REVIEW

Lifestyle Components and Primary Breast Cancer Prevention

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Abstract

Breast cancer primary prevention is a high research priority due to the high psychological and economic costs. The disease is a multistep process and several risk factors have been recognized. Over the past three decades numerous studies have investigated the association of lifestyle with breast cancer, showing independent effects of various factors. We report here a summary of the present state of knowledge on the role of lifestyle patterns, such as physical activity, diet, smoking, hormone therapy, and experience of psychological stress in the modulation of breast cancer in women, and discuss commonly accepted biological mechanisms hypothesized as responsible for the associations. The findings indicate that regular physical activity of moderate to vigorous intensity is probably linked with the decreased breast cancer risk among postmenopausal females and suggestive for a decrease of the risk in premenopausal women. In contrast, the consumption of high-fat diet, alcohol intake, and use of combined estrogen and synthetic progestagen hormonal therapy may increase the risk. Epidemiological findings dealing with a role of smoking and experience of psychological stress are conflicting.

Keywords: Breast cancer - lifestyle factors - review

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Introduction

Breast cancer (BC) is the most common malignancy in women in the world. The disease is caused by multiple genetic defects that can be due to infectious and non-infectious factors, environmental and lifestyle factors, e.g. diet, physical inactivity, obesity, alcohol consumption, tobacco smoking (Hussain et al., 2003; Nahleh et al., 2011). According to the recent estimates 1.38 million women were diagnosed with breast cancer and 485,000 died worldwide in 2008 (Jemal et al., 2011). Breast cancer is one of the most frequent diagnosed cancer among women in the economically developing countries (Jemal et al., 2009; 2011; Ferlay et al., 2010). The incidence rate of this disease vary around the world. For example, the age-standardized incidence rates per 100,000 are: North America 126 (Toriola and Colditz, 2013); Taiwan 81.36 (Wang et al., 2013); Singapur 54.9, Malaysia 39.3 (Sulaiman et al., 2011); Poland 44.5 (Bruzewicz, 2008); Russia 43.2, Japan 42.7, China 21.6, Mongolia 8.0 (Troisi et al., 2012); Saudi Arabia 11.4 (Amin et al., 2014). According to the analysis of trends in the breast cancer incidence and mortality in USA, carried out by Toriola and Colditz (2013) over the past 70 years, the stable incidence rates are monitored after 2003 (126 per 100,000). Although, the 5-years relative survival rate of the breast cancer cases has reached a high percentage (77-90%) (Siegel et al., 2012) owing to new breast cancer fighting but, unfortunately, the disease is associated with side effects and high economic costs (Kruk, 2014a). It is suggested that about 90% of cancers is linked to the environmental exposure (Moore and Sobue, 2010; Givennikow et al., 2010). Therefore, the main strategy for a control of breast cancer would be through primary prevention, followed by the identification of risk factors for cancer. There is a large amount of evidence that the strongest factors that increase breast cancer risk in women are: age above 65 years, genetic mutations in *BRCA1* and/or *BRCA2* genes, high mammographic breast density, atypical hyperplasia (relative risk, PR>4); exposure to endogenous sex hormones, exposure to high-dose of ionizing radiation (RR=2.1-4.0); age at menarche <12 years, menopause above 55 years, no full-term pregnancies, postmenopausal obesity, personal history of colon or other gynecological cancers, long-term use of hormones containing estrogen and progestin (RR=1.2-2.0) (Weir et al., 2007; ACS, 2011).

However, the epidemiologic studies suggest that the recognized breast cancer factors can explain only about 40% of all breast cancer cases (Bleiker and van der Ploeg, 1999). In addition, Lacey et al. (2009) supposes that an identification of risk factors in the majority of breast cancer patients is impossible. As it is seen from the cancer statistic (Jemal et al., 2011) both the incidence and mortality rates of breast cancer in developing countries may rise to the level of the developed countries. Moreover, according to an estimation of Jemal et al. (2011) about 50% incidence and 60% deaths occurred in the developing countries. A high speed of both incidence and mortality of breast cancer may be partially described to a change of lifestyle patterns

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depressing healthcare. The considerable differences between western and eastern countries in the breast cancer incidence rates indicate that the environmental and economic factors may contribute to breast cancer risk independently on the established risk factors presented above.

During the past 20 years, there has been growing interest in the lifestyle determinants and breast cancer risk. Strong evidence exists that physical inactivity, some nutritional factors, such as an increased intake of fat and red meat are associated with a higher risk of breast cancer (Murthy and Mathew, 2004; Kushi et al., 2006; Kruk, 2007a; Kellen et al., 2009; Bernstein et al., 2010; Friedenreich et al., 2010; Lynch et al., 2011; Kamineni et al., 2012; Kushi et al., 2012; Sangrajrang et al., 2013; Schmid et al., 2014).This paper examines the results of the recent scientific research concerning the role of lifestyle components in breast cancer and the biological mechanisms through which the "healthy" lifestyle can perform its beneficial action.

Physical Activity

Physical activity (PA) is defined as any bodily movement produced by skeletal muscles that results in energy consumption (Caspersen et al., 1985). The simplest description of PA in epidemiological studies should include types of activity (recreational, household, occupational, transportation), duration, frequency, and intensity in all domains (Schmid et al., 2014). Additionally, the total amounts of energy expenditure during individuals engaging in a particular PA should be calculated. The energy expenditure dose is a combination of the duration and intensity of activity, and is the most frequently measured using a resting metabolic score (MET) (WCRF/AICR, 2007). One MET is equivalent to quiet sitting, which for the average adult is approximately equals to 4.184 kJ • kg^{-1} body weight • h^{-1} or 3.5ml of oxygen • kg body $weigh^{t-1}$ • min^{-1} (Ainsworth et al., 2000; Ainsworth et al., 2011). Based on the MET score, the intensity of activity is often stratified in epidemiologic studies into four levels (Norton et al., 2010): *sedentary* or *inactive* for MET 1.0-<1.6 (e.g. sleeping, eating, sitting, watching television, working using computer, Internet use); *light* for MET 1.6-<3.0 (e.g. balance, yoga); *moderate* for MET 3.0-<6.0 (e.g. walking, gardening), and *vigorous*, for MET ≥6.0 (e.g. running, swimming, jogging).

According to the World Health Organization Report physical inactivity is the fourth leading reason for global mortality, responsible for 6% of deaths worldwide (WHO, 2010; Lee et al. (2012). In a recent analysis of the disease burden and life expectancy estimates physical inactivity is responsible for 10% of breast cancer. The authors conclude that a 25% decrease in physical inactivity may result in the reduction of 1.3 million deaths every year. Physical inactivity is seriously growing among individuals worldwide, and is considered in the literature on this subject as "the biggest public health problem of the 21st century" (Blair, 2009, p.1). The significance of physical inactivity as a main factor of civilization diseases was highlighted in numerous research that focused on the relationship between PA and human health, and the scale of inactivity was estimated as pandemic in 2012 (Piggin and Bairner, 2014).

In the past two decades the observational and randomized controlled trials (RCTs) have presented a large evidence on the protective role of physical activity against chronic diseases. However, findings from observational studies are often conflicting. This is due to the heterogenity of methods applied to assess physical activity across studies, adjustment for confounding variables selection criteria of individuals and a sample size, different populations studied or incomplete consideration of confounding factors (Lynch et al., 2011; Clague and Bernstein, 2012; Nunan et al., 2013).

Earlier review by Monninkhoff et al. (2007) regarding the relationship between PA and BC risk found an average risk reduction of 30% in case-control studies and a 20% risk reduction in cohort studies. The authors noticed an estimation of a dose-response relationship PA-BC in 41 studies of the 51 studies reporting a decrease of the risk, and the dose-response relation was confirmed in 33 studies. The risk reduction was demonstrated for recreational, occupational and household activity, being the strongest for moderate-vigorous recreational activity, for women with BMI<30 kg/m^2 and was stronger in postmenopausal women. Furthemore, Lynch et al. (2011) reviewed 73 studies published from 1993 to 2009. In this review physically active women vs the least active women were associated with a 25% average risk reduction. The risk reduction was strongest for recreational activity, for lifetime timing, for exercise performed after menopause and regularly, and for exercise of moderate to vigorous intensity. The authors concluded that the protective effect of activity was stronger in women who were normal weight, non-Caucasian, parous and had no family history of BC. In turn, in a review of 76 studies (72 studies conducted among women and four in men) published from 1989 to 2011, Loprinzi et al. (2012) found that 53% of the studies reviewed demonstrated the protective effect of regular PA on BC risk. The group concluded that the greatest reduction in the risk may be achieved by the regular activity exhibited from childhood throughout the lifespan. The next study by Wu et al., (2012) reviewed 31 prospective studies demonstrating that the risk reduction was seen for occupational and non-occupational activity of moderate and vigorous intensity. In a recent meta-analysis, Guo et al. (2013) summarized three cohort and 12 case-control studies published between 2003-2012, involving 10,290 cases and 84,259 controls. They found a significant protective effect of PA on BC risk (OR=0.73, 95%CI=0.63-0.85). In turn, the recent meta-analysis of 43 prospective studies of Schmid and Leitzmann (2014) (68,936 cancer cases among >4 million individuals) demonstrated that the sedentary lifestyle increased risk of colon, endometrial, and lung cancers but not of breast. The authors concluded that in the case of cancers related with obesity the relationship of PA-BC may be indirect, i.e. to occurs through the effect of activity on obesity (Yang and Colditz, 2014). Although, different methodology was applied in the meta-analyses or pooled analyses in order to provide the summary estimates of relationship

between PA and BC and also, citing Clague-Bernstein's, 2012 p.551 "one must interpret results of this studies cautiously", the summary estimates well document the benefits of moderate-vigorous PA in relation to BC risk. This evidence finds confirmation in a few recent studies on this topic not included in the reported analyses above. For example, Kobayashi et al. (2012) in a case-control study (1,011 cases, 1,014 controls) conducted in Vancouver found that lifetime leisure-time and household moderate-to vigorous PA decreased BC risk by about 50% among postmenopausal women engaged in running for 3h/week and active in household work for 21h/week. The risk reduction was seen in all age periods across lifetime being the strongest during adulthood. The authors observed that the protective effect of leisure-time activity was restricted to human epidermal growth factor receptor-2 (HER-2). In turn, household activity appeared to reduce BC risk for ER^+/PR^+ tumors regardless of HER-2 status. Further, occupational PA performed during ages 18-34 increased the risk in premenopausal women two times.

Steindorf et al. (2013) have addressed the association between PA-BC risk in the European prospective study (257,805 women from eight countries among them 8,034 incident invasive BC identified during 11.6 years). The study results showed that adjusted hazard ratio (HR) for BC risk was negatively associated with moderate and high levels of total activity (HR=0.92, 95%CI=0.86-0.99 and HR=0.87, 95%CI=0.79-0.97) compared with the lowest level. The group further showed that for women with BC diagnosed before age 50 the decrease in risk was observed for moderate total PA, while in women aged >50 years the risk reduction was the largest for the vigorous activity (HR=0.78, 95%CI=0.64-0.94 and HR=0.86, 95%CI=0.77-0.97, respectively). In this study no relationship between occupational activity and BC was found. Further, a subgroup analysis by hormone receptor status, using data from 6,007 cases, showed a 16% significant decrease in the risk in women with ER^+/PR^+ receptors for combined recreational and household activities and a 38% decrease for household activity alone in women with EP^-/PR^- receptors type, as compared the highest vs the lowest tertile of activity. The authors concluded that PA of moderate and vigorous levels can protect modestly against breast cancer. Another prospective study included 73,615 postmenopausal women participating in the CPS-II Nutrition Cohort (Hildebrand et al., 2013). After 14.2 years follow-up time 4,760 incident BC cases were identified. This study also supported the protective effect of total recreational activity on BC as follows: RR=0.75, 95%CI=0.63-0.89 for women reporting >42 MET-hours/week activity vs those reporting 0-<7 MET-hours/week; RR=0.86, 95%CI=0.75-0.98 for women reporting only walking as their recreational activity for ≥7 hours/week vs those walking ≤3 hours/week. The authors reported null associations for any hormone receptor type. In contrast, the Norwegian Women and Cancer Study with 80,202 postmenopausal women including 1,767 invasive BC cases, identified during 8.2 years of follow-up, did not confirmed findings of consistent inverse association between PA and BC risk in the Norwegian postmenopausal women (Borch et al., 2014). This lack of consistency may be attributable to the limitation in the PA assessment. Firstly, the self-reported PA data were collected for three periods of life (at age of 14, 30 years, and at enrollment), and not for lifetime. Secondly, the authors did not collect the basis information on type, intensity, frequency and duration of activity. However, the authors in their conclusion maintain that PA has a potential to decrease the risk. In contrast, the previous case-control study in Tunisia that evaluated the association between lifetime PA and BC risk (400 cases, 400 controls) found significant strong risk reductions (OR=0.27, 95%CI=0.18-0.52 and OR=0.42, 95%CI=0.26-0.73 for the highest *vs* the lowest level of activity measured in hours/week/year and MET-hours/week/year, respectively (Awatef et al., 2011).

A number of multiple biological interrelating pathways have been proposed to explain the association between PA and BC risk. Briefly, PA decreases overweight/obesity, decreases concentration of sex hormones, reduces insulin resistance and insulin-like growth factor 1 (IGF-1), reduces levels of leptin and adiponectin, increases level of sex hormone binding globulin (SHBG), stimulates the immune systems and decreases inflammation (reviewed recently by Montaruli et al., 2012). These hypothesized pathways may impact all stages of carcinogenesis (initiation, promotion, progression) because BC is a multifactorial disease (Rundle, 2005; Wetmore and Ulrich, 2006; Kruk, 2007b; McTiernan, 2008; Neilson et al., 2009; Thompson et al., 2009; Friedenreich, 2011; Lynch et al., 2011; Goh et al., 2012; Montaruli et al., 2011). The mechanism that can predominate may be dependent on subtype and stage of carcinogenesis, intensity of PA, and a woman's characteristic (e.g. race/ethnicity). Exercise and PA can increase detoxification of both chemical carcinogens and ROS, thus may reduce DNA damage caused by environmental pollutions (Rundle, 2005; Kruk and Aboul-Enein, 2006). In addition to the detoxication capacity, PA can increase DNA repair activity through up-regulating the potential of antioxidant defense systems (Leeuwenburgh and Heinecke, 2001) which, in turn would prevent against DNA mutation and cancer initiation. Exercise and regular physical training has also positive effect on homeostasis (Rundle, 2005; Wartburton et al., 2006; Sachdev and Davies, 2008; Kruk, 2012). The role of ROS in the expression of a number of genes and cell signalling and a possible participation in the development and progression of BC was suggested in several research (Lander 1997; Allen and Tresini, 2000; Valko et al., 2007; Liou and Storz, 2010; Nourazarian et al., 2014). Signals to the transcriptional apparatus in nucleus are regulated by transcriptional factors, among them are those sensitive to ROS, such as nuclear transcription factors (NF-ϰB) participating in regulation of apoptosis, differentiation, inflammation, cell growth, and survival; a tumor suppressor p53; hypoxia-inducible factors HIF-1 and HIF-2, and others (Davies et al., 1981; Liou and Storz, 2010). Research relating to this topic has demonstrated the ability of PA to reduce the growth factors concentration (Rundle, 2005). Thus, PA can reduce the initiation and promotion stages of carcinogenesis. One of the most frequently reported beneficence of PA for postmenopausal women is associated with its effect through body weight.

The World Cancer Research Found (WCRF) and the American Institute for Cancer Research (AICR), based on the world literature on this topic, concluded that there is convincing and consistent evidence between body fatness and BC in postmenopausal women (WCRF/AICR, 2007). The hypothesized link between obesity and BC includes hormonal systems: sex hormones, insulin and IGFs (particularly IGF-1) and adipokines (Renehan et al., 2008). Overweight/obesity increases concentrations of: leptin, insulin, IGF-1, estrogens, androgens, inflammatory markers, such as IL-6 and tumor necrosis factor (TNF-α), and elevates the insulin resistance. Additionally, overweight/obesity decreases sex hormone binding globulin (SHGB). Epidemiologic data have shown that the association between PA and BC risk varies depending on BMI; greater decreases in the risk were seen in women with a lower BMI when compared the highest to the lowest level of PA, as reviewed by Lynch et al. (2011). According to the results of this comprehensive review, women with BMI <22kg/m^2 who reported the highest level of activity had the average risk reduction 27%, those with high BMI (≥25kg/m^2)-18% and those with BMI ≥30kg/m^2-less than 1%, compared to the least active. In this contest, it is noteworthy that randomized controlled trials (RCT) have confirmed the effect of exercise on a primary outcomes (body weight) and on secondary outcomes (e.g. waist circumference, glucose metabolism variables). For example, the RCT studies of Irvin et al. (2003), McTiernan et al. (2004), Friedenreich et al. (2010) reported a decrease of abdominal fat and estradiol and an increase of the SHBG concentration. In turn, in the next RCT study, Velthuis et al. (2009) observed reduction of body fat and waist circumference in trial participants in comparison with the control group. Also, a later systematic review of clinical trials demonstrated a small to moderate effect of PA on insulin, leptin, estrogens levels, and an apoptosis regulation (Winzer et al., 2011). Similarly, the previous research presented that exercise of suitable dose might cause significant reduction of serum estrogens and androgens (Irwin et al., 2003; McTiernan et al., 2004; Jasieńska et al., 2006). Consistent with these findings, fat loss is hypothesized as a key factor in the preventive action of PA against BC in postmenopausal women. Strong and coherent evidence exists for effect of increased levels of PA on sex hormones concentration. Renehan et al. (2008) have suggested that hormonal systems, such as insulin and IGFs especially IGF-1, sex hormones, and adipokines link overweight/obesity and BC risk. Physical activity, especially of vigorous intensity, decreases sex hormones concentration and their cummulation, for example through a disturbance of the menstrual cycle (Tworoger et al., 2007). Moreover, PA can influence on the estrogen transformation favoring its metabolism to 2-hydroxyestrone that has a weak affinity to the estrogen receptor (reviewed previously in Kruk and Aboul-Enein, 2006). There are several pathways suggesting the role of hormones in the carcinogenesis stages, such as oxidative stress induced by metabolic redox reactions of catecholestrogens, formation of the estrogenquinones-DNA adducts, replication errors caused by proliferation (Rundle, 2005). It is now widely accepted that BMI is positively, and PA negatively correlated with the sex steroids in postmenopausal women (McTiernan et al., 2004; Neilson et al., 2009). Also, a concentration of adipokines (e.g. tumor necrosis factor-α, TNF- α; interleukin-6, IL-6), agents known to influence on biosynthesis of estrogen, is lowered due to PA. These polypeptides are produced by adipocytes or adipose tissue and represent a group of inflammatory blood markers implicating in BC development (Lee and Pratley, 2005). Some of adipokines can directly promote cancer by an alteration of cell growth and promotion of metastasis or indirectly by affecting insulin resistance (Neilson et al., 2009). Insulin resistance and hyperinsulinemia are positively correlated with obesity and central fatness. In case of obesity, concentration of adiponectin-the hormone that regulates metabolism of fatty acids and glucose is decreased (Shahar et al., 2010). The group further showed statistically important decrease in the serum adiponectin concentration in BC cases compared to controls among Malaysian women. Thus, low levels of adiponectin and SHBG and higher levels of insulin are related to obesity. In turn, higher levels of PA, reduction of overweight/obesity and caloric intake are a means for reduction of insulin and IGFs. It is noteworthy, that insulin resistance and IGF-1 may act synergically in development of BC (Malin et al., 2004). A special attention has been put on the role of PA in antitumor immune defenses and in the effect of regular exercise training on adaptation to oxidative stress; PA increases the number and activity of macrophages, lymphokine-activated cells, interleukins and levels of the antioxidant enzymes. Several research have demonstrated that regular exercise can increase resistance of tissues against the ROS damage (Kruk, 2011). For example, reduction of the oxidants and ROS during oxidative phosporylation and prevention against glutathione oxidation were reported (Vina et al., 2000; Leeuwenburgh and Heinecke, 2001). A CRT study by Campbell et al. (2010) confirmed a reduction of C-reactive protein (an inflammatory marker) among obese women (BMI ≥ 30 kg/m^2) during 12 months exercise of moderate intensity. It is important to note that elevated levels of ROS are detected in many types of the cancer cells and considered to participate in regulation of signaling pathways (e.g. cell growth/proliferation, differentiation, cell inflammation, metabolism of glucose, inflammation (Klauning et al., 2010; Liou and Storz, 2010; Reuter et al., 2010; Valluru et al., 2014). Hen et al. (2010) found that after 6 months participation in the PA programme obese women experienced of a significant increase of total antioxidant capacity (an increase of Total Antioxidant Status, due to waist circumference reduction). Although some of unresolved questions related to the mechanisms how activity influences BC risk exist, the Second Panel judgments categorized level of scientific evidence of the PA protection against postmenopausal BC as probably and limited suggestive in premenopausal women, with the averages risk reduction 20-30% and 27%, respectively (WCRF/AICR, 2007; Friedenreich, 2011; Lynch et al., 2011). Given these relationships, current PA guidelines for healthy adults recommend accumulation of 60 min of moderate intensity or 30min of vigorous intensity intentional exercise per day, above normal daily activity

for the BC protection (WCRF/AICR, 2007; Kushi et al., 2012).

Diet

Due to international variance in cancer rates, geography-related dietary habits, importance of diet in the development of cancers including BC, the association between dietary pattern and BC risk has been suggested and hundreds of studies have examined this association during last 35 years. According to previous research, dietary factors were thought to be responsible for about 30% of all cancers in developed countries and for 20% in developing countries (Key et al., 2004; Linos et al., 2007; Nahleh et al., 2011). It is commonly accepted that a diet of the Western developed countries is high in animal products, fat and sugar. In contrast, a diet of developing countries is more "healthy" basing on starchy staple foods with low consumption of animal products, fat and sugar (Key et al., 2002b; 2004). Considering the proposed mechanisms for BC development, the diet may impact all stages of carcinogenesis. For example, chemical carcinogens, such as heterocyclic amines, polycyclic aromatic hydrocarbons, and nitrites that may be produced in a high temperature processed meat can damage DNA and initiate carcinogenesis. In addition, the compounds present in an unhealthy diet may stimulate formation of IGF-1, increase concentrations of circulating endogenous sex hormones, thus influence the initiation, promotion and progression of tumor stages. In turn, red meat is rich in heme iron which is necessary for production of hydroxyl radical via the Fenton reaction-the most biologically toxic oxygen species involved in oxidative stress. Thus, iron ions may indirectly influence on cytoplasmic and nuclear signal transduction pathways (Liou and Storz, 2010; Nourazarian et al., 2014). In contrast, the healthy diet (rich in antioxidants) may influence on DNA repair, metabolic detoxification and decrease of estrogens (Michels et al., 2007). Up till now, the evidence concerning nutrition and BC risk is not clear. Previously Key et al. (2002b) had reviewed the studies concerning nutrition and common cancers and reported that the best-defined is effect of diet and dietary-related factors on obesity. The direct dietary protective effect of fruits and vegetables was estimated as *none established* at this time. In contrast, a meta-analysis that included mainly case-control studies reported a modest increased BC risk in subjects with the highest intake level of fat vs the lowest level of intake (RR=1.13, 95%CI=1.03-1.25) (Boyd et al., 2003).

A compiled evidence from 11 large prospective studies on total and saturated fat consumptions and BC risk concluded that adult diet may be important for breast neoplasia, and excess energy intake in comparison to PA energy expenditure may be a factor for BC in postmenopausal women. Also, these researchers did not observed of association between carbohydrates and the risk (the conclusion was based on 7 prospective studies). Furthermore, a latter systematic review and meta-analysis of cohort and cases studies (Brennan et al., 2010) basing on 16 studies (bearing date 2001-2009) demonstrated a 11% significant small decrease in the risk (OR=0.89, 95%CI=0.82-0.99) in adults with the highest compared with the lowest level of the prudent/healthy dietary patterns (a diet rich in fruit, vegetables, poultry, fish, low fat dairy, and whole grains). Although, the authors did not found the association between Western/unhealthy dietary patterns and BC risk. In a recent systematic review and meta-analysis of 33 studies (31 case-control and two cohort studies), published during 1987-2013 conducted in Chinese female (9,299 cases and 11,413 controls) considering the association between nutritional constituents (soy, fruits, vegetables, fat) and BC risk, Liu et al. (2014) found that a high intake of fat was significantly associated with an increased risk (OR=1.36, 95%CI=1.13-1.63) (data based on six studies). In contrast, a high intake of soy and fruits decreased the risk by 35% (OR=0.65, 95%CI=0.43-0.99 and by 34% (OR=0.66, 95%CI=0.47-0.91, respectively), based on 13 studies. In addition, the researchers found significantly decreased risk (OR=0.49, 95%CI=0.27-0.89) for vegetables intake in four papers published during 2007 year and later, and a lack of the association considering five research carried out before 2007. Inconsistencies between previous studies, as noted above, are also seen in the recent studies on this topic that were not included in the reported reviews. For example, Buck et al. (2011) addressed the association between dietary patterns and postmenopausal BC risk among the German women (2,884 cases and 5,509 controls). They found that both kinds of dietary patterns "healthy" (diet rich in vegetables and vegetable oil) and "unhealthy" (a diet including processed meat, red meat, and deep-frying fat intake) were not associated with BC risk. Similarly, a case-control study in Malaysia (382 breast cancer cases and 382 control group) carried out by Sulaiman et al. (2011) reported a lack of association between total fat and fat subtypes intake and BC risk in premenopausal and postmenopausal women. On the other hand, Ronco et al. (2012) observed an increased risk with a high consumption of red meat and fried food (OR=2.20, 95%CI=1.35-3.60 and OR=1.79, 95%CI=1.12-2.84, respectively) in premenopausal Uruguayan women. Contrary to these observation, a high intake of plant food exhibited a protective effect (OR=0.41, 95%CI=0.25-0.65). Also, the recently published prospective study of 337,327 women living in 10 European countries (10,062 BC cases) reported that a high consumption of total and saturated fat was linked with greater risk of ER^+/PR^+ BC risk (Sieri et al., 2014).

Over the past three decades numerous studies have documented that products of natural origin play a critical role against cancer (Pauwels, 2010; Patel, 2012; Tsuji et al., 2012; Alegre et al., 2013; Ma et al., 2013). For example, Zheng et al. (2013) have maintained that a high caloric and fat intake, low consumption of vegetables and fruits, alcohol drinking and environmental pollution are the major risk factors for BC in Asian population. In turn, a high antioxidative capacity of the mediterranean diet as reach in vegetables, legumes, fruits, olive oil, fish, red wine has been reported (Liu et al., 2014). Alegre et al. (2013), based on the recent literature within this topic, reported that olive oil has potential not only to decrease BC risk but also aggressiveness of this disease. Zhu et al.

(2011) found that postmenopausal women declaring the highest intake of soy experienced of the reduced BC risk even by 58%. Similarly, a case-control study of Zhang et al. (2011) (438 cases, and 438 controls) reported a 74% decreased risk in women included in the highest quartile of the vegetable-fruit-soy-milk-poultry-fish dietary pattern (OR=0.26, 95%CI=0.17-0.42). In contrast, the researchers observed an increased BC risk in women with a high consumption of the refined grain-meat-pickle pattern (OR=2.58, 95%CI=1.53-4.34). Another recent case-control study (858 causes, 1,085 controls) conducted in Poland reported strong significant decrease in BC risk for the highest vs lowest quartile of vegetables and fruits in women characterized by the lowest level of PA (63% and 53%, respectively). Women that declared a high level of PA also experienced beneficial effect of high intakes of vegetables and fruits on BC risk (47% and 53%, respectively) (Kruk, 2014b). This study also focused on the relationship between carbohydrate intake and BC risk, not finding of a support for the relationship between a diet high in this component and BC among examined women. However, the recently published meta-analysis of 10 prospective studies on the role of dietary glycemic index (GI) and glucemic load (GL) in relationship to BC risk, demonstrated a 8% increased summary RR for the highest GI intake compared to the lowest (Dong and Qin, 2011). A diet reach in GI can increase glucose concentration in blood and also insulin-the hormone being positively associated with BC (Minatoya et al., 2013) by an increase of IGF-1 that has strong proliferative and antiapoptic effects on mammary cells. Given these findings, it may be suggested that some components of diet e.g. olive oil, soy products may help in the reduction of BC. This is due to a fact that the plant food is reach in monounsaturated fat acids, fibres, anthocyanins and polyphenols, and additionally posses the capacity of removing ROS and prevention against oxidative stress (Gupta et al., 2012; Tsuji et al., 2012). Vegetables and fruits contain flavonoids that show significant anti-inflammatory and antioxidant potential, thus, they are able to reduce the risk of cancer (Guo et al., 2013). According to the previous meta-analysis of 17 studies for vegetables and 12 studies for fruits, a high intake of vegetables but not fruits resulted in 25% significant decrease of the risk (Gandini et al., 2000). In turn, the recent meta-analysis by Gao et al. (2013) has observed that a high intake of green tea has a capacity to decrease BC risk. The authors noticed a 21% decrease in the risk among regular tea drinkers comparing with non-drinkers. It is noteworthy that the leaf is rich in flavonoids and simple polyphenols, hence may directly scavenge the ROS (Chu and Juneja, 1997).

Alcohol Intake

A previous report of the Collaborative Group on Hormonal Factors in Breast Cancer (2002), basing on 53 epidemiological studies, found that alcohol drinking causes an increase in BC risk by a 32% in women drinking 0.35-<44g daily and by 46% in those drinking 44g and above daily. The risk was found to be a 2-fold increased in postmenopausal women consuming ≥2 drinks weakly. The recent review of the literature on this topic by Scoccianti et al. (2014) basing on papers with the publication data 2007-2012 maintains that alcohol-related disease including BC is an important public health problem. Schutze et al. (2011) estimated that 5% of all BC cases in 8 European countries is causally associated with the consumption of alcoholic beverages. Moreover, an analysis of alcohol consumption dimensions and types of alcoholic beverage intakes showed the positive effect of alcoholic beverages on the BC development even at low level of their intake. Further, a magnitude of BC risk was noticed to be dependent on age at start of drinking, menopausal status, portion of ingested alcohol, and polymorphism in individual's genes. For a daily intake of 10-20g of pure ethanol, the reported BC risks in the evaluated literature ranged from 0.97 to 2.07 in postmenopausal women and from 0.85 to 1.66 in premenopausal women. The recent prospective study basing on 1,609 BC cases also found that alcohol intake between menarche and first pregnancy had elevated RR by 11% per 10g/day intake. In turn, women who started alcohol drinking after first pregnancy had increased risk by 9% per 10g/day intake (Liu et al., 2013). A toxicity of ethanol is due to acetylaldehyde originated during oxidation of alcohol, of a compound capable to induce DNA damage, of the formation of DNA adducts and chromosomal aberrations. Ethanol is also metabolized to ROS. The products of ethanol metabolism interfere with steroidal estrogen metabolism leading to carcinogenic products (Reichman et al., 1993; Seitz and Stickel, 2007, 2010). Moreover, ethanol has been found to stimulate cell proliferation and to induce the expression of ER and PR hormone receptors. Suzuki et al. (2009) observed a 12% increase in magnitude of the risk in women with ER^+ tumors for each additional drink, a small increase in those with ER^- tumors (7%), and a lack of relationship with ER^-/PR^- or ER^-/PR^+ receptors. Similarly, Kabat et al. (2011) reported that alcohol consumption may be moderately linked to an increased risk of ER^+ BC, basing on 2,479 ER^+ postmenopausal cases which reported ≥7 drinks/week.

It is also important to mention about an individual susceptibility to BC, i.e. polymorphisms in genes involved in ethanol metabolism and elimination of acetylaldehyde. Polymorphism may be a modulator of an individual's susceptibility to BC. The evidence concerning diet and cancer is not clear, due to inconsistency of epidemiological studies, resulting, in part, from the methodology of the diet-BC estimation and not established mechanisms of the causal relationship diet with cancer. Nevertheless, recommendations of the Second Report on Food, Nutrition and Cancer Prevention obey: *i)* limitation of consumption of the energy-dense foods (energy content >225-275 kcal per 100g) with advancing of a diet of an average energy density 125 kcal per 100g (without drinks) and also avoiding of drinks with added sugars, *ii)* consumption at least of five portion/servings (400g) of non starchy vegetables and fruits daily, *iii)* consumption of unprocessed cereals and/or pulses with every meal, *iv)* limitation of refined starchy foods, *v)* consumption less that 500g of red meat/week, avoiding of consumption of meat preserved by smoking, currying/salting or with an addition of chemical preservatives, *vi)* limitation of

consumption to one drink/day (10-15 grams of ethanol) for the women consuming alcoholic drinks (WCRF/AICR, 2007). Additionally, the Expert Report does not recommend dietary supplements (vitamins, minerals) as a means of cancer prevention.

Smoking

Tobacco smoking is a debatable risk factor of BC, although at least 40 carcinogens, tumor initiators or promoters, such as nitrosoamine 4-(methylnitrosoamino-1-(3-pyridyl)-1-butanone)-the most strong toxic agent are present in the cigarette smoke (Maser, 1997). There is evidence that carcinogens present in tobacco smoke may be transported to the breast through lipoproteins and albumin of plasma (Shu and Bymun, 1983; Plant et al., 1985). Most observational studies on association between cigarette smoking and BC have failed to find a strong association. For example, Moore and Sobue (2010) in a study on strategies for cancer control in the various regions of Asia reported that cigarette smoking can play a minor role in BC risk. The previous reanalysis of 53 epidemiological studies (Collaborative Group on Hormonal Factors in Breast Cancer, 2002), focusing on smoking status, also concluded that tobacco has no effect on overall risk of BC, but its effect on certain subgroups of women could not be excluded. Analysis of findings of the latter studies on this topic indicates that the link of smoking with BC may be dependent on several factors including age of smoking initiation, duration, amount of cigarette smoking per day, genotype, estrogen level, suggesting that early age at smoking initiation, longer duration of smoking and greater numbers of cigarettes are linked with increased risk (Hulka and Moorman, 2001; Reynolds et al., 2004; Gram et al., 2005; Olson et al., 2005; Terry and Goodman, 2006; Ha et al., 2007; Ahern et al., 2009; Pieta et al., 2009; Young et al., 2009; McKenzie et al., 2013). For example, Olson et al. (2005) reported increased BC risk by 27% in women who started smoking before the first delivery and by 39% in those who started smoking between first menarche. In turn, Nagata et al. (2006) reviewed three cohort and 8 case-control studies and found that the majority of examined studies reported increased BC risk in smoking women. Also, significantly increased risk was observed in case-control study (848 cases, 1085 controls) of the Polish women (Kruk, 2007a). According to this study both premenopausal and postmenopausal active smokers experienced increased risk for the intensity of smoking ≥10 cigarettes/day as compared with non-smokers (OR=2.55, 95%CI=1.81-3.60, OR=1.78, 95%CI=1.33-2.37, respectively). Also, a recent small study (191 cases, 191 controls) conducted in Serbia reported significantly increased BC risk among former smokers (Ilic et al., 2013). The group showed that BC risk was increased in women who quit smoking at ≤50 years of age (OR=3.29, 95%CI=1.07-5.24) and in those who stop smoking <5 years before diagnosis of the disease (OR=5.46, 95%CI=1.34-22.28) when compared with nonsmokers. Another recent prospective study of Kabat et al's (2011) (148,030 women including 300 triple-negative BC cases and 2,479 women with ER^+ BC) reported HR=1.24, 95%CI=1.06-1.44 for women with ER^+ and with ≥40 pack-years of smoking, presenting a modest increase in the risk. In turn, in a recent case-control study carried out in Japan (1,263 cases and 3,160 controls), Nishino et al. (2014) found no significant relationship between history of smoking and BC risk for any ER/PR subtype. However, the authors observed the significantly increased risk among postmenopausal women with ER^-/PR^- status who started to smoke at of ≤19 years (OR=7.01, 95%CI=2.07-23.73). Further, the results of their analysis indicated that intensity of smoking, duration of smoking, and start of smoking before the first birth were not associated with the risk independently on the receptor subtype. Also, the researchers did not found of association between passive smoking from husbands and BC risk for any of the ER/PR subtypes. Concerning cigarette smoking-BC risk, two competing mechanisms are suggested (Hulka and Moorman, 2001). The first deals with carcinogens present in cigarette smoke as initiating and promoting cancer agents directly, as presented above. The second-preventive may result from a fact that women who smoke are often leaner, experience earlier menopause and have lower levels of estrogen. This may in part explain conflicting epidemiological findings reporting positive, negative and null relationships.

Exogenous Estrogens

Because estrogen status is commonly hypothesized as an important factor for BC risk (Key et al., 2002a), the association between exogenous hormones usage (mainly hormonal contraceptives, OCP, and hormone replacement therapy, HRT) has been studied extensively. The first reanalysis of data of 54 epidemiological studies by Collaborative Group on Hormonal Factors in Breast Cancer (1996) showed a 7% increase in BC risk in women which ever used OCP. The risk reached the largest value in current users (OR=1.24, 95%CI=1.15-1.33) compared with women who did not report using OCP, and those using OCP within 4 years prior to diagnosis. Ten years after stopping use of OCP non increase in the risk was observed. We also found an increased risk among premenopausal sex hormones users vs nonusers (OR=1.65, 95%CI=1.15-2.36), and a lack of association in postmenopausal users (Kruk, 2007a). Prevalence of HRT use is relative high and increases due to recognition of the benefits in relieving of menopause symptoms, preventing of heart diseases and osteoporosis (Hulka and Moorman, 2001), and usage of hormone therapy in the treatment of urogenital atrophy (Lambrinoudaki, 2014). The previous studies suggested the positive relationship between long-term use of HRT (≥5 years) and BC risk in current or recent users. For example, the Million Women Study (Million Women Study Collaborators, 2003) showed that the current use of HRT was associated with a 66% increase in BC risk in the British women. The study group reported no increase in the risk for the past users, i.e. after 10 years and more. Other report basing on quantitative estimates demonstrated a 2.3% increase of the risk per year for HRT usage exceeding 5 years. Currently, there are few findings available to evaluate the HRT-BC risk relation.

For example, Dieli-Conwright et al. (2011) have estimated the beneficial effect of PA on BC risk among non-users and users of HRT among postmenopausal women (1,908 cases, 2,013 controls). They found evidence for a dose-response association between increasing levels of PA and decreasing BC risk among never HRT users, fewer than 5 years HRT users, and among current estrogen-alone users. In contrast, PA was without effect on the risk in long-term and past HRT users and in current estrogen plus progestin users. These data confirmed the findings of Howard et al. (2009) that PA decreases postmenopausal BC in women who had never used HRT in comparison with those who had ever used HRT. Some findings of other studies suggested that the protective effect of PA against BC in former HRT users was dependent on time since last therapy use and therapy duration, other indicated a lack of modification by the HRT use (Dieli-Conwright et al., 2011). The findings from observational studies published up 2002 were not able to demonstrate statistically important data, whether HRT use modifies the PA-BC association due to differences across these studies in the methods used to assess PA, and a category of HRT users. It should be noted that preparations applied in menopausal hormone therapy differed in composition. Before 2002 most preparations contained estrogen alone. Due to observed of increase in endometrial cancer, described to the use of estrogen, the combined estrogen and progestagen therapy have been applied for the prevention and treatment of endometrial disease (Thom et al., 1979). However, there is also a large variety of synthetic progestagens that differ in their pharmacological properties according to their molecular structure. The compounds added to estrogen can act differently on hormone receptors. In 2002, the Writing Group for Women Health Initiative (WHI, 2002) in their report from a randomized clinical trial, demonstrated that the use of preparations containing estrogen and synthetic progestagen was linked with an increased BC risk. Other studies presented findings showing that the mode of HRT administration may have impact on magnitude of BC risk (Bakken et al., 2011). For example, the recent case-control study in France (739 cases, 816 controls) found an increased BC risk among estrogen-synthetic progestin therapy users (OR=1.57, 95%CI=0.99-2.49) and among estrogen-testosterone users (OR=3.35, 95%CI=1.07-1.04) (Cordina-Duverger et al., 2013). According to review of clinical trials and epidemiologic studies the combined estrogen-progestagen therapy causes a higher BC risk compared to estrogen-alone therapy (Lambrinoudaki, 2014). The author reported further that natural progesterone and dydrogesterone are linked with a lower risk compared with other progestins. Currently, the IARC Group, basing on epidemiological evidence concerning the association between estrogen and progestagen hormonal therapy and BC risk classified the combined therapy as carcinogenic to women (IARC, 2012).

Psychological Stress

Epidemiological observations concerning the influence of psychological stress on health have suggested that the people who experience the severe life events, such as a loss of a spouse, a close relative or friend or who experience psychological distress repeatedly over a long time may have mental and/or physical problems. The association between psychological stress and the onset of cancer was first reported in 19 century (Snow, 1893). Snow observed that 150 out of 250 BC cases experienced severe life events because of loss of a close relative. Since 1893 year several epidemiological studies have reported a causal link between life event stress and BC. For example, Dalton et al. (2002) compiled the available evidence from the research published between 1967 and August 2001 on influence of family illness, death of close relatives, divorce, job loss, and depression on cancer risk. The research has shown weak relationships, equivocal dose-response trends, and a lack of consistency of the results. Similarly, in a previous meta-analysis, Petticrew et al. (1994) concluded that recent severe life events did not affect BC risk. In contrast, later cohort and case-control studies of the large sample size and estimation of the cumulative effect of life events which controlled the association for the confounding variables confirmed the positive association between cummulation of life events and BC development (Jacobs and Bovasso, 2000; Lillberg et al., 2003; Kruk and Aboul-Enein, 2004; Peled et al., 2008; Kruk, 2012). For example, Peled et al. (2008) studied the relationship of a cumulative number of life events, psychological distress and BC risk. According to this study, experience of two or more events was positively associated with BC risk (OR=1.62, 95%CI=1.09-2.40). In addition, in their estimation a feeling of happiness and optimism significantly decreased BC risk (OR=0.75, 95%CI=0.64-0.86). In turn, Santos et al. (2009) in their meta-analysis including the latter findings reported statistically significant increased BC risk among women who had reported experience of stressful life events of high intensity. In the recent Polish case-control study (858 cases, 1085 controls) women with four to six individual major life events had over 5-times higher risk for BC compared with those not reporting major life events experience (OR=5.33, 95%CI=4.01-8.21) (Kruk, 2012). Also, women who reported cummulation of a life change stress score greater than 210 had elevated BC risk compared to women who reported scores in the range 0-70. Another recent case-control study in Taiwan (157 cases and 314 controls) found that a high perceived stress increased BC risk by a 65% (OR=1.65, 95%CI=1.10-2.47) (Wang et al., 2013). Given the epidemiological evidence, findings on an association between psychological stress and BC risk are inconclusive, similar as those on psychosocial work stress and the risk (Heikkilä et al., 2013). Heikkilä et al. in their meta-analysis of prospective studies of European cohorts in 12 countries which identified 1,010 breast cancer cases found no evidence for the relationship between job strain and BC risk (OR=0.97, 95%CI=0.82-1.14). However, an association between experience of crude psychological events and BC risk is still a highly controversial topic, this relationship is biologically plausible and multiple mechanisms, such as immune-down regulation, DNA damage and faulty of the acid repair, influence on endocrine parameters, inhibition of apoptosis, and somatic mutations have been hypothesized (Cohen and Herbert,

1996; Kiecold-Glaser and Glaser, 1999; Forlenza and Baum, 2000; Sloan et al., 2010). For example, Cohen and Herbert (1996) and Kiecold-Glaser and Glaser (1999) suggested that stress plays a role in the initiation or progression of cancer through immune down regulation. This hypothesis have been supported by other researchers who observed that chronic stress increases concentration of cortizol, which disturbs immune functions, considered as important for elimination of mutated cells (Lutgendorf et al., 1999; Kemeny and Schedlowski, 2007). Some studies have shown that psychological stress may alter endocrine characteristics (Forlenza and Baum, 2000), e.g. noradrenaline, the catecholamine which may stimulate the cancer cells by releasing vascular endothelial growth factor-an agent that can participate in the growth of the blood vessels by supplying cancer cells. Thus, the noradrenaline release may lead to the growth and spread of the cancer (Moreno-Smith et al., 2010; Sloan et al., 2010).

Conclusions

In conclusion, there have been rapidly growing body of evidence on the independent effect of lifestyle factors on the BC development. However, the references cited here consist only a small fraction of the publication in this topic. Knowledge of the association between BC risk and lifestyle factors and benefits of a given lifestyle component allows to change lifestyle habits. At present, it is commonly accepted that some lifestyle patterns, like physical inactivity, diet reach in animal fat, processed foods, and increased intake of alcohol or usage combined estrogen-synthetic progestin therapy may significantly affect the BC development. The world literature strongly underlines an important role of exercise of moderate to vigorous intensity, diet reach in antioxidants and poor in animal fats, minimized alcohol intake as the key modifiers low-costly, and approachable means against cancer. Sanchez-Zamorano et al. (2011) based on a large population case-control study, have proposed so-called "healthy lifestyle index" which "was defined as the combined effect of moderate and/or vigorous-intensity physical activity, low consumption of fat, processed foods, refined cereals, complex sugars, and the avoidance of tobacco smoking and alcohol consumption". The researchers reported that these behavioral patterns were significantly associated with a decreased BC risk by 50% in premenopausal women and by 80% in postmenopausal women. As concluded by this study, the primary prevention against BC should focuses not on a single lifestyle determinant, but on the integrated lifestyle components. Although, considering various hypotheses of the biological pathways through which particular lifestyle determinants can impact on the development of the breast neoplasms and the cancer stages, regular moderate/vigorous PA has the highest potency. This property results with a capacity of body weight and central adiposity reduction through balancing caloric intake with energy expenditure and of a help to combatant psychological stress, thus prevent directly. Data from observational epidemiological studies and randomized exercise intervention trials allow to propose the biochemical mechanisms through PA exerts effects, such as decrease of sex hormone levels, insulin level and its resistance; decrease of leptin and adiponectin levels; decrease of growth factors concentration; reduction of oxidative stress; detoxification of chemical carcinogens; reduction of systemic inflammation; DNA repair and improvement of immune function.

Future epidemiological and laboratory studies on lifestyle behaviors and BC risk are needed to be continued. These studies should include data on race/ethnicity, cancer subtypes, time spent in the sitting and lying down positions, menopausal status, and other potential risk factors as confounding variables. A large sample of cases and detailed outcome measures including behavioral determinants can explain the potential reasons of inconsistency of epidemiological studies and provide more information on causal link between lifestyle determinants and BC risk. This will help to focus more precisely on future public health interventions for enhance perceived healthy lifestyle behaviors needed to reduce BC risk.

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