MINI-REVIEW

Repercussions of Breastfeeding by Diabetic Women for Breast Cancer

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Abstract

Diabetes represents a serious health problem. In the diabetic state, alterations in metabolism, increased susceptibility to infections and immunological changes occur. The suppression of the immune response has been identified as a relevant factor that contributes to the increase in the rate of infections in these patients. At the same time, breast cancer is the most frequent malignant tumor in women. The molecular and cellular mechanisms underlying cancer development have revealed that immune cells functionally regulate epithelial cancer development and progression. Breastfeeding has been hypothesized to reduce the risk of breast cancer. However, early systematic reviews have not yielded consistent findings for this association. The demand for human milk is increasing due to the promotion and consumer acceptance of the health benefits of consuming a natural product rich in bioactive components. However, due to changes in glucose metabolism, the components of the milk from diabetic women are modified depending on the time of evaluation. In this literature review, we summarize important new findings revealing the paradoxical role of breastfeeding in preventing the onset of breast cancer in diabetic mothers. We hypothesized that the milk component production in diabetic mothers is affected by changes in glucose metabolism. Therefore, adequate maternal glycemic control and an adequate duration of breastfeeding for diabetic mothers are crucial to ensure that the immunity components are able to confer protection against breast cancer.

Keywords: Diabetes - breast cancer - breastfeeding - chronobiology - immunology

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Introduction

Diabetes mellitus is a metabolic disease characterized by elevated blood glucose levels. It results from the absence of or inadequate pancreatic insulin secretion with or without concurrent impairment of the action of insulin (ADA, 2012). Diabetes mellitus represents an important public health problem. The increase in the incidence of diabetes and other chronic diseases in contemporary society have required the formulation of public policies covering a variety of factors related to its incidence. The prevalence of diabetes is increasing worldwide, leading to an epidemic resulting largely from the aging population. Changes in lifestyle brought about by urbanization and an aging population are the main aspects related to the increase in diabetes and a number of other chronic diseases (Zimmet et al., 2001).

Diabetes is linked to an increased risk for various types of cancer, such as colon cancer, pancreatic cancer, bladder cancer, prostate cancer, non-Hodgkin's lymphoma and breast cancer (Coughlin et al., 2004). Breast cancer is the most frequent gynecological tumor and the second most common cancer worldwide. The etiology of breast cancer is still poorly understood, with known breast cancer risk factors explaining only a small proportion of cases (Dumitrescu and Cotarla, 2005). Diabetes is associated with many types of tumors, but its links with breast cancer remain controversial (Liao et al., 2011).

Postmenopausal women have an increased risk of developing breast cancer, particularly if they display an android-type pattern of adiposity, which is also associated with increased risks of diabetes mellitus, hypertension and cardiovascular disease (Ronco et al., 2012). On the other hand, studies have also indicated the long-term health benefits of lactation for mothers. A long-term reduced incidence of breast cancer has been well-documented in breastfeeding on mothers. In this review, we discuss the evidence for the relationship between diabetes and breast cancer, as well as the role of the duration of breastfeeding involved in this association.

Diabetes Mellitus

Diabetes mellitus is a metabolic disease characterized by elevated blood glucose levels. It results from the absence of insulin or inadequate pancreatic insulin

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secretion with or without concurrent impairment of the action of insulin (ADA, 2012), and it has been linked to changes in metabolism (Balda and Pacheco-Silva, 1999).

Diabetes is considered one of the predominant threats to human health in this century. The global epidemic of diabetes is largely due to population growth, aging, urbanization, and the scourge of obesity and physical inactivity. The total number of people worldwide with type II diabetes is expected to increase from 171 million in 2000 to 366 million in 2030 (Wild et al., 2004).

Type 1 diabetes is an autoimmune disease that is untimely caused by the destruction of insulin-producing pancreatic β-cells by autoreactive T cells. The development of the pathology involves several cell types of both the innate and adaptive immune systems. This disease is under the control of several genetic loci for susceptibility, but it is also influenced by environmental factors such as infectious agents (Diana et al., 2001).

Type 2 diabetes is a chronic, progressive and multifactorial disease, with insulin resistance and decreased β-cell function playing dominant roles in its genesis. The disease is a major cause of early mortality due to atherosclerosis and cardiovascular disease, and it is the leading cause of blindness, leg amputations, and chronic renal disease (Ismail-Beigi, 2012).

The morbidity and mortality of diabetes are related to complications associated with chronically increased levels of glucose in the blood. These complications can be macrovascular and microvascular. The macrovascular complications are mainly ischemic heart disease, stroke and peripheral vascular disease. The microvascular complications can manifest as damage to the retina or diabetic retinopathy, with the possibility of progression to permanent blindness; kidney damage, known as diabetic nephropathy; or by distal sensory neuropathy, which can lead to the requirement for amputation of limbs, especially the lower limbs (Gross and Nehme, 1999).

The incidence of diabetes has been increasing in recent years, and several studies have associated a lower immune response and increased rates of infection with diabetes. The complications due to infections can lead to chronic inflammation and degenerative diseases, such as cancer (Rabinovitch, 1999).

The literature has shown that diverse immune functions, especially antigen non-specific processes, are affected by diabetes (Lau et al., 2005). Little is known, however, about the influence of diabetes on specific tissues or organs, as the mammary gland. Diabetic patients have reduced phagocytic activity, low microbicidal activity and high reactive oxygen species production due to changes in the antioxidant systems (França et al., 2011; 2012; Morceli et al., 2011). The reduction in the phagocytic and microbicidal activity of leukocytes is likely related to an increase in blood glucose levels (Alba-Loureiro et al., 2007).

Understanding the immunological mechanisms associated with diabetes is essential to establish the possible immunotherapeutic strategies for the prevention and cure of disease, and, above all, it is an important strategy for providing support and assistance to patients with this disorder.

Breast Cancer

Breast cancer is the most common female cancer. Annually, more than one million new patients are diagnosed worldwide (Chu and Lu, 2008). The breast cancer incidence has increased steadily in developed countries over the past few decades, but the mortality caused by breast cancer has decreased because of improvements in diagnosis and treatment (Watanabe et al., 2010).

Several risk factors have been identified for breast cancer and can be divided into those that cannot be modified and those that are potentially modifiable. Diet is one of the modifiable risk factors, together with adiposity, physical activity, smoking, alcohol consumption, and the use of hormonal replacement therapy (Mahoney et al., 2008; Romieu, 2011). Heterozygous carriers of mutations in the hereditary breast cancer genes BRCA1 or BRCA2 have a 60-80% lifetime risk of breast cancer (Cantor and Guillemette, 2011).

Breast cancer is a heterogeneous disease encompassing multiple subgroups with differing molecular signatures, prognoses, and responses to therapies. Breast tumors evolve via a sequential progression of defined stages, starting with epithelial hyperproliferation and progressing to in situ, invasive, and metastatic carcinomas. Both clinical and experimental data suggest that ductal carcinoma in situ is a precursor to invasive ductal carcinoma (Burstein et al., 2004; Espina and Liotta, 2011). Ductal carcinoma in situ lesions contain proliferating neoplastic cells confined to the duct. A critical, but poorly understood, step in breast cancer progression is the transition from in situ to invasive ductal carcinoma, which is defined by the loss of the myoepithelial cell layer and basement membrane. The subsequent spread of tumor cells to distant sites results in metastatic disease. The tumor microenvironment has been implicated in each of these steps of cancer progression (Place et al., 2011).

A major challenge to human breast cancer research has been the identification of the molecular and immunological alterations linked with the different stages of breast cancer progression. Until recently, progress in attaining this goal has been hampered by technical limitations associated with applying advanced molecular technologies to the microscopic preinvasive stages of breast tumorigenesis (Bombonati and Sgroi, 2011).

During the past decade, insights have been gained regarding the mechanisms underlying the dynamic interplay between immune cells and tumor progression. The accumulated data indicate that the outcome of an immune response toward a tumor is largely determined by the type of immune response.

Breast cancer tumors are infiltrated by a heterogeneous population of immune cells consisting of different proportions of T cells, B cells, natural killer (NK) cells and macrophages (Georgiannos et al., 2003). Although components of the immune system are present, many breast tumors progressively grow and spread; therefore, the role of tumor-infiltrating leukocytes in the tumor microenvironment is unclear (Marsigliante et al., 1999). The association of tumor-infiltrating CD4+ T lymphocytes

with lymph node metastases suggests a role for these cells in the spread of tumor cells to the lymph nodes in patients with early breast cancer (Macchetti et al., 2006).

The balance between a protective cytotoxic response and a harmful response can be regulated systemically by the general immune status of the individual (DeNardo and Coussens, 2007). Comprehensive analysis of immune effector functions at different stages of tumor metastasis is fundamental to the design of effective immune intervention.

Diabetes and Breast Cancer

Diabetic state changes in metabolism, increased susceptibility to infections, immunological changes. A reduction in the immune response has been identified as a relevant factor and contributes to the increase of infections and chronic diseases, such as breast cancer, in these patients.

A meta-analysis of diabetes mellitus, cancer, and the prognostic outcome evaluated the prognostic outcome by diabetes status in a cancer population (Peairs et al., 2011). A meta-analysis of pre-existing diabetes and its effect on all-cause mortality in patients with breast cancer and qualitatively summarized other prognostic outcomes. Of 8.828 titles identified, eight articles met the inclusion/exclusion criteria and described the outcomes in patients with breast cancer and diabetes. Pre-existing diabetes was significantly associated with all-cause mortality in six of seven studies. In a meta-analysis, patients with breast cancer and diabetes had a significantly higher all-cause mortality risk compared with their nondiabetic counterparts. Three of four studies found pre-existing diabetes to be associated with a more advanced stage at presentation. Diabetes was also associated with altered regimens for breast cancer treatment and increased toxicity from chemotherapy (Peairs et al., 2011).

Another meta-analysis was conducted including 16 studies published between 2000 and 2010 and summarized the relative risks. The combined evidence indicates that diabetes is associated with a statistically significant 23% increased risk of breast cancer, especially in postmenopausal women. The correlation between diabetes and breast cancer was the most obvious in Europe, followed by Americas. In Asia, the result was not significant. Diabetes also increased the mortality from breast cancer overall (Liao and Wei et al., 2011).

The Long Island Breast Cancer Study Project evaluated the effect of self-reported diabetes on breast cancer incidence and mortality. This study included 1.447 breast cancer cases and 1.453 controls. Follow-up data for all-cause (n=395) and 5-year breast cancer-specific mortality (n=104) through December 2005 were determined for case women from the National Death Index. Postmenopausal women with diabetes were at increased risk of developing breast cancer, as were those who were not of white race regardless of their menopausal status. Among the case women, diabetes was associated with a modestly increased risk of death from all causes, an association that was stronger in women who were obese at the time of breast cancer diagnosis (Cleveland et al., 2012).

The hyperinsulinemia, a hallmark of insulin resistance, and the increase in bioavailable insulin like growth factor I (IGF-I) appear to have a role in tumor initiation and progression in insulin-resistant patients. Insulin and IGF-I inhibit the hepatic synthesis of sex-hormone binding globulin, whereas both hormones stimulate the ovarian synthesis of sex steroids, whose effects in the breast epithelium and endometrium can promote cellular proliferation and inhibit apoptosis. It is possible that the abundance of inflammatory cells in diabetic patients may promote systemic inflammation, which can result in a protumorigenic environment. Furthermore, an increased risk of cancer among insulin-resistant patients may be due to over production of reactive oxygen species that can damage DNA contributing to mutagenesis and carcinogenesis (Arcidiacono et al., 2012).

Excessively high levels of free radicals cause damage to cellular proteins, membrane lipids and nucleic acids, which eventually culminates in triggering the cell death pathways (Maritim et al., 2003; Ferrari et al., 2009). Immune cells produce a high amount of superoxide radical anion during oxidative stress (Ferrari et al., 2009; 2011; França et al., 2010) an important protective mechanism during infectious processes and chronic disease. Clinical and experimental study showed that the high blood glucose level determined changes in the functional activity of macrophages. These cells are more active, as shown by an increased oxidative metabolism and the consequent enhanced production of the superoxide anion (França et al., 2009; 2012; Honorio-França et al., 2009). Various mechanisms have been suggested to contribute to the formation of these reactive oxygen-free radicals. Glucose oxidation is believed to be the main source of free radicals (Jiang et al., 1990). Hyperglycemia has also been found to promote lipid peroxidation by a superoxide-dependent pathway, resulting in the generation of free radicals (Kawamura 1994; Tsai et al., 1994). Another important source of free radicals in diabetes is the interaction of glucose with proteins, leading to the formation of various products that contributed to the production and release of free radicals (Maritim et al., 2003).

The alterations in glucose metabolism and increased oxidative metabolism may be linked to changes in the tissue mammary glands, compromising the integration of the breast and increasing the breast cancer risk. Molecular and cellular mechanisms underlying cancer development have revealed that immune cells functionally regulate epithelial cancer development and progression. Moreover, accumulated clinical and experimental data indicate that the outcome of an immune response toward an evolving breast neoplasm is largely determined by the type of immune response (DeNardo and Coussens, 2007).

The inflammatory responses necessary for enabling an immune reaction may, however, also set the stage for promoting neoplastic disease. In diabetic patients the increase of free radical production by phagocytes plays an important role in the host defense system, which produces the superoxide. Superoxide is essential for microbicidal killing (França-Botelho et al., 2011; França et al., 2011; 2012) and crucial to the success of the immune response. It also promotes the inflammatory reactions and may favor breast cancer evolution.

The Effect of Breastfeeding on Breast Cancer and Diabetes

Studies have attempted to elucidate the effects of lactation on maternal glucose metabolism (Taylor et al., 2005). There is evidence that human milk may confer long-term benefits, such as a reduced risk for certain autoimmune diseases, inflammatory bowel disease and certain malignancies. Breastfeeding even reduces the incidence of acute illnesses and likely decreases the risk of a number of chronic diseases. Several studies have investigated the association of breastfeeding with a variety of chronic diseases, including diabetes (Davis, 2001; Kent, 2007). A reduced incidence of breast cancer is the most well documented long-term effect of breastfeeding on mothers and it has been shown to affect blood pressure, obesity/overweight and diabetes (Horta, 2007).

Human milk has been demonstrated to possibly affect the components involved in metabolic syndrome. An increasing number of studies have indicated that breastfeeding offers protection against ovarian cancer, rheumatoid arthritis and type II diabetes (Løland et al., 2007). Due to medical advances that have allowed for improved metabolic control of glucose, diabetic women are more likely to become pregnant. However, due to alterations in glucose metabolism, the components in the milk they produce are changed (França et al., 2011; 2012; Morceli et al., 2011).

The effects of breastfeeding on breast risk have been difficult to study due to the high correlation with parity (Barnett et al., 2008; Alsaker et al., 2011). Reproductive factors may induce permanent changes in the mammary gland epithelium or surrounding stromal tissue (Russo et al., 2005; Russo et al., 2008). It is most likely that the tissue changes can make the breast more or less susceptible to carcinogenic factors (Russo et al., 2005).

Although the mechanisms have not been entirely elucidated, breastfeeding has been hypothesized to reduce the risk of breast cancer primarily through two mechanisms: the differentiation of breast tissue and a reduction of the lifetime number of ovulatory cycles; however, a previous study examining the association between breastfeeding and breast cancer did not consistently find that breastfeeding reduces the risk of breast cancer (Yang and Jacobsen, 2008).

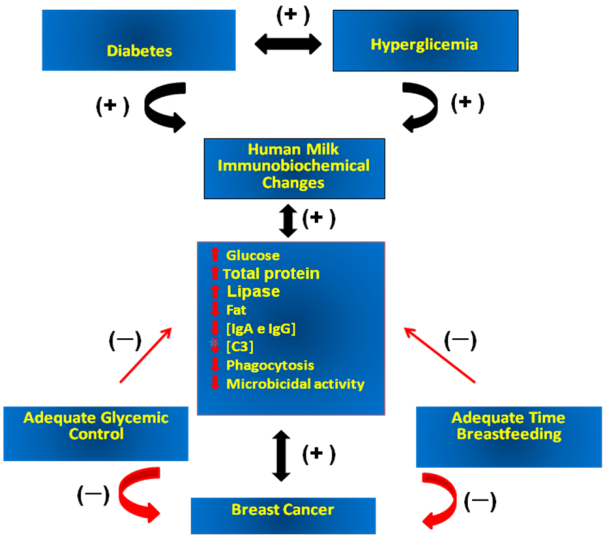

Figure 1. Relationship between Diabetes, Breast Cancer and Breastfeeding

Non-breastfeeding mothers have been shown in previous studies to have a higher risk of reproductive cancers. Breastfeeding for longer periods results in statistically significant reductions in the risk of developing breast cancer, the most common gynecological tumor in young women, the second most common cancer and the most frequently diagnosed cancer among women worldwide. There is strong evidence that breastfeeding reduces the risk of breast cancer; however, further studies must be conducted to further elucidate the mechanisms involved in the protective effects of breastfeeding (França-Botelho et al., 2012).

Clinical studies have reported that a combination of longer breastfeeding duration and a lower parity seemed to reduce the risk of breast cancer (Redondo et al., 2012). On basis of epidemiologic studies conducted throughout the world and biological evidence, some studies conclude a protective effect of breastfeeding on breast cancer risk (Nagata et al., 2012). Even, clinical, epidemiological and experimental studies suggest that diet is implicated in the etiopathogenesis of diabetes (Horta et al., 2007) and breastfeeding is in fact associated with a decreased risk for type 2 diabetes later in life (Taylor et al., 2005).

There is an ever-increasing interest in understanding the effects of breastfeeding on diabetes as well as the mechanisms involved. A number of studies show the role of breastfeeding in promoting growth and protecting against infections and diseases such as diabetes (Taylor et al., 2005; França et al., 2011; 2012; Morceli et al., 2011). Breastfeeding may modify the natural development of type I diabetes because it protects against a number of viral diseases, preventing or delaying disease onset (Bognetti et al., 1992). Breastfeeding is also associated with improved maternal outcomes, including a reduced risk of breast and ovarian cancer, type 2 diabetes. These reductions in acute and chronic illness help to decrease health-care-related expenses and productive time lost from work (ADA, 2009).

Short-term breastfeeding followed by early introduction of bovine milk is a known risk factor for type 1 diabetes in infants (Gerstein and VanderMeulen, 1996). The lack of breastfeeding also increases the risk of type 1 diabetes (Malcova et al., 2006) whereas prolonged breastfeeding duration likely reduces the risk of future type 2 diabetes (Stuebe et al., 2005).

On the other hand, lactating mammary glands are part of the integrated mucosal immune system, and milk antibodies reflect antigenic stimulation of Mucosa Associate Limphoid Tissue (MALT) both in the gut and airways (Brandtzaeg, 2010).

The innate defense factors present in milk include components such as lysozyme, lactoferrin, peroxidase, complex oligosaccharides (receptor analogues), fatty acids (lipids), and mucins (Brandtzaeg, 2003; 2010). Moreover, a variety of leukocytes occur in colostrum (1×10^9/mL) and in milk (1×10^5/mL). Macrophages (55-

60%) and neutrophilic granulocytes (30-40%) are more prevalent lymphocytes (5-10%), the latter being mainly (75-80%) T cells (Islam, 2006; Brandtzaeg, 2010). Oral administration of macrophages in newborn mice showed the survival of these cells for several hours in the gut and even some mucosal uptake. The macrophages contain engulfed SIgA, which they may release on contact with microorganisms in the gut (Honorio-França et al., 1997; 2001; França-Botelho et al., 2006, França et al., 2009; 2010; 2011). These milk cells may also secrete an array of important immunoregulatory factors (França-Botelho et al., 2006; Brandtzaeg, 2010).

Due to alterations in glucose metabolism diabetics, the components of the milk are altered (Figure1). Milk from diabetic mothers is high in glucose, total protein, and lipase, and it is lower in fat antibody, complement protein and microbicidal activity (França et al., 2011; 2012). Adequate glycemic control in diabetic mothers is crucial to correct any abnormalities in the milk composition (Vanbeusekom et al., 1993; França et al., 2011).

There are many benefits for the mother. The degree to which some of these health benefits may be realized depends on the breastfeeding duration, breastfeeding frequency, breastfeeding exclusivity, and other personal factors. Despite the abnormalities in biochemical and immunological components, women with diabetes should be strongly encouraged to extend their breastfeeding. Furthermore, the milk is an excellent source of immunological components, and the lactating mammary glands become part of the integrated mucosal immune system. Therefore, it is possible that breastfeeding may reduce the risk of breast cancer. In addition, the extent of the protection against breast cancer provided by breastfeeding can be related to the duration of breastfeeding rather than the concentration of immunological cells and proteins in the milk.

Conclusion

Despite great advances in medicine, including improvements in the methods of detection, diagnosis and treatment, breast cancer is still a disease that has a high mortality rate; in developing countries, these rates are even higher. The incidence of diabetes and breast cancer has increased substantially, and they have become important risk factors threatening womens' health.

Overall, breastfeeding represents a remarkable immunologic interaction between the mother and her baby, and in developing countries it is the best defense against mucosal infections. Breast milk is an excellent source of immunological components, and it decreases the high rates of maternal and infant complications.

Our findings support the hypothesis that the production of milk components differs in diabetic mothers due to alterations in glucose metabolism. Therefore, adequate maternal glycemic control and breastfeeding duration in diabetic mothers is crucial to ensure the immunity components acts against the breast cancer.

Considering the numerous immunologic constituents of breast milk and that the breast tissue is in constant and direct contact with the soluble and cellular immune components in milk, this period contributes to the surveillance against cancer. Extending the period of breastfeeding can be considered an alternative mechanism for generating protection against breast cancer in diabetic mothers.

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