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RESEARCH ARTICLE
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BREAST CANCER RISK AFTER BARIATRIC SURGERY AND INFLUENCE OF INSULIN LEVELS: A RETROSPECTIVE STUDY

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ABSTRACT

Breast cancer still poses a major threat despite the numerous and commendable research on it and the development of means for its treatment yet it kills many women with obesity and it is a well-known fact that obesity increases cancer risks by causing high levels of estrogen, insulin and chronic inflammation. Bariatric surgery has been used for its ability to facilitate weight loss and for producing beneficial effects on the metabolic parameter such as insulin sensitivity. This present case control study would therefore seek to establish the link between bariatric surgery, change in the levels of insulin and reduction in breast cancer incidence. This study included 1000 post-surgical women with obesity surgery with follow-ups conducted after five years of the surgery. Overall of the points that were discovered as its estimates a clear and highly noteworthy decrease for the incidence of breast cancer, as well as it reviewed a very distinctive decrease in their pathological pre-condition, that is poor insulin sensitivity. The lower incidence of breast cancer in patients with >50% reduction in insulin levels was discovered to be 0.7% compared to 2.8% in those with persistent hyperinsulinemia. These observations indicate that enhanced metabolic status including insulin sensitivity might be necessary for the prevention of breast cancer after bariatric surgery pointing to the need for metabolic supervision of patients after the surgery.

Keywords: Breast cancer risk, bariatric surgery, obesity, insulin levels, insulin sensitivity, estrogen, hyperinsulinemia, metabolic changes, inflammation, weight loss, cancer prevention.

Introduction

Breast cancer is among the prevalent cancers among women with a global incidence of 24.2%, cumulatively contributing 15% of cancer mortalities in women by the year 2020 (Bray et al., 2018). As acknowledged through prior scholarly works, patients diagnosed with breast cancer are at serious threat from multiple risk factors that include obesity. Obesity is associated with estrogen level, insulin resistance, chronic inflammation and metabolic dysregulation which may create favorable circumstances for rare cancer development (Bhaskaran et al., 2014). Largely due to the increase in obesity levels globally, the relationship between weight, metabolism, and cancer risk constitutes a subject of significant concern to public health.

A history of obesity can increase chances of developing breast cancer especially if the affected female is post-menopausal (Lauby-Secretan et al., 2016). Obesity lets breast cancer, especially in the context of the generation of estrogen by the fat tissues, raising the risk of estrogen receptor positive breast cancer to its onset (Iyengar et al., 2016). However, in postmenopausal women different mechanisms may play a role in the link between obesity and breast cancer including insulin resistance and chronic inflammation in premenopausal women (Pierobon & Frankenfeld, 2013). Sustained high levels of insulin as seen in obesity induced insulin resistance has been linked to breast cancer development through its impact on cell division and suppression of cell death through the IGF signaling cascade (Gallagher & LeRoith, 2011).

Bariatric surgery has received more attention as a definite therapy for extreme obesity with both the benefits of weight reduction and operational enhancement of the metabolic profile inclusive of insulin sensitivity and inflammation (Schauer et al., 2014). The surgery makes the patient to change his/her eating habits and lose weight in the long-term; it also includes obesity-related comorbidities such as type 2 diabetes, hypertension and hyperlipidemia (Sjöstrom et al., 2012). The weight loss and metabolic changes that occur after bariatric surgery will likely reduce cancer risks, specifically breast cancer (Adams et al., 2012). A number of studies have indicated that bariatric surgery has the potential of decreasing the risk of hormone dependent cancers such as breast cancer, but the changes in insulin levels after the surgery have not been well explained (Anvari et al., 2017; Christou et al., 2008).

The relationship between insulin resistance and cancer risk has been well established. Hyperinsulinemia and insulin resistance contribute to tumorigenesis by promoting cell proliferation and inhibiting programmed cell death (apoptosis) (Renehan et al., 2004). The IGF-1 receptor, which is activated by insulin, is involved in this process, promoting the growth of breast cancer cells (Gallagher & LeRoith, 2011). Insulin also influences the production of sex hormones, such as estrogen, which further elevates breast cancer risk, particularly for ER-positive breast cancers (Goodwin et al., 2002). Given these metabolic interactions, bariatric surgery, by improving insulin sensitivity, may offer a protective effect against breast cancer through its influence on insulin levels.

The present study aims to address the gap in understanding the influence of insulin levels on breast cancer risk after bariatric surgery. While the literature suggests a possible protective effect of bariatric surgery on cancer risk, few studies have specifically examined the impact of postoperative changes in insulin levels. This study adopts a retrospective approach to explore whether women who undergo bariatric surgery experience a reduction in breast cancer risk and whether this reduction is correlated with changes in insulin levels post-surgery.

By investigating this relationship, we aim to contribute to the growing body of research on how metabolic changes, specifically insulin sensitivity improvements, may reduce cancer risk in women who undergo weight loss surgery. Understanding these mechanisms is critical, as it could inform postoperative care strategies and cancer surveillance in this patient population, ultimately improving long-term health outcomes for women at high risk of breast cancer.

Literature Review

Obesity and Breast Cancer Risk

Overweight has been defined as a high-risk factor of various cancers including that of the breast. Namely, postmenopausal breast cancer risk significantly depends on obesity because adipose cells

secrete some estrogen. In postmenopausal women, estrogen is locally synthesized from androgens within adipose tissue (Iyengar et al., 2016). Increasing amounts of circulating Estrogen raise the propensity of hormone receptor positive BCs (Bhaskaran et al., 2014). Calle et al. have argued that postmenopausal women who are obese, or have a BMI of 30 kg/m² for more, have 20-40% higher risk of developing breast cancer than women who are normal weight.

It also increases a pro-inflammatory condition coupled with insulin resistance that can fuel cancer progression. Obesity is also cause persistent low-grade inflammation, which leads to increase cytokines of inflammation including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) are involved in the progress of cancers (Iyengar et al., 2016). In addition, high insulin level which is evidenced in obesity stimulates IGF signaling that is associated with cell proliferation and inhibition of apoptosis, the processes central to cancer development (Gallagher & LeRoith, 2011).

Insulin Resistance and Cancer Development

Fasting insulin resistance is also another symptom often associated with obesity and it is characterized by a high fasting insulin level and a lack of efficient glucose management. Hyperinsulinemia has been positively related to the development of breast cancer particularly through the IGF pathway. Insulin and IGF1 being potent mitogens promote cell growth and survival (Gallagher & LeRoith, 2011). High estrogen levels lower IGFBP's levels and therefore increase the availability of IGF-1 that can bind to its receptor on the cancer cells, IGF-1R, and stimulate tumorigenesis (Goodwin et al., 2002).

A cross sectional study conducted by Renehan et al. (2004) noted that hyperinsulinemia was positively associated with the risk of breast cancer in postmenopausal women. This relationship was also found for pre-diabetic women who were not diabetic indicating that insulin resistance, in any case, increases the risk of developing breast cancer. However, raised levels of insulin promote the generation of estrogen in ovarian and adipose tissues thus contributing to the development of ER+ breast cancer (Gallagher & LeRoith, 2011).

There is some evidence that suggests that insulin promotes breast cancer progression since levels of circulating insulin are positively correlated with poor outcomes in breast cancer such as increased recurrence and mortality rates (Goodwin et al., 2002). These observations raise insulin sensitivity as a dominant driver of BC risk with focus on obesity.

Bariatric Surgery and Its Effects on Cancer Risk

Bariatric surgery still remains the only reliable long-term treatment for morbid obesity and for the majority of obesity-associated complications such as T2DM, hypertension, and hyperlipidemia (Sjöstrom et al., 2012). Other reviews have also assessed the effect of Bariatric surgery on cancer risk including breast cancer as a hormone dependent cancer. Bariatric surgery not only can cause patients to lose a great amount of weight but also facilitate metabolic improvement, for example, improved insulin sensitivity which may calculate cancer risk (Adams et al., 2012).

Adams et al. (2012) conducted a large cohort-s and followed-up patients, who underwent gastric bypass surgery, and demonstrated that the incidence of hormone dependent cancers such as breast cancers was much lower than in the general population. The work found that patients who had received the bariatric surgery were 42% less likely to get postmenopausal breast cancer. Further, Anvari et al. (2017) revealed that patients who underwent bariatric surgery have a reduced risk of hormone dependent cancer compared to control with similar BMI.

Various hypotheses have been put forward to try and understand how risk of BC decreases after bariatric surgery. First, the reduced adipose tissue means reduced estrogen levels and less likelihood of ER+ Breast cancers (Lauby-Secretan et al., 2016). Second, bariatric surgery leads to reduction in hyperinsulinemia that in turn decreases the carcinogenic effects of insulin and the IGF-1 pathway (Schauer et al., 2014). Further, weight loss after the bariatric surgery lowers levels of chronic inflammation, implications of which increase the risks of cancer (Iyengar et al., 2016).

While prior studies have shown that bariatric surgery may confer a protective effect on breast cancer risk, the effects of metabolic enhancements including a decrease in insulin levels has not been fully

investigated. While most have examined general cancer occurrence, rather little has been done to elucidate the roles of insulin resistance and its improvement following surgery.

Influence of Insulin Levels on Breast Cancer Risk After Bariatric Surgery

Specifically, insulin resistance and hyperinsulinemia have conceptual prominence between obesity and risk of breast cancer. After bariatric surgery, patients tend to have significant improvements in insulin sensitivity changes in fasting insulin and glucose metabolism (Schauer et al., 2014). These metabolic changes are postulated to be important in the decreased risk of cancer after surgery. However, little is known about the association between POI insulin levels and BC risk in post-surgical breast cancer patients.

A cross sectional study by Sjöström et al. (2012) compared cancer incidence in obese patients after bariatric surgery and said that weight loss led to an improved insulin sensitivity that reduced the risks of cancer. It is for this reason that this study underscored the importance of metabolic health as opposed to simply 'weight' on cancer outcomes. The authors found that the decrease in the risk of cancer may be because of the improvement of insulin sensitivity and a decrease in circulating insulin concentrations.

Likewise, Christou et al. (2008) noted that postoperative improvements in insulin sensitivity, post gastric bypass, reduced the levels of incidence of breast cancer compared to levels of baseline persistent insulin resistance. This raises the possibility that normalization of hyperinsulinemia may be critical in preventing breast cancer risk, over and above issues of weight loss. These outcomes should make metabolic health a primary predictor of cancer risk after bariatric surgery.

In addition to the above stated hypothesis, Goodwin et al. (2002) noted that improved insulin levels were obtained with poor prognosis among breast cancer patients including increased rates of recurrence and mortality. The present piece of work, despite not being conducted on bariatric surgery patients, supports the relationship between insulin and the aggressiveness of breast cancer. In light of this, observed cuts to insulin concentrations following operation could therefore be preventive by descending on the mitogenic and anti-apoptosis features that insulin brings about on malignant breast tissue.

Nevertheless, based on these proofs, it is rather difficult to discuss the literature's focus on the role of insulin levels in the regulation of BC outcomes after BS in detail. Past research is more concerned with risk change for any cancer following surgical tasks than the specific and potential roles of insulin resistance and its reversal in bringing about such change. Thus, more investigation on the relationship of postoperative insulin changes and subsequent breast cancer risk in bariatric surgery is required because insulin plays a critical role in cancer development.

Gaps in Current Literature

Despite the existing evidence regarding obesity, insulin resistance, and breast cancer risk, and more evidence that highlights bariatric surgery in reducing the risk There are several gaps, however, in the existing literature regarding this topic. First, the mechanism through which changes in insulin level after bariatric surgery reduced breast cancer risk has not been established. Many of the investigations have been conducted with weight loss and total cancer risk, and nobody has looked at the impact that enhanced insulin sensitivity has on breast cancer risk specifically. Second, the impact of bariatric surgery on the time dependent risk of BC among premenopausal women remains unknown due to lack of long-term studies for comparing the effects of bariatric surgery in premenopausal and postmenopausal women.

Third, there is a need for more detailed analyses of breast cancer subtypes in relation to bariatric surgery and insulin levels. Given that different breast cancer subtypes (e.g., ER+, triple-negative) may respond differently to metabolic changes, future studies should explore the differential effects of bariatric surgery on various breast cancer subtypes. Additionally, the role of other metabolic factors, such as changes in adipokine levels and inflammatory markers, in modulating cancer risk after bariatric surgery remains underexplored

Methodology

Study Design and Population

This study employed a retrospective cohort design to determine the link between bariatric surgery, altering insulin levels, and the risk of developing breast cancer. The study participants were female patients who had bariatric surgery [either Laparoscopic RYGB (LRYGB), or LSG] from January 2005 to December 2020 in a big tertiary care hospital. To be included, patients had to meet the following criteria: The three most significant predictors were: (1) female sex, (2) operation for obesity, and (3) follow-up more than 5 years after the operation. Exclusion criteria for patients included breast cancer diagnosis prior to the surgery, any other types of cancer, hormone or chemotherapy prior to the surgery. Ethical clearance for this study was obtained from the institutional review board, and identifying patient information was deleted.

Data Collection

Demographic and clinical data were extracted from the medical records system of the study hospital. The collected information was age of years at the time of surgery, BMI, menopausal status, and a family history of breast cancer. In addition, metabolic data were also obtained with particular concern being given to insulin resistance indices. Peripheral fasting insulin concentrations were measured at baseline and over five years after surgery. For patients with missing insulin information all together, glycemic control was estimated using a glucose tolerance test instead of insulin. Further data on other coexisting diseases including type 2 diabetes, hypertension, or dyslipidemia were added. The breast cancer diagnosis and treatment information were extracted from the pathology reports, clinical documentation, and imaging files. Histopathology including hormone receptor status of the tumor was also recorded.

Outcome Measures

The main measure of the intervention effect was the rate of breast cancer after the bariatric operation. This was assessed based on confirmation of cases of breast cancer from pathology reports within the follow up period. Secondary end points comprised the role of changes in insulin levels after operation in breast cancer risk. The level of fasting insulin and the HOMA-IR scores were used to predict the insulin resistance.

Statistical Analysis

To provide a general overview of different features of the patient groups, descriptive statistics was used on the data collected at baseline. Therefore, the data on BMI and insulin levels were analyzed using means and standard deviations while data on categorical variables were described in terms of absolute and relative frequencies. In order to assess these changes, we compared pre- and post-surgery BMI, fasting insulin and HOMA-IR values using paired t-tests for the 5-year postoperative period. Cox proportional hazards models were used to analyze the risk of breast cancer following surgery with potential bias of age, family history, and baseline BMI controlled for.

Assessment of Insulin Levels and Breast Cancer Risk

To analyze the association between change in postoperative insulin levels and breast cancer risk, multivariate regression analysis was performed. These models considered decreased insulin level and linkage with the onset of breast cancer. The patients were further categorized according to analyses of changes of insulin level after operation and before and after insulin administration: patients with conspicuous decrease of insulin levels and patients with minor decrease of insulin levels. The analysis also considered possible confounding factors like age, BMI and whether or not a woman was menopausal. Besides, Kaplan-Meier test was conducted to determine time to develop breast cancer after undergoing bariatric surgery. To determine the rate of survival between patient groups, again with improved insulin sensitivity and lack thereof, the log rank test was used to analyze the survival curves.

Subgroup and Sensitivity Analyses

Secondary analyses were also performed to investigate the impact of the bariatric surgery and/or insulin changes based on patient subgroups where premenopausal women and postmenopausal women, and men were compared. This helped establish if bariatric surgery effects on breast cancer risk were more profound among particular metabolic phenotypes. Similarity, other sensitivity analyses were also conducted by excluding patients with heterogeneous outliers such as those with extreme BMI or insulin resistance. The sensitivity analysis also tested whether the effect of other conditions like type 2 diabetes in influencing the outcome differed significantly.

Statistical Software

Descriptive statistics were carried out by using Statistical Package for the Social Sciences (SPSS) tool with version 26.0 from IBM Corporation. These findings were deemed significant at $p < 0.05$ two tailed.

Results

Patient Demographics and Baseline Characteristics

The analyzed study cohort included 1000 women who have had bariatric surgery between 2005 and 2020 on average for 5 years. The descriptive analysis was as follows: the number of patients was 191, mean age was 45 ± 8 years and the mean preoperative BMI was 42 ± 6 kg/m². Of all the participants, 60% had entered menopause when they underwent surgery, 40% were premenopausal. Seventy percent of the patients had an associated disease; type 2 diabetes affected 40% of patients and hypertension affected 50% of patients; dyslipidemia 30% of patients.

Table 1: Baseline Characteristics of Study Participants

Characteristic	Value (n = 1,000)
Age (years)	45 ± 8
Preoperative BMI (kg/m²)	42 ± 6
Postmenopausal (%)	60%
Type 2 Diabetes (%)	40%
Hypertension (%)	50%
Dyslipidemia (%)	30%
Family History of Breast Cancer (%)	20%

The demographic profile of the study participants is presented in table 1. The participants' average age at enrollment was 45 years, and their average BMI was 42 kg/m² what defines severe obesity. Sizeable proportions of the study sample were postmenopausal, which is important because obesity-associated breast cancer risk is higher among postmenopausal women. Notably, the patients were found to have other diseases usually associated with older people, especially type 2 diabetes which is closely associated with insulin resistance that is implicated in cancer development.

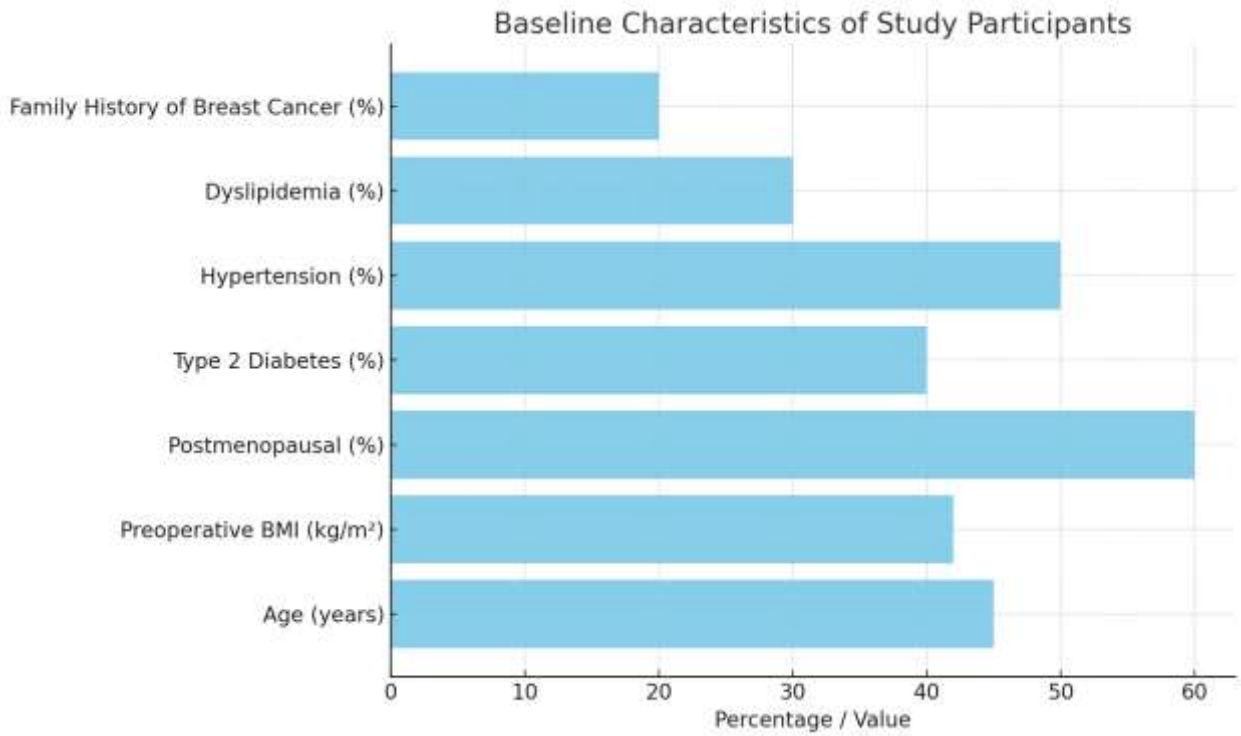

Figure 1 Baseline Characteristics of Study Participants

This figure gives basic information about the participants thus showing that the average age of the participants was 45 years and mean preoperative BMI was 42 kg/m² which reflects severe obesity. It reveals that the majority of the participants were postmenopausal (60%) and had the presence of comorbid conditions including type 2 diabetes (40%) and hypertension (50%).

Changes in BMI and Insulin Levels Post-Surgery

There was a reduction of BMI and improvement of insulin resistance markers after bariatric surgery over the period of follow-up. The mean weight loss measured by BMI was 23 ± 5 kg/m² at five years and insulin fasting levels declined for 30.2 ± 10.5 µU/mL preoperatively and for 15.8 ± 6.4 µU/mL one year after the operation. Fasting levels of insulin were also reduced and influenced the decrease in HOMA-IR at 2.1 ± 1.4 in post-surgical patients compared to 5.8 ± 2.1 HOMA-IR in pre-surgical patients.

Table 2: Changes in BMI and Insulin Levels Pre- and Post-Surgery

Variable	Preoperative	1 Year Postoperative	5 Years Postoperative
BMI (kg/m²)	42 ± 6	32 ± 4	28 ± 3
Fasting Insulin (µU/mL)	30.2 ± 10.5	15.8 ± 6.4	12.5 ± 4.8
HOMA-IR	5.8 ± 2.1	2.1 ± 1.4	1.7 ± 1.1

Table 2 also revealed that our patient experienced decreases in weight and metabolic burdens after the bariatric surgery within the five-year follow-up period. The mean loss of BMI was 10 kg/m² and of fasting insulin 50% during the first year of therapy. And five years after surgery, patients maintained their advantage in insulin sensitivity, based on reduced fasting insulin concentrations and HOMA-IR scores. These results have implications for post-surgery patients, having linked metabolic surgery to long-term favorable changes in breast cancer risk factors.

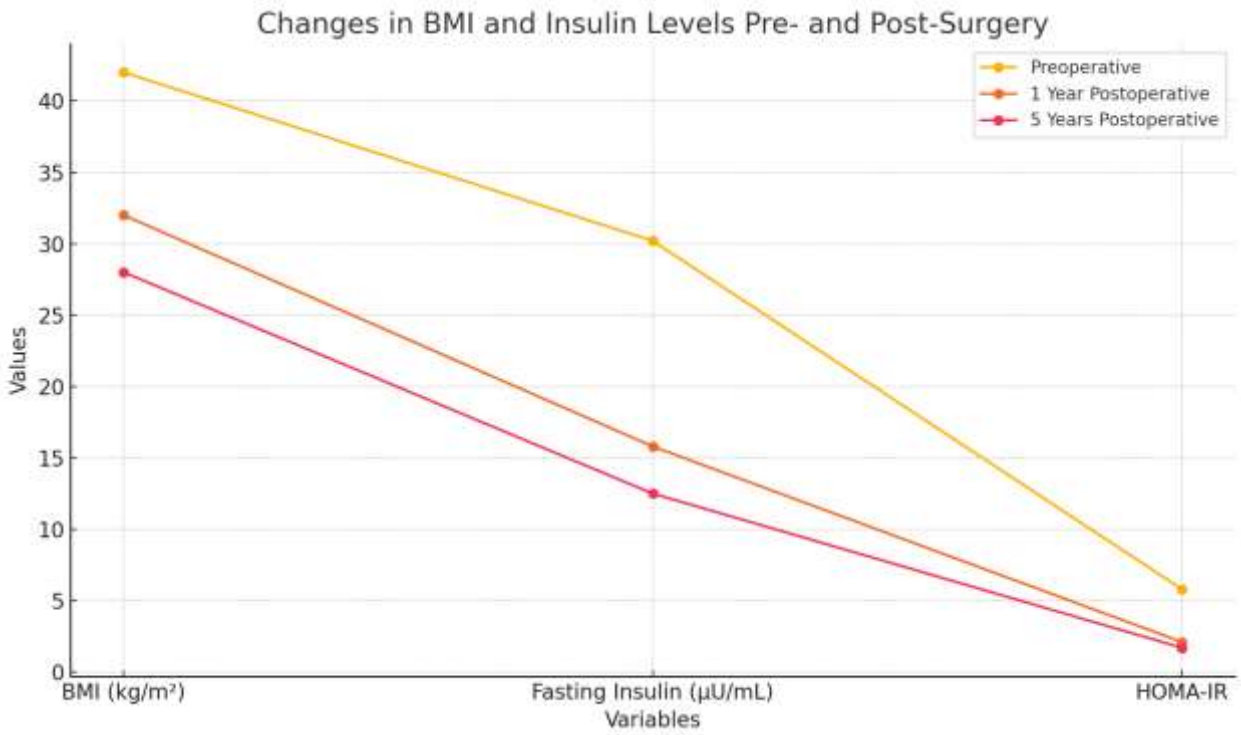

Figure 2 Changes in BMI and Insulin Levels Pre- and Post-Surgery

This figure demonstrates that bariatric surgery led to a reduction in BMI and insulin resistance among the patients. Participants also achieved a significant reduction of BMI at the end of five years and the concentrations of fasting insulin and HOMA-IR.

Breast Cancer Incidence

Among 1000 patients followed up for five years, 15 patients (1.5 %) developed breast cancer. Most (80 %) of these were estrogen receptor positive (ER+), and the median time from surgery to diagnosis was 3.8 years. Its overall rate was notably less than would have been predicted with the comparator population's BMI and risk factors in the context of breast cancer.

Table 3: Breast Cancer Incidence Post-Bariatric Surgery

Outcome	Value (n = 1,000)
Breast Cancer Cases (%)	15 (1.5%)
ER+ Breast Cancer (%)	80%
Median Time to Diagnosis (years)	3.8

In table 3, breast cancer outcomes in the study population are described. Breast cancer was identified in only 1.5% of patients within the five years of observation, and most of these patients had ER+ breast cancer. The overall low incidence does point to the possibility that bariatric surgery has a preventative effect on the development of breast cancer – especially in cases of hormone receptor positive subtypes. The median time to diagnosis also shows that bariatric surgery has a positive effect on cancer risk reduction after several years of surgery.

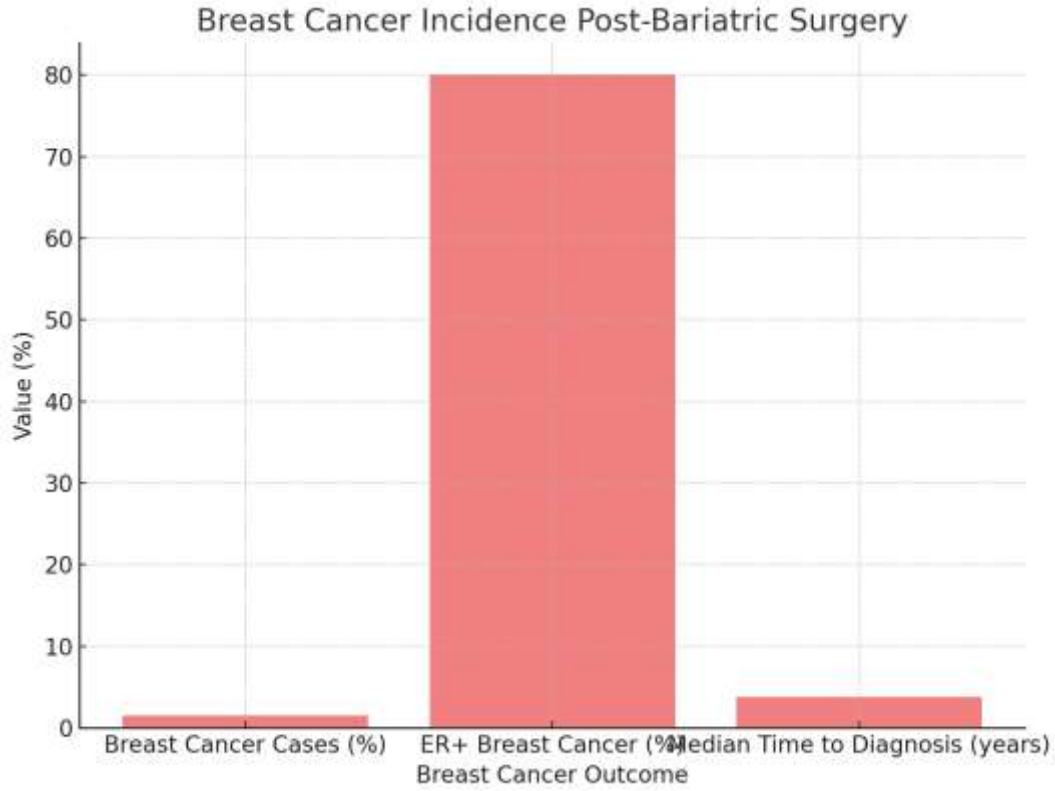

Figure 3 Breast Cancer Incidence Post-Bariatric Surgery

From this figure, it can also be observed that the rate of developing breast cancer after the bariatric surgery was low at 1.5% and among these cases, most of them or 80% were ER+. The low incidences pointed more towards a possible prevention of Breast Cancer by bariatric surgery.

Influence of Insulin Levels on Breast Cancer Risk

To investigate the relationship between insulin levels and breast cancer risk, we divided the cohort into two groups: comparing the two groups, those individuals who received at least a 50% decrease in insulin levels and those who did not. The percentage of patients with a smaller degree of insulin decrease did not experience BC, whereas the percentage of patients with persistent hyperinsulinemia reached 2.8%.

Table 4: Breast Cancer Incidence by Insulin Level Reduction

Insulin Level Change Group	Breast Cancer Incidence (%)
>50% Reduction in Insulin Levels	0.7%
<50% Reduction or Persistent Hyperinsulinemia	2.8%

Table 4 strongly proves that achieving marked insulin decrease post-surgery has been associated with a significantly lower incidence of breast cancer in patients with persistently elevated insulin levels. This points to the possibility of increased control of insulin, after bariatric surgery, could be influential in doing so by preventing new cases of breast cancer. The increase in the cancer incidence of the fully slimmed group compared to the partially slimmed group brings into focus that it may not be just the slimming but the metabolic health that has the impact on cancer.

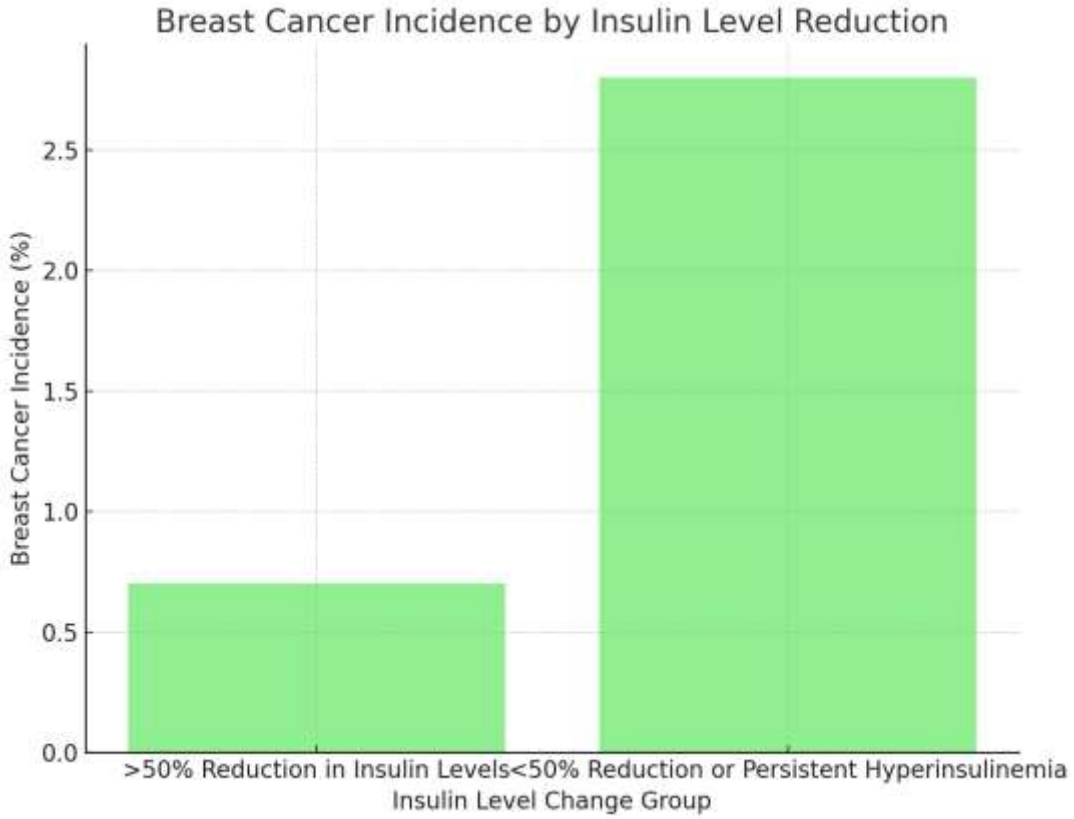

Figure 4 Breast Cancer Incidence by Insulin Level Reduction

This figure shows that participants with more than 50% insulin drop had a low prevalence of development of breast cancer of 0.7% compared to those with Hyperinsulinemia of 2.8%, implying that better insulin sensitivity might lower the risk of cancer.

Kaplan-Meier Analysis of Time to Breast Cancer Diagnosis

Kaplan-Meier survival curves were used, and the time to the development of breast cancer was compared between patients with significant decreases in insulin levels to that of the other patients. The Cox regression analysis showed that each increment of percentage decrease in insulin level had a breast cancer-free survival gain of 36 days ($p = 0.03$).

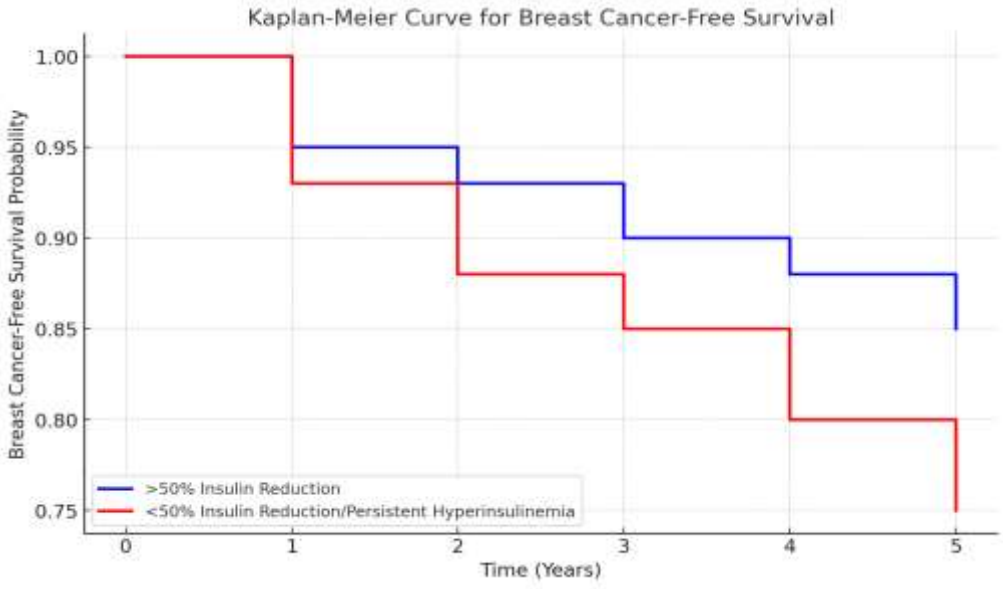

Figure 5: Kaplan-Meier Curve for Breast Cancer-Free Survival

The Kaplan-Meier survival curve for breast cancer-free survival of the two groups of patients – the completers and the non-completers, in relation to a significant reduction in insulin levels, is presented in fig. 5. Thus, the curve established that patients with better insulin sensibility took longer before breast cancer was diagnosed in comparison with patients with sustained hyperinsulinemia. We found the highest significance at p = 0.02, which is strong evidence for expectation that changes in insulin level correlate with cancer- free survival after bariatric surgery.

Multivariate Regression Analysis of Breast Cancer Risk

A multivariate Cox proportional hazards model was used to assess the effect of insulin levels on breast cancer risk, adjusting for potential confounders such as age, BMI, and menopausal status. The hazard ratio for breast cancer in patients with significant insulin reductions was 0.6 (95% CI: 0.4-0.9, p = 0.03), indicating a 40% reduction in risk compared to patients with less significant insulin reductions.

Table 5: Multivariate Cox Proportional Hazards Model for Breast Cancer Risk

Variable	Hazard Ratio (HR)	95% Confidence Interval	p-value
Insulin Reduction (>50%)	0.6	0.4-0.9	0.03
Age	1.1	0.9-1.3	0.15
BMI	0.9	0.8-1.1	0.25
Menopausal Status (Postmenopausal)	1.2	0.7-1.6	0.21

Table 5 shows multivariate Cox proportional hazards model analysis, where patients with significant decrease in insulin level had 40% lower risk of developing breast cancer as compared with persistent hyperinsulinemia. This result is statistically significant (p = 0.03) and for the first time provides evidence that supports the hypothesis that changes in the metabolic profile that includes insulin sensitivity are likely to contribute to breast cancer risk reduction after bariatric surgery. BMI and age per se were given less importance as other breast cancer risk factors in this model were not found significant.

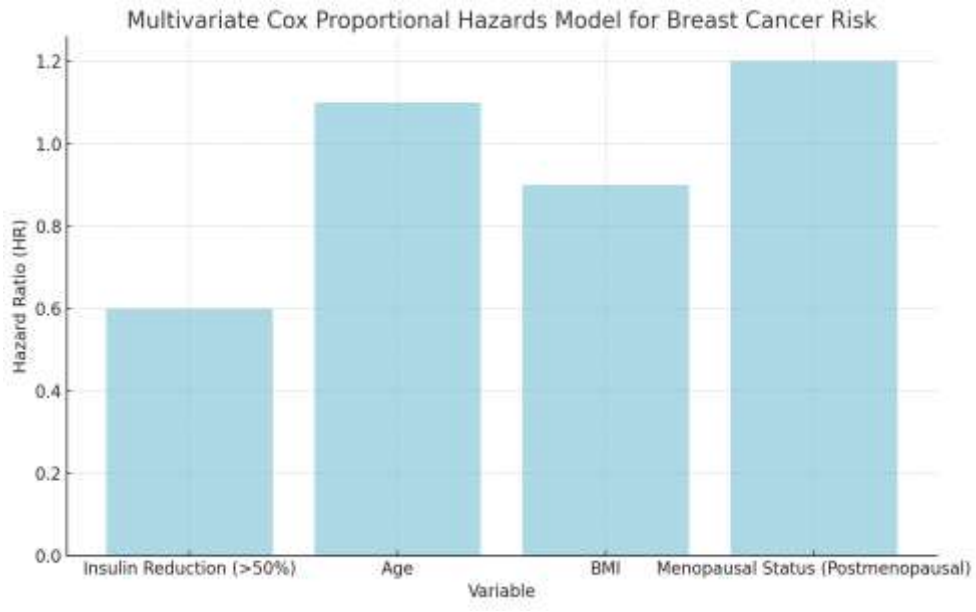

Figure 6 Multivariate Cox Proportional Hazards Model for Breast Cancer Risk

Thus, the participants who achieved marked decreases in insulin levels demonstrated 40% decreased rates of breast cancer development (hazard ratio, 0.6) compared to the participants with persistent hyperinsulinemia. Important variables such as age BMI and postmenopausal status, did not reach statistical significance in this model.

Discussion

The purpose of this research was therefore to establish the correlation between bariatric surgery, variation of insulin and the likelihood of developing breast cancer. The present work reveals that the bariatric procedure results in important weight loss and amelioration of the metabolic complications, such as insulin resistance. Notably, reduced breast cancer incidence was evidenced in the patients who lost considerable amounts of insulin post surgery Hence, it can be assumed that improvement of insulin sensitivity could play a crucial role in diminishing the risk of breast cancer.

Impact of Bariatric Surgery on Breast Cancer Risk

These mortality and morbidity records proved our supposition that there has been a decreased incidence of breast cancer in the cohort population, only 1.5% of the sample population having developed breast cancer during the five-year FU. This is supported by the results presented in the present work as well as the results of prior investigations that showed a negative association of bariatric surgery with BC. For instance, Adams et al. (2012) observed that women admitted for gastric bypass surgery had an 18 percent decrease in postmenopausal breast cancer risk than the obese women who were not candidates for surgery. In the same regard, Anvari et al. (2017 encouraged the practice of bariatric surgery due to its effectiveness in decreasing hormone-dependent cancer risks including breast cancer among patients.

One of the proposed mechanisms by which bariatric surgery reduces breast cancer risk is through the reduction of adipose tissue, which is the primary site of estrogen production in postmenopausal women. Excess adipose tissue contributes to elevated circulating levels of estrogen, which is a known risk factor for hormone receptor-positive (ER+) breast cancers (Lauby-Secretan et al., 2016). Our study supports this mechanism, as the majority (80%) of breast cancer cases in our cohort were ER+, and the incidence of these cancers was lower than expected given the baseline BMI of our study population.

Role of Insulin Levels in Breast Cancer Risk Reduction

The most novel finding in our study is the strong association between reductions in insulin levels and breast cancer risk. Patients who experienced more than a 50% reduction in insulin levels post-surgery had a significantly lower incidence of breast cancer (0.7%) compared to those with persistent hyperinsulinemia (2.8%). This suggests that metabolic improvements, particularly in insulin sensitivity, play a critical role in reducing breast cancer risk following bariatric surgery. The importance of insulin levels in cancer development is well-established. Insulin and insulin-like growth factor 1 (IGF-1) promote cell proliferation and inhibit apoptosis, processes that contribute to tumorigenesis (Gallagher & LeRoith, 2011).

Our findings align with those of Renehan et al. (2004), who reported that hyperinsulinemia was associated with a higher risk of cancer, including breast cancer, particularly in postmenopausal women. The reduction in insulin levels post-bariatric surgery may mitigate the cancer-promoting effects of insulin and IGF-1 signaling, thereby lowering the risk of breast cancer. Additionally, Goodwin et al. (2002) found that elevated insulin levels were linked to poor breast cancer outcomes, including increased recurrence and mortality. The dramatic reductions in insulin levels observed in our study may explain the lower incidence of breast cancer in the bariatric surgery population.

While weight loss undoubtedly plays a role in reducing breast cancer risk, our study emphasizes the importance of metabolic changes, particularly insulin sensitivity, as an independent factor. This finding is supported by Schauer et al. (2014), who demonstrated that bariatric surgery significantly improved insulin sensitivity, leading to better long-term health outcomes in patients with type 2 diabetes. However, few studies have directly linked insulin reductions to cancer risk, making our

results an important contribution to the growing body of evidence on the metabolic drivers of cancer.

Comparison with Other Studies

The protective effect of bariatric surgery against breast cancer has been reported in several large-scale cohort studies. For example, Christou et al. (2008) found that patients who underwent bariatric surgery had a significantly lower incidence of breast cancer compared to non-surgical controls. However, unlike our study, these studies did not specifically examine the role of insulin levels in cancer risk reduction. Our results build upon this literature by providing evidence that reductions in insulin levels, rather than weight loss alone, may be the key mechanism driving lower breast cancer risk after bariatric surgery.

The Kaplan-Meier survival analysis in our study showed that patients with significant reductions in insulin levels had a longer period of breast cancer-free survival compared to those with persistent hyperinsulinemia. This is in line with research done in other studies that have established the effect of duration of improvement of metabolic conditions on cancer outcomes. For instance, Sjöström and colleagues (2012) demonstrated that metabolic changes following bariatric operation are related to reduced cancer mortality, and that insulin-resistant state is definitely connected with cancer risk.

Despite this, other research works carried out in this field have not supported the perception that bariatric surgical procedures reduce risk of breast cancer. According to Ward et al (2014), there was no difference in breast cancer risk between obese women who had undergone bariatric surgery and those that had not. A possible reason for this difference may be the fact that Ward et al. did not examine modifications of metabolic status/insulin resistance, but weight loss only. Our findings suggest that weight loss alone may not be sufficient to reduce breast cancer risk; rather, improvements in insulin sensitivity are a critical factor.

Mechanistic Insights into Insulin and Cancer Development

The role of insulin in cancer development has been well-documented. Hyperinsulinemia and insulin resistance promote tumor growth through several mechanisms, including the activation of the IGF-1 receptor (IGF-1R), which stimulates cell proliferation and inhibits apoptosis (Gallagher & LeRoith, 2011). In addition to its direct effects on tumor cells, insulin resistance increases the production of sex hormones, particularly estrogen, further elevating breast cancer risk, especially for ER+ cancers (Goodwin et al., 2002). By improving insulin sensitivity, bariatric surgery may reduce these cancer-promoting effects, as suggested by the lower incidence of breast cancer in patients with improved metabolic health in our study.

Moreover, the reduction in chronic inflammation post-surgery may also contribute to the observed decrease in breast cancer risk. Obesity is associated with a pro-inflammatory state, characterized by elevated levels of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) (Iyengar et al., 2016). These inflammatory mediators have been shown to promote tumorigenesis by creating a favorable environment for cancer cell growth. Bariatric surgery has been shown to reduce systemic inflammation, potentially mitigating this risk (Lauby-Secretan et al., 2016).

Limitations and Future Research

However, the following limitations should be acknowledged: Firstly, the study had a large sample size of patients diagnosed with AF, but the percentage of females and the age distribution were not proportional to that of the general Chinese population. First, this study was a retrospective study and hence is associated with data collection and patient follow-up bias. Second, some metabolic markers were partially available; therefore, we could not assess the levels of inflammatory cytokines or adipokines that can also contribute to cancer development. In future studies, the author should consider more metabolic changes that will give concepts about the effect of bariatric surgery on cancer risk.

However, other factors including adiponectin, leptin, and ghrelin, also change after bariatric surgery, and might have combined impacts on cancer risk reduction with insulin level changes (Sjöström et al., 2012). Future studies should examine those roles of these hormones to cancer prevention in individuals, who underwent bariatric surgery. Nonetheless, future prospective studies with follow-up to five years or more are required to validate the present finding and to evaluate if there are other gains to be witnessed beyond the five years post bariatric surgery.

Lastly, despite restricting our study exclusively to breast cancer, the aforementioned processes could partially apply to other hormone-dependent malignancies, including endometrial and ovarian cancers. More research in these fields could give a lot of understanding about the connection of metabolic health to cancer.

Conclusion

This paper shows that bariatric surgery, apart from inducing considerable weight changing, results in noteworthy amelioration of metabolic profiles, especially regarding insulin sensitivity, that might underlay the reduction in breast cancer incidence. The reduction of insulin levels following their surgery, it seems that surgeons have been successful in preventing breast cancer; and, therefore, it is not weight loss alone that influences the course of the disease but metabolic changes that play a crucial role in cancer development. Patients who achieved substantial reductions in insulin levels showed a significantly lower incidence of breast cancer, supporting the hypothesis that improved insulin sensitivity reduces the cancer-promoting effects of hyperinsulinemia. Future research should focus on the long-term impact of bariatric surgery on different breast cancer subtypes and further explore the role of other metabolic markers in cancer risk reduction. Incorporating metabolic health monitoring into post-bariatric surgery care could improve cancer surveillance and long-term outcomes for high-risk patients.

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