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# Association between body composition and genetic polymorphism of tumor necrosis factor alpha in women with breast cancer

## Abstract

The change in body composition can affect the treatment of women who are undergoing treatment. The increase in body composition may present a state of chronic low-grade inflammation that is determined by the increase in fatty acids, produced by inflammatory cytokines such as Tumor Necrosis Factor (TNF-α), which has negative consequences for women with breast cancer. The study aimed to understand the association between body composition and inflammatory processes (TNF-α genetic polymorphism) in women with breast cancer. The research was developed through a literature review. The search was carried out in the SciElo, Pubmed, Lilacs and Google academic databases. 130 articles were found. The selected scientific texts were reduced to 11 for use in the review. There was a predominance of quantitative study design. The strategy used to search for studies were combinations of "oncology", "polymorphisms", "obesity", "body composition" and "inflammatory process". In the investigations of the high incidence of breast cancer in women and the inflammatory process activated by their own health conditions and treatment, the number of studies found was small. In all studies, the authors confirm that the TNF-α inflammatory process is a fundamental tool for planning cancer care. Future research is needed in order to analyze the habit of life and the environment that the individual is inserted to elucidate the association of altered body composition and breast cancer.

**Keywords:** breast cancer, TNF-α polymorphism, body composition, health Sciences

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## Introduction

Breast cancer is the most common type of disease among women in the world. The morbidity and mortality rate expresses the highest number in the female population, representing a public health problem. In Brazil, neoplastic diseases account for an estimated 57,960 cases per 100,000 women. In view of the growing estimate of new cases in Brazil, although the disease is considered to have a relatively good prognosis, the mortality rate (13.68% per 100,000 women). Studies have shown that health care networks in the Unified Health System (SUS) establish actions to guarantee women's access to cancer treatment. In 2012, Law No. 12,732 of the Presidency of the Republic was sanctioned, which determines the time of 60 days for the start of the first treatment stage.[1]

Epidemiological studies with women with an average age of 52 years with histopathological diagnoses of breast cancer were conducted by several studies related to body composition. Patients were referred to the oncology service and subsequently scheduled assessments of body mass index (BMI), waist/hip and waist circumference. The results of the studies have shown that body composition is associated with the appearance of mammary tumors in postmenopausal women. Excess weight can be considered a worldwide risk for new cases of breast cancer. In the seventies and eighties, the predominance of overweight in women over 20 years old was 28.7%. The risk was evidenced by several studies that examined overweight and increased levels of free IGH-I (insulin-like growth factor), which may be responsible for cell proliferation.[2] A study carried out in a public hospital, belonging to the Federal University of Uberlândia with a sample of 150 women with breast cancer, showed that obesity has a greater conversion of androstenedione to estrogen in adipose tissue and a decrease in the level of sex hormone-binding globulin, which may contribute to the release of estrogen at the tissue level. These hospital patients were over 18 years old and had a high BMI, especially in the abdominal region, which in turn can induce side effects when the patient is being treated with chemotherapy. The following evaluations of the study were the analysis of tetrapolar bioimpedance, abdominal circumference (WC) and hip circumference (QC), anthropometric data, waist-to-hip ratio (WHR), body mass index (BMI), systemic blood pressure and biochemical analysis. Considering weight changes during treatment. In general, body composition influences the lives of women undergoing treatment for breast cancer.[3]

A study of 5,254 women examined the association between overweight and cancer, found that obese women had a high mortality rate for cancer when compared to women who were not overweight. However, 3.5 million women survivors of breast cancer in the USA had a BMI considered normal, which shows that body composition influences the recovery of women with cancer.[4]

Obesity stimulates the production of hormones in a state of short-term inflammation. The production of these hormones is linked to certain types of cancer. The origin of this state of chronic low-grade inflammation is determined by the increase in fatty acids, produced by inflammatory cytokines as a tumor necrosis factor (TNF-α), and their high circulating concentrations are related to BMI. When body composition increases, the production of these cytokines by adipose tissue is increased and, consequently, the high circulation of inflammatory cytokine levels characterizes a low-grade chronic inflammation.[5]

Inflammation in a short period of time can be beneficial to health, since it can chronically present conditions that are harmful to health. Chronic inflammation in the etiology of cancer has gained strength, since studies have shown the intervention of macrophages within the neoplastic tissue.[6]

Epidemiological studies have shown that inflammatory drugs in individuals with several types of cancer, in which the level of inflammation was lower, were more likely to be alive compared to individuals who had a higher level of inflammation. In breast cancer, the chronic inflammatory response due to excess weight determines the increase in production at high levels of prostaglandins, mediator of inflammatory cytokines.[7]

Studies show the importance of studies related to obesity, cancer and the additive effect of the chronic inflammatory process. Study with 151 women diagnosed with breast cancer, divided into obese and non-obese women with inflammatory status. Sociodemographic profiles, characteristics of the neoplasia and measurements of Interleukin (IL)-1β and Tumor Necrosis Factor (TNF)-α were compared with the BMI (Body Mass Index). Laboratory tests were also measured in order to assess markers of insulin resistance and menopausal status. The cytokine levels of the culture supernatants were quantified using the Cytometric Bead Array (CBA) system. The analyzes were carried out at the Center for Technological Platforms at the Aggeu Magalhães Research Center (CPqAM)/Fundação Oswaldo Cruz (Fiocruz). The study showed an association between BMI and TNF-α in women with high body composition.[8]

In this sense, chronic inflammation related to body composition, specifically obesity, may partly explain the association of obesity and breast cancer. However, this article aims to understand the association between body composition and inflammatory processes (TNF-α genetic polymorphism) in women with breast cancer, based on a review of scientific articles that consists of a survey of the impact of body composition and its relationship with chronic increase in inflammation of women diagnosed with breast cancer.

## Method

The review procedure was guided by the systematic review of a bibliographic study about the importance of weight control for the inflammatory process in women with breast cancer, and among so many types of studies available, qualitative research presents appropriate sources for the main focus. The bibliographic search was conducted using standardized terms indexed in the scientific databases: Scielo, Pubmed, Lilacs and Google Scholar. Great research content was made available in English and Portuguese: "oncology", "polymorphisms", "obesity", "body composition" and "inflammatory process".

The initial selection of articles was carried out through a review that assessed the adequacy of articles based on the information provided in the title and abstract. Subsequently, the same reviewers evaluated the full texts of the articles and made the final selection, according to the established criteria, independently. For registration, a standardized form was used, in which the review was carried out independently, the extraction of the following data: author (s); year of publication; study design; population (sex, place of recruitment, age/age range, sample size, country of study); objective; methods for measuring breast cancer diagnostic criteria; inflammatory processes evaluated; synthesis of the main results related to obesity; conclusion of the study; studies with women with cancer and/or studies involving the diagnostic criteria for breast cancer in women. In the case of divergences in the selection of article (s), the author also read it, opting for the inclusion or exclusion of the same (s).

The strategy used to search for studies were combinations with those presented above, to achieve more scientific content that would investigate in detail the performance of the significant results of body composition in women with breast cancer. Thus, the first access was on August 15, 2019, using the following combinations/keywords: Breast cancer, TNF alpha genetic polymorphism and body composition. Altogether, 130 scientific texts were found with the researched combinations, of which 74 articles in Pubmed served for the theoretical basis and for the explanation of this review; in Scielo, 25 texts were found; in Lilacs, 13 articles were found and in Google Scholar, 18 texts were reached.

All clinical trials and observable studies were included in which general survival data were reported according to the number of women with breast cancer research in one or more domains on the topic (prognosis, mortality, expression of genetic polymorphisms, obesity in the cancer treatment), in addition, original articles published in the last 10 years (2010 to 2020) were selected. The exclusion criteria were: elimination of articles whose abstracts were not available in the electronic databases; texts that addressed the body composition of women who did not have breast cancer, women with other cancer; articles that did not address polymorphisms in breast cancer; and qualitative articles that the individuals' samples were less than or equal to 15; articles that had only the abstract; other types of publications: lectures, conferences etc.

The selected scientific texts were reduced to 11, with 4 articles obtained from Pubmed, 2 from Scielo, 1 from Lilacs, 4 from the Academic Google, all found on websites, as shown in Table I. After the review process of abstracts and full texts of the articles, the following information from the journals was read. The first revised axis was the protective effect of TNF alpha polymorphism in women with breast cancer. The aim of the study was to identify studies related to these aspects. It is worth mentioning that the theme encompasses scientific productions that identify the impact on patients' quality of life. According to the revised axis, it was the inflammatory process in patients with different body composition, with the objective to be achieved or as a proposal for good nutrition and physical activity in their health. Last axis, elaboration of the productions that identified the scarcity of studies that relate obesity and cancer.

## Results

The searches in the six databases initially provided 936 abstracts. We identified 130 articles related to the research topic. However, the studies were mostly observational designs of the transversal type in Portuguese and English in the databases. Of the 130 found, 119 were excluded, and 54 were excluded by duplicate, that is, they were present in more than one database. The other 10 were excluded because they did not fit the inclusion criteria: breast cancer in men (n=08), articles with other polymorphism (n=10), review articles (n=10), studies with experimental models (n=4), only with plasma oxytocin (n=04), studies with TNF alpha polymorphism, but associated with another psychopathology (n=8), studies with breast cancer only. Thus, only 11 articles were included in the present study. The flowchart for selecting articles is shown in figure 1.

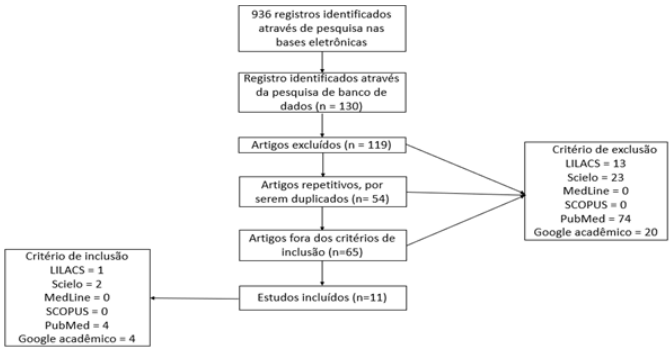


**Figure 1** Prism flow diagram for article retrieval.

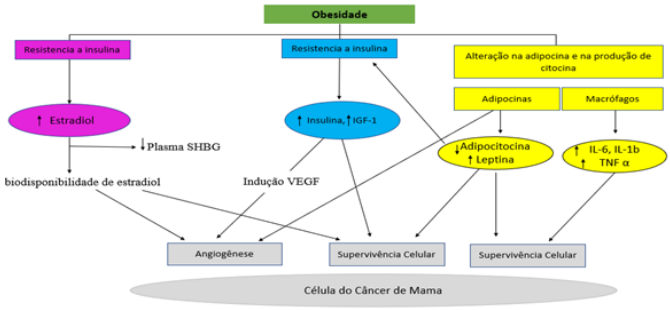


**Figure 2** Paths that link obesity and breast cancer. Reproduced with permission from Sinicrope and Dannenberg.

In the analysis of possible factors related to obesity as adjustment variables in association with the measures of inflammatory response, studies show an increase in body composition, percentage of fat, lipids and glucose metabolism after chemotherapy. The women who underwent chemotherapy, decreased the intake of nutrients, systemic metabolic dysfunction (unbalanced metabolism between carbohydrates, proteins and lipids), inflammation (expression of TNF alpha) and increased energy expenditure. In the search for articles that associated increased body composition and cancer, studies have shown that chronic inflammation promotes the induction of angiogenic factors by cells of the tumor microenvironment, which increases metastasis.

There was an association between excess body weight and cancer risk, which can be explained by changes in hormone metabolism. However, several studies have shown a suspicion of a relationship between cancer and inflammation of obesity for thousands of years. It was observed in the published works, women with excess weight, said to be high producers of TNF-alpha, had an increased risk of breast cancer (Figure 2).

Several inflammatory mediators are associated with breast cancer, the tumor necrosis factor is known to positively regulate the expression of homeostasis through specific chemical reactions. Increasing its levels can lead to improved and regulatory estrogenic biosynthesis of a target gene. Many cancers are recognized for their origin related to inflammation, such as tumors of the colon, esophagus, bladder, prostate, among others, this link is much clearer in breast cancer. Studies have shown a positive relationship between the increased size of adipocyte tissue and cell death in breast tissue. For this reason, the presence of the tumor is associated with increased levels of TNF-α.[7]

In relation to breast cancer, all the most relevant studies found identified that obesity is associated with an inflammatory state in all women over 18 years of age (see Table 1). However, few molecular studies indicate that obesity promotes an increase in pro-inflammatory cytokines, unfortunately, the search for quality assessment has only provided few studies in relation to breast cancer and the release of pro-inflammatory cytokines (TNF-α), without providing criteria to classify the studies as “high quality”, “medium quality” or “low quality”.

**Table 1** Clinical studies in humans on the inflammatory status in obese women with breast cancer

| Reference | Study designer | Study objective | Sample | Main conclusions |
|---|---|---|---|---|
| Araújo et al.,[3] | Randomized clinical study Breast cancer | Impact of chemotherapy not on women with breast eating | 76 women initiating or treatment for body cancer 18 to 70 years | Chemotherapy can induce weight loss and reduce inflammation |
| Felden et al.,[2] | Case-control proceedings | Association between distribution of body fat and cancer of body fat and eaten cancer From 18 to 65 years | 400 women with breast cancer diagnosis | Or accumulation of fat in the upper part of the body and preditor of breast cancer and reduction of inflammatory cytokines (TNF-α) |
| Freitas et al.,[5] | Randomized and controlled clinical trial | Effect of obesity and related diseases to the levels of cytokines that form pro-inflammatory (TNF-α) and anti-inflammatory (adiponectin) submetations | 55 obese women in common bariatric surgery from 18 to 63 years old | Weight is related to the inflammatory state of obese women |
| Miliniak et al.,[4] | Longitudinal clinical study between 1992 and 2013 | Association of obesity and physical activity with specific mortality from breast cancer | 4226 women with breast cancer eaten from 30 to 65 | Higher BMI, was associated with a higher risk of mortality specific to breast cancer |
| Paiva et al.,[11] | Descriptive, observational, cross-sectional study on weight | Investigate the prevalence of lymphedema in mastectomized women with | 100 women with breast cancer eaten from 45 to 71 years | Higher body mass index higher probability of lymphedema |

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The role of TNF-α in carcinogenicity, incentivized various researchers to study or use inflammatory agents in the prevention of cancer in people with obesity, new investigations are in progress aiming to reinforce the immune system to combat tumors. Women with a BMI>25 with a diagnosis of breast cancer have increased in recent years in Brazil, and how this aspect can be associated with the expression of TNF-α.

The results are based on epidemiological studies that link body composition, cancer, and the inflammatory process. Some of the studies show that the inflammatory markers and the risk of various breast cancers make it plausible to hypothesize that the molecular mechanisms of carcinogenesis can be mediated by inflammatory pathways.

## Discussion

Forces detected strong evidences of the inflammatory process in obese women, but there are still some inconsistencies, there are no evidences that obesity is directly related to or aggravated in mortalities of women with breast cancer.

The inflammatory system is made up of a complex network of cells and molecules dispersed throughout the body. As inflammatory adipokines are proteins of low molecular weight, which participate in inflammation, these adipokines are present not breast cancer.[9] In literature we find the main sources of adipokines that are subcutaneous and visceral adipose tissues, not which role and produce certain bioactive substances like TNF-α. As the quantity of adipose cells increases, as metabolic and endocrine functions are altered, or even, these alterations can aggravate the health of patients with breast cancer.[10]

The alteration in the body composition of BMI has been widely studied in literature as an importance in public health in failure not in the area of care for two individuals. It was considered that with 1000 women with breast cancer and with high levels of BMI, it was necessary to specify a greater quantity of blood in circulation to maintain a constant flow. Therefore, the study has shown that alterations in body composition in women with breast cancer can increase the risk of lymphedema.[11]

It requires more randomized clinical studies that show differences in relation to the years given from the base line in the experimental and control groups. Just as the known confusion factors can be controlled, there may still be residual confusion factors. Furthermore, a theoretical framework is lacking to guide the research. Therefore, more randomized clinical trials with theoretical reference are necessary in future studies. Furthermore, the number of participants enrolled in the included studies was generally small, larger populations are necessary to conform to the results of obesity and inflammation in women with obesity. Or use of different questionnaires and appraisals could be a potential factor of inconsistent flaws. As a result, the measurement instruments used in the future must be sensitive or sufficient to measure changes in our research results.[12]

Since the results of these studies are still not enough, we now find an association between body mass index and TNF alpha polymorphism with several types of cancer, including breast cancer. In addition, it is also essential to take into account environmental and emotional conditions, these factors can alter the expression of cytokine polymorphisms affecting the synthesis and release of inflammatory substances.[13]

## Conclusion

The studies obtained on body composition and breast cancer have enabled us to explain some of the aspects that may contribute to the medical and biological understanding of breast cancer. Therefore, the increase in body composition showed a strong interaction between the inflammatory process and breast cancer.

The results of the present study strongly support the change in habits as a powerful tool in the rehabilitation of women with breast cancer; in addition, it brings to health professionals and researchers the ability to elucidate which protocols are most effective in assessments. Future research with participants in different living environments is necessary in order to analyze the environmental influence to which the individual is inserted to elucidate the association between changes in BMI and breast cancer. It is also important to consider the instruments for tumor tracking, and the sample size of each study performed.

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## Conflicts of interest

Authors declare that there is no conflict of interest.

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