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Rethinking the carcinogenesis of breast cancer: The theory of breast cancer as a child deficiency disease or a pseudo semi-allograft☆

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ABSTRACT

The theory of breast cancer as a *child deficiency disease* is an *inversion of the current paradigm*, which considers full-term pregnancies to be a protective factor and uses nulliparous women as the reference group. Instead, the theory of breast cancer as a child deficiency disease says that women with the highest parity (about 20, which is the limit of human fertility) are those with the lowest risk and should be used as the reference group in risk estimations. This theory is explained biologically by converting parity from the simple value of number of children into an understanding of the long-lasting biological and immunological effects of pregnancy. These effects can be reflected, as measured by functional genomics, in gene expression of the immune cells in the blood. Each pregnancy represents a unique *fetus or semi-allograft*, which provokes the creation and deposit of memory cell clones in the mother. Gene expression levels have been found to change linearly with number of full-term pregnancies in healthy women, *but not in breast cancer patients*. High hormone levels are necessary for a successful pregnancy, as they modulate the immune response from adaptive to innate in order to protect the fetus (considered as a semi-allograft) from rejection. At the end of the pregnancy, hormone levels drop, and the immune system recognizes the semi-allograft, but not in time for rejection to occur before birth. High hormones levels are also classified as carcinogens illustrating that carcinogenesis in the breast could be viewed as a war or balance between later exposures to hormonal carcinogens and the protection of the immune system. We propose that breast tumors are *pseudo semi-allografts* made up of transformed breast tissue cells. Assuming that the sensitivity to the exposure to increased levels of endogenous or exogenous hormones in women with breast cancer mimic those that occur in pregnancy, these *breast tumor cells are protected* against the body's immune reaction, just as the fetus is during pregnancy. However, with more pregnancies, the potential to eradicate the pseudo semi-allograft might increase due to enhanced immune surveillance. The theory of breast cancer as a child deficiency disease proposes that the protective effect of pregnancy on breast cancer incidence via the immune system is independent of other risk factors.

The theory

The theory of breast cancer as a *child deficiency disease* proposes that breast cancer is the result of immune deficiency in low-parity women combined with a dual effect of hormone levels. Moreover, the theory considers breast cancer as a *pseudo semi-allograft*.

Background

Despite many decades of research, there is still no general or consistent theory of breast cancer. Nor is there any unifying concept that explains the mechanism of pregnancy-related breast cancer protection. However, there are some main theories, such as decreased number of mammary stem cells; increased differentiation of breast epithelial cells; and increased estrogen responsiveness [1]. Most of these theories focus on local changes in the mammary gland.

Most studies on parity and breast cancer have been conducted in low-parity countries like Western Europe, including Norway, or the US. In international consortia, like the European Prospective Investigation into Cancer and Nutrition (EPIC) [2] and the Oxford Collaborative

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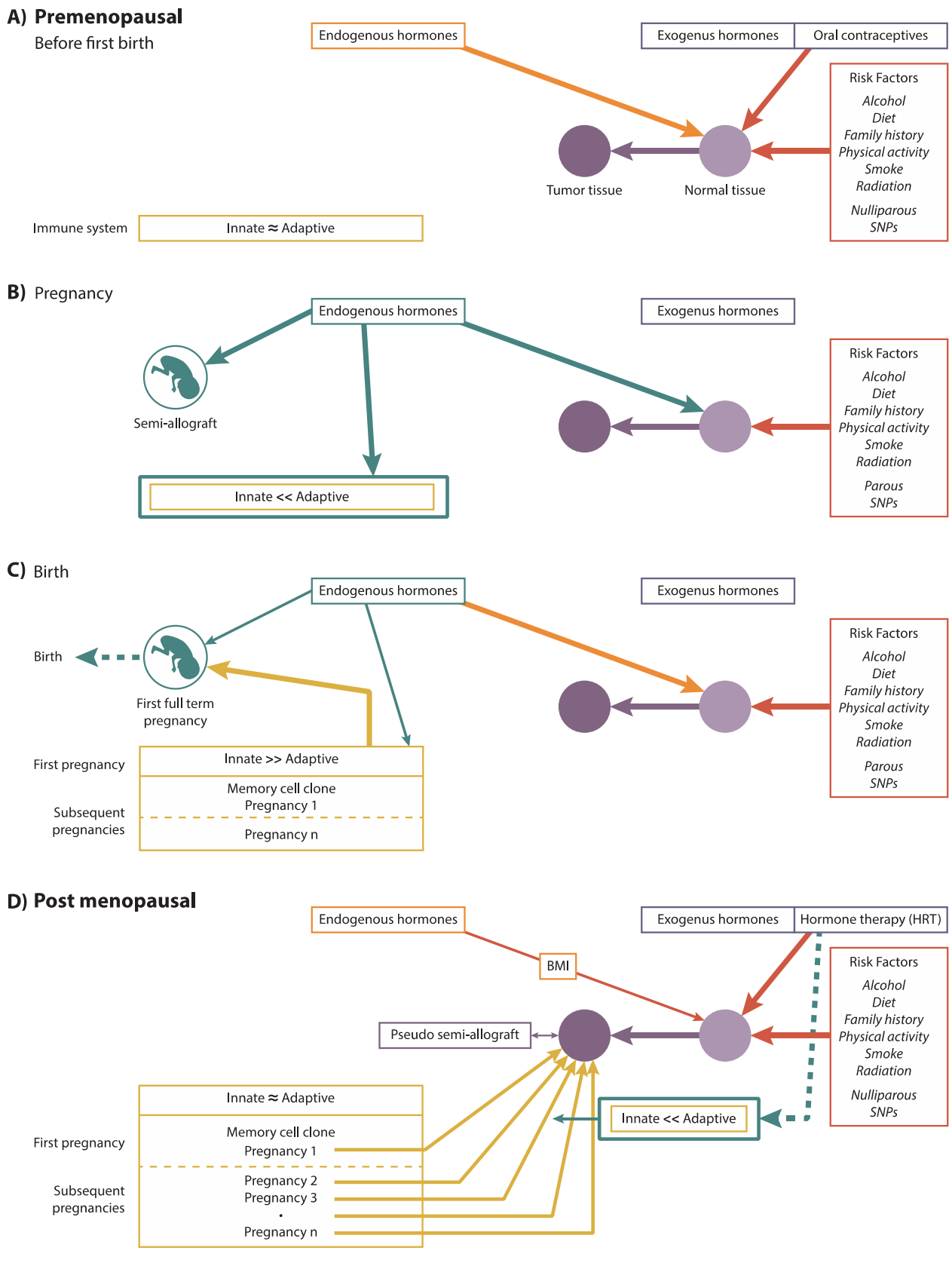

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Group on Breast Cancer [3], the average number of children per woman is 2–3. Moreover, nulliparous women have been traditionally selected as the reference group, and have been compared with the so-called high-parity group (4+ or 5+ children). These studies are limited in their capacity to explain breast cancer incidence, since the major protective factor, parity, is not measured to its full extent.

In the absence of a coherent theory, a wide variety of risk factors has been explored [4]. Body mass index has been revealed to be a weak risk

Fig. 1. Illustration of the complicated interactions between the immune system and hormone levels that occur during each pregnancy are given panels A–D. Red lines indicate increased risk, green lines indicate support for the pregnancy, yellow lines the immune surveillance. A) Before first pregnancy, premenopausal: -endogenous and exogenous hormones act as carcinogens. B) During pregnancy: -the pregnancy and the immune shift depend on high levels of endogenous hormones. -the pseudo semi-allograft (fetus) is protected from rejection through these hormonal effects. -each pregnancy changes the overall immune reaction to increased innate and reduced adaptive responses. -each fetus or pseudo semi-allograft differs from the next. C) At the end of the pregnancy and birth: -hormone levels drop abruptly. -decreasing levels of hormones increase the immune reaction to increased adaptive and reduced innate responses. -the immune system recognizes the pseudo semi-allograft, starting a rejection process. -the child is born before the immune system would be able to harm the pseudo semi-allograft by rejection mechanisms. -during this late phase, the immune response produces memory cell clones directed against fetus-derived antigens, giving the mother lifelong immunity against these antigens. -these procedures are repeated for each full-term pregnancy, not in abortions. D) Postmenopausal: -high-parity women will have more memory cell clones to raise specific immune responses against overlapping epitopes from former fetuses and cancer-associated antigens expressed in novel neoplastic cells – the clone war. -use of exogenous hormones like hormone replacement therapy might shift the immune system in a manner that mimics changes that occur during pregnancy, resulting in reduced adaptive responses and enhanced susceptibility to breast cancer. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

factor, with an effect that can be related to an increased production of estrogens in fat tissue. Other factors include genetic factors, which are independent of other risk factors. Diet has also been investigated heavily over the last 30 years, but findings have been mostly negative [5,6], save those for alcohol consumption. Smoking might be a risk factor in young women, and radiation is also a risk factor for breast cancer. The complicated and dynamic changes in hormone levels related to menopausal status and pregnancies are illustrated in Figure 1.

Combined exogenous hormones like oral contraceptives and hormone replacement therapy have also been classified as human carcinogens [7]. Estrogens alone are weak carcinogens, while gestagens alone might increase the risk of specific subtypes of receptor-positive breast cancer [8]. Large nested case-control studies, like those carried out in the EPIC cohort [2], have shown that increased plasma or serum concentrations of almost all female hormones are related to an increased risk of breast cancer. The relative risk estimates of high versus low concentrations (measured in tertiles) could be in the order of two–three among postmenopausal women. Interestingly, there was no evidence of a relationship between levels of the same hormones and number of children, indicating that, as a risk factor for breast cancer, hormone levels are independent of parity [9].

Endogenous hormones act as breast carcinogens throughout a woman's life. In this respect, both early menarche and late menopause increase the risk of breast cancer, early age at first full-term pregnancy decreases the risk, and older age at first full-term pregnancy increases the risk. Furthermore, it has been shown that abortions have no protective effect on breast cancer [10].

The immune system and hormones during pregnancy

Since pregnancy is unequivocally the most common alloimmunization event in humans [11], multiparous women likely have higher gene expression levels than nulliparous women. Fetal antigens can be found in maternal tissue many years after pregnancy [12,13]. The woman's immune status changes during pregnancy, during which fetal antigens are presented to maternal major histocompatibility complex in secondary lymphoid organs, indicating a systematic priming of the mother to indirect allo-recognition. [14]. Although data on primed T cells in maternal tissue are mainly derived from animal experiments it has been shown that primed human T cells can be hyporesponsive, with limited capacity for proliferation and cytokine production [15].

Background evidence for the theory: Epidemiology

The original observation in favor of the theory of breast cancer as a child deficiency disease, which is an inversion of the parity-breast cancer paradigm, was the lack of cohort and age-specific mortality rate change in Norway based on corresponding figures from 1951 to 85. Indeed, during this period there were no changes in breast cancer treatment [16], but parity changed dramatically from the end of the 19th century to the end of the Second World War. This led to stable age-specific breast cancer mortality and birth cohort-cumulated breast cancer mortality rates. No association was observed between these changes in parity and breast cancer mortality when the range of exposure was defined as a parity of 0, 1, 2, 3, or 4+. However, if the maximum parity was changed to around 20, and that maximum was used as the reference group, considering a parity of 0 as high risk, the change (20–4 = 16) would be only 1/5 of the exposure range. These relatively small changes were not expected to affect mortality rates in an association analysis.

To test the theory of breast cancer as a child deficiency disease, information on parity and age at first full-term pregnancy from the 1970 Census were linked to the register of death certificates in Statistics Norway [17]. In the 1970 census, Norwegian women were interviewed at home by trained interviewers. Using women with 8–9 children as the unexposed (to lack of childbirths) reference group, the relative risk for nulliparous women was 4.6 (95% CI; 2.3–7.9) and the relative risk for uniparous women was around 3.8–4.5, with a population attributable risk of 72% due to low parity. The analysis showed that for high-parity women, age at first and last birth did not matter. There was evidence for a further decrease in RRs among women with 10–11 children, but this could only be calculated for women aged 65–74 years at the start of follow-up, due to the lack of high parity in younger age groups.

The next step was to test the theory in a nationally representative study. The Norwegian Women and Cancer (NOWAC) study was chosen for this. Women were recruited into the NOWAC study between 1991 and 2007 [18]. The last update included 6536 incident cases of breast cancer. In a linear additive model, the decrease in breast cancer incidence was 8% per child. We found the same absolute difference between nulliparous and uniparous women as between women with five or six children, in agreement with an additive model effect. The effect of pregnancy was independent of all established risk factors in stratified analyses. Tests for heterogeneity between strata were not significant except for a borderline significance of history of breast cancer in the mother ($p = 0.06$). Regarding exogenous hormones, use of hormone replacement therapy increased the incidence levels, but did not change the protecting effect conferred by each full-term pregnancy. Oral contraceptives had no long-term effects. Advanced age at first full-term pregnancy had the same effect as one full-term pregnancy, and lactation showed no interaction with parity. Increased body mass index showed no effect, but the NOWAC study contains few very obese persons. Women with six children had an adjusted, multivariate relative risk of 0.49 (Cox regression). There were too few women in the cohort for further analyses beyond 6 children.

Adding novel results from integrated systems epidemiology analyses

We proposed the term of systems epidemiology in 2008 as a new scientific discipline [19] aimed at understanding the carcinogenic process through the incorporation of functional genomics into the prospective design. To carry through this idea, within the NOWAC study of 172 000 Norwegian women, we created a postgenome biobank, which contains blood samples buffered for conservation of mRNA from

50 000 NOWAC participants selected randomly [20]. The addition of functional genomic analyses in both the blood and tissue of breast cancer patients and healthy controls have shown the potential of functional analyses [21,22]. Each woman has answered from two to four questionnaires about lifestyle, with a focus on exposures to endogenous and exogenous hormones, fertility, and diet.

Our term *integrated systems epidemiology approach* combines the standard epidemiological analysis with functional analyses. A major problem in genomic research is the high dimensional data, which can increase the potential for false-positive results. This can be handled by false detection rate (FDR) techniques or through test–retest approaches, but our approach for dimension reduction is to explore the model of the relationship between the exposures, in this case parity, and the outcome, in this case breast cancer, in a large prospective study and then perform strict hypothesis testing in the functional data. In the whole NOWAC study, the mathematical model for the relationship between parity and breast cancer were decided through statistical analyses that included all women in the cohort [23]. The described 8% linear reduction per child based on an additive model was tested by investigating differences in blood gene expression between breast cancer patients and controls in the postgenome biobank. The novel findings of gene expression in relation to parity in these groups were unexpected.

Among controls, we found linear changes in the expression of hundreds of genes for each child, while no changes were observed in women who were later diagnosed with breast cancer.

The number of up-/downregulated genes for controls (FDR 5%) was 501/255 compared to the number of up/downregulated genes for cases (FDR 5%) of 0/0.

Similar analyses of endometrial cancer showed the same relationships with changes in gene expression following parity [24]. However, for ovarian cancer no such relationship was found (data not shown).

Of the 10 most significant genes among controls, four were tumor promotors, one was a tumor suppressor, and five were not known to be related to carcinogenesis. It is worth repeating that the information on function was mainly derived from studies of cancer tissues or reductionist experiments with small animals like mice and other rodents. Locally, a tumor promotor appears to be important in tumor growth. However, the interpretation of immune cells in the blood could be different: it could imply that the organism has increased its gene expression as an alert, or there may be simply more immune cells as a consequence of more memory cell clones. This view was supported by analyses of the correlations between gene expression in the blood and cancer tissue of women with breast cancer in the NOWAC study. After gene clustering was performed, only tumors with high immunological profiles showed a relationship with blood gene expression [21]. There is *a priori* no reason to assume that immune cells in the blood should mirror tumor tissue gene expression or that the functionality described as relevant for immune cells in tissue studies would also be relevant in blood due to highly different functions and biological material.

Proposing breast cancer as a pseudo semi-allograft

Breast tumor cells correspond to altered woman's cells. The tumor is obviously different from a fetus semi-allograft, and therefore is referred to as a "pseudo" semi-allograft here. The cumulative incidence rates or absolute risk among NOWAC participants with six children was half of that of nulliparous women. From the immune system standpoint, one could speculate that the immune effect was able to remove almost half of potential tumors when moving from nulliparity to a parity of six.

Discussion

By inverting the traditional use of each full-term pregnancy as a protective factor to the use of each deficient child as a risk factor, we propose to change the paradigm of parity in epidemiology. In this new paradigm, we were able to describe the importance of high parity in the protection against postmenopausal breast cancer through analyses of population-based studies. By shifting the focus from number of children to full-term pregnancies, and by viewing the fetus as a semi-allograft, we were able to document the linear relationship between full-term pregnancies and breast cancer incidence. We were also able to observe the relationship between full-term pregnancies and blood gene expression in women without breast cancer, while no such relationship was found in breast cancer patients. The concept of the breast cancer as a pseudo semi-allograft was a natural expansion of the theory. In breast cancer, the pseudo semi-allograft may be "protected" by high levels of hormones similar to those that protect the fetus during pregnancy, demonstrating the dual effect of hormones. Clearly, breast cancer development is opposed by the immune system in a dynamic balance over time. Since the effect of childbirth on cancer risk could be confirmed only for endometrial cancer and not for ovarian cancer it would be hard to justify a more general theory for the carcinogenesis.

The interpretations of the breast cancer hypothesis have several limitations. Due to lack of samples the analysis was run with all case-control pairs under one hypothesis with no retest analysis as part of the design. Dividing data into a test–retest design would reduce the power of the hypothesis testing. In addition, the preservation method bof the whole blood samples reduced the potential for a biological interpretation related to specific immune cell types.

The introduction of gene expression into the analysis of breast cancer changed the context from just counting the number of children to a more functional analysis, in which the relevant information on parity includes the pregnancy-dependent changes and later changes in immunology or biology. This is an important conceptual change.

Several methods could explain the observational findings. The concept of immune surveillance is more than 60 years old. Today, it is well accepted that parous women have functional, long-lived memory cell clones and effector T cells that react against multiple tumor-associated antigens (TAA), which are not found in nulliparous women. TAA-specific Treg cells suppress strong effector T cell responses after birth [25]. Specific T cell responses during pregnancy could be a product of enhanced expression of shared pregnancy- and cancer-associated antigens discovered in the breast tissue, placenta, and fetus. Lymphocytes accumulate in pregnant women and develop in breast tissue simultaneously with increased expression of cancer-associated antigens, supporting the hypothesis that pregnancy induces life-long immunization against a variety of cancer-associated antigens.

A recent study of human immune cells after vaccination showed that the long-term memory effects originate from CD8 T cells that divided extensively after infection and some are maintained as quiescent cells that last for decades with a very long doubling time [26].

Pregnancy is also associated with increased immune tolerance mechanisms, which prevent the mother's immune system from reacting against the fetus [27]. Cancer-specific memory T cells clones created by fetal antigens in pregnant women might therefore be inhibited by T regulatory cells in later breast cancer development. This could be one mechanism behind the lack of relationship between blood gene expression and parity among women who develop breast cancer.

A population-based study showed that 25–50% of parous women have detectable alloantibodies in their blood [28]. Although the amount of antibodies against fetus HLA is an imprecise estimation of total allo-immunization, it is obvious that there is a range in the quality and quantity of pregnancy-induced immunization among women. This might partly explain why some women do not obtain any pregnancy-related advantages against breast cancer. However, there is a lack of knowledge related to B cells, T cells, and especially the innate immune system during and after pregnancy.

Another mechanism could be the fetal microchimerism, which is defined as the long-term persistence of a few fetal-derived allogeneic cells in the mother [29]. Each pregnancy could leave a clone of different

fetal microchimerism cells.

A possible mechanism behind the protective effect of young age at first pregnancy could be a longer duration of the immune protection compared to women who are older at first pregnancy.

The concept of immune evasion could be part of the explanation of the findings [30]. Immune evasion was considered as a hallmark of cancer [31] covering many potential mechanisms.

Historically, before the Second World War, breast cancer was reported to have been “cured” by violent spontaneous or intentionally introduced infections. This link with the immune system was forgotten for more than a half decade, but was recently reviewed [32].

This proposed theory that the biological memory of each pregnancy lasts for decades is based on the existence of different memory T cell clones created by the mother at the end of each full-term pregnancy.

Future studies should concentrate on an improved design for gene expression related to the specific immune cells. Another important aspect would be the exploration of changes in the breast cells depending on the number of pregnancies as indicators of a potential stem cell mechanism. Through comparison between tumor tissue and normal tissue the effects of intragenic mutations that promote or “drive” tumorigenesis [33] could be studied.

Conflict of interest

There is no conflict of interest for any of the authors.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.mehy.2018.08.015.

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