radical damage induced by normal metabolism [39]. Antioxi-

dant-rich foods may postpone the accumulation of cell damage in the body and protect against cardiovascular disease, diabetes and the consequences of aging. A number articles in the literature have suggested that olive oil consumption is inversely related to risk of breast and ovarian cancer [40].

Another important feature of the Mediterranean diet is the diversity of seafood from the Mediterranean Sea. Long-chain omega-3 (n-3), eicosapentaenoic and docosahexaenoic fatty acids in seafood help improve cardiovascular health by decreasing risk factors such as blood pressure, triglyceride concentrations, heart arrhythmias and platelet aggregation [41]. These acids are thought to inhibit breast cancer [42, 43]. Fish like sardines and mackerel are an important part of the Mediterranean diet and are rich in omega-3 fatty acids. Other foods rich in omega-3 are nuts like walnuts, almonds, pumpkin and other seeds. These help prevent cancer progression by moderating cell proliferation, angiogenesis, metastasis and inflammation [44].

One or two glasses of wine per day, taken with food, are usually part of the Mediterranean diet. Although alcohol generally has negative effects on health, The Copenhagen Prospective Population Studies (2000) demonstrated that moderate wine intake may have a beneficial effect on human health as it contains various polyphenols. Resveratrol in particular increases expression of the sirtuin 1 (*SIRT1*) gene [45]. Changes in *SIRT1* expression are critical in diseases such as neurodegeneration, metabolic syndrome, cardiovascular disease and cancer. Moderate intake of red wine can be protective and decrease proliferation of breast cancer cells, while the antioxidant polyphenols modify ROS production and target steroid receptors [46]. There are studies indicating an inverse relationship between vegetable consumption and hormone-related tumors, including breast, ovarian and endometrial cancer (Pelucchi et al., 2009). The abundance of fruit and vegetables in the Mediterranean diet, such as apples, citrus, onions, broccoli, rich in flavonol polyphenols and fibre, is suggested to protect against carcinogenesis [14]. The vegetable component of the Mediterranean diet, specifically non-starchy vegetables, regulates steroid hormone concentrations and metabolism, activating antioxidant enzymes, stimulating the immune system and protecting against cancer [47]. The Mediterranean diet contains high concentrations of phytoestrogens, estrogen-like agents which may compete with estrogens for estrogen receptors, with antiestrogen effects [48]. Some studies demonstrate an association between significantly close observance of the Mediterranean diet and lower risk of endometrial cancer, providing evidence of a protective effect [49].

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Conflicts of interest statement

Authors declare no conflict of interest.

Author's contributions

Literature review: G.T., Q.H.; Collected the data: G.T., Q.H., G.M., M.C.E.; Contributed data: G.T., Q.H., G.M., M.C.E.; Performed the analysis: G.T., Q.H.; Wrote the paper: G.T., Q.H., revised the paper: G.T., Q.H., G.M., M.C.E; supervised the project: M.C.E.

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