Commentary

Heightened Risk of Breast Cancer Following Pregnancy: Could Lasting Systemic Immune Alterations Contribute?

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Abstract

The protective effect of having a first full-term pregnancy (FFTP) at a younger age on women's lifetime risk of breast cancer is well known. Less appreciated is the increased risk seen in the years immediately following pregnancy. This adverse effect is more pronounced and more prolonged in women with later age at FFTP. The mechanisms responsible for this increased risk are still poorly understood. In the present paper, we put forward the hypothesis that the marked peripheral immune changes induced by pregnancy may account for these effects. We highlight immune changes that characterize the unique immune state of pregnancy (a combination of cellular immunosuppression and enhanced inflammatory response), note the resemblance of these changes to cancer escape mechanisms, and discuss why such immune changes may be critical for the development of breast cancer following pregnancy. We further support this idea by initial findings from our own laboratory that the age at FFTP is negatively related to natural killer cell cytotoxicity many years later and propose possible models for the kinetics of the immune changes during and following pregnancy. The effect of age at FFTP on the immune function is currently understudied. Its potential relevance to the development of breast cancer stresses the need for further research. (Cancer Epidemiol Biomarkers Prev 2007;16(6):1082–6)

The widely known protective effect of having a first full-term pregnancy (FFTP) at an earlier age on women's lifetime risk of developing breast cancer has been extensively documented over the past 30 years and is included as a factor in the classic Gail model of breast cancer risk (1). Less widely appreciated are more recent data from large-scale studies indicating that this protective effect is preceded by a period of increased risk for breast cancer, especially among women with later age at FFTP (2-8). This increased risk of developing breast cancer is both more pronounced and more prolonged in women with later age at FFTP (3-5, 8). Indeed, the crossover from increased to decreased risk of breast cancer following pregnancy, which occurs after about 10 years for women whose FFTP was before the age of 25, occurs only after about 20 years for women whose FFTP was between 25 and 29, and may never crossover for women whose FFTP occurred after the age of 35 (3, 10).

The mechanisms underlying what has been termed the ''dual'' effect of pregnancy on breast cancer risk are largely unknown. Reduced susceptibility to carcinogenesis due to terminal differentiation of mammary gland stem cells is increasingly recognized as a likely mechanism for the long-term reduction of risk following an early pregnancy (2, 11, 12). To date, speculation concerning the mechanisms responsible for the initial increased risk of breast cancer following pregnancy has also centered on possible effects on breast tissues, including the extracellular matrix (2, 13). These effects are most commonly attributed to the high proliferative rate of breast cells during pregnancy and to the carcinogenic effects of estrogen metabolites (14, 15). Pathways that may be involved in the effects of estrogen on breast cells have received research attention (16, 17), and additional pathways that may be involved in the effect of pregnancy on breast tissues have also begun to be explored by some investigators (13, 18, 19). Largely overlooked is the possibility that lingering effects of the profound alterations in immune function associated with pregnancy (including both systemic cellular immunosuppression and enhanced inflammatory response; refs. 20-24) may contribute to the increased risk of breast cancer. The purpose of this paper is to highlight lines of evidence from the current literature on reproductive immunology and cancer immunology that are consistent with the hypothesis that systemic effects of pregnancy on the immune system may contribute to the increased risk of breast cancer after delivery and to the long-lasting higher risk in women with later age at FFTP (see Fig. 1). To spur research interest in this possibility, we also present preliminary evidence from our own laboratory of lasting consequences of FFTP on a classic immune effector mechanism, natural killer cell cytotoxicity (NKCC), and emphasize the need for additional hypothesis-generated research.

Immunomodulation Associated with Pregnancy

A voluminous research literature now indicates that pregnancy introduces broad and marked modulation of both innate and adaptive immune function (20-24). Interest in those immune alterations stemmed from the recognition that they are key factors in understanding how the semiallogeneic embryo escapes from rejection. The lack of a cellular maternal immune response toward the fetus is attributed not only to the unique expression of HLA molecules on the trophoblast (classic HLA class I molecules are absent, and certain trophoblast cells express the nonclassic HLA-E and HLA-G molecules; ref. 25), but also to various immunomodulatory factors that are expressed or released by the placenta. These include indoleamine 2,3-dioxygenase (IDO), an intracellular enzyme that promotes T cell tolerance (25); estrogen and

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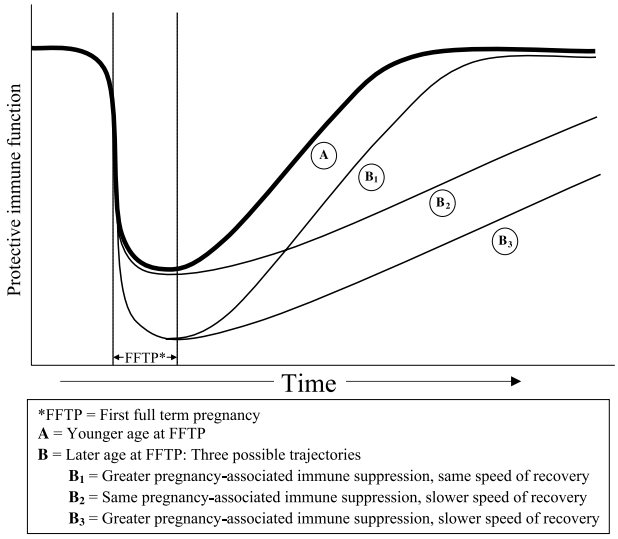

Figure 1. Models of the severity and recovery patterns of pregnancy-induced immune changes in women with early versus late age at FFTP.

progesterone, which directly and indirectly regulate various immune functions (26); and soluble MHC chain-related proteins A and B (MICA/B), molecules that down-regulate the activatory NKG2D receptor on NK cells and CTLs (27). Over the years, it has become apparent that various aspects of immune function are also essential to actively promote trophoblast growth, control its invasion into the uterine wall, and provide adequate blood supply to the placenta (through angiogenesis and remodeling of the spiral arteries; refs. 25, 28, 29). Decidual NK cells, which comprise 70% of the leukocytes in the uterus, have gained most interest in this respect (22, 25, 28, 30).

Although most interaction between fetal cells and the maternal immune system takes place in the feto-maternal unit, interactions also occur systemically as fetal cells and microparticles shed into maternal circulation during pregnancy (31). It has recently been suggested that these fetal microparticles are at least partly responsible for the strong systemic inflammatory response during pregnancy (21). The shed fetal cells may have a continuing effect on immune function as they persist in the circulation for many years after delivery (microchimerism; ref. 32).

Regardless of where most interactions initiate, considerable immune modulation is observed systemically. An interesting aspect of this systemic immunomodulation is that it simultaneously embraces cellular immunosuppression, immunotolerance to various antigens, and enhanced inflammatory response. In humans, it is specifically characterized by (*a*) an increase in WBC counts (23); (*b*) a suppression of NKCC that is strongest in the third trimester (33-36); (*c*) a decrease in the ratio of Th1/Th2 cytokines, especially in the third trimester (23, 24); (*d*) an increase in certain proinflammatory cytokines [e.g., interleukin-6 (IL-6), tumor necrosis factor-α], especially in the second half of pregnancy (21); (*e*) an increase in the number of regulatory T cells (37, 38); (*f*) an increase in asymmetrical immunoglobulin G (IgG) antibodies, which can bind antigen but are unable to activate effector function (39, 40); (*g*) a decrease in various breast cancer–related antibodies, such as anti-MUC1 IgM (41, 42); and (*h*) an increased expression of various activation-associated adhesion molecules on granulocytes and monocytes (23).

That these pregnancy-associated immune changes are biologically significant is supported by evidence of effects of pregnancy on the course of various immune-related diseases. It has been recognized, for example, that pregnancy ameliorates the clinical course of multiple sclerosis and rheumatic arthritis (43), aggravates systemic lupus erythematosus (44), increases the risk of infectious diseases, including influenza (45) and plasmodium falciparum malaria (46), and accelerates the progression of HIV and increases morbidity in HIV (47).

Relatively rare in the reproductive immunology literature are systematic studies examining potential lasting consequences of pregnancy-associated alterations in immune function. If and when the various immune changes associated with pregnancy return to baseline levels remains largely unknown. Although some functions may fully recover within few months after delivery, there is initial evidence that at least some aspects of immune function, for example NKCC (35, 48), may be altered for a prolonged period of time following pregnancy.

Also notably lacking in this literature are studies examining the possible impact of women's ages at FFTP on either the severity, or recovery patterns, of pregnancy-associated immune changes. As shown in Fig. 1, three scenarios are logically possible. First (B_1), immunosuppression during pregnancy may be more severe in women with later age at FFTP, but speed of recovery may be similar to that of women at younger age. Second (B_2), immunosuppression may be identical during pregnancy, but recovery may be slower in women with later age at FFTP. Third (B_3), immunosuppression during pregnancy may be greater in women with later age at FFTP, and their recovery slower. Some indirect evidence consistent with greater immunosuppression during pregnancy comes from studies showing that older age at pregnancy (primiparous status not reported) is associated with increased susceptibility to influenza infection and increased mortality from infections overall (49, 50).

With the intent of stimulating future studies on this topic, we conducted an exploratory analysis of NKCC data collected from 58 parous women (mean age = 41 $\pm$ 8, range = 26-63) in our laboratory. Blood samples from these healthy women were collected by venipuncture for blind assessment of NKCC using standard Cr release, whole blood, protocols with K562 targets (51). Consistent with the hypothesis, NKCC was negatively related to age at FFTP ($P < 0.005$) using a general linear model (GLM) approach with statistical software (SAS). This relationship remained significant after inclusion of current age, family history of breast cancer, and number of children (mean = 2.1 + 1.3) in the model ($P < 0.01$). These findings are striking because women were on average 18 years after the birth of their first child. Consistent with the preponderance of the literature on age and peripheral blood NKCC levels (52), the women's age at the time of blood collection was not found to be related to NKCC. When analysis was limited to premenopausal women (conservatively defined as women under 45), similar results were found ($P < 0.05$). These results must be interpreted with caution because the study was not specifically designed for this purpose, and no data were collected on: birth spacing, possible fertility problems, or time since the women's most recent pregnancy. Nonetheless, these initial findings suggest that the suppressive effects of pregnancy on NKCC may be particularly severe and/or long lasting in women with older ages at FFTP. These findings stress the importance of additional research to explore the contribution of reduced NKCC to pregnancy-associated risk of breast cancer.

The Role of the Immune System in the Development of Breast Cancer

The role of the immune system in nonviral cancers and particularly in breast cancer has been debated for a long time. Studies in mice and in humans suggest that the immune system has a complex role, and that it can both promote cancer and eradicate tumor cells, depending on a number of factors,

including the time course of the interaction and the specific immune components that are activated (53). For example, proinflamatory processes in the tissue microenvironment have been identified during mammary gland involution (postpregnancy or following cessation of breast-feeding), raising the possibility that such processes could contribute to increased risk of breast cancer initiation and/or progression (13), consistent with an emerging appreciation of the possible role of inflammatory processes in cancer more generally (53). Interestingly, there have been reports that the use of nonsteroidal anti-inflammatory drugs is associated with reduced incidence of breast cancer (54, 55). Proinflammatory cytokines could mediate these effects by causing DNA damage, increasing cell proliferation, stimulating the production of angiogenic factors, and suppressing adaptive antitumor immune responses (53).

On the other hand, there is also evidence supporting the existence of both cellular and humoral immunity that may protect against breast cancer. Findings include (*a*) breast cancer cells express various tumor-associated antigens (e.g., MUC1; ref. 56); (*b*) some breast cancer patients spontaneously mount both cellular and humoral immune responses toward these tumor antigens, and having these responses is associated with improved prognosis (42, 57-59); some of these antigens are currently being targeted for the development of immunotherapies; (*c*) indices of cell-mediated immunity are often impaired in women with breast cancer, and greater impairment is associated with increased risk of recurrence, even after controlling for stage of disease (60-62); (*d*) various polymorphisms in cytokine genes have been associated with altered risk of breast cancer (63-65); (*e*) healthy women at familial risk for breast cancer have been reported to exhibit low NKCC and reduced cytokine production (66-68); (*f*) although controversial, several studies have reported increased prevalence of breast cancer in women exposed to immunosuppressive drugs for organ transplantation (69-71); (*g*) immunotherapy has shown some promise if given to breast cancer patients at an early stage of the disease (e.g., immunization with oxidized mannan-MUC1; ref. 9); (*h*) breast tumors often evidence adaptive mechanisms that allow escape from immune surveillance (e.g., increased expression of HLA-G, reduced expression of HLA-A, refs. 72, 73; release of immunosuppressants that modulate the expression of the NKG2D receptor on various lymphocytes, ref. 74). The existence of such mechanisms is in accordance with the immunoediting theory, which proposes that tumor cells are initially immunogenic, and that the immune response to these tumors results in the natural selection of tumors with lower immunogenicity. The escaping tumor cells continue to proliferate and turn into cancers that are immune resistant (75).

Does the Effect of Pregnancy on Immune Function Render Women More Susceptible to Breast Cancer?

As noted above, pregnancy is a unique immunomodulatory state that is systemically characterized by marked immunosuppression, increased tolerance to various foreign antigens, and an increase in inflammatory cytokines (21, 23). Despite the profound changes in immune function associated with pregnancy, little attention has been paid to the possibility that such immune change may increase the risk of breast cancer. Most attention on the possible consequences of pregnancy-induced immune alteration has focused on the possibility that pregnancy could immunize against tumor antigens that are also expressed by trophoblast cells (e.g., MUC-1) and thus protect against breast cancer (76). The possibility that the unique immune state of pregnancy may open a window for breast cancer to develop has only been briefly mentioned (2, 11, 77-79) and has received relatively little attention in the empirical literature.

The similarity of many escape mechanisms used by the fetal trophoblast cells to those employed by cancer cells is striking. These include not only alterations in expression of various molecules and enzymes that affect local immune response (e.g., down-regulation of the classic HLA class I molecules, and expression of IDO; refs. 25, 29, 80, 81), but also the release of various immunomodulatory molecules that have a systemic effect. MICA/B, s-HLA-G, IL-6, IL-10, transforming growth factor-β, and progesterone-induced blocking factor are often found at increased level in the circulation of both cancer patients and pregnant women and are thought to assist the tumor and the fetus to escape attack by the immune system (20, 27, 80, 82).

In cancer, such mechanisms are thought to evolve due to the selective pressure the immune system puts on tumor cells. These mechanisms can be observed in advanced tumors after natural selection has taken place and are unlikely to be present on newly transformed tumor cells (75). Pregnancy may, however, create unique circumstances: because the immune alterations at this time period are similar to those employed by tumor escape mechanisms, tumor cells that would otherwise be recognized and destroyed by the immune system may have greater chance to survive and proliferate. Thus, the systemic immune modulation that occurs during pregnancy and is essential for proper development of the embryo may render women more susceptible to the development of cancer during this time period.

Although the altered immune state of pregnancy is likely to influence various cancers, it may be particularly influential in the development of breast cancer. Breast cells are rapidly proliferating during pregnancy to prepare the breast for lactation. The increased rate of proliferation, together with the simultaneous exposure to high levels of proinflammatory cytokines, may increase the mutation rate in breast cells. Immune suppression at this critical time period may lower immune surveillance, and as a result, the mutated cells will have an increased chance to proliferate and potentially metastasize.

The idea that the immunomodulation during pregnancy may increase breast cancer risk is further supported by observations showing that the elevated risk is not observed immediately after delivery, but only 3 to 5 years later. According to the immunoediting hypothesis, the immune system eliminates tumor cells that are relatively at their early phase of development and does not eradicate cells that have already experienced Darwinian selection and are currently at an ''escape phase.'' Consequently, the progression of relatively advanced carcinomas *in situ* will not be affected by this immunosuppression, and a delay between the time of immunosuppression caused by pregnancy and the detection of tumor cells is expected.

The association between NKCC and age at FFTP observed in our preliminary data raises the possibility that the altered immune function during pregnancy may also drive the long-lasting difference in breast cancer risk between women with younger versus older age at FFTP. The protective effect later observed in women with young maternal age may be due to a different mechanism. This protective effect may not be observed in women with late age at FFTP simply because it does not balance the long-lasting deleterious effect of pregnancy on immune function in these women.

Summary and Conclusions

In the present paper, we have attempted to highlight evidence consistent with the hypothesis that the unique state of immunosuppression and increased inflammatory response during pregnancy may increase the risk of breast cancer. The deleterious effect of pregnancy may be stronger for women

with later age at FFTP because they may have greater immunosuppression (or stronger inflammatory response) during pregnancy and/or they take longer to recover. Our preliminary findings that NKCC is related to FFTP even years later highlight the importance of further research in this area.

Although we focused on the development of primary breast cancer, lingering immune effects of pregnancy may also have implications for the treatment and recurrence of breast cancer, as well as for the development of other cancers and immune-related disorders. These considerations raise the possibility, for example, that immunotherapy may better benefit women with late age at FFTP because such cancers may be more immunogenic. In addition, because immune mechanisms are thought to also control metastasis and dormant tumor cells, lingering immune effects of pregnancy may pose a risk for recurrence, particularly in women with late age at FFTP. In support of this hypothesis, women diagnosed with stage II or III breast cancers during or close to pregnancy have a lower rate of survival (83).

The lasting systemic effects of FFTP at different ages on immune function are currently not known. Also unknown are the effects of subsequent pregnancies on the immune function and its recovery patterns. The potential relevance of such knowledge to our understanding of the risk of breast cancer, as well as other health outcomes following pregnancy, strongly supports the need for systematic research in this respect. Because the balance between positive and negative effects of parity on the development of breast cancer is increasingly recognized to depend on women's age at FFTP, future studies should examine the differential effect of parity and age at FFTP on immune function during and after pregnancy.

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