

PRIMAL HEALTH RESEARCH

A NEW ERA IN HEALTH RESEARCH

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BREAST CANCER

FROM A PRIMAL HEALTH RESEARCH PERSPECTIVE

Twenty years ago, when anticipating 'Primal Health Research' as a new generation of research¹, I could not find any published pioneering study exploring risk factors for breast cancer during the 'primal period'. In 2006, an overview of the primal health research database reveals an accumulation of recent data that indicates a new vision of the genesis of this disease.

An Inevitable Perspective

In the current scientific context, we can state that some women inherit an increased *risk* of breast cancer, but not the disease itself. It is well-known that women who have inherited certain mutations in particular genes (such as BGRCA1 and BRCA2) have a high risk of developing breast cancer over their lifetimes; but not all women who inherit mutations in these genes will develop this cancer. Thus, it is necessary to improve our understanding of the interaction between genetic and early environmental factors. In other words we need the primal health research perspective all the more, since established risk factors such as nulliparity, age at menarche, age at first birth, breastfeeding, exposure to the synthetic oestrogens diethylstilbestrol (DES) in adulthood, and dietary habits are insufficient to explain adequately the occurrence pattern of this cancer.

Today, Primal Health Research offers an inevitable perspective if we are to compare the importance of multiple risk factors.

Learning from Sweden

The first large authoritative study to take this perspective was Swedish.² This study, published in 1997, illustrates the sort of research that is feasible only in Sweden. The authors had at their disposal the birth records of all deliveries at five different hospitals from 1874 through 1961 (there is no other country where such data is available). They also had access to the National Cancer Registry and the Uppsala Regional Cancer Registry from 1958 through 1994 (this, too, cannot be done outside Sweden). Thus, they could collect data from birth records regarding 1068 women who developed breast cancer and 2727 controls individually matched for date of birth.

The authors found a markedly and significantly reduced risk in women whose mothers had 'toxemia' (pre-eclampsia or eclampsia): the odds ratio was 0.41. They found

a significant excess risk (odds ratio 2.16) in women who had neonatal jaundice or who were born before 33 weeks (odds ratio 3.96). There was also an increased risk in non-identical twins, but the excess was at the limit of statistical significance. There was no evidence in these data of a statistically significant or even substantial association of breast cancer risk with birth size indicators (weight and length at birth and placental weight). Because pregnancy toxæmia is associated with low levels of oestrogens, while neonatal jaundice, severe prematurity, and dizygotic twins are associated with high levels, the authors could suggest that oestrogens play a critical role during the intrauterine period.

As early as 1992, the same team of Uppsala University Hospital had published a smaller study using the same method, of 458 breast cancer cases and 1197 matched controls.³ Pre-eclampsia/eclampsia when the mother gave birth to her daughter was already associated with a highly-significant reduction in the risk of breast cancer. The trends for increased breast cancer incidence with increasing birth weight, birth length, and placental weight were not statistically significant.

More recently, the same Swedish team conducted two studies to clarify the risk of breast cancer in prematurely-born women. According to a first study the risk in women born before 31 weeks' gestation was significantly increased⁴, but a further enlarged study could not confirm the statistical significance of the previous results.⁵

Not only did the Uppsala epidemiology team explore pre- and perinatal risk factors, they also conducted studies and suggested interpretations that could reinforce the plausibility of the correlations they had brought to light. Data regarding all 115,670 women born between 1858 and 1958 that was reported to the Swedish Cancer Registry in 1958-89 as having breast cancer, identified a significant seasonal pattern for women born between 1880 and 1920: women born in June had a 5% higher risk of breast cancer than those born in December.⁶ In contrast, there was no evidence of birth seasonality among 440,948 women with cancer at other sites.

One can conclude that pre- and peri-natal factors influence breast carcinogenesis, since exposures relevant to breast cancer risk later in life are unlikely to be related to month of birth. On the other hand birth outcomes and particularly pre-eclampsia, are influenced by the season of birth. In Scandinavian countries giving birth in winter is a risk factor for pre-eclampsia.

One may also wonder if pre-eclampsia exposure could be an indirect causal factor, by affecting, for example, pubertal development and adult morphology. Uppsala researchers offered answers to this question by interviewing 230 women with verified pre-eclampsia exposure during fetal life and 359 non-exposed women.⁷ While babies of women who had pre-eclampsia were lighter and shorter for gestational age, in young adulthood there were no differences in height, body mass index, waist-to-hip ratio, or age at menarche. The variance in final height was to a great extent explained by parental height. These data indicate that neither adult anthropometry nor age at menarche is significant in the causal pathway between intra-uterine pre-eclampsia exposure and the reduced risk of breast cancer.

Such conclusions are reinforced by the results of another study by the same team of researchers. They retrieved mammograms for 370 women aged 40 to 74 years old with no history of breast cancer, for whom birth weight, birth length, placental weight and other birth characteristics were indicated in their birth records at the Uppsala University hospital.⁸ Blind evaluation of the mammographic parenchymal patterns allowed the subjects to be classified as high- risk versus low-risk. The high-risk pattern was significantly associated with a high weight of the placenta, i.e. the main oestrogen-producing organ during pregnancy. These results are compatible with hypotheses suggesting that pregnancy oestrogens influence the risks of breast cancer in the offspring.

A more recent American study found that birth weight was positively associated with mammographic breast density among postmenopausal women and more weakly among premenopausal women.⁹ In this study the prenatal and perinatal risk factor data were ascertained by mailed questionnaires only.

The unrivalled data available at Uppsala Hospital have also been analysed by British epidemiologists.¹⁰ First, they investigated whether size at birth and rate of fetal growth influence the risk of breast cancer in adulthood in 5358 women born during 1915-1929, alive and traced with the 1960 census. They could conclude that size at birth, particularly length and head circumference, is associated with risk of breast cancer in premenopausal

women. Fetal growth rate, as measured by birth size adjusted for gestational age, rather than size at birth, may be the aetiologically-relevant factor in premenopausal breast cancer. Then, they enlarged the study by looking at 11,166 women born during 1915-1929 and investigated the incidence of all sorts of cancer in relation to birth characteristics.¹¹ They found that women who had higher birth weights had increased rates of breast cancer under age 50 years, but reduced rates of endometrial (corpus uteri) cancer at all ages. There was no evidence of associations with other cancer sites.

Outside Sweden

The same researchers completed their enquiries among a British population in order to interpret the association between birth weight with premenopausal breast cancer.¹² They examined data from 2176 women born in 1946 for whom there were prospective measurements of birth weight and body size throughout life. During follow-up, 59 breast cancer cases occurred (21 premenopausal). The authors concluded that the association of birth weight with premenopausal breast cancer risk was not mediated through childhood growth.

It is notable that, outside Sweden, birth weight has usually been the only proxy measurement available to evaluate the effects of prenatal environmental factors. This is the case with a large Danish study investigating a cohort of 106,504 women.¹³ A total of 2,334 cases of primary breast cancer was diagnosed among women with birth weight between 500-6000g. Of these, 40% was diagnosed with primary breast cancer at the age of 50 years or older. A significant association between birth weight and breast cancer was found, equivalent to a 9% increase in risk per 1,000g increase in birth weight. This statistic was observed for all age groups, representing both pre- and postmenopausal women, and irrespective of tumour characteristics. Adjustment for age at first birth and parity did not influence the results.

When birth weight is the only criterion available to evaluate early risk factors, the results provided by different epidemiological teams can be ambiguous. The history of studies exploring correlations between birth weight and risks of breast cancer started in Honolulu, with a paper published as early as 1988.¹⁴ Comparing 153 cases and 461 controls, the authors found that cases had a smaller mean birth weight (3120g) than controls (3162g).

Another study in the USA found that the association between birth weight and breast cancer in women aged 21-45 years followed a 'J'-shaped curve, with an odds ratio of 1.3 for women whose birth weight was less than 2,500g, and an odds ratio of 1.7 for women whose birth weight was 4000g or more.¹⁵ Surprisingly, women aged 50-64 years who weighed 4,000g or more at birth appeared to be at slightly-reduced risk of breast cancer. The authors of a similar study, looking at women aged 14-37 years, also found a J-shaped association between birth weight and breast cancer risk;¹⁶ very high birth weight (more than 4,500g) was associated with the greatest elevation.

Another American study could not reach statistical significance regarding the correlations between birth weight and the risks of breast cancer.¹⁷ We must also mention the Shanghai Breast Cancer Study in 1996-98, involving 288 cases and 350 controls: after adjustment for confounding factors, women who were 4000g or more at birth were not at increased risk of premenopausal breast cancer relative to women whose birth weight was 2500-2999g.¹⁸

Complementary Data

We stress the importance of data that indirectly identify the prenatal period as a critical period for genes-environment interaction, where the risk of breast cancer is concerned.

It is worth interpreting an investigation of cerebral asymmetry among 79 women with breast cancer and 97 controls.¹⁹ Women with breast cancer had a reversed pattern of cerebral asymmetry significantly more often than did controls for both frontal and occipital widths. We have previously compiled a great diversity of data suggesting that handedness, and therefore brain asymmetry, is also to a great extent determined during fetal life.²⁰ Among such data we have mentioned studies of handedness in relation to maternal emotional states in pregnancy, studies of laterality among women exposed

prenatally to Diethylstilbestrol (DES)²¹ and to ultrasound, and studies relating laterality and birth complications.

It is significant that prenatal exposure to DES is a factor influencing both the process of laterality and the risk of breast cancer. A preliminary American study, looking at a cohort of 4821 exposed women and 2095 unexposed women, followed for an average of 19 years, found an overall 40% excess risk; however the differences were not statistically significant.²² After a longer follow-up it appeared that the excess risk was statistically significant after age 40 years.²³

Recently, the possible genetic effects of DES on human breast tissue have been examined. Prenatal DES exposure does not significantly increase genomic instability in breast epithelium.²⁴ This leads us to the conclusion that the consequences of prenatal DES exposure are probably mediated by the proliferative effects of oestrogens, rather than by 'somatic mutations'. 'Somatic mutations' are acquired during a person's lifetime and are present only in certain cells; they are not inherited.

Learning From Negative Findings

To this accumulation of data that led us to include the genesis of breast cancer in the framework of 'womb ecology', we must add the negative findings of two large studies regarding exposure to breast milk in infancy.

The authors of the two "nurses' health studies" (Harvard Medical School) did not observe any association between having been breastfed and the development of breast cancer later in life among premenopausal women or postmenopausal women.²⁵ No significant trend was observed with increasing duration of breastfeeding. The conclusions of another large American study were similar;²⁶ interestingly it appeared that breast cancer risk was not increased by having been breastfed by a mother who later developed breast cancer, compared to having been breastfed by a mother who never developed breast cancer. Two previous smaller studies had suggested that exposure to breast milk might reduce the risks of breast cancer, but the results were at the limits of statistical significance.^{27,28} Such negative findings regarding postnatal life are important to confirm the limits of the period that is critical in the pathogenesis of breast cancer.

There are two reasons why we focused on female breast cancer. First, the prevalence of male breast cancer is less than 1% of total cases. Also, we could find only one study of male breast cancer from a primal health research perspective. Primal Health Research is still a new branch of epidemiology.

The Future

We have reached an historical phase when the pathogenesis of breast cancer has become a chapter of "womb ecology". The way is open for a new subgroup of studies. Today, we all have in our adipose tissue hundreds of synthetic fat-soluble chemicals that did not exist some decades ago. We understand that many of them behave like endocrine disruptors, and more precisely mimic oestrogen.

We need studies exploring the long-term consequences of prenatal pollution. Until now we must rely on a small number of animal experiments. For example, according to a recent study, intrauterine exposure of rats to bisphenol A at 2.5 parts per billion can induce breast cancers detectable at age 50 and 95 days.²⁹

It is more and more obvious that causes of endocrine-related cancers or susceptibility to cancer is more likely to be a result of developmental exposures rather than exposures existing at, or near the time, of tumour detection.

Michel Odent

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