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Review

Potential protective role of bariatric surgery against breast cancer in postmenopausal women

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Abstract

Obesity is a major public health problem worldwide especially due to the metabolic disorders which seem to be induced by an excessive amount of adipose tissue. Therefore attention was focused on evaluating the role of bariatric surgery in order to offer a better control of the comorbidities such as diabetes mellitus, arterial hypertension or dyslipidemia which are widely accepted as causes of increased morbidity and mortality among obese patients.

Once these benefits have been widely demonstrated, attention was focused on studying the potential protective role of bariatric surgery against development of various malignancies such a breast, endometrial, pancreatic or even colorectal cancer. This is a literature review regarding the potential protective role of bariatric surgery against breast cancer among obese women worldwide.

Keywords: breast cancer, bariatric surgery, obesity, protective role

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Introduction

Obesity has become a major health problem worldwide, especially due to the associated comorbidities such as dyslipidemia, arterial hypertension, sleep apnea or diabetes mellitus (1-3). Overweight (defined as a body mass index greater than 25 kg/m2) and obesity (defined as a body mass index greater than 30 kg/m2) represent common conditions currently, 65% of the adults in the United States of America being overweight and 30% of the same population being classified as obese persons (4). All these findings associated with the observation that most patients submitted to conservative, dietary regimens fail to report a consistent, long term weight loss leaded to the apparition of the concept of bariatric surgery. The most common types of surgical bariatric procedures consist of restrictive methods (the most frequently performed being laparoscopic sleeve gastrectomy) or malabsorbtive procedures (such as laparoscopic gastric bypass or duodenal switch). Once the benefits in terms of consistent, permanent weight loss and the amelioration of the associated comorbidities have been widely reported in cases submitted to this kind of surgical approach, bariatric surgery has become the gold standard in treating obese patients (5-7).

Another important pathological correlation was the one between obesity and the development of certain malignancies, most often obese patients being diagnosed with gastrointestinal malignancies (especially colorectal cancer), genitourinary malignancies (such as breast, endometrial, cervical, ovarian, prostatic or kidney carcinomas) and even hematological malignancies (such as lymphomas) (8, 9). Although the first data suggesting this association originates in the early '90's, the first studies demonstrating the strong correlation between obesity and malignant conditions were published in the past few years. These observations, in association with the spectacular improvement of metabolic disorders after bariatric surgery encouraged the surgeons worldwide to study the potential benefits of bariatric surgery in order to provide a protective role against various malignancies.

In the study conducted by Plecka et al. the authors demonstrated that for obesity related cancers (such as breast, prostate, endometrial, kidney or colorectal cancer)the overall incidence ratio is 1,04 for all subjects who were submitted to bariatric surgery compared to general population, demonstrating in this way that bariatric surgery might decrease the malignancy risk in formerly obese patients to a comparable rate with the one reported by normal weight patients (7).

Association between obesity and breast cancer

In postmenopausal women there is a strong level of evidence that obesity is associated with an increased risk of breast cancer due to an increased level of estrogen (9). In the meantime association of hormone therapy in obese postmenopausal women leads to a higher incidence of breast cancer. Administration of hormone therapy is usually associated with an alteration of hepatic protein synthesis, including an insufficiency of glucose metabolism related proteins (10). Oppositely to postmenopausal women, in premenopausal women things are not so clearly defined: while some studies report an inverse association between obesity and breast cancer risk in premenopausal women (8), or the absence of any kind of correlation (11), other studies consider that obesity might provide a protective role against breast cancer. This phenomenon is explained through the fact that in obese patients severe modifications of the menstrual cycles (leading even to anovulatory infertility) might occur; in consequence a decreased number of ovulations and a reduced estrogen exposure is incriminated (12).

However, in obese postmenopausal women not only a higher estrogen level leads to a higher incidence of breast cancer. Another important aspect is related to the fact that in this particular situation (obese, postmenopausal woman, with breast malignant tumor) the level of hormone receptors at the tumor level is higher than in normal weight patients. A meta-analysis which was conducted on nine cohorts and 22 case-control studies demonstrated that each five unit increase of the medium BMI was associated with a 33% increased risk of positive estrogen and progesterone receptors (13): this fact increases the sensibility of the tumoral cells to the circulant hormones (which are also present in a higher amount due to the presence of a higher amount of aromatase originating in the adipose tissue) (9). The main mechanisms of action of estrogens which were incriminated for the carcinogenic role consists of an antiapoptotic action of the estrogens in breast tissue in association with the mutagenic effect of the estrogen metabolites. Other hormones which might influence the tumor growth are the androgens; the androgens are also found in a higher amount in obese women and can be easily transformed in estrogens under the action of aromatase (14).

Another important modulator of the mitogenic activity of the cells is insulin. It is well known the fact that obese patients usually have a higher level of plasmatic glucose in association with a higher level of insulin due to the development of insulin resistance. In the meantime, a higher level of plasmatic insulin is associated with a higher mitotic and antiapoptotic effect which comes to accelerate the tissular growth, stimulating the tumoral development (15). The positive correlation between the higher levels of circulating insulin and breast cancer has been also demonstrated by the fact that administration of oral antidiabetic drugs such as metformin is associated with a lower risk of breast cancer. Metformin is a substance which inhibits liver gluconeogenesis leading to a better control of the plasmatic levels of circulating glucose, and, in the meantime, decreasing the insulin resistance. Consequently, the insulin plasmatic levels will decrease and so will happen with its' antiapoptotic effect. Another important mechanism that leads to a lower risk of carcinogenesis in diabetic patients is by modulating the protein kinase activity especially in mTOR cancer-related pathway (9, 16).

Other incriminated substances in tumoral development in obese patients are adipokines such as leptin and adiponectin; it has been demonstrated that in obese patients a higher level of leptin can be encountered, which has been also proved to have a mitogenic and antiapoptotic role. In the meantime, a lower level of adiponectin (an adipokine with antimitotic properties) is also usually seen. However the specific influence of adiponectin and leptin on breast cancer development has not been widely recognized, conflicting results being reported so far (17-19).

The role of bariatric surgery in decreasing the breast cancer risk in postmenopausal women

Once the correlation between obesity and breast cancer in postmenopausal women has been widely accepted, the attention was focused on the possible benefits of bariatric surgery on this special situation. The effect of bariatric procedures on the main mechanisms which are supposed to be responsible for this correlation (decreasing the amount of adipose tissue, decreasing the insulin resistance and modifying the levels of adipokines) transformed this surgical approach in a successful weapon in order to prevent the apparition of breast cancer in obese postmenopausal women.

The retrospective study conducted by McCawley *et al.* included 1482 patients submitted to bariatric surgery; among these cases 53 patients were also diagnosed with associate malignancies, breast and endometrial cancers representing the most frequently encountered cancers (in 15 and 9 patients respectively). Thirty four patients were diagnosed and treated for their malignancies before performing a

bariatric procedure, the mean interval between cancer diagnosis and bariatric surgery being of 9,9 years. Other 17 patients were diagnosed with a malignant tumor after bariatric surgery, the mean interval being of 4,2 years. One patient was diagnosed during the preoperative workup while in another case the moment of cancer diagnosis remained unknown. Breast cancer was diagnosed during the preoperative workup for bariatric surgery in 46,7% of cases and after bariatric surgery in 53,3% of cases. These patients had a mean age of 46 years at the moment of breast cancer diagnosis and a mean BMI of 50,8 kg/m^2. The results were compared to the ones reported in a control group constituted by obese patients who were not submitted to bariatric surgery. Among these patient breast cancer was diagnosed in 9,4% of cases, while the mean age at diagnosis of breast cancer was 57,3 years. The authors demonstrated that bariatric surgery decreased breast cancer development in these patients; however it was not well established if the lower rates of breast cancer after performing a bariatric procedure were related to the metabolic changes induced by weight loss or if decreasing the patients' BMI leaded to an earlier diagnosis of a potential breast tumor (20).

In one of the most popular studies regarding the benefits of bariatric surgery the authors included 2010 patients submitted to bariatric procedures after 1987 and the results were compared with 20137 matched controls. After a median follow up of 10,9 years the hazard ratio of malignancy development in women who had been submitted to bariatric surgery was 0,58 as compared with those who were treated in a conservative manner. Similarly to McCawley's study, breast cancer and endometrial cancer were the most frequently encountered (in 23% and 22% of cases respectively) but data did not suggest a significant benefit for each type of malignancy individually (21).

Adams *et al.* demonstrated that the hazard ratio of developing any malignancy in obese women after a mean follow up of 12,5 years (after performing a bariatric procedure) was 0,73 (95% confidence interval 0,62-0,87); however the data regarding breast cancer was not significant (22).

Other studies demonstrate an even closer connection between bariatric surgery and risk reduction of breast cancer; bariatric surgery proved to lower the risk of breast cancer development by 80% during the 5 years postoperatively (23).

Conclusions

Although the protective role of bariatric surgery against breast cancer development in obese postmenopausal women is not well defined yet, a decrease of the incidence has been suggested in the studies conducted so far. The main incriminated mechanisms are related to the modulation of estrogen, insulin and adipokines' synthesis. However, large studies are still needed to offer a better analysis of this subject.

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