MINI-REVIEW

Mechanics behind Breast Cancer Prevention - Focus on Obesity, Exercise and Dietary Fat

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Abstract

Cancer prevention is rapidly emerging as a major strategy to reduce cancer mortality. In the field of breast cancer, significant strides have recently been made in the understanding of underlying preventive mechanisms. Currently, three major strategies have been linked to an increase in breast cancer risk: obesity, lack of physical exercise, and high levels of saturated dietary fat. As a result, prevention strategies for breast cancer are usually centered on these lifestyle factors. Unfortunately, there remains controversy regarding epidemiological studies that seek to determine the benefit of these lifestyle changes. We have identified crucial mechanisms that may help clarify these conflicting studies. For example, recent reports with olive oil have demonstrated that it may influence crucial transcription factors and reduce breast tumor aggressiveness by targeting HER2. Similarly, physical exercise reduces sex hormone levels, which may help protect against breast cancer. Obesity promotes tumor cell growth and cell survival through upregulation of leptin and insulin-like growth factors. This review seeks to discuss these underlying mechanisms, and more behind the three major prevention strategies, as a means of understanding how breast cancer can be prevented.

Keywords: Breast cancer - obesity - physical exercise - diet - prevention

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Introduction

Breast cancer is among the most frequently studied diseases in oncology (Siegel et al., 2012). In fact, breast cancer accounts for nearly 1 in 3 female cancers, and consequently is the number one most frequently diagnosed cancer in women. Fortunately, the 5-year relative survival rate of breast cancer patients has increased to 77-90% today (Siegel et al., 2012). However, despite recent advances in our understanding of cancer, breast cancer incidence rates have generally remained stable (Siegel et al., 2012). These statistics show that while there has been great improvement in detection, treatment options, and survival, there remains a great need to reduce breast cancer incidence rates through prevention.

There are several factors which have shown promise in reducing breast cancer incidence rates. Some of the most popular preventative measures relate to lifestyle choices, especially changes in diet. Despite the fact that the American Cancer Society recommends consuming a diet high in fruits and vegetables, there remains some controversy regarding the role of diet in cancer prevention (Kushi et al., 2012). Most of this controversy comes from inconsistent results obtained from studies involving either single foods or single nutrients (Magalhaes et al., 2012). The truth behind these conflicting studies is better understood by analyzing their underlying mechanisms.

Many of the lifestyle choices thought to help prevent breast cancer are either directly or indirectly related to energy balance. Energy balance is most often described as calories consumed verses those expended during physical activity (Hall et al., 2012). For this reason, caloric intake and physical exercise are among the energy balance lifestyle choices which may have the greatest potential to reduce breast cancer risk. Other factors which are indirectly related to energy balance have also shown some potential with regards to breast cancer prevention. Those factors include maintaining a healthy diet of fruits and vegetables, moderate intake of red wine, and eating "good fats". In the past it has been unclear whether these factors have independent potential to reduce breast cancer rates, or whether they are simply a means of controlling overall caloric intake, another possible prevention strategy. Rather than focusing on epidemiological studies, this review will focus on the underlying mechanisms behind breast cancer prevention to more fully understand the science behind these controversies.

Obesity

Traditionally, the most common indicator of energy balance is body mass index (BMI) which estimates body fat using an individual's height and weight. Obesity, as defined by a BMI greater than 30, is a known risk factor

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for a variety of diseases including cancer. This is especially true for breast cancer in which the proximity of the adipose tissue may have a direct influence on the tumor (Brown and Simpson, 2012; Wang et al., 2012; Zhao et al., 2012). Unfortunately, the evidence linking BMI and breast cancer appears complex. For example, obesity during pre-teen years (ages 5-10) is inversely related to breast cancer risk (Baer et al., 2010). On the other hand, obesity after menopause is positively related to breast cancer incidence (Bates and Carmichael, 2004; Lahmann et al., 2004; Cheraghi et al., 2012; Phipps et al., 2012; Xu et al., 2012). Although this is fairly well established, the relationship between premenopausal obesity and breast cancer risk remains less clear. The majority of studies report that obesity, before menopause, is inversely related to premenopausal breast cancer (Carmichael and Bates, 2004; Palmer et al., 2007). However, a few studies report either no association or a positive association with breast cancer (Eng et al., 2005; Cecchini et al., 2012; Ogundiran et al., 2012). This complexity warrants a discussion regarding the obesity-related signaling pathways.

One of the mechanisms by which obesity is now thought to contribute to breast cancer is through the increased presence of leptin. Leptin is an adipose-tissue derived signaling molecule and is overexpressed in breast cancer, particularly in high-grade tumors (Artac and Altundag, 2011). Leptin contributes to cancer proliferation through activation of the mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K) signaling pathways as well as the JAK/STAT3 pathway (Frankenberry et al., 2006; McCormack et al., 2011). These pathways are often associated with tumor formation due to their involvement in cell proliferation and apoptosis. Additionally, Valle et al. (2011) reported that leptin may also increase the mitogenic effects of estrogen through the alteration of the estrogen receptor alpha and beta ratio (Valle et al., 2011). This ratio increased as a result of chronic exposure to leptin, which also enhanced estrogen-dependent transcriptional activity and increased cell growth (Valle et al., 2011). In addition to activating cell proliferation, leptin also poses a risk to breast cancer patients through its ability to influence epithelial to mesenchymal transition (EMT). Yan et al. (2012) demonstrated that leptin increases beta-catenin levels which are essential for promoter recruitment which leads to leptin-induced EMT and tumor formation. Beta-catenin levels are increased through leptin-induced phosphorylation of glycogen synthase kinase 3 beta (GSK3 beta) by both activated Akt and by activation of Wnt signaling through MTA1 (Yan et al., 2012).

Another obesity-related signaling pathway which may contribute to breast cancer is insulin-like growth factors (IGFs), especially IGF-1. Obesity is known to increase circulating insulin and IGF-1 which has been linked to tumor cell growth (Brown and Simpson, 2012; D'Esposito et al., 2012). Consequently, it plays a major role in obesity-related breast cancer. In fact, Creighton et al. (2012) analyzed the transcription signature of primary breast tumors of obese patients compared to non-obese patient's tumors. They reported a transcriptional signature of 662 genes in the obesity-associated tumors, most of which were involved in IGF signaling (Creighton et al., 2012). This illustrates the importance of the IGF signaling pathway in obesity-related breast cancer. Overall, IGF-1 has been linked with cell survival (anti-apoptosis) in addition to tumor cell growth (Yu and Rohan, 2000; Godsland, 2010). This occurs primarily through activation of PI3K/Akt and MAPK/p38 pathways (Sung et al., 2011). D'Esposito et al. (2012) reported IGF-1's release from adipocytes can be regulated by the presence of glucose and fatty acids such as palmitate or oleate (D'Esposito et al., 2012). IGF-1, IGF-2, and IGF-1 receptors (IGF-1R) have also been linked to estrogen (Mawson et al., 2005). For example, IGF-2 is recognized by IGF-1R and activates both estrogen receptor-alpha and estrogen receptor-beta (Richardson et al., 2011). Additionally, Song et al. (2010) demonstrated that estrogen can utilize either the IGF-1R or the estrogen receptor (Song et al., 2010). These underlying mechanisms, especially their link to estrogen, may help us better understand the controversy of premenopausal obesity-related breast cancer.

Diet

Monounsaturated fats and olive oil

Dietary choices and calorie reduction are lifestyle choices which may help lower the risk of breast cancer (Omodei and Fontana, 2011; Nogueira et al., 2012). The 'Mediterranean diet' and its components have been investigated for their potential to reduce an individual's risk for cancer. The 'Mediterranean diet' includes food generally consumed within this region including nuts, fruits, vegetables, legumes, whole-wheat bread, fish, olive oil (OO) and red wine (Pauwels, 2010). Within this diet, olive oil appears to reduce breast cancer risk specifically (Tsuji et al., 2012). Other aspects of the 'Mediterranean diet' have beneficial properties and may protect against other types of cancer, but are discussed thoroughly in other reviews (Egeberg et al., 2009; Taylor et al., 2009; Kabat et al., 2010; Alexander et al., 2011; Fortes and Boffetta, 2011; Fu et al., 2011; Hardy and Tollefsbol, 2011; Hauner et al., 2011; Jansen et al., 2011; Shanmugam et al., 2011; Magalhaes et al., 2012).

Olive oil has two major components which are studied in relation to breast cancer: the fatty-acid component, especially oleic acid and the antioxidant component containing polyphenols. Several studies have reported an inverse relationship between olive oil or other monounsaturated fats consumption and breast cancer (Wolk et al., 1998; Thiebaut et al., 2007; Psaltopoulou et al., 2011; Tsuji et al., 2012). There are also several studies which report either no or weak association between monounsaturated fat and breast cancer (Sieri et al., 2008; Zhang et al., 2011). Therefore, it is imperative that we understand the mechanisms by which monounsaturated fats such as olive oil influence breast cancer.

The underlying mechanism by which OO affects breast cancer is primarily through human EGFR type 2 (HER2/neu) (Colomer et al., 2008; Menendez et al., 2008; 2009). Since HER2-positive breast tumors are known to be more aggressive than their counterparts, OO specifically protects against the more aggressive

breast cancer tumors while having only minimal or no effect on HER2-negative breast tumors (Colomer et al., 2008). Early work by Menendez et al. (2008) with breast cancer and HER2 demonstrated that the tumoricidal effects of OO polyphenols are blocked when the HER2+ tyrosine activity is blocked, and OO is responsible for the depletion of the HER2 protein (Menendez et al., 2008). This indicated that tyrosine kinase might play a major role in the mechanism of OO and HER2. Their follow-up study indicated that OO polyphenols did not significantly decrease tyrosine kinase activity, but they did trigger more apoptosis in HER2 over-expressing MCF10A cells. Additionally, they determined that despite the fact that OO doesn't regulate tyrosine kinase activity, the protective effects of OO specifically target breast tumors which over-express the type 1 receptor tyrosine kinase HER2 (Menendez et al., 2009).

The polyphenols or antioxidant component of OO is also known for its ability to help protect against DNA damage, thereby reducing the risk of breast cancer. Two of the major antioxidants that have been studied in relation to breast cancer prevention are hydroxtyrosol and tyrosol. One recent study demonstrated that hydroxtyrosol is a more potent antioxidant than tyrosol due to its ability to lower the concentration of reactive oxygen species (ROS) in MCF10A cells more compared with tyrosol (Warleta et al., 2011). Furthermore, they also showed that hydroxtyrosol was able to prevent oxidative DNA damage in three breast cancer cell lines while tyrosol did not.

Although polyphenols represent a major component of OO, other major components of OO are also known to play a role in the protection against breast cancer. Specifically, the protective effect of certain dietary fats has been linked to regulating the amount or activity of transcription factors. This is especially true regarding OO and breast cancer. For example, Menendez et al., made the observation that oleic acid found in OO is known to repress the transcriptional activity of the HER2 gene. They also showed the HER2 promoter was essential for this repression and that oleic acid also up-regulates PEA3, a transcriptional repressor of the HER2 gene (Menendez, 2006). Mendendez and Lupu (2006) later found that oleic acid also down-regulates the fatty acid synthase gene (FASN) which decreases the risk that precursor lesions will become invasive (Menendez and Lupu, 2006). Overall, it appears that OO has potential to reduce the risk of breast cancer formation, especially of the more aggressive types including HER2-positive and over-expressing FASN tumors.

Although most of the work involving breast cancer prevention and OO has been in vitro, there is also in vivo evidence to support the protective effects conferred by OO. For example, Escrich et al. (2011) determined that breast cancer-induced mice that were fed a diet rich in OO showed a slight protective effect over mice that were fed a high-corn diet. Additionally, the tumors in mice fed with an OO-rich diet were less aggressive, compared to controls (Escrich et al., 2011). Furthermore, OO led to modifications in the tumors which corresponded with lower proliferation, higher apoptosis and lower DNA damage, compared to control tumors. Costa et al. (2004) demonstrated that adenocarcinomas which arose from rats fed a high-OO diet were of a lower histological grade compared with adenocarcinomas from rats fed a high-corn diet. These high-OO diet adenocarcinomas were also associated with fewer necrotic and invasive areas (Costa et al., 2004). Overall, it appears that OO as a source of monounsaturated fat has the potential to decrease both breast cancer incidence rates as well as breast cancer aggressiveness.

Physical Exercise

Physical exercise as a prevention strategy against cancer is most often associated with a means of reducing the negative effects of obesity or in other words, energy imbalance. This may be one reason why the connection between breast cancer prevention and physical exercise is less well established and understood than other preventative strategies. However, new evidence has demonstrated that physical activity may confer breast cancer-specific protection beyond reducing obesity (Bernstein et al., 1994; Bernstein, 2009; Shin et al., 2009; Friedenreich et al., 2010; Morris et al., 2010; Lynch et al., 2011; Albrecht and Taylor, 2012).

Recent evidence has indicated that physical exercise prevents breast cancer primarily through its ability to reduce sex hormone levels in women. This mechanism is crucial since estrogens promote the risk of breast cancer development due to the stimulation of mitosis and regulation of cell proliferation. Friedenreich et al., sheds further light on this mechanism as it showed that physical exercise initiated a significant decrease in estradiol and increase of sex-hormone binding globulin (SHBG), with no significant impact on levels of estrone, androstenedione, and testosterone (Friedenreich et al., 2010). Furthermore, Kossman et al. (2011) conducted a study involving seven healthy premenopausal women at high risk for breast cancer resulted in a beneficial reduction of estrogen (18.9%) and progesterone (23.7%) after 300 minutes of vigorous physical exercise per week for seven menstrual cycles (Kossman et al., 2011). Despite these encouraging results, there remains some controversy regarding the effect of exercise and hormone levels in premenopausal women. For instance, in the 16-week WISER study, no significant differences in sex hormones or SHBG were demonstrated between exercise and sedentary groups (Smith et al., 2011). The results of the study involving the high-risk premenopausal women may be due to the increased length of the study, the performance of vigorous activity opposed to moderate exercise, or the doubled duration of physical activity compared with the WISER study. Nonetheless, varied results were noted. One principle behind many of these studies is the fact that an exposure to higher levels of sex hormones increases breast cancer risk. Evidence for this claim is a study by Morris et al., which correlated an increased risk of breast cancer with earlier onset of ovulation in young women who were not physically active and underwent menarche at an earlier age (Morris et al., 2010). Overall, these studies demonstrate that physical activity may play an important role in lowering breast cancer risk, through lowering the levels of sex hormones, especially as a result of lifelong

physical activity.

Conclusions

Several studies have demonstrated the importance of maintaining beneficial lifestyle choices throughout an individual's lifetime to reduce breast cancer risk (Bernstein et al., 1994; Hilakivi-Clarke et al., 2010; Cabanes et al., 2011; Escrich et al., 2011; Lynch et al., 2011; Kark et al., 2012). One possible explanation for this is that the initial accumulation of driver mutations which have the potential to ultimately lead to malignancy, occur in young adults. Unfortunately, few studies address this important issue. This may be a possible explanation why some diet or physical exercise studies report insignificant correlations. Perhaps the effect of these factors on breast cancer risk was not seen due to the limited time of the study, or that the potentially beneficial agents could not reverse the effects of previous poor lifestyle choices. It may be premature to disregard these factors without long-term studies which include young adults.

Overall, there are several lifestyle factors which appear to aid in breast cancer prevention. Obesity is one factor which has shown a consistent and strong correlation with increased breast cancer risk. Dietary choices, especially the type of fat consumed, and physical exercise have shown considerable promise in reducing risk. Despite some conflicting epidemiological studies, it is clear that obesity, dietary fat, and physical exercise each have underlying mechanisms which may help protect against breast cancer. A thorough understanding of these mechanisms will no doubt lead to the discovery of novel targets and therapies which may extend the protective effects of these lifestyle choices.

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