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Reproduction and Breast Cancer Risk

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Summary

Reproduction is doubtlessly one of the main biological meanings of life. It is therefore not surprising that various aspects of reproduction impact on breast cancer risk. Various developmental levels may become targets of breast tumorigenesis. This review follows the chronologic sequence of events in the life of a female at risk, starting with the intrauterine development. Furthermore, the influence of both contraceptive measures and fertility treatment on breast cancer development is dealt with, as well as various pregnancy-associated factors, events, and perinatal outcomes. Finally, the contribution of breast feeding to a reduced breast cancer risk is discussed.

Introduction

Breast cancer is the most common malignant disease in women. A significant cause for concern are incidence rates which have been rising since at least 1935–1939. Overall, age-adjusted incidence rates rose by 25% from the early 1980s to 1993 and an additional 15% through 2001, then dropped by 18% until 2004 and finally edged upwards in 2006 [1]. It has been proposed that reproductive factors are amongst the most relevant contributors to personal risk, and that the approximated 1% annual incidence rise [2] is mainly due to reproductive factors.

Since there are so many different aspects of reproduction to be considered, this review cannot deal with every aspect in detail but will focus on the most interesting perspectives. In order to propose an elucidating model of reproductive factors in the development of breast cancer, we decided to follow the chronologic sequence of events in the life of a female at risk with the following, admittedly somewhat arbitrary, stages:

i) The person at risk as a product of procreation (prenatal life)
ii) The pre-reproductive phase in life (preventing pregnancy, infertility treatment)
iii) Pregnancy and breast feeding as influencing factors

The Person at Risk as a Product of Procreation (Prenatal Life)

'I propose...' (the hypothesis)... 'that increased concentrations of estrogens in pregnancy (possibly with increased concentrations of other hormones in pregnancy) increase the probability of daughters getting breast cancer by creating a 'fertile soil' for subsequent cancer initiation' (Trichopoulos, 1990) [3]. Trichopoulos stated that factors which increase the risk of cancer during adult life might also increase the risk of cancer when they act in utero (e.g. ionizing radiation and diethylstilbestrol in human beings and other chemicals in animals). To him, the existing empirical data seemed compatible with the hypothesis that increased concentrations of estrogens in pregnancy (and might we add today: 'and other growth-promoting factors') increase the probability of future occurrence of breast cancer in daughters.

This early proposal by Trichopoulos is as thought-provoking and elucidating as ever: The concept explains that the development of breast cancer can start during prenatal life with a functional imprint on the developing breast tissue leading to increased susceptibility of the tissue to further hits, ultimately leading to breast cancer. It should however be kept in mind

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Table 1. Mean age at first birth in West Germany

Year	Maternal age at first birth, years
1965	24.9
1970	24.3
1985	26.2
1995	28.2
2010	30.2

Source: *www.bpb.de/nachschlagen/zahlen-und-fakten/soziale-situation-in-deutschland/61556/alter-der-muetter*

that breast tissue does not achieve final differentiation before the first full-term pregnancy followed by a significant period of lactation. After this, the terminal ductulo-lobular unit reaches a finally differentiated state in which breast tissue has been experimentally shown to be much less vulnerable to induction of preneoplastic lesions [4, 5].

Accepting this concept, at least 2 new insights can be reached:

Firstly, a solid part of the historically proven rise in breast cancer incidence can be explained by the continuing postponement of first pregnancy to older age (table 1), which extends the vulnerable period of postnatal life, resulting in increased chances for initiating events to occur in the breast tissue [6, 7]. What the newly opened door of 'social freezing' might lead to can now be anticipated. Beyond that, many women remain without any full-term pregnancy, exposing themselves to a lifelong threat of cancer induction.

Secondly, a possible avenue of prevention emerges: if a hormonally mimicked sham pregnancy can be induced, and a limited time of pseudo-lactation could be endured, childless women may be able to achieve the same reduced risk as young mothers [8]: the authors describe in their recent review the main changes in morphology and gene expression levels of the mammary gland of Sprague-Dawley rats exposed to known cancer-preventative conditions (pregnancy, human chorionic gonadotropin (hCG) and progesterone + estrogen). In addition, they postulate a protective mechanism induced by hCG that could reduce the cells' potential to be transformed by carcinogens.

Following the logical path of Trichopoulos' hypothesis, and searching for evidence that prenatal growth promotion might be associated with increased postnatal breast cancer risk, immediately several distinctive groups of growth modulators come to mind. To name just a few: hormonal (steroidal) influences (e.g. estrogens, progestins), growth factors (non-steroidal, e.g. insulin), and physical influences (e.g. heat (fever), ionizing radiation).

Placental Steroids

Only recently, it became possible to more precisely define steroid levels in umbilical cord blood [9]. It was shown that contrary to common belief levels of all estrogens (E1–E4) examined were reduced in twin as compared to singleton pregnancies. Further, E1 and E2 concentrations were not associated with preeclampsia in the current pregnancy, but E3 and E4 concentrations were lower in pregnancies complicated by preeclampsia.

Table 2. Daughters' risk with various prenatal conditions

Item	Effect	Ref.
Twin pregnancy	divergent results, slightly elevated risk	[10]
Twin pregnancy	decreased risk	[9]
Preeclamptic pregnancy	decreased risk	[19]
Preterm delivery	no elevated risk	[49]
Increasing birth weight	consistently elevated risk	[10] [16]
Increasing birth length	elevated risk	[50]
Ever maternal diabetes mellitus	decreased risk, especially pre-menopausal	[51]
Maternal age	divergent results, slightly elevated risk	[10]
Paternal age	case control study: trend for increased risk	[52]
Maternal pre-pregnancy body mass index and weight gain in pregnancy	no association	[53]
Season of birth summer/winter in Sweden	1880–1920: 5% higher risk if born in June	[54]

Xue et al. [10] investigating the preconditioning relevance of prenatal estrogen exposure as hypothesized by Trichopoulos performed a systematic review in 2007 and noted a decreased risk of breast cancer for maternal preeclampsia and eclampsia (0.48 (0.30–0.78)) and twin pregnancy (0.93 (0.87–1.00)). Park et al. [11] however found in their review somewhat divergent and in summary slightly contradictory trends for twin pregnancies. Table 2 summarizes prenatal conditions and their effects on later breast cancer risk.

Exposure to Estrogens or Agents with Estrogen-Like Activity (Xenoestrogens)

In the 1950ies and 1960ies, when pregnant women at risk of miscarriage were treated with the synthetic estrogen diethylstilbestrol (DES), their daughters were imprinted to develop rare clear cell adenocarcinoma of the vagina. This disaster was the first proven example of transplacental carcinogenesis in humans. Since then, it is a matter of debate whether breast cancer risk in DES daughters is consistently elevated above background level. In a very recent review, Hilakivi-Clarke [12] addressed the mechanisms that may explain why DES daughters have a 2 times higher breast cancer risk than women who were not exposed to it. The mechanisms most likely involve epigenetic alterations, such as increased DNA methylation and modifications in histones and microRNA expression. It appears that these alterations target genes that regulate stem cells and prevent differentiation of their daughter cells. The

author reports that recent findings in a preclinical model suggest that not only women exposed to DES in utero are at increased risk of developing breast cancer, but this risk may extend to their daughters and granddaughters as well.

As with thalidomide, the catastrophe of DES could have been foreseen if animal data would have been taken into account or had been collected in the first place. Today, it has been recognized that in rats prenatal exposure to DES results in increased mammary cancer incidence during adulthood when these animals are challenged with the chemical carcinogen dimethylbenzanthracene (DMBA) in puberty [13]. Soto et al. [14] have repeatedly warned that animal data suggest that bisphenol A, a widespread environmental man-made chemical contaminant with xenoestrogeneic activity, predisposes rodent mammary glands to the development of breast cancer when exposure takes place in the womb or through lactation. Previously, in analytical work, we repeatedly detected xenoestrogeneic activity in surface water in Germany [15, 16].

Growth Factors (Non-Steroidal, e.g. Insulin)

Troisi et al. [17] carried out a population-based study to correlate perinatal characteristics of girls with their later life risk of developing breast cancer. Breast cancer risk rose by 7% with every 500 g (roughly 1 standard deviation (SD)) increase in birth weight and 7% for every 1 SD increase in birth length. The association with birth length was attenuated after adjustment for birth weight, while the increase in risk with birth weight remained after adjustment for birth length. Risk was not associated with maternal education, gestational duration, delivery type or birth order, or with several pregnancy complications including preeclampsia.

One of the driving mediators of fetal growth is without any doubt insulin. Disturbed glucose tolerance is frequently encountered in pregnant women and is about to become yet more frequent as maternal age at first pregnancy and body mass index are continually rising. Gestational diabetes mellitus (GDM), just like various forms of disturbed glucose tolerance including type 2 diabetes, is accompanied by hyperinsulinemia. Type 2 diabetes is a risk factor for breast cancer in postnatal life [18]. Therefore, it is justified to suspect that hyperinsulinemia could also be a risk factor for daughters from GDM pregnancies. However, no literature clarifying this notion could be found.

It is worth mentioning that the determination of placental growth factor (PlGF) (and soluble vascular endothelial growth factor receptor sFlt-1) has recently become a clinical method of estimating a woman's risk for preeclampsia. While sFlt-1 inhibits vascular growth, PlGF promotes it. In preeclampsia, sFlt-1 is increased in relation to PlGF. What are the implications for breast cancer risk? PlGF is produced by malignant tissue enhancing breast cancer cell mobility [19]. Although the available data are somewhat conflicting [17] (Table 2), as mentioned above in the context of reduced placental steroids, there is evidence for a reduced risk for daughters born from preeclamptic pregnancies. Ekbom et al. [20] found a markedly and significantly reduced risk for breast cancer in women whose mothers had 'pregnancy toxemia', i.e. preeclampsia. Additionally, a meta-analysis has shown that among all women, preeclampsia-born offspring had a 52% lower risk of breast cancer [10].

Physical Influences

Ionizing radiation administered prenatally can readily induce initiation just as it can postnatally, particularly in childhood. The atomic bomb disasters in Japan prove that young girls are at particular risk: the 'in-utero cohort' is composed of about 3,300 individuals who were in their mother's womb at the time of the bombings. The cohort was followed up for mortality and cancer incidence, and a subset is being clinically monitored with biennial clinical examinations [21]. A recent report compared the risk estimates for those exposed in utero and during childhood with respect to the incidence of solid cancer at ages 12–55 years. Although there was a statistically significant dose dependence for the in-utero group, the cancer risk was nominally smaller overall than in the childhood-exposure group. The authors concluded that in-utero exposure does not appear to confer greater adult cancer risk than childhood exposure, but further follow-up to older ages was recommended. Goto et al. [22] investigated cancer mortality among atomic bomb survivors exposed as children. Standardized mortality ratios were significantly higher for exposed girls for all cancers; however, a dose distribution for various types was found. For breast cancer, exposure to higher doses conferred a significantly elevated risk. Evidently, ionizing radiation can prime for cancer in the unborn.

The Pre-Reproductive Phase in Life (Preventing Pregnancy)

As indicated above, age at first full-term pregnancy is a powerful denominator of future breast cancer risk [7] as it determines the length of time the undifferentiated breast tissue remains particularly vulnerable. However, instead of securing breast cancer protection for future life, most young women are trying to prevent an early pregnancy. While non-hormonal methods would not as such be under suspicion of modulating breast cancer risk (aside from the precarious delay of breast tissue differentiation), hormonal interventions could cause such a risk modulation.

A differential approach appears appropriate here: while modern oral contraceptives (OC) expose breast tissue to lower estrogen peaks than would be encountered in normally cycling women, this could in principle be either beneficial or detrimental: i) detrimental in the way that a pseudopregnant state with high estrogen and progesterone levels is avoided, depriving hormonal contraception of the inherent option of inducing final differentiation and thereby lowering future vul-

nerability to breast cancer; ii) beneficial in the way that breast epithelial proliferation is without question driven by estrogens, and lower estrogen peaks of modern OC could in principle reduce risk.

Epidemiological studies show that 'taking the pill' does modify a woman's risk of developing breast cancer. Compared with never use, ever use of OC is significantly associated with a decrease in colorectal and endometrial cancers and an increase in breast cancer. Although the elevation in breast cancer risk was small, the relatively high incidence of breast cancer and the very high number of exposed women mean that OC may contribute to a substantial number of cases [23]. Beaber et al. [24] presented data from a very recent nested case-control study using ascertained OC use information from electronic pharmacy records. Recent OC use was associated with an increased breast cancer risk (odds ratio (OR) 1.5) relative to never or former OC use. The association was stronger for estrogen receptor-positive disease, although not statistically significant. Recent OC use involving high-dose estrogen (OR 2.7), ethynodiol diacetate (OR 2.6), or triphasic dosing with an average of 0.75 mg of norethindrone (OR 3.1) was associated with particularly elevated risks, whereas other OC types including low-dose estrogen were not (OR 1.0; 95% confidence interval (CI) 0.6–1.7).

These data show that it appears prudent to look with caution on the various synthetic progestins as part of modern OC. Little is known about the differential ability of these agents to drive breast cancer risk. Preclinical experimental [25], and epidemiological and experimental data of the Womens' Health Initiative (WHI) study suggest that in postmenopausal hormone therapy it is the progestins that pose the pharmacological risk [26]. In humans, these differential progestin effect data are only sparsely available. An in depth review of animal and preclinical data is beyond the scope of this paper.

Finally, the timing of the onset of OC use is of clinical importance: a database review of 1,010 breast cancer patients produced evidence of a linear trend between age at OC start and age at breast cancer diagnosis. Women who started using the OC aged 18 years or younger were on average 4 years younger at the time of breast cancer diagnosis than women who started using the OC over the age of 30 years [27].

If an unwanted pregnancy occurs, it may result in spontaneous miscarriage or an induced abortion might be resorted to. Beral et al. [28] carried out a collaborative reanalysis of data from 53 epidemiological studies including 83,000 women with breast cancer to study the effects of previous miscarriages/abortions. They concluded that pregnancies that end by spontaneous or induced abortion do not increase a woman's risk of developing breast cancer. In Chinese women, essentially the same was found, specifically for induced abortion [29].

In some women discontinuation of contraceptive measures does not result in the then desired conception, and for various reasons assisted reproductive interventions become necessary. The reasons why reproductive medical measures have to be applied might in themselves modulate future breast cancer risk in the affected individuals:

Hormonally 'healthy' women that have to resort to assisted reproductive therapy for andrologic or purely mechanical (e.g. after tubal ligation) reasons might have a different susceptibility to induction of breast cancer than women with endocrine problems requiring medical intervention.

Women with longstanding hypoestrogenic dysfunctions (e.g. hypothalamic ovarian failure) should experience a reduced risk similar to women who were ovarectomized at a young age.

Women with impaired intraovarian regulation (e.g. polycystic ovarian syndrome PCOS) with excess of free circulating androgens and constantly slightly elevated levels of estradiol and anovulation have to be viewed separately. Barry et al. [30] performed a systematic review of studies of women with and without PCOS. Their data suggested that women of all ages with PCOS are at an increased risk of endometrial cancer, but the risk of ovarian and breast cancer was not significantly increased overall. However, the available evidence was classified as 'far from robust'.

Women with repeated ovarian stimulation with antiestrogens (clomiphene citrate) or urinary or recombinant gonadotropins are again a different risk group. Zreik et al. [31] reviewed the literature and found that the risk of breast cancer was not significantly associated with fertility drug treatment. Brinton et al. [32] conducted an extended follow-up among a cohort of 12,193 US women evaluated for infertility between 1965 and 1988. During 30 median years of follow-up, 749 breast cancers were observed. Ever use of clomiphene citrate among 38.1% of patients was not associated with risk (hazard ratio (HR) = 1.05; 95% CI 0.90–1.22) compared to never use. However, somewhat higher risks were seen for patients who received multiple cycles, with the risk for confirmed invasive cancers being significantly elevated (HR = 1.69; 95% CI 1.17–2.46). This risk remained relatively unchanged after adjustment for causes of infertility and multiple breast cancer predictors. Gonadotropins, used by 9.6% of patients mainly in conjunction with clomiphene, showed inconsistent associations with risk, although a significant relationship of use with invasive cancers was seen among women who remained nulligravid (HR 1.98). The authors felt that this increased breast cancer risk among nulligravid women associated with gonadotropins most likely reflected an effect of underlying causes of infertility, and that additional evaluation of long-term fertility drug effects on breast cancer was warranted.

Along the same lines are the findings of Sergentanis et al. [33] who systematically reviewed the literature and concluded that controlled ovarian hyperstimulation for in vitro fertilization does not seem to confer an increased breast cancer risk. However, before definite conclusions concerning the safety of this treatment can be drawn, the authors would like to see longer follow-up periods, appropriate controls and comparisons, and adjustment for various confounders.

Pregnancy and Breast Feeding as Influencing Factors

Pregnancy

Conception opens up a new chapter in our considerations on reproductive factors in the development of breast cancer. A number of influences have already been mentioned, albeit from a different perspective: that of the developing fetus. Now the focus is on the pregnant mother herself. The situation of an unsuccessful pregnancy resulting in miscarriage/abortion has already been dealt with.

It has been known for a long time that the age at first pregnancy has a very profound influence on future breast cancer risk. MacMahon et al. [6] deduced that the reduced risk of breast cancer in women having their first child at an early age explains the previously observed inverse relationship between total parity and breast cancer risk, since women having their first birth early tend to become ultimately of high parity. Recently, it was reconfirmed that age at first birth also has an impact on molecular subtypes if breast cancer arises: Horn et al. [34] found that older age at first birth and low parity were associated with increased risk for luminal breast cancer subtypes.

Further conceivable influencing factors could be multifetal pregnancies that expose the mother to high amounts of placental growth factors and hormones different from those in singleton pregnancies, GDM accompanied by hyperinsulinemia, and preeclampsia with reduced placental mass and function. A possible consequence might be fetal retardation and/or preterm delivery. Finally, timing of delivery, postterm delivery, and mode of delivery are also conceivable factors. An overview of the current knowledge is given in table 3. To go into further details about all these aspects would go beyond the scope of this review.

To clarify the conflicting data from individual studies on maternal breast cancer risk and preeclamsia or pregnancy-induced hypertension, Kim et al. [35] performed a meta-analysis and found non-significantly reduced relative risks (RR) for both preeclamsia (RR 0.86) and pregnancy-induced hypertension (RR 0.83).

Equally, the available data on the impact of having twins was conflicting so that a meta-analysis was necessary. Kim et al. [36] detected an RR of 0.94 ($p = 0.127$) suggesting that twin pregnancy does not significantly decrease the maternal risk of breast cancer.

It would appear plausible that GDM could pose a cancer risk in affected mothers, and indeed there is a strong association with pancreatic cancer but not with breast cancer. Tong et al. [37] reviewed a total of 9 articles documenting 5 cohort and 4 case-control studies comprising 10,630 cancer cases and 14,608 women with a history of GDM. Taken together, the pooled OR between GDM and breast cancer risk was 1.01 (0.87–1.17). These results should however be interpreted with caution because of certain methodological flaws.

Table 3. Maternal breast cancer risk in association with own obstetric history

Item	Effect	Ref.
Increasing age at first pregnancy	linearly increasing risk	[6]
Parity	inverse relationship	[55]
Abortions	no elevated risk	[27]
Twin pregnancy	no significantly decreased risk	[35]
At first multifetal pregnancy	slightly elevated risk	[37]
Gestational diabetes mellitus	no elevated risk	[36]
Nausea/vomiting	decreased risk	[56]
Preeclampsia	non-significantly reduced risk	[34]
Pregnancy-induced hypertension	non-significantly reduced risk	[34]
Delivering small for date baby	non-significantly reduced risk	[48]
Extreme premature delivery (< 32 weeks)	significantly elevated risk	[37]
Smoking during first pregnancy	significantly elevated risk	[47]

Innes et al. [38] hypothesized that first pregnancy would be likely to have a significant impact on a woman's BC risk, and examined first pregnancy characteristics in a large New York cohort. Extreme prematurity (< 32 weeks gestational age) was associated with elevated maternal breast cancer risk (adjusted OR 2.1; 95% CI 1.2–3.9), as were abruptio placentae (OR = 1.8) and multifetal gestation (OR 1.8). Preeclampsia was associated with a marked reduction in breast cancer risk among women who bore their first child after age 30 (OR 0.3) and in the first 3 years after delivery (OR 0.2).

No data could be retrieved on the association of breast cancer risk and postmaturity or mode of delivery including caesarian section. It should be kept in mind that all these imponderabilities in pregnancy might be acting as modulators of the preexisting individual breast cancer risk or could be in themselves mere indicators of underlying processes that are accompanied by an increased or lowered likelihood to develop breast cancer.

Breast Feeding

After pregnancy, an extended period of breast feeding contributes to the functional ripening of the glandular tissue. The duration of breast feeding within certain limits is believed to have an influence on breast cancer risk. In order to unravel the impact of breast feeding on breast cancer risk (reduction) within the complex topic of childbearing, the Collaborative Group on Hormonal Factors in Breast Cancer [39] retrieved individual data from 47 epidemiological studies in 30 countries that included information on breast feeding patterns and other aspects of childbearing for 50,302 women with invasive breast cancer and 96,973 controls. The RR for breast cancer decreased by 4.3% ($p < 0.0001$) for every 12 months of breast feeding in addition to a decrease of 7.0% ($p < 0.0001$) for each

birth. The authors estimated that the cumulative incidence of breast cancer in developed countries would be reduced by more than half, from 6.3 to 2.7 per 100 women by age 70, if women had the average number of births and lifetime duration of breast feeding that had been prevalent in developing countries until recently. Breast feeding could account for almost two-thirds of this estimated reduction in breast cancer incidence. A recent workshop on postpartum remodeling, lactation, and breast cancer risk held by the National Cancer Institute stated that breast feeding may provide greater protection against triple-negative, basal-like, and BRCA1 mutation-associated breast cancer, suggesting particular protection against aggressive types of breast cancer [40].

Within this context, it should be noted that breast feeding has positive effects on maternal breast cancer risk beyond mere terminal differentiation of the glandular tissue: Exclusive breast feeding suppresses hypothalamic activity leading to hypogonadotropic hypoestrogenism through anovulation. This dormant endocrine state in itself is associated with decreased breast cancer risk. While hypoestrogenicity may be seen as a direct influence of breast feeding on breast cancer risk, the following indirect influences also play a role.

Diabetes Mellitus

Jäger et al. [41] extensively investigated the interrelationship between breast feeding and a mother's later risk of developing type 2 diabetes. The HR for each additional 6 months of breast feeding was 0.73. A meta-analysis of 3 previous prospective studies and their own study revealed an inverse association between breast feeding duration and risk of diabetes. Type 2 diabetes mellitus, again, is a risk factor for breast cancer. Data reported by Onitilo et al. [42] support the notion that hyperinsulinemia, rather than hyperglycemia, as a major diabetes-related factor is associated with increased risk of breast cancer.

RANKL Pathway Activation

On the other hand, extensive breast feeding can lead to skeletal demineralization if calcium is taken up insufficiently to replenish internal stores. Such a deficit is accompanied by activation of the RANKL pathway. Experimental results by Xiong et al. [43] demonstrate that RANKL produced by osteocytes contributes to the increased bone resorption and bone loss caused by secondary hyperparathyroidism. RANKL pathway activation has been found to play a role in the risk modulation for postmenopausal breast cancer [44]. In order to minimize osteoporosis and its many unwanted sequelae, it is therefore advisable to secure a sufficient supply of calcium and vitamin D3 (sun exposure).

Depletion of Xenoestrogen Stores

The role of persistent organo-halogen compounds with xenoestrogeneic activity stored in adipose tissue for breast cancer development has been a matter of debate [45]. Once taken up, mainly via the oral route, it is virtually impossible to get rid of these persistent hormonally active agents (HAA), except via breast feeding: since adipose tissue is broken down in order to provide the basis for fatty acids and fat droplets in breast milk, mothers transfer significant amounts of HAA unto their infants [46]. Whether this decontamination process contributes to a reduced breast cancer risk is unknown and a matter of speculation. On the other hand, it could be hypothesized that this transfer of persistent HAA unto the child could possibly pose a risk for, in this context, breast cancer in the nursed child. However, nursing as a main source of infantile energy uptake has undisputed advantages, e.g. a lowered risk of later diabetes mellitus which in itself is a risk factor for breast cancer, or the prevention of obesity in later life as compared with bottle-fed children. Here, too, obesity as a risk factor for breast cancer (mortality) is avoided or ameliorated. It is, however, in this very complicated interplay of divergent influences extremely difficult to detect a truly existing effect: Wise et al. [47, 48] were unable to show an influence of being breast-fed as a baby on later breast cancer risk.

Summary

Reproduction is an important functional complex in our lives, hence it comes as no surprise that reproductive factors play a role in many other concepts such as the development of breast cancer as the most common malignant disease in women. Some factors could at least theoretically be incorporated into a risk-minimizing lifestyle while others are absolutely beyond the control of the individual at risk. What can be recommended is care when selecting OC with respect to the progestins involved and possibly a critical appraisal of the indication in young women, careful dietary advice in pregnancy to avoid GDM, and exclusive breast feeding for the recommended amount of time. In this way, mother and child will both benefit.

Disclosure Statement

With respect to this particular work, the authors have no conflicts of interest to declare.

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