Risk of Breast Cancer in Prematurely Born Women

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Epidemiologic studies of breast cancer [reviewed in (1)] have for several decades focused on the role of reproductive factors during adult life. A new line of research opened when it was suggested that perinatal events and conditions may influence a woman’s breast cancer risk throughout her life (2,3). Five separate epidemiologic studies (4–8) have tested this hypothesis. Besides a weak association between increasing birth weight and increased risk for breast cancer [seen in four studies (4–7)], most pronounced in women with premenopausal breast cancer, two studies (4,7) also demonstrated an inverse association between preeclampsia during pregnancy and breast cancer in the offspring out of three that examined this hypothesis. This finding supports indirectly that early hormonal exposures affect risk of breast cancer, since preeclampsia is characterized by decreased levels of pregnancy hormones (9,10).

Two independent observations led to the present investigation. One study (7) indicated that female babies born prematurely (before the 33rd gestational week) had an increased risk for breast cancer. Girls born before the 33rd gestational week have markedly increased levels postnatally of gonadotropins (11) that stimulate the ovaries to produce excessive amounts of estradiol during several months after birth (12,13). Since women born before the 33rd gestational week during the first half of the 20th century constitute a very small fraction, 10 of 1068 case patients, of breast cancer patients in the study mentioned above, this will not affect the results in the studies analyzing the association between birth weight and breast cancer risk. However, women born extremely preterm are an ideal group in which to test the hypothesis of an association between early exposures to elevated estrogen levels and breast cancer.

In the city of Stockholm, Sweden, there were two major delivery centers covering defined geographic areas from 1925 through 1934. There were around 60,000 deliveries uniformly documented on charts where names and addresses of the parents, gestational age calculated from the date of last menstruation, and birth weight could be retrieved. The charts have been saved in the city archive. We were able to trace the offspring by using church parish ledgers up to January 1, 1947, when all Swedish residents were assigned a national registration number, which is used as an identifier in the Swedish databases. The study was approved by the local ethical committee in Stockholm.

Extremely premature children during this time period were treated in a uniform manner. They stayed at the maternity ward for about 24 hours, and survivors were then transferred to a pediatric ward, where they were offered nutritional support. No other care or diagnostic procedures, such as x-ray examination of the lung, were provided. The children stayed at the ward for 2–3 months. The 1st year after birth, the mortality was extremely high but did not differ substantially from that expected in the rest of the population.

We examined manually and individually all 60,000 delivery charts to identify girls born before the 35th gestational week and those with a birth weight under 2000 g—regardless of gestational age. (Girls within the highest 1% of birth weight for the specific gestational week were excluded.) The study was restricted to women still alive on January 1, 1958, the starting date of the Swedish Cancer Registry.

A total of 273 women met our eligibility criteria; their distribution by gestational age is shown in Table 1. The occurrence of breast cancer was ascertained through the Swedish Cancer Registry for the period from 1958 through 1992. We calculated the expected number of breast cancer cases under the assumption that the risk was similar to that of the background population (also derived from the Swedish Cancer Registry). Person-time at risk (from January 1, 1958, until the end of follow-up, December 31, 1992) was calculated with allowance for death or emigration, both of which were ascertained through the Swedish registry. The standardized incidence ratio, i.e., the rates of observed-to-expected numbers of cancers, was used as a measure of risk. The 95% confidence interval (CI) was calculated under the assumption that the observed number of cancers followed a Poisson distribution.

In the analysis, we stratified the women into one of four groups: 1) born gestational weeks 29–30, 2) born gestational weeks 31–32, 3) born gestational weeks 33–34, or 4) born after the 34th gestational week but with a birth weight less than 2000 g. (In this last group, we also included deliveries where the girls weighed <2000 g without any information of gestational age.)

During follow-up, breast cancer was diagnosed in 12 women, seven of whom were younger than 50 years (Table 1). In women born before the 31st gestational week, the risk for breast cancer was increased 6.7 times (95% CI = 1.4–19.5), and the risk before the age of 50 years was increased 12.2 times (95% CI = 1.5–45.1). A twofold to fourfold increased risk was observed among women born in the 31st or 32nd gestational week. With longer gestational time, the relative risk of breast cancer declined. There was even some evidence that women born small (i.e., birth weight <2000 g) and after the 34th gestational week were at lower risk, in accordance with the results of previous studies (2,4).

Our main finding—that women born before the 33rd gestational week run a higher risk of breast cancer—is consistent with the observation that women born extremely small are at increased risk (9,10). Extremely premature children during this time period were treated in a uniform manner. They stayed at the maternity ward for about 24 hours, and survivors were then transferred to a pediatric ward, where they were offered nutritional support. No other care or diagnostic procedures, such as x-ray examination of the lung, were provided. The children stayed at the ward for 2–3 months. The 1st year after birth, the mortality was extremely high but did not differ substantially from that expected in the rest of the population.

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Our main finding—that women born before the 33rd gestational week run a
Gestational age substantially increased risk of breast cancer—supports the hypothesis of a relationship between the perinatal hormonal environment and the risk for breast cancer. Selection bias cannot explain the results because the study was essentially a population-based study, since the two centers at which the children were delivered in Stockholm encompass two defined areas where, as a rule, all deliveries from these areas were supposed to take place. Moreover, the study was prospective, with complete, nondifferential follow-up. Misclassification of gestational age is possible but would only attenuate the results. We did not identify any plausible confounding factor; most importantly, none of the children had undergone frequent or high-dose x-ray exposures to the chest (14). Chance findings cannot be ruled out, but the results were in accordance with observations made in our previous case–control study (7). Indeed, the excess breast cancer risk among the extremely prematurely born, low birth weight notwithstanding, suggests that the unusual endocrinology that characterizes extremely premature girls is the most likely explanation.

We can only speculate about the mechanism(s). An immature hypothalamic–pituitary feedback system might entail increased stimulation of the ovaries by high levels of gonadotropins leading to an excessive secretion of estradiol. Estrogens could favor the development of mutations through enhanced cell proliferation when the breast tissue is partly undifferentiated. Evidence (15) also indicates that high levels of estrogen have a direct mutagenic potential.

In our study base, girls born before the 33rd gestational week constituted approximately 0.2% of all survivors as of January 1, 1958. Today in Sweden, children born before the 33rd gestational week constitute about 1% of all live births. In the 1970s, 50% survived, whereas today more than 80% survive (16). If our risk estimates are correct, those women will, in the next 10–20 years, constitute close to 5% of all women with a new diagnosis of breast cancer.

REFERENCES


NOTE

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