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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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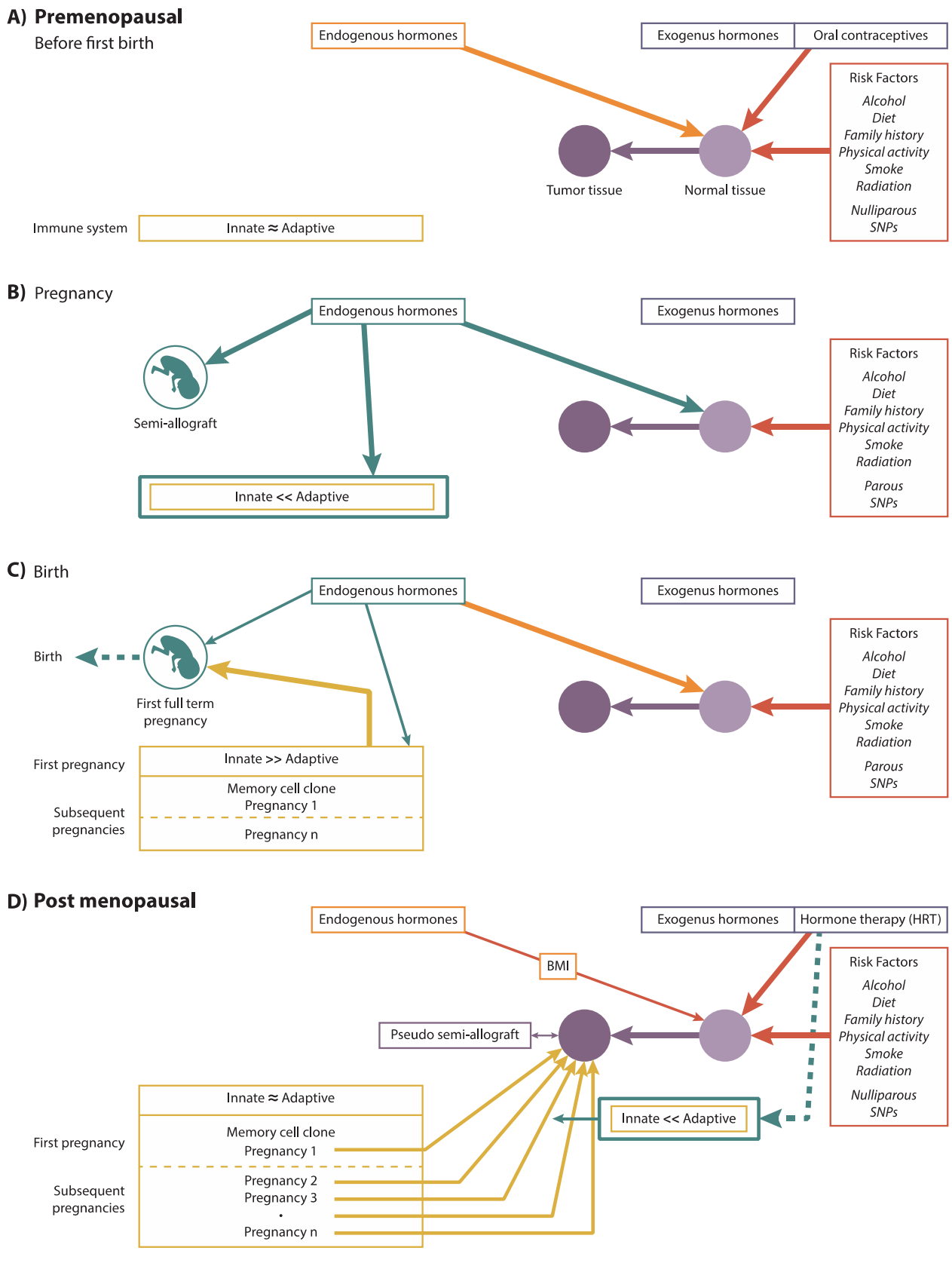

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Group on Breast Cancer [3], the average number of children per woman is 2–3. Moreover, nulliparous women have been traditionally selected as the reference group, and have been compared with the so-called high-parity group (4+ or 5+ children). These 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