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Breast cancer in individuals with type 2 diabetes; a mini-review to the recent concepts

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Abstract

Introduction: Pieces of evidence indicate a relationship between breast cancer and type 2 diabetes (T2D) which is a potential risk factor for breast cancer development and progression. Hyperinsulinemia, insulin resistance, chronic inflammation, inflammatory cytokines, and hormonal factors are possible explanations for this association. T2D may also affect the breast cancer treatment course. Neoplastic cells are more chemo-resistant, and chemotherapy adverse effects are more prominent in patients with diabetes and breast cancer at the same time. Diabetic nephropathy is one of the T2D complications that should be considered prior to choosing a therapeutic protocol for breast cancer patients. Hence, collaboration between oncologists, endocrinologists, and nephrologists is essential to provide comprehensive care for T2D and breast cancer patients.

Keywords: Type 2 diabetes, Breast cancer, Obesity, Malignancy, Chronic inflammation, Diabetic kidney disease

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Introduction

Breast cancer is a common malignancy affecting about one-fourth of women worldwide. One out of six women (15.5%) who died from cancer in 2020 had breast cancer. On the other hand, type 2 diabetes (T2D) is a chronic metabolic disorder that affects millions of people globally. In 2017, the estimated population suffering from T2D was more than 460 million. Several epidemiological studies have suggested an association between T2D and an increased breast cancer risk. Compared to the general population, T2D prevalence is dramatically higher among patients with breast cancer (1-3).

Type 2 diabetes may be correlated with a 10% to 20% excess relative breast cancer development risk. The link between T2D and breast cancer may vary by breast cancer subtype. This correlation is frequently observed in women who have been diagnosed with estrogen receptor-positive breast cancer. Obesity coupled with/aligned with old age is a significant risk factor for both T2D and breast cancer (4). These factors contribute to the increased risk observed in individuals with T2D. Women with T2D who are diagnosed with breast cancer have a two-fold higher mortality rate compared to individuals without diabetes (5). Diabetes is associated with a 50% death rate from breast cancer and a high risk of renal toxicity caused by chemotherapy (1). Metformin is a well-known medication for T2D treatment and may suppress the development of estrogen receptor-positive breast cancer. Thiazolidinediones are another anti-diabetic medication that may reduce breast cancer risk by enhancing insulin sensitivity. Insulin, insulin analogs, and sulfonylureas which increase insulin in the circulating blood, possibly increase breast cancer development risk (6). Despite similar treatment rates, patients with breast cancer suffering from T2D have higher all-cause (+40%) and cancer-specific (+25%) mortality rates. Patients affected by T2D for a longer duration or those with cardiovascular complications have the highest mortality rate (7). This review discusses different aspects of the association between breast cancer and T2D.

Insulin resistance

Insulin resistance is defined as a declining cellular response to insulin due to long-term exposure to excessive insulin amounts. Insulin resistance is a hallmark feature of T2D results in elevated insulin levels in the blood. Insulin resistance may explain the increased risk of breast cancer in individuals with T2D. Compensated insulin receptor gene overexpression in insulin-resistant cells is linked to malignant cell proliferation in breast tissue.

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Implication for health policy/practice/research/ medical education

It is well known that breast cancer is a significant global health concern for women. In conjunction with T2D, women are at an increased risk of developing this disease. Individuals with T2D have a strengthened breast cancer development risk, particularly estrogen receptor-positive breast cancer. Insulin resistance in T2D creates a hyper-insulinemic state, a favorable environment for neoplastic cell growth and proliferation. Diabetes also impacts patients' response to treatment and prognosis. Since a common diabetes complication is diabetic nephropathy, which may limit drugs of choice and medication dosage, nephrologists may play a crucial role in managing these patients, especially those with kidney-related complications or undergoing cancer treatment.

Another consequence of insulin resistance is decreased sex hormone-binding protein (SHBG). This condition increases free estrogen and testosterone as another risk factor for breast neoplasm development. Studies have shown that hyperinsulinemia promotes cell proliferation and inhibits apoptosis, both of which contribute to the development of breast cancer. High inflammatory cytokines levels such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) in T2D are also linked to different neoplastic states (8,9).

Insulin resistance and T2D can increase the hazard of metabolic complications during chemotherapy with drugs such as doxorubicin and cisplatin by increasing reactive oxygen species production. High insulin levels induce neoplastic cell proliferation and increase these cells' chemo-resistance (10,11). T2D metabolic complications affect overall health while worsen chemotherapy side effects. Insulin resistance and diabetes can impair wound healing, which can be a concern during chemotherapy treatment. Insulin resistance and also diabetes affect both treatment efficacy and decrease chemotherapy side effects tolerance (12). Chemotherapy can cause skin reactions, mucositis, and impaired wound healing. Insulin resistance and diabetes can weaken the immune system and consequently, make individuals more susceptible to infections. Also, Chemotherapy can suppress the immune system, and increase the infection risk, especially in females with T2D (13,14).

Hormonal factors

As discussed above, excessive insulin and IGF-1 amounts are linked to inhibiting SHBG production in the liver, while these hormones may increase sex hormones production in the ovaries. High levels of sex hormones may induce proliferation and inhibit apoptosis in breast tissue. A further consequence of hyperinsulinemia is an increase in the rate of androgen-to-estrogen synthesis. This imbalance may cause carcinogenesis in organs with high estrogen uptake, such as the breast (1,8,15).

Chronic inflammation

Both T2D and breast cancer are related to chronic inflammation which can promotes the growth and spread of cancer cells. The inflammatory responses in T2D may contribute to breast cancer development and progression (16,17).

Chronic inflammation in women with T2D has several impacts on the breast tumor microenvironment. It leads to the recruitment and activation of immune cells, such as macrophages, into the tumor microenvironment. These immune cells release pro-inflammatory cytokines and growth factors that promote tumor growth and progression (18,19).

Moreover, inflammation stimulates new blood vessel formation, a process known as angiogenesis. This process improves the tumor's blood supply, allowing it to receive nutrients and oxygen. Chronic inflammation can lead to changes in the extracellular matrix, the network of proteins and molecules surrounding and supporting cells (19,20). These changes create an environment that facilitates tumor cell migration and invasion. Chronic inflammation may contribute to immunosuppression in the tumor microenvironment which will impair the immune system's ability to distinguish and eliminate cancer cells, allowing the tumor to evade immune surveillance (16,21).

Chronic inflammation may produce pain, swelling, and redness in the affected area. Women with breast cancer may experience these symptoms like swelling in the affected area due to inflammation Chronic inflammation can also cause fatigue, which is a prevalent symptom in women with T2D and breast cancer (22-24).

Adipocytokines and inflammatory mediators

Type 2 diabetes affects adipocytokines and inflammatory mediators. These changes increase breast cancer risk. Adiponectin is an adipocytokine with anti-inflammatory and anti-tumor properties. In individuals with T2D, adiponectin levels are often decreased, which can contribute to insulin resistance and inflammation that promote tumor growth. Leptin is another adipocytokine involved in appetite and energy balance regulation (25,26). In individuals with T2D, the leptin level is usually elevated. Furthermore, high levels of leptin have been associated with increased breast cancer risk and tumor growth. IL-6 is an inflammatory mediator involved in immune response regulation. In individuals with T2D, there is often an increase in IL-6 levels, which can contribute to chronic inflammation and promote breast cancer development and progression (27,28).

Moreover, tumors linked to diabetes may secrete considerable amounts of IL-6, which is accompanied by insulin resistance and inflammatory signaling in the body. Insulin-like growth factor (IGF) is a significant cell growth and proliferation hormone. In individuals with T2D, there may be insulin-like growth factor receptor (IGFR) gene over-expression, which can contribute to breast cancer development (29, 30). TNF-α is an inflammatory cytokine involved in immune response regulation. In individuals

with T2D, there may be an increase in TNF-α levels, which can contribute to chronic inflammation and promote breast cancer development. These adipocytokines and inflammatory mediators, along with dysregulation in individuals with T2D, can create an environment/situation that promotes tumor growth and progression in the breast simultaneously (31,32).

A nephrology point of view on women with breast cancer and T2D

From a nephrology perspective, it is imperative to note that both T2D and breast cancer have an impact on kidney health. Individuals with T2D are at an increased risk of developing diabetic kidney disease (diabetic nephropathy), which leads to kidney dysfunction or failure (33). Additionally, certain cancer treatments, such as chemotherapy or certain targeted therapies, can be harmful to the kidneys. Although these treatments are effective at combating cancer, they may cause acute kidney injury or long-term kidney damage. In managing individuals with breast cancer and T2D, collaborations between oncologists, endocrinologists, and nephrologists are essential to provide comprehensive care (34,35).

Conclusion

There is a growing body of documents linking T2D and breast cancer. T2D affects patients with breast cancer in different aspects, from breast neoplasm development and progression to treatment and its adverse effects. Nephrologists should be aware of this association and play an active role in the management of individuals with T2D and diabetic kidney disease. Regular breast cancer screening tests should be performed in this population to ensure early detection and treatment of breast cancer.

Authors' contribution

Conceptualization: Rezvan Ebrahimi, Yasaman Vahdani.
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Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

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