

Review paper

## The influence of risk factors associated with lifestyle on the development of breast cancer

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### ABSTRACT

Breast cancer is the most common result of mutual correlation between hormonal determinants, environmental and genetic. Mechanisms of its development include: high estrogen concentration, impaired glucose metabolism, hyperglycemia, hyperinsulinemia, high levels of insulin-like growth factor 1, persistent inflammation and oxidative stress, and impaired cellular apoptosis.

The aim of the study was to analyze data on the risk factors of breast cancer, which have been divided according to the period of diagnosis for pre-menopausal and postmenopausal.

Due to the fact that a large part of the determinants of the occurrence of this cancer is modifiable, it is necessary to raise the awareness of the population about it. Maintaining proper body mass through the use of a balanced diet rich in calcium, non-starch vegetables and products rich in carotenoids, while limiting alcohol consumption and care for physical activity, are the best prevention of breast cancer. At the same time, further research is needed to explain the uncertainty of current observations.

**Key words:** risk factors, breast cancer, lifestyle

## INTRODUCTION

Neoplasm is defined as a system's homeostasis disorder in terms of proliferation, growth and differentiation of body cells. It is a pathological condition, characterized by excessive, uncontrolled cell proliferation and the possibility of neoplasm cells to locally infiltrate and to spread. A loss of control over cell proliferation occurs when the protein coding genes, which take part in the cell cycle, are subject to mutation or expression change. These in turn disrupt or completely prevent the cell from receiving signals and responding appropriately. The irregularities that arise in the organism accumulate and increase the risk to occur one of 100 types of neoplasms diagnosed so far. What is important, carcinogenesis is a multifactorial process. It can be distinguished in endogenous determinants, arising as a result of processes taking place in the organism, and exogenous, from the environment (fig. 1) [1].

For example, breast cancer development mechanisms include among others high levels of estrogen hormone, glucose metabolism impairment, hyperglycaemia, hyperinsulinaemia, high levels of IGF-1 (insulin-like growth factor-1), persistent inflammation, oxidative stress and impaired cell apoptosis. The above components are influenced by factors of varied background [2–4].

Neoplasms remain second, after cardiovascular system diseases, global death cause. Breast cancer in turn, according to IARC (International Agency for Research on Cancer) most recent data from year 2012, is the fifth cause of mortality due to oncological

reasons in general and second cause of death in highly developed countries – just after lung cancer. At the same time, it is the second most common cancer in the world and the most common cancer among women – it accounts for about 25% of new cases in all neoplasms [5]. ACS (American Cancer Society) estimated that in year 2017, 316,000 women and 2470 men will be diagnosed with breast cancer in United States of America alone. In the same year it will cause the death of approximately 316,000 women and 460 men. Thanks to this data, it can be observed that breast cancer occurs mainly in women. Reports however, indicate that their morbidity among men gains a small but steady increase [6].

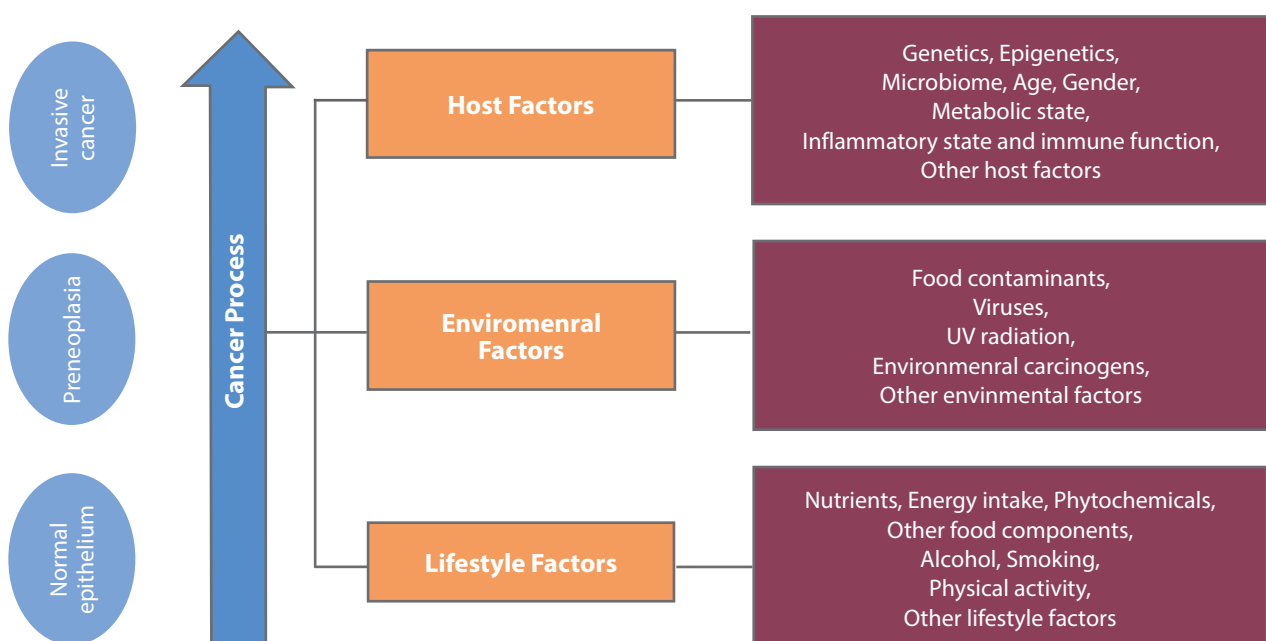
As a result of a number of studies, independent risk determinants have been designated that predispose to the development of various types of neoplasm. The following summary will analyze the impact of selected lifestyle factors on the risk of breast cancer.

## THE INFLUENCE OF SELECTED RISK FACTORS ON THE DEVELOPMENT OF BREAST NEOPLASM

Breast cancer belongs to heterogeneous diseases, but most of its subtypes are hormone-dependent (approx. 60–90%). In this case, active estrogen (ER+) and/or progesterone (PR+) receptors are found in cancer cells. The presence of oncogene HER2 (human epidermal growth factor receptor 2) and antigen Ki-67 (which is an indicator of proliferation) are also not without significance. Based on the carried out diagnostic tests of aforementioned

FIGURE 1.

Postulated effect of risk factors on the cancer development process (own elaboration based on [1]).



markers, one of four clinically relevant molecular phenotypes of breast cancer can be identified: luminal type A (ER+, PR+, HER2-, low Ki-67 level), luminal type B (ER+, PR-, HER2-, high Ki-67 level), TNBC (triple-negative breast cancer ER-, PR-, HER2-) and with *HER2* gene overexpression (HER2+). In addition, the diagnosis based on these tests allows for better identification of the patient's therapeutic options and prognosis. In the case of hormone-dependent breast cancers, prognosis is relatively optimistic, which is associated with greater sensitivity to treatment and less tumor invasiveness [6–9].

In addition, specific patterns of the occurrence of particular molecular bases of breast cancer in terms of age, ethnicity, socio-economic status or geographical location can also be noticed. For example, young women present the most common subtypes of TNBC disease (in 26%, compared with 12% of the total occurrence) or HER +, which is associated with worse prognosis [7, 9].

According to the latest analyses, breast cancer can also be divided due to the diagnosis period: premenopausal and postmenopausal. This is particularly related to the hormonal changes in the women's organism during menopause. It is believed that hormones affect the risk of breast cancer by increasing cell proliferation, thus increasing the likelihood of DNA damage as well as promoting cancer development [1, 6].

Genetic loads, belonging to non-modifiable risk factors for breast cancer, play an important role in the process of carcinogenesis. Molecular studies show that *BRCA1* and *BRCA2* genes have a strong association with breast cancer (and ovarian cancer), and the carrier-state of those genes increases the risk of developing cancer by about 70%. They constitute an estimated 5–10% of all breast cancer in women, 5–20% of male breast cancers and 15–20% of breast cancers related to family burden (first-degree relatives). In addition, in women with gene mutations, the risk of breast cancer increases with age. Importantly, the risk of developing breast cancer also increases significantly (up to 4 times) if the first-degree relatives (parents, siblings, children) had this disease, even in the absence of gene mutations. It is concluded that this is related to the interaction between lifestyle factors and low-risk genetic changes, which currently include about 150 genetic variants [6, 9].

Data included in the latest report on breast cancer, focusing on the relationship between specific lifestyle components and the risk of developing this neoplasm, were divided according to the period of cancer diagnosis into premenopausal

and postmenopausal. In relation to both types of breast cancer, the determinants increasing and decreasing the risk of cancer development with strong and limited scientific evidence were identified, which will be presented in the tables (tabs 1 and 2), and selected ones described below.

TABLE 1.

Factors influencing the risk of breast cancer development, when the diagnosis occurred before menopause (own elaboration based on [1]).

		↓ risk	↑ risk
Breast cancer – premenopausal diagnosis			
Strong scientific evidence	Convincing		Height achieved in adulthood*
	Likely	Energetic physical activity Body fatness (according to BMI, WHR) Lactation (breast-feeding)	Alcohol Higher birth mass
Limited scientific evidence	Suggestive	Non-starch vegetables (ER-breast cancer) Milk products Products rich in carotenoids Diet rich in calcium Physical activity	
	No clear conclusions	Cereal products, dietary fiber, potatoes, non-starch vegetables (ER+ cancer), fruits, legume seeds, red and highly processed meat, poultry, fish, eggs, fats and fatty acids, and their relative amounts to each other, sugar and other sweeteners, coffee, tea, glycaemic index and load, vitamins and minerals, energy charge, environmental factors, etc.	

\* It is an indirect marker – genetic, environmental, hormonal and nutritional factors influencing the growth in the period from conception to reaching the final height.

TABLE 2.

Factors influencing the risk of breast cancer development when the diagnosis occurred after menopause (own elaboration based on [1]).

		↓ risk	↑ risk
Breast cancer – postmenopausal diagnosis			
Strong scientific evidence	Convincing		Alcohol Body fatness (according to BMI, WHR) Weight gain in adulthood Height gained in adulthood*
	Likely	Physical activity Lactation (breast-feeding)	
Limited scientific evidence	Suggestive	Non-starch vegetables (ER-breast cancer only) Products rich in carotenoids Diet rich in calcium	
	No clear conclusions	As in the case of premenopausal breast cancer	

\* It is an indirect marker – genetic, environmental, hormonal and nutritional factors influencing the growth in the period from conception to reaching the final height.

## EXCESSIVE BODY WEIGHT

An intriguing example in the case of pre- and postmenopausal breast cancer remains excessive body mass and its fatness. In the first case, with the increase of these anthropometric indicators, the risk of morbidity decreases, in the second case – just the opposite [9, 10].

Undeniably, the influence of overweight and obesity on the occurrence of breast cancer is a complex process, resulting mainly from the accompanying metabolic disorders [11, 12]. These in turn lead to the development of the metabolic syndrome, which usually includes the following disorders: hypertension, insulin resistance, obesity and dyslipidaemia. Study results suggest that the listed components of the metabolic syndrome, particularly low HDL cholesterol level and high triglyceride levels, are associated with an increased risk of breast cancer. A noticeable trend of recent decades also remains the simultaneous increase in the incidence of breast cancer and the multiplication of the frequency of occurrence of metabolic syndrome [13].

In addition, excess fat causes increased estrogen production, which leads to an increased risk of development and recurrence of hormone-dependent neoplasms. Obesity is also accompanied by chronic inflammation, secondary disorders associated with deregulation of lipid and insulin levels, decrease in the production of sex hormone binding globulin (SHBG) and the excess of proinflammatory cytokines produced by fat cells [9, 11, 12, 14].

Some researchers, in turn, claim that the distribution of body fat and specific markers integrated with it may be more related to the development of breast cancer than obesity itself [10, 15]. For example, the results of one of the last meta-analysis indicate that abdominal obesity, measured as a waist circumference, is associated with both types of breast cancer, regardless of the general degree of obesity, interpreted in the form of BMI (body mass index) [16].

Another meta-analysis of studies showed, however, that women aged 40–49 with overweight and obesity (categorization according to BMI) showed a lower risk of premenopausal breast cancer compared to women with normal body mass and underweight [17].

Interestingly, also obesity in childhood and adolescence seems to reduce the risk of developing pre-menopausal breast cancer. In addition, this is not related to body weight

during diagnosis [18, 19]. The results of the meta-analysis of prospective studies conducted by Chen et al., in turn, indicate that the relationship between BMI and breast cancer diagnosed at a young age differs statistically depending on the race of the studied women [16].

These relationships present themselves in yet another way, when the WHR (waist-hip ratio) parameter is taken into analysis instead of BMI, which is a better parameter of the amount of visceral fat, which is considered to be more metabolically active. In this case, every increase in WHR by 0.1 unit is associated with an 8% increase in the risk of premenopausal breast cancer [20]. At the same time, it should be remembered that mechanisms lying at the basis of these relations are ambiguous and require further research.

In turn, the risk of breast cancer after menopause is about 1.5 times higher in women who are overweight and about two times higher in obese women, compared with slim women. This is probably partly due to the higher estrogen concentration (fat tissue is the largest source of it in postmenopausal women), but it can also refer to other mechanisms, including the often occurring hyperinsulinaemia in women with excessive body mass. Increased IGF-1 synthesis, by increasing cell proliferation and inhibiting apoptosis, can lead to the development of breast neoplasm. It is also important that women with excessive body weight have diagnostic difficulties, delayed wound healing, an increase in the number of complications and an increased risk of relapse within the next 5 years [15, 21–23]. In addition, a meta-analysis of 82 clinical trials conducted in 2014 showed that the increase in BMI by 5 kg/m<sup>2</sup> in three reference points (before, < 12 months and ≥ 12 months after breast cancer diagnosis) increased mortality by 17%, 11% and 8%, respectively and was associated with 18%, 14% and 29% increase in mortality caused by neoplasm [24].

## Products rich in carotenoids

A systematic review and meta-analysis of prospective clinical trials regarding the comparison of carotenoid consumption and blood carotenoid levels and the risk associated with the occurrence of breast cancer did not confirm the relationship between the consumption of carotenoids from vegetables and fruits and the risk of this cancer. The exception was only a weak reduction in the risk of breast cancer associated with the intake of  $\beta$ -carotene with food.

In turn, the total concentration of carotenoids,  $\beta$ -carotene,  $\alpha$ -carotene and lutein in the blood showed a stronger asso-

ciation with the reduction of the risk of developing breast cancer. Importantly, the above results may be the effect of measurement errors related to the amount of carotenoids absorbed from food products, but they may also indicate large losses of these compounds during changes occurring in the gastrointestinal tract. However, this has no effect on the demonstrated relationship between blood carotenoid levels and the risk of developing breast cancer [25].

Eliassen et al. received similar results. They indicated that women with high level of carotenoids in blood plasma have a statistically lower risk of breast cancer by 18–28% [26]. Earlier analyses of authors showed a 22% risk reduction for lycopene concentration, 17% for  $\beta$ -carotene, 13% for  $\alpha$ -carotene and 19% for carotenoids in total [27]. It is believed that carotenoids in breast cancer cells can inhibit proliferation and induce epithelial cell differentiation. In addition, as antioxidants, they can protect DNA against damage caused by reactive oxygen species (ROS) [15].

In one of the parts of the EPIC (European Prospective Investigation into Cancer and Nutrition) study, involving 10 European countries, the focus was on the impact of prediagnostic plasma concentrations of carotenoids in relation to the risk of breast cancer. Analysis of the results showed that a higher blood concentration of  $\alpha$ -carotene and  $\beta$ -carotene may lead to a reduction in the risk of neoplasm development by 39–59% in the case of ER- breast cancer. In turn, the studied hormone-dependent tumors did not show this correlation, which may be related to the strong influence of endogenous factors. Additionally, it has been suggested that a stronger effect of the corresponding plasma carotenoids concentration occurs for breast cancer diagnosed in the pre-, rather than postmenopausal period. At the same time, no effects on the above relationships were observed after the introduction of data on smoking, alcohol use or BMI [15, 28]. In another study, it was shown that low consumption of  $\alpha$ -carotene and  $\beta$ -carotene was associated with an increased risk of breast cancer only among smokers [29].

### Diet rich in calcium

The meta-analysis of prospective cohort studies published in 2016 regarding the relationship between calcium intake and the risk of breast cancer was based on the results of 11 observations, conducted over a period of 7–25 years among 26,606 women diagnosed with this cancer. The review of the results confirmed the inverse relationship between calcium intake and the risk of developing breast cancer, thus obtain-

ing a similar result to previous reviews. In addition, dose-response analysis showed that each increase in calcium intake by 300 mg/24 h was significantly associated with 2%, 8% and 2% reduced risk of occurrence adequately complete, diagnosed before and after menopausal breast cancer. It is also important that this relationship turned out to be stronger in the group of people consuming calcium with diet, in comparison to people who supplement it [30].

Although the exact mechanisms by which calcium can reduce the risk of breast cancer remain unclear, the ability of calcium to regulate cell proliferation, differentiation and apoptosis makes it biologically reliable as a potential protective determinant against breast cancer. There is also evidence that low levels of calcium are common in women with breast cancer [22, 30].

### Alcohol

The mechanism lying at the basis of the relationship between alcohol consumption and the risk of developing breast cancer has not been clearly defined. It is postulated, however, that this may be related to the effect of alcohol on the endocrine system. Its abuse leads to damage to liver cells that metabolize estrogen, thereby leading to increased levels of these hormones in the organism and their carcinogenic action. In addition, the metabolite of alcohol, acetaldehyde, has a genotoxic effect that may contribute to the development of cancer. Other proposed mechanisms include folic acid metabolism disorders due to the antagonistic effect of alcohol leading to abnormalities in the absorption and transformation of folate, and thus also DNA synthesis and methylation. Results of research occur showing the relationship between folic acid levels, alcohol use and the risk of breast cancer – the lower the concentration of folate, the greater the risk of developing cancer. It is also suggested that this issue may be associated with increased appetite, increased body weight, and thus increased hormonal activity. The above findings seem to confirm the fact that alcohol use is more associated with an increased risk of hormone-dependent breast cancer, compared to types of cancer independent of hormone activity [6, 8, 22, 31, 32].

Numerous studies have confirmed that alcohol consumption increases the risk of breast cancer by about 2–15% for every 10 g of alcohol consumed daily. Also, the comparison of research results of women who do not use alcohol and those who report (even small) intake allows to conclude about a lower risk of developing the disease in the first group presented [6, 15, 32, 33]. The issue of the interaction between alcohol consumption and breast cancer mortality remains



unclear [34–36], however, the additional incentive of tobacco smoking seems to increase this rate [35].

Alcohol is undeniably a determinant of the risk of developing breast cancer, however, due to the observed multifactorial interactions (including excessive body weight, age, type of cancer, time, amount and type of alcohol used, genetic polymorphisms) and significant heterogeneity of the designed analyses, further research should be carried out in order to better understand the mechanisms involved and the influence of individual fractions on them [22, 33, 37, 38]. Similar conclusions can also be drawn from analyses regarding the impact of alcohol consumption on the mortality rate of breast cancer [34].

It should be remembered that in the case of other groups of food products, the results of meta-analyses remain ambiguous. However, these postulates are not definitive, but rather encouraging, so that the influence of particular components of the diet on the risk of breast cancer remains an active area of research.

### Physical activity

Physical activity, through many biological paths connected with one another, remains consistently associated with a reduction in the risk of developing breast cancer, both in young and old women (by about 10–30%). This is confirmed by one of the last meta-analyses carried out in this topic, which showed a relationship between higher levels of physical activity and lower incidence of breast cancer among both women before and after menopause. In addition, no differences depending on the intensity of the exercises were found in any of the groups. Similar results were noted in another meta-analysis [39, 40].

Another meta-analysis, carried out in 2016, indicated a 3%, 6% and 14% drop in the risk of developing breast cancer in people with low activity (600–3999 MET min/wk), moderately active (4000–7999 MET min/wk) and highly active ( $\geq 8000$  MET min/wk) in comparison to people who are not active enough, according to the records of the World Health Organization (WHO) [41]. WHO recommends at least 600 metabolic equivalents (MET, metabolic equivalent) min/wk, defined as the amount of oxygen consumed at rest. In this case, 600 MET min/wk means six hundred times more energy expenditure than staying at rest, eg about 75 minutes of running/week or 150 minutes of fast walking/week [42].

Furthermore, there is evidence to suggest that an adequate amount of physical activity during adolescence and early

adulthood may lower the risk of breast cancer both before and after menopause [43]. It is claimed that the risk of breast cancer related to physical activity decreases by 16% during adolescence, 8% in early adulthood, 15% in middle age and 17% over 50 years of age [44].

The relationship between physical activity before and after diagnosis and mortality due to breast cancer seems to be an extremely important issue. Multivariate analyzes have proved that the lower number of deaths caused by the disease occurred only in women who maintained a dynamic pattern of activity or increased it after diagnosis, but did not concern inactive or active people before the diagnosis, which reduced the amount of movement after it. In the 2016 study, it was shown that physical activity, performed after the diagnosis, corresponding to at least 2.5 hours of fast walking/week, reduced mortality by as much as 32%, as compared to lower activity level. Similar results were obtained in another meta-analysis – a 34% drop in mortality and a 24% reduction in the risk of disease recurrence among women active after breast cancer diagnosis [39, 45, 46].

Bearing in mind the data presented in the report on breast cancer, in addition to the factors described above, the risk of this neoplasm may also be affected by: early first menstrual bleeding (before age 12), late natural menopause (after age of 55) and the late first pregnancy (after 30 years old). In addition, it is claimed that exposure to even low doses of ionizing radiation as a result of medical treatment, especially during adolescence, increases the risk of developing breast cancer. Also, the use of hormonal therapy and oral contraceptives, especially those containing a combination of estrogen and progesterone preparations, results in an increased risk of breast cancer. In the case of contraception, it is observed mainly in young women currently or recently using [1, 7, 19].

### CONCLUSION

Breast cancer is most often the result of mutual correlations between hormonal, environmental and genetic determinants. What's more, a significant proportion of the risk factors for this cancer are modifiable. At the same time, it should be remembered that lifestyle determinants are a complex combination of interactions that should be taken into account when conducting further dependency analyses. However, this does not change the need to introduce preventive strategies that increase public health awareness. This is aimed at limiting behaviours affecting the development of breast cancer and the number of deaths caused by it.

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