

Obesity in breast cancer patients after oncological treatment. How to conduct a nutritional intervention?

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Obesity in breast cancer patients is a significant predictor of morbidity as well as adverse treatment outcomes. It correlates with poorer response to treatment, particularly affecting survival length and quality of life. This paper aims to describe the relationship between obesity and breast cancer prognosis, highlighting the importance of integrated prehabilitation strategies. Prehabilitation, which includes nutritional counseling, psychological support, and physical activity, is proposed as a proactive approach to prepare patients for the rigors of cancer treatment, such as surgery, chemotherapy, and radiation therapy. The results emphasize the need to maintain optimal weight and body composition through dietary adjustments, particularly high protein intake, and physical rehabilitation. An interdisciplinary approach, including the involvement of oncologists, nutritionists, psychologists, and physiotherapists, is crucial for successful treatment outcomes.

Keywords: obesity breast cancer, prehabilitation

Obesity among patients with breast cancer

Obesity is defined as a pathological increase in adipose tissue in women exceeding 25% of ideal body weight (IBW), which increases the risk of breast cancer by up to 3-fold [1, 2]. Insulin resistance, hyperglycemia, and hyperinsulinemia are key factors leading, on the one hand, to obesity, and, on the other, to the development of cancer. Therefore, it is not surprising that, despite the disease, 15–45% of the European population's cancer patients are overweight and obese [3].

Obese women have the pooled relative risk (RR) of breast cancer 1.41, while overweight women have a much lower risk 1.07, according to a Chan et al. [4] study. Another important

factor is the timing of obesity onset: when it occurs before menopause it increases the risk of breast cancer (BC) more than in the postmenopausal period (RR pre-menopause 1.75, post menopause 1.34) [4]. Increased body weight is not only associated with a more frequent diagnosis of breast cancer but also with an unfavorable treatment outcome. An increase in body weight (by 5 kg/m²) before diagnosis of BC is associated with a 17% increase in total risk of death, up to 12 months after diagnosis and over this time by 11% and 8% respectively [4]. Both the time of gaining weight and the intensity of this process are important. Women with obesity in II and III class have a 58% increased risk of breast cancer [5]. Interestingly,

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women with a body mass index (BMI) > 35 kg/m² had a higher risk of breast cancer with the expression of estrogen (ER) and progesterone receptors (PR). There was no association between weight gain and an increased risk of cancer without the estrogen receptors expression. Additionally, no correlation was found between premenopausal hormone therapy, BMI, and breast cancer [5].

In the case of patients with a higher BMI, tumors of larger dimensions, less differentiation and more frequent lymph node metastases were diagnosed [5].

Obesity after oncological treatment

The body composition of female patients undergoing and after oncological treatment undergoes dangerous changes [6]. Catabolic processes, prolonged periods of weakness or bedrest, increased inflammatory state, loss of appetite, and changes in taste during the disease causes reduction in nutrient intake and an inability to engage in regular physical activity. This leads to unfavorable changes in body composition [7, 8] such as:

- loss of muscle mass (LBM) and strength;
- decreased physical performance;
- increase in fat tissue content.

These changes are characteristic for sarcopenia or sarcopenic obesity and have a negative impact on treatment course. The International guidelines for the assessment of nutritional status (GLIM) highlight the importance of assessing muscle mass by including its measurement as one of the phenotypic criteria for this assessment on a par with weight loss (> 5% within six months, or > 10% beyond six months), low BMI (< 20 if < 70 years, or < 22 if > 70 years) [9]. Assessing malnutrition using only BMI is insufficient because loss of lean body mass may be masked by excess fat mass [10]. Therefore, an obese patient according to the GLIM criteria (due to loss of muscle mass) could also be considered a malnourished patient.

The incidence of sarcopenia in breast cancer patients varies, depending on the measurement techniques from 15.9% to 47.8% (dual X-ray absorptiometry scans vs. CT scans), event to 58% [10, 11]. Sarcopenia increases the risk of complications (postoperative complications, chemotherapy toxicity, cardiovascular disease e.g., hypertension — the reduction in muscle mass also reduces the expression of myokines, including irisin, involved in the maintenance of vagal tone and in the parasympathetic modulation of cardiac function) and prolongs rehabilitation. It reduces the percentage of patients responding to treatment, overall survival (OS), progression-free survival (PFS), quality of life (QoL), increases the risk of depression, and overall mortality in breast cancer survivors [12].

Unintentional loss of body weight, which is often accompanied by loss of muscle tissue, should automatically alert the therapeutic team. Monitoring patients (weight, muscle mass) and promptly addressing any abnormalities in body weight and body composition is crucial to providing optimal care [13]. Adequate nutrient supply, particularly protein, and regular

physical activity are crucial during and after treatment, as the adverse effects of chemotherapy and radiotherapy may result in undesirable changes in body composition that have been demonstrated to persist for months or even years [14].

Prehabilitation as a method of supporting therapy

Prehabilitation is a comprehensive process that prepares patients for surgery and long-term oncological treatment, including chemotherapy, immunotherapy, and radiotherapy (Fig. 1). The fundamental premise of this process is to ensure the optimal state of health of patients, enabling successful surgical procedures without complications. Prehabilitation facilitates the implementation of therapy, helps minimize adverse events (AE) and contributes to a faster return to optimal psychophysical condition [15, 16]. The effectiveness of this process depends on the cooperation between the interdisciplinary prehabilitation team, which should include: a physician (surgeon, oncologist, anesthesiologist), clinical dietitian, physiotherapist, psychologist, nurse, and the patient. Prehabilitation is based on four inseparable pillars:

- elimination of addictions;
- psychological support;
- nutritional preparation;
- physical activity.

Every single pillar has an individual character and guidelines which are adapted to the patient's current condition and the expected effect [17]. Each element of prehabilitation is crucial, but special attention is focused on nutritional and physical preparation for treatment.

Nutritional preparation is an extremely important pillar of prehabilitation, although it is often overlooked. The patient's nutrition in the perioperative period, before and during chemotherapy and radiotherapy, has a direct impact on the course and effectiveness of treatment [17]. All patients before starting any planned treatment should be under the supervision of a clinical dietitian. The clinical dietitian will determine the patient's nutritional status and individual needs (for macro-, micronutrients and fluids). Particular attention should be paid during this period to patients with low muscle mass (malnourished according to the GLIM criteria [9] and high body mass which are associated with worse treatment outcomes [11, 12, 19, 20]. American studies indicate that if breast cancer patients > 50 years of age maintained a BMI < 25 kg/m², approximately 11–18 thousand deaths could be avoided per year [21]. Therefore, both during preparation for surgery and other oncological treatments, in the case of obese patients, the goal is to reduce body weight with maintaining or rebuilding muscle mass [22]. For this purpose, nutritional treatment should focus on an adequate supply of protein and supplementation of omega-3 fatty acids.

The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines on nutrition in cancer patients

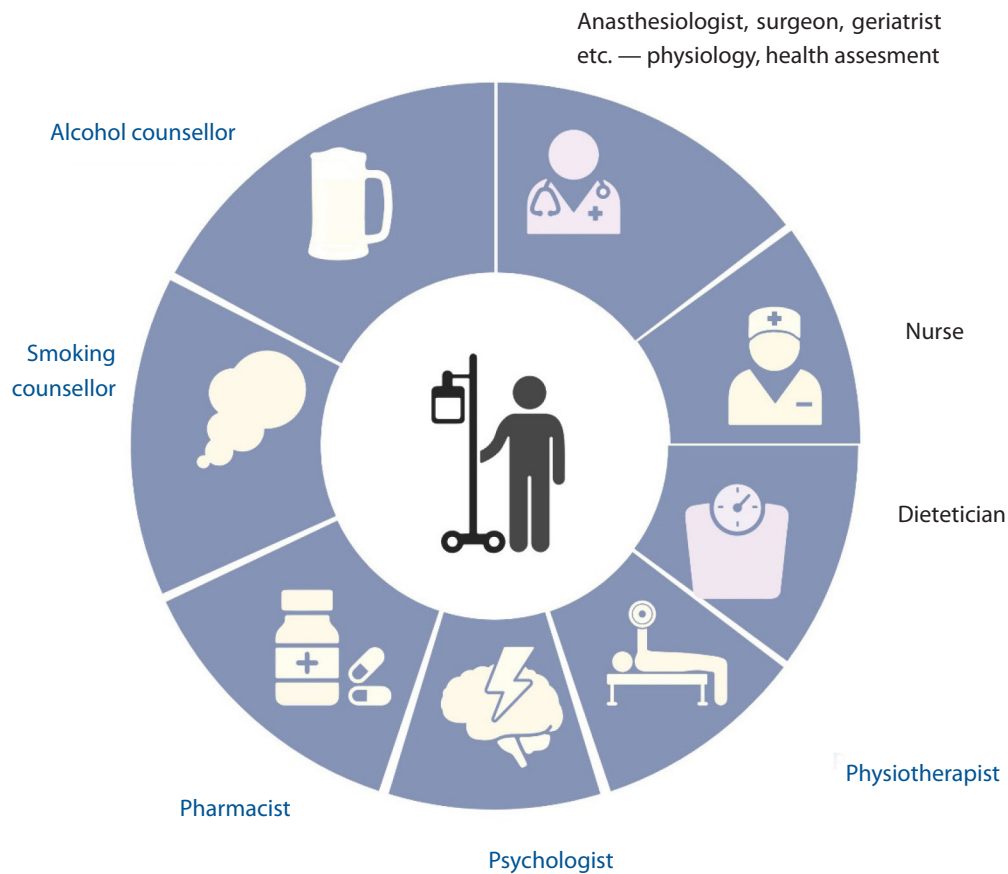


Figure 1. Multidisciplinary team, Durrand J. et al., 2019 [18]

recommends protein intake above 1 g/kg body weight/day and if possible, up to 1.5 g/kg body weight/day [23]. The synthesis of muscle tissue in oncological patients is extremely difficult due to the inflammation associated with the disease. It is also important to consider that the synthesis of muscle tissue in the geriatric population requires an increased supply of protein per kilogram of body weight compared to younger individuals. This is due to several factors, including disturbed intracellular signalling, impaired circulation of nutrients in the blood, the presence of chronic inflammation, and reduced physical activity [24]. In this population, to maximize skeletal muscle protein synthesis, an intake of 25–30 g of high-quality protein per meal is required [25].

One of the amino acids that is often used in the perioperative period is arginine. This amino acid contributes to the wound healing process at every stage (synthesis of nitric oxide, growth factors, collagen), and is an essential amino acid for the proliferation and activation of immune system cells. Due to this effect, it is used as a common component of immunonutrition. However, it must be noted that arginine supplementation is not recommended for routine use. Some types of cancer cells are dependent on external arginine sources (arginine auxotrophy) due to the inability of its synthesis to internally. In other words,

some type of cancer cells may respond to Arg supplementation with growth. Deficiencies of the key enzymes in the synthesis of arginine [arginine succinate synthetase (ASS1)] have been found in some cancer types e.g., hepatocellular, prostate, pancreatic, head and neck carcinoma, malignant melanoma [26]. Moreover, breast cancer expresses high levels of another enzyme arginase (ARG1), which is associated with polyamine production (growth factors) and inhibition of the NO generation by macrophages. This leads to cancer cell proliferation, Arg deprivation in the tumor microenvironment, inhibition of T-cell proliferation and impairment of their functions [27]. Other components of immunomodulatory diets are beta-glucans, or more precisely, the dectin-1 receptor, which are responsible for triggering immunostimulatory effects. Immunonutrition also uses ingredients such as selenium, zinc, and vitamin C, which will regenerate wounds and support the immune system [2].

Supplementation with omega-3 fatty acids (another immunomodulatory component) is recommended in patients with advanced cancer undergoing chemotherapy and at risk of weight loss or malnourished (ESPEN, Clinical Nutrition in cancer, 2021) [23]. The consumption of omega-3 fatty acids improves appetite, food intake, increases lean body mass and body weight. These fatty acids, on the one hand, reduce

Proposed multi-level approach to prehabilitation intervention

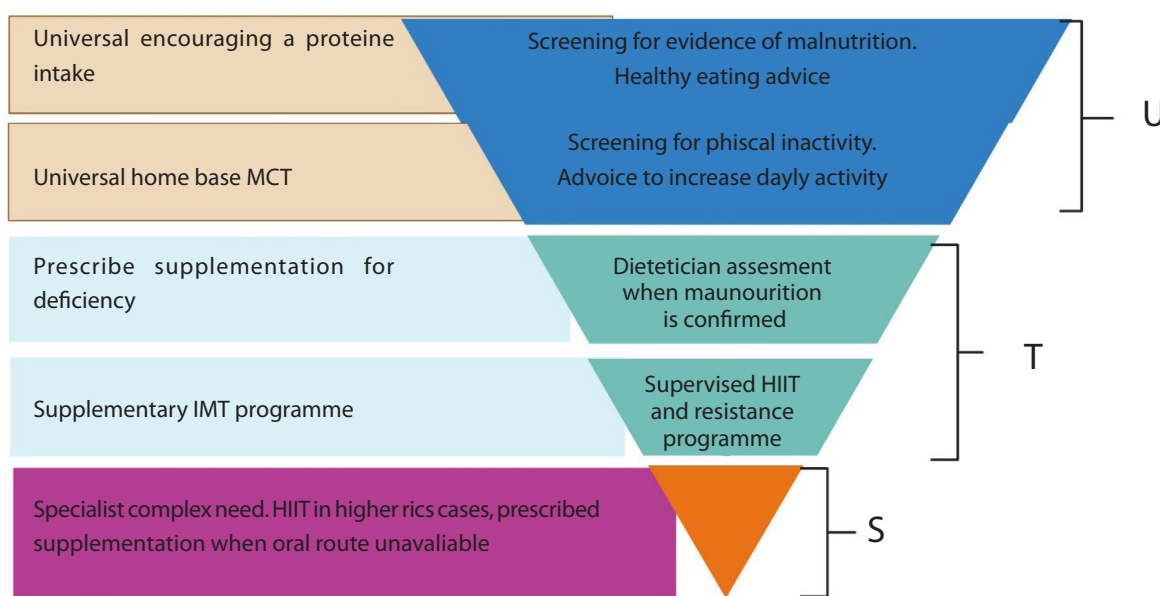


Figure 2. Proposed multi-level approach to prehabilitation intervention (nutritional support and exercise used as examples) (Durrand et al., 2019 [18]); HIIT — high intensity interval training; IMT — inspiratory muscle training; MCT — moderate continuous training; S — specialist; T — targeted; U — universal

synthesis of pro-inflammatory mediators [2], and, on the other, have the ability to increase (even double) the anabolic response in reaction to increased amino acid and insulin concentrations [28]. However, the anabolic effect of omega-3 fatty acids requires long-term intervention. A change in the structure of the myocyte cell membrane and, therefore, a change in their sensitivity to anabolic signals (increased concentration of amino acids in the blood) occurs over a period of 4–6 weeks, with supplementation of 5 g of omega-3/day [28] (Fig. 2).

The diet of a prehabilitated patient should, first be individually tailored to the patient's health condition and needs. The frequently used intervention is a modification of the usual diet (often a reduction diet) with high protein content and supplementation with omega-3 acids (1–2 g/d). Doses exceeding 2 g/day of eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA) are generally required to reduce levels of prostaglandin E₂. In the treatment of hypertriglyceridemia or inflammatory disorders, the most commonly administered dosage is 3.0 to 3.5 g/day of EPA + DHA. The European Union has established that doses of EPA and DHA up to 5 g per day are safe [29, 30]. As long as BC patients consume an adequate amount of protein and follow dietary recommendations, dietary fortification is rarely required. It is also worth noting that each patient should be educated on the importance of hydration which influence e.g., taste perception, especially during chemotherapy. It is recommended that oncology patients should drink 30–40 ml/kg body weight/day [8, 31].

According to ESPEN and Enhance Recovery After Surgery Society (ERAS Society) recommendations, providing increased

nutritional support (especially protein intake) prior to planned surgery is beneficial in many clinical situations but depends on a number of variables. However, if the patient is malnourished or at risk of malnutrition, surgery can be postponed for 10–14 days [32]. On the day before surgery and 2–3 hours before the procedure, it is recommended that the patient should consume an oral carbohydrate solution. This approach minimizes the body's response to injury, postoperative insulin resistance and hyperglycemia, and has a protective effect on muscle tissue [32, 33].

The fourth pillar of prehabilitation is physical activity. Lack of physical strength the sensitivity of muscle cells to anabolic signals such as an increase in amino acid concentration in the blood. Additionally poor physical function is a predictor of adverse events in the perioperative period [34] and poor outcomes in the long term. Moderate physical activity (3–5 h/week) will influence the effectiveness of treatment, including OS, especially in patients with hormone-dependent cancer [35] and it is a cost-effective procedure [36]. Muscle tissue has an important impact on the functioning of the immune system, mediated by myokines. Physically active patients after diagnosis of breast cancer have a higher survival rate than physically inactive patients, and these effects are mediated by regulation of natural killer cells. The breast cancer survivors can also mobilize NK cells to the circulation to the same degree as age-matched healthy controls by exercise [37, 38].

Therefore, each patient should have an individually prescribed set of exercises adapted to their health condition and physical predispositions aimed at changing the body mass

composition (resistance training), and increasing the patient's aerobic capacity (aerobic training). Most patients preparing for surgery or the entire treatment process, require consultation with a physiotherapist [39]. Appropriately selected physical exercises performed daily for a minimum 2 week period (optimally 4–6 weeks) will help eliminate the side effects of surgical treatment e.g., the most common respiratory complications. These is why a form of resistance training of the diaphragm, respiratory muscles, and intercostal muscles — inspiratory muscle training should be especially included in the prehabilitation exercise program [40]. Physical activity may also be an effective remedy for chronic fatigue frequently reported by BC patients [41].

Treatment methods and effects on body weight

Treatment of breast cancer includes a wide range of interventions as surgical treatment, radiotherapy, and systemic treatment [hormone therapy (HT), immunotherapy, chemotherapy (CT) as neoadjuvant or adjuvant treatment]. There are

many regimens due to dynamic development of personalized treatment which are based on receptor expression on cancer cells [42]. Due to such a large variety of therapies and drugs used to treat breast cancer, we can expect various adverse events and, consequently, different effects on body weight.

Weight gain during treatment is most common in hormone receptor (HR)-positive_(HR+) breast cancer treatment, however studies indicate an ambiguous relationship between e.g. tamoxifen (TMX) therapy and weight gain (Tab. I). It is also worth noting that patients with adjuvant CT prior to TMX for the first 3 years were more obese than those who had not undergone CT and this may be due to the prolonged effects of chemotherapy [43].

Other adverse events accompanying oncological treatment which affect nutritional status (body weight and body composition) are vomiting [19, 44, 45], decreased appetite [44, 46–48], anorexia [49], feeling of fullness [50], xerostomia [51], diarrhea [19, 44, 46, 47, 52], constipation [53], loss or change of taste [47, 48, 54], mucositis [55]. These events, through

Table I. Adverse events affecting body weight in distinct therapeutic regimens

Breast cancer type	Author	Therapy	AE affecting body weight	
HR+	Nyrop et al., 2016 [56]	TMX	Weight gain	<ul style="list-style-type: none"> • 18–52% of patients in 1st year • 7–55% of patients in the 5th year
	Raghavendra et al., 2018 [57]			<ul style="list-style-type: none"> • in pre-menopausal patients weight gain > 5% is 1.4 times higher than post-menopausal
HR+ recurrence	Baselga et al., 2012 [47]	Steroidal aromatase inhibitor (SAI) + mTOR inhibitor (everolimus)	Weight loss	<ul style="list-style-type: none"> • 19% of patients in everolimus + exemestane • 5% of patients in placebo + exemestane
			Other AE	<ul style="list-style-type: none"> • stomatitis • decreased appetite • diarrhea • dysgeusia
HER+ advanced, metastatic	Swain et al., 2020 [48]	Pertuzumab + trastuzumab + docetaxel	Diarrhea	<ul style="list-style-type: none"> • 68.4% of patients: mild to moderate • patients > 65 years of age > probability of diarrhea
			Other AE	In pertuzumab arm: <ul style="list-style-type: none"> • nausea • stomatitis • loss or change of taste • decreased appetite
Unresectable HER+ or HER2–low (IHC1+ OR IHC 2+/ISH–)	Hurvitz et al., 2023 [44]	Second line: T-Dxd (conjugated deruxtecan with trastuzumab)	Weight loss	<ul style="list-style-type: none"> • 23% of patients in group T-Dxd • 9% trastuzumab–emtansine
			Other AE	<ul style="list-style-type: none"> • nausea 77% • vomiting 52% • diarrhea 32% • lack of appetite 30%
TNBC	Cortes et al., 2022 [58]	ICI: pembrolizumab (neoadjuvant or adjuvant [58]) Atezolizumab with nab-paclitaxel	Other AE	Pembrolizumab: <ul style="list-style-type: none"> • nausea • abdominal pain • diarrhea • decreased appetite [46] Atezolizumab: <ul style="list-style-type: none"> • decreased appetite • nausea • diarrhea • vomiting (19)

AE — adverse events; HER+ — human epidermal growth factor receptor positive; HR+ — hormone receptor (HR)-positive; ICI — immune checkpoint inhibitors; IHC1+ or 2+ — immunohistochemistry evaluation of the degree of protein expression; ISH — *in situ* hybridization; TMX — tamoxifen; TNBC — triple negative breast cancer

Table II. Differences between diet with preventive effects, lowering breast cancer (BC) recurrence, cancer-related mortality

Diet with preventive effects and lowering breast cancer recurrence, breast cancer-related mortality [71–73]	Diet increasing breast cancer risk (pro-inflammatory), elevating risk of cancer recurrence [71, 72, 74]
Diet rich in: <ul style="list-style-type: none">• fresh vegetables (green-leafy, cruciferous)• fruit• nuts• fish (EPA, DHA)• dietary fiber• soy• whole grain products• eggs• lean meats	Diet rich in: <ul style="list-style-type: none">• highly processed foods (with salt and sugar)• high glycemic index, including fruit juice• red and processed meat• alcohol• saturated fatty acids• total fat

DHA — docosahexaenoic acid; EPA — eicosapentaenoic acid

their negative impact on adequate protein and energy intake affect the results of oncological treatment.

Nutritional guidelines for obese patients during and after completion of therapy

Diet may, on the one hand, be a factor influencing the risk of developing breast cancer and, on the other hand, be a factor influencing the course of oncological treatment (Tab. II) [59]. Weight gain (overweight or obesity) during or after cancer treatment increases the risk of the disease (HR+), is a predictor of poor prognosis, increases recurrence, and reduces the OS [60]. Moreover, women who survive breast cancer have a 30% higher risk of developing another type of cancer [61]. For this reason, the oncologist should recommend a reduction diet, with adequate protein intake by a clinical dietitian [62], and lifestyle changes including physical activity and psychosocial support.

Inadequate protein supply will affect the functioning of the immune system both during treatment [e.g., with checkpoint inhibitors (ICI)] and after its completion. Lack of sufficient protein delivery leads to atrophy of the thymus, reduction of thymus-dependent areas in lymphatic organs, a decreased number of T lymphocytes, inability to produce responses to T-dependent antigens, cell-mediated responses, activity of macrophage system, complement system (C1, C2, C4, C3) [63]. Insufficient protein intake not only weakens the immune system, but also contributes to the depletion of muscle tissue. Muscle mass loss is associated with high neutrophil to lymphocyte ratios or proteolytic cascades (increase TNF- α), which promote tumor migration and invasion [11]. If one considers that muscle tissue has an important impact on the function of the immune system (mediated by myokines), the need to preserve this tissue becomes obvious. Interventions such as adequate protein and energy supply and physical activity (“exercise oncology”) are necessary, and it should be perceived as multidisciplinary supportive care during and after treatment [64].

Maintaining the appropriate energy balance and thus proper body weight is related to improving BC patient prognosis and quality of life [65–69]. Consumption of foods rich in dietary fiber, soy, lower consumption of saturated fatty acids and total fats are related to higher survival after BC [60, 65]. A meta-analysis by Xing et al. [70] suggests that following a low-fat diet after a BC diagnosis can improve survival by reducing the risk of disease recurrence by 23%. Breast cancer survivors whose diet was characterized by the highest dietary quality index had a 23% lower mortality rate compared to women with the lowest dietary quality index category [65, 71–74].

A meta-analysis by Lee et al. [75] showed that following the DASH diet and Chinese Pagoda Guidelines can reduce breast cancer-related mortality. This relationship turned out to be particularly important in older people, physically fit and women with cancer cell with estrogen (ER+) and human epidermal growth factor 2 receptors expression (HER2+), and without progesterone receptor expression (PR-) [75]. A diet based on the Mediterranean model was able to improve the body’s antioxidant capacity as well as the glycemic profile [76].

The above-mentioned dietary models are based on the consumption of vegetables, fruit, whole grain products, eggs, fish, lean meats, and dairy products, as well as limiting the consumption of salt, fat, sugar, and alcohol. The Pagoda guidelines additionally recommend at least: 150 minutes of physical activity per week and performing at least 6000 steps a day [1, 6, 77].

The study, conducted as part of the Nurses’ Health Study (NHS; 1980–2010) and NHSII (1991–2011) involved 8,927 women with stage I-III breast cancer, concluded that total fruit and vegetable (green, leafy, and cruciferous vegetables) intake was associated with lower all-cause mortality (ACM) but not with breast cancer-specific mortality. It is worth highlighting that a higher consumption of fruit juices (except orange juice) was associated with worse breast cancer- and non-breast cancer-related survival [4].

The composition of the microbiota found in the mammary glands seems to be diverse and may influence both the development of BC and the course of treatment. Researchers will confirm the hypothesis that intestinal dysbiosis is the source of the development of BC. Disturbed microbiota activate mast cells in the breast, which will facilitate the spread of cancer cells [78]. Diets rich in dietary fiber may have a beneficial effect on composition (increased diversity) and functioning of the intestinal microbiota and therefore on the functioning of the immune system [79, 80]. For this reason, the consumption of various sources of fiber is crucial before and after BC treatment.

Better diet quality after cancer diagnosis appears to be associated with lower levels of inflammation measured by the C-reactive protein (CRP), regardless of BMI or physical activity [5, 78, 81, 82] the association between DII and cancer recurrence and mortality among patients with breast cancer has not been investigated. Therefore, the present study aimed to investigate whether DII was positively associated with risk for cancer recurrence and overall mortality among patients with breast cancer. Among 511 women (51.9 ± 10.7 years; stage 0–3). On the other hand, the high risk of cancer recurrence in obese patients may be caused by pro-inflammatory cytokines e.g., CRP, IL-3, IL-6, IL-8, as well as TNF α [83].

Conclusions

Increased body weight is not only associated with a more frequent diagnosis of breast cancer but also with an unfavorable treatment outcome [decreased QoL, disease free survival (DFS), and OS]. The time of gaining weight (before or after menopause) and the intensity of this process influences treatment results. Therefore, maintaining the appropriate energy balance and proper body weight and composition of BC patients is crucial. In this area, the support of a clinical dietitian and physiotherapist is necessary. The oncologist should recommend a reduction diet with adequate protein intake (1,2 g/kg body weight/day and if possible up to 1.5 g/kg body weight /day) by a clinical dietitian and lifestyle changes including physical activity. Clinical dietitians' support during and after breast cancer treatment is an essential element that can improve the patient's prognosis.

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Authors contributions

Ewa Stachowska — conceptualization, writing — review and editing.

Nikola Janowska — writing — original draft preparation.

Agata Łyczek — writing — original draft preparation.

Natalia Komorniak — writing — review and editing.

Natalia Jakubiak — visualization.

Karolina Siedlecka-Kaźmierczak — writing — review and editing.

Conflicts of interest

None declared.

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