Introduction

The incidence of breast cancer (BC) is influenced by age, genetics, ethnicity, diet, socioeconomic status, and reproductive history. The latter is the strongest and most reliable risk factor besides age and genetic susceptibility (1). Reproductive factors have been associated with risk for BC since the seventeenth century, when the disease was noted to be more prevalent among Catholic nuns. It is now a well-established fact that a full-term pregnancy early in life is associated with a long-term risk reduction for developing BC. A woman who has her first child after the age of 35 has approximately twice the risk of developing BC as a woman who has a child before age 20 (see current NCI Cancer Fact Sheet on Pregnancy and BC Risk). Despite this long-term reduction in BC risk in parous women, epidemiologists agreed at a recent NCI-sponsored workshop on “Early Reproductive Events and Breast Cancer” (http://nci.nih.gov/cancerinfo/ere) that each gestation increases temporarily the likelihood for developing BC (2). This transient increase in BC risk lasts for a few years after a full-term pregnancy.

Pregnancy and Breast Cancer

Pregnancy has a very similar dual effect on the etiology of mammary cancer in animal models. Like humans, parous rats and mice have a greatly reduced susceptibility to chemically induced mammary tumorigenesis compared with their nulliparous siblings (3). Humans who carry germ line mutations in tumor susceptibility genes do not benefit from the protective effects of pregnancy, but have a significantly greater risk of developing the disease following one or multiple gestation cycles (4). There are, however, conflicting reports whether lactation influences the onset of BC in women with BRCA1 mutations.

The current view on BC as a stem cell disease is founded on compelling evidence that many BCs may arise as clonal expansions from epithelial progenitors with an infinite lifespan (5). It has been hypothesized that unique properties of mammary stem cells, such as self-renewal, make this population a prime target for
transformation and tumorigenesis. Several experimental BC models support this hypothesis. The most venerable is the mammary tumor virus (MMTV) (6) model in mice, where MMTV proviral insertions produce mutated mammary cells, which attain immortality (escape from growth senescence) and produce clones of mammary cells with increased propensity to develop mammary cancer. Serial transplantations of these preneoplastic lesions result in the formation of hyperplastic/dysplastic ductal trees, suggesting that multipotent cells are affected by MMTV transformation and that they pass on their neoplastic properties to their descendants (7). Morphologically undifferentiated cells, reminiscent of stem/progenitor cells are present in both premalignant and malignant mammary populations (Fig. 1). Reproductive history has a profound impact on breast tumorigenesis, thus it is

Fig. 1 This electron micrograph depicts an ultra thin section through one of the acini in an MMTV-induced alveolar hyperplasia. There is evidence of virus replication (MMTV) of secretory activity leading to secretory granule formation in the apical cytoplasm of the luminal cells and release into the lumen. An undifferentiated suprabasal cell (SLC) is present and proximal to it, a differentiated myoepithelial cell (arrow). Bar equals 1.0µM