

MINI-REVIEW

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

Melissa Marie Alegre, McKay Hovis Knowles, Richard A Robison, Kim Leslie O'Neill*

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

Asian Pacific J Cancer Prev, 14 (4), 2207-2212

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 versus 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

Department of Microbiology and Molecular Biology, Brigham Young University, Provo, UT, USA *For correspondence: kim_oneill@byu.edu

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 hydroxytyrosol and tyrosol. One recent study demonstrated that hydroxytyrosol 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 hydroxytyrosol 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.

References

Albrecht TA, Taylor AG (2012). Physical activity in patients with advanced-stage cancer: a systematic review of the literature. *Clin J Oncol Nur*, **16**, 293-300.

Alexander DD, Weed DL, Cushing CA, Lowe KA (2011). Meta-analysis of prospective studies of red meat consumption and colorectal cancer. *Eur J Cancer Prev*, **20**, 293-307.

Artac M, Altundag K (2011). Leptin and breast cancer: an overview. *Med Oncol*, **29**, 1510-4.

Baer HJ, Tworoger SS, Hankinson SE, Willett WC (2010). Body fatness at young ages and risk of breast cancer throughout life. *Am J Epidemiol*, **171**, 1183-94.

Bernstein L (2009). Exercise and breast cancer prevention. *Current Oncol Reports*, **11**, 490-6.

Bernstein L, Henderson BE, Hanisch R, Sullivanhalley J, Ross RK (1994). Physical exercise and reduced risk of breast cancer in young-women. *J Nat Cancer Institute*, **86**, 1403-8.

Brown KA, Simpson ER (2012). Obesity and breast cancer: Mechanisms and therapeutic implications. *Front Biosci (Elite Ed)*, **4**, 2515-24.

Cabanes A, Pastor-Barriuso R, Garcia-Lopez M, et al (2011). Alcohol, tobacco, and mammographic density: a population-based study. *Breast Cancer Research and Treatment*, **129**, 135-47.

Carmichael AR, Bates T (2004). Obesity and breast cancer: a review of the literature. *Breast*, **13**, 85-92.

Cecchini RS, Costantino JP, Cauley JA, et al (2012). Body mass

index and the risk for developing invasive breast cancer among high-risk women in nsabp p-1 and star breast cancer prevention trials. *Cancer Prev Res*, **5**, 583-92.

Cheraghi Z, Poorolajal J, Hashem T, Esmailnasab N, Irani AD (2012). Effect of body mass index on breast cancer during premenopausal and postmenopausal periods: a meta-analysis. *Plos One*, **7**, 51446.

Colomer R, Lupu R, Papadimitropoulou A, et al (2008). Giacomo castelvetro's salads. Anti-her2 oncogene nutraceuticals since the 17th century? *Clinical and Translational Oncology*, **10**, 30-4.

Costa I, Moral R, Solanas M, Escrich E (2004). High-fat corn oil diet promotes the development of high histologic grade rat dmba-induced mammary adenocarcinomas, while high olive oil diet does not. *Breast Cancer Res and Treatment*, **86**, 225-35.

Creighton CJ, Sada YH, Zhang YQ, et al (2012). A gene transcription signature of obesity in breast cancer. *Breast Cancer Res and Treatment*, **132**, 993-1000.

D'Esposito V, Passaretti F, Hammarstedt A, et al (2012). Adipocyte-released insulin-like growth factor-1 is regulated by glucose and fatty acids and controls breast cancer cell growth in vitro. *Diabetologia*, **55**, 2811-22.

Egeberg R, Olsen A, Loft S, et al (2009). Intake of whole grain products and risk of breast cancer by hormone receptor status and histology among postmenopausal women. *Int J Cancer*, **124**, 745-50.

Eng SM, Gammon MD, Terry MB, et al (2005). Body size changes in relation to postmenopausal breast cancer among women on long Island, New York. *Am J Epidemiol*, **162**, 229-37.

Escrich E, Moral R, Solanas M (2011). Olive oil, an essential component of the mediterranean diet, and breast cancer. *Public Hlth Nutrition*, **14**, 2323-32.

Fortes C, Boffetta P (2011). Nutritional epidemiological studies in cancer prevention: what went wrong, and how to move forwards. *Eur J Cancer Prev*, **20**, 518-25.

Frankenberry KA, Skinner H, Somasundar P, McFadden DW, Vona-Davis LC (2006). Leptin receptor expression and cell signaling in breast cancer. *Int J Oncology*, **28**, 985-93.

Friedenreich CM, Woolcott CG, McTiernan A, et al (2010). Alberta physical activity and breast cancer prevention trial: Sex hormone changes in a year-long exercise intervention among postmenopausal women. *J Clin Oncol*, **28**, 1458-66.

Fu Z, Deming SL, Fair AM, et al (2011). Well-done meat intake and meat-derived mutagen exposures in relation to breast cancer risk: The nashville breast health study. *Breast Cancer Res Treat*, **129**, 919-28.

Godsland IF (2010). Insulin resistance and hyperinsulinaemia in the development and progression of cancer. *Clin Sci*, **118**, 315-32.

Hall KD, Heymsfield SB, Kemnitz JW, et al (2012). Energy balance and its components: Implications for body weight regulation. *Am J Clin Nutrition*, **95**, 989-94.

Hardy TM, Tollefsbol TO (2011). Epigenetic diet: Impact on the epigenome and cancer. *Epigenomics*, **3**, 503-18.

Hauner D, Janni W, Rack B, Hauner H (2011). The effect of overweight and nutrition on prognosis in breast cancer. *Dtsch Arztebl Int*, **108**, 795-801.

Hilakivi-Clarke L, Andrade JE, Helferich W (2010). Is soy consumption good or bad for the breast? *J Nutrition*, **140**, 2326-34.

Jansen RJ, Robinson DP, Stolzenberg-Solomon RZ, et al (2011). Fruit and vegetable consumption is inversely associated with having pancreatic cancer. *Cancer Causes and Control*, **22**, 1613-25.

Kabat GC, Cross AJ, Park Y, et al (2010). Intakes of dietary iron

- and heme-iron and risk of postmenopausal breast cancer in the national institutes of health-aarp diet and health study. *Am J Clin Nutr*, **92**, 1478-83.
- Kark JD, Goldberger N, Kimura M, Sinnreich R, Aviv A (2012). Energy intake and leukocyte telomere length in young adults. *Am J Clin Nutr*, **95**, 479-87.
- Kossman DA, Williams NI, Domchek SM, et al (2011). Exercise lowers estrogen and progesterone levels in premenopausal women at high risk of breast cancer. *J Appl Physiol* **111**, 1687-93.
- Kushi LH, Doyle C, McCullough M, et al (2012). American cancer society guidelines on nutrition and physical activity for cancer prevention. *CA: A Cancer J Clinicians*, **62**, 30-67.
- Lahmann PH, Hoffmann K, Allen N, et al (2004). Body size and breast cancer risk: Findings from the european prospective investigation into cancer and nutrition (epic). *Int J Cancer*, **111**, 762-71.
- Lynch BM, Neilson HK, Friedenreich CM (2011). Physical activity and breast cancer prevention. *Recent Results Cancer Res*, **186**, 13-42.
- Magalhaes B, Peleteiro B, Lunet N (2012). Dietary patterns and colorectal cancer: Systematic review and meta-analysis. *Eur J Cancer Prev*, **21**, 15-23.
- Mawson A, Lai A, Carroll JS, et al (2005). Estrogen and insulin/igf-1 cooperatively stimulate cell cycle progression in mcf-7 breast cancer cells through differential regulation of c-myc and cyclin d1. *Molecul Cellular Endocrinol*, **229**, 161-73.
- McCormack D, Schneider J, McDonald D, McFadden D (2011). The antiproliferative effects of pterostilbene on breast cancer in vitro are via inhibition of constitutive and leptin-induced janus kinase/signal transducer and activator of transcription activation. *Am J Surg*, **202**, 541-4.
- Menendez JA, Lupu R (2006). Mediterranean dietary traditions for the molecular treatment of human cancer: Anti-oncogenic actions of the main olive oil's monounsaturated fatty acid oleic acid (18: 1n-9). *Current Pharmaceutical Biotechnology*, **7**, 495-502.
- Menendez JA PA, Vellon L, Lupu R (2006). A genomic explanation connecting "mediterranean diet", olive oil and cancer: oleic acid, the main monounsaturated fatty acid of olive oil, induces formation of inhibitory "pea3 transcription factor-pea3 DNA binding site" complexes at the her-2/neu (erbb-2) oncogene promoter in breast, ovarian and stomach cancer cells. *Eur J Cancer*, **42**, 2425-32.
- Menendez JA, Vazquez-Martin A, Garcia-Villalba R, et al (2008). Tabanti-her2 (erbb-2) oncogene effects of phenolic compounds directly isolated from commercial extra-virgin olive oil (evoo). *BMC Cancer*, **8**, 377.
- Menendez JA, Vazquez-Martin A, Oliveras-Ferraro C, et al (2009). Extra-virgin olive oil polyphenols inhibit her2 (erbb-2)-induced malignant transformation in human breast epithelial cells: Relationship between the chemical structures of extra-virgin olive oil secoiridoids and lignans and their inhibitory activities on the tyrosine kinase activity of her2. *Int J Oncology*, **34**, 43-51.
- Morris DH, Jones ME, Schoemaker MJ, Ashworth A, Swerdlow AJ (2010). Determinants of age at menarche in the uk: Analyses from the breakthrough generations study. *Bri J Cancer*, **103**, 1760-64.
- Nogueira LM, Dunlap SM, Ford NA, Hursting SD (2012). Calorie restriction and rapamycin inhibit mmtv-wnt-1 mammary tumor growth in a mouse model of postmenopausal obesity. *Endocrine-Related Cancer*, **19**, 57-68.
- Ogundiran TO, Huo DZ, Adenipekun A, et al (2012). Body fat distribution and breast cancer risk: findings from the nigerian breast cancer study. *Cancer Causes Control*, **23**, 565-74.
- Omodei D, Fontana L (2011). Calorie restriction and prevention of age-associated chronic disease. *Febs Letters*, **585**, 1537-42.
- Palmer JR, Adams-Campbell LL, Boggs DA, Wise LA, Rosenberg L (2007). A prospective study of body size and breast cancer in black women. *Cancer Epidemiol Biomarkers Prevent*, **16**, 1795-802.
- Pauwels EKJ (2010). The protective effect of the mediterranean diet: Focus on cancer and cardiovascular risk. *Med Principles Practice*, **20**, 103-11.
- Phipps AI, Buist DSM, Malone KE, et al (2012). Breast density, body mass index, and risk of tumor marker-defined subtypes of breast cancer. *Ann Epidemiol*, **22**, 340-8.
- Psaltopoulou T, Kostis RI, Haidopoulos D, Dimopoulos M, Panagiotakos DB (2011). Olive oil intake is inversely related to cancer prevalence: A systematic review and a meta-analysis of 13800 patients and 23340 controls in 19 observational studies. *Lipids in Health and Disease*, **10**.
- Richardson AE, Hamilton N, Davis W, Brito C, De Leon D (2011). Insulin-like growth factor-2 (igf-2) activates estrogen receptor-alpha and -beta via the igf-1 and the insulin receptors in breast cancer cells. *Growth Factors*, **29**, 82-93.
- Shanmugam MK, Kannaiyan R, Sethi G (2011). Targeting cell signaling and apoptotic pathways by dietary agents: Role in the prevention and treatment of cancer. *Nutrition Cancer*, **63**, 161-73.
- Shin A, Matthews CE, Shu XO, et al (2009). Joint effects of body size, energy intake, and physical activity on breast cancer risk. *Breast Cancer Res Treat*, **113**, 153-61.
- Siegel R, Naishadham D, Jemal A (2012). Cancer statistics, 2012. *CA: A Cancer J Clinicians*, **62**, 10-29.
- Sieri S, Krogh V, Ferrari P, et al (2008). Dietary fat and breast cancer risk in the european prospective investigation into cancer and nutrition. *Am J Clin Nutrition*, **88**, 1304-12.
- Smith AJ, Phipps WR, Arikawa AY, et al (2011). Effects of aerobic exercise on premenopausal sex hormone levels: Results of the wiser study, a randomized clinical trial in healthy, sedentary, eumenorrheic women. *Cancer Epidemiol Biomarkers Prevent*, **20**, 1098-106.
- Song RXD, Chen YC, Zhang ZG, et al (2010). Estrogen utilization of igf-1-r and egf-r to signal in breast cancer cells. *J Steroid Biochem Molecul Biol* **118**, 219-30.
- Sung MK, Yeon JY, Park SY, Park JHY, Choi MS (2011). Obesity-induced metabolic stresses in breast and colon cancer. *Nutrition and Physical Activity in Aging, Obesity, and Cancer*, **1229**, 61-8.
- Taylor VH, Misra M, Mukherjee SD (2009). Is red meat intake a risk factor for breast cancer among premenopausal women? *Breast Cancer Res Treat*, **117**, 1-8.
- Thiebaut ACM, Kipnis V, Chang SC, et al (2007). Dietary fat and postmenopausal invasive breast cancer in the national institutes of health-aarp diet and health study cohort. *J Natl Cancer Inst*, **99**, 451-62.
- Tsuji M, Tamai Y, Wada K, et al (2012). Associations of intakes of fat, dietary fiber, soy isoflavones, and alcohol with levels of sex hormones and prolactin in premenopausal japanese women. *Cancer Causes Control*, **23**, 683-89.
- Valle A, Sastre-Serra J, Oliver J, Roca P (2011). Chronic leptin treatment sensitizes mcf-7 breast cancer cells to estrogen. *Cellular Physiology Biochemistry*, **28**, 823-32.
- Wang YY, Lehuede C, Laurent V, et al (2012). Adipose tissue and breast epithelial cells: a dangerous dynamic duo in breast cancer. *Cancer Lett*, **324**, 142-51.
- Warleta F, Quesada CS, Campos M, et al (2011). Hydroxytyrosol protects against oxidative DNA damage in human breast cells. *Nutrients* **3**, 839-57.
- Wolk A, Bergstrom R, Hunter D, et al (1998). A prospective study of association of monounsaturated fat and other types

Melissa Marie Alegre et al

- of fat with risk of breast cancer. *Arch Int Med*, **158**, 41-5.
- Xu YL, Sun Q, Shan GL, et al (2012). A case-control study on risk factors of breast cancer in China. *Arch Med Science*, **8**, 303-9.
- Yan D, Avtanski D, Saxena NK, Sharma D (2012). Leptin-induced epithelial-mesenchymal transition in breast cancer cells requires beta-catenin activation via akt/gsk3- and mta1/wnt1 protein-dependent pathways. *J Biol Chem*, **287**, 8598-612.
- Yu H, Rohan T (2000). Role of the insulin-like growth factor family in cancer development and progression. *J Natl Cancer Inst*, **92**, 1472-89.
- Zhang CX, Ho SC, Lin FY, et al (2011). Dietary fat intake and risk of breast cancer: a case-control study in china. *Eur J Cancer Prev*, **20**, 199-206.
- Zhao M, Sachs PC, Wang X, et al (2012). Mesenchymal stem cells in mammary adipose tissue stimulate progression of breast cancer resembling the basal-type. *Cancer Biol Ther*, **13**, 782-92.