

Understanding Mechanisms of Breast Cancer Prevention

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Several relatively strong risk factors for breast cancer that affect large proportions of the general population have been known for some time. Nevertheless, few effective preventive interventions have been developed, probably because most of the recognized risk factors relate to reproductive factors that are, in a practical sense, nonmodifiable. The response to this situation has been enthusiasm for identifying the underlying biologic mechanisms associated with these recognized risk factors, with the expectation that these mechanisms could be exploited directly rather than altering the risk factors responsible for them. An example is the solid evidence from both laboratory and population studies of the growth-promoting action of estrogen relatively late in carcinogenesis, which led to the studies of tamoxifen as a chemopreventive agent. Risk-benefit considerations have limited the applicability of this regimen to those women at the highest risk of breast cancer, but the success among this group has created considerable enthusiasm for the development of selective estrogen receptor modulators with much lower toxic effects.

Some of the most powerful determinants of breast cancer risk are related to parity, particularly the age of a woman at her first full-term pregnancy. The potential preventive implications of understanding the biology underlying the one-half to two-thirds reduction in breast cancer risk associated with parity at a young age are profound. Although this risk reduction has been recognized for more than 30 years, and a number of potentially explanatory hypotheses—ranging from molecular alterations in breast cells (1) to a permanently altered hormonal milieu (2)—have been developed, we remain ignorant of the underlying mechanisms. Certainly, one of the factors inhibiting this discovery process is the long interval between the exposure and the manifestation of disease. It is not practical (or timely) to attempt to measure all biochemical and molecular parameters of interest in a large group of pregnant women and then follow them for 30–40 years to determine which parameters are associated with reduced risk.

An example of a first step toward a possible solution to this conundrum appears in a report by Cohn et al. (3) in this issue of the Journal. Making creative use of data from a study developed more than 40 years ago to investigate the prenatal determinants of pregnancy outcome, Cohn et al. have examined the associations of some of these same pregnancy characteristics with subsequent breast cancer risk in the mothers. Given previous suggestions of a protective effect of preeclampsia (4–6), Cohn et al. focused on the group of 3804 women for whom information on blood pressure changes during pregnancy and placental characteristics at delivery had been collected. Relatively strong, statistically significant, and apparently independent reductions in the rate of subsequent breast cancer were associated with increases in blood pressure between the second and third trimesters, infarctions of the maternal floor of the placenta, low placental weight, and small placental diameter. Characterizing pregnan-

cies according to important biologic parameters (e.g., placental characteristics) and then assessing the impact of these parameters on breast cancer risk offer the prospect of uncovering clues to the actual underlying mechanisms of breast carcinogenesis and the protective effect of parity.

Although the potential effects on breast cancer risk of pregnancy characteristics reported by Cohn et al. (3) are provocative, at this time they should be viewed as hypotheses awaiting testing. In general, variables selected for presentation were chosen to maximize apparent protective effects after inspection of the data. For example, the highest quartile of placental diameter was compared with the lowest three categories combined, whereas the highest three quartiles of placental weight were compared with the lowest quartile. These comparisons were used to best characterize what looked like protective associations. These associations, however, did not show consistent trends when all four quartiles were considered individually. This analytic approach is entirely appropriate when attempting to best describe an apparent relationship, but it is not appropriate for formal hypothesis testing. In addition, although the most impressive protective relative hazards were those for women with combinations of several factors, these hazards were not those actually observed in the study but were rather expectations modeled from the estimates of the single factors, based on a rather limited sample size (146 cases). Thus, investigations testing the hypotheses using the metrics proposed here are needed, and it would be useful if they could be based on larger numbers of cases.

If the breast cancer rate reductions associated with increased maternal blood pressure, maternal floor infarction of the placenta, low placental weight, and small placental diameter are confirmed, the next step in discovering the biologic mechanisms that might be responsible and, thus, gaining possible insights into the risk reduction associated with parity itself, is to identify the relevant biochemical and molecular differences associated with these pregnancy characteristics. Cohn et al. (3) explore some of these possibilities, particularly circulating estrogens, androgens, and α -fetoprotein. To this list could be added a number of other hormones as well as possible resultant molecular changes in the breast. Their discussion also illustrates the major impediment to this process, the remarkable paucity of relevant data. Often, little is known in detail about the range of physiologic and molecular changes associated with breast cancer risk factors that might be relevant to breast carcinogenesis. As Cohn et al. note, it was only recently that elevated androgens, rather than reduced estrogens, were suggested as the most prominent

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feature of circulating hormones in preeclamptic mothers. Fortunately, this lack of relevant data is readily addressed. For example, the variables suggested by Cohn et al., such as placental size and blood pressure changes, are present in all pregnancies, and their impact on a variety of hormonal and other parameters could feasibly be studied.

This process—identification of more refined features of recognized breast cancer risk factors through epidemiologic studies, followed by detailed characterization of the relevant physiologic and molecular impact of these factors—should be a high priority for those interested in understanding human breast carcinogenesis. These data, combined with our rapidly evolving understanding of basic molecular mechanisms, should produce much more promising preventive opportunities than the current, less systematic approaches to such discovery.

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