EDITORIAL

Chemoprevention for Breast Cancer: Are We Ready?

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Despite recent advances in the management of breast cancer, there has been no noticeable improvement in the mortality rate. In fact, the reported incidence of breast cancer is rising (1,2). Although early detection through mammography screening may contribute to this increase, the main causes have yet to be delineated (3). Factors that concern many investigators include changes in dietary habits and the tendency of a delayed first pregnancy (4). Prospective epidemiological studies to determine whether a reduction in dietary fat intake may curb the increase in incidence are expensive and difficult to perform (5). Another approach is to undertake hormonal chemoprevention for breast cancer.

In rodent mammary cancer models, hypophysectomy or ovariec-tomy has been shown to prevent or markedly reduce tumor development induced by various carcinogens (6,7). Additive hormonal therapies are also being investigated extensively in animal studies; among them are estrogen plus progesterin (8), estriol (9), contraceptives (10), and antiestrogens such as ethamoxytriphetol (MER-25) (11) or tamoxifen (12). All of these agents have been effective when applied during the early reproductive life. The study by Jordan et al, reported in this issue of the Journal (13), represents one of the latest efforts utilizing tamoxifen, an antiestrogen, in prevention of rodent mammary tumorigenesis. As adjuvant therapy for human primary breast cancer, tamoxifen, at a dose of 40 mg daily for 2-5 years, can reduce cancer incidence in the contralateral breast by 45% (14).

Thus, accumulating evidence has confirmed that endocrine manipulation is effective in preventing the development of ro-dent and human breast cancers. The uncertainty remaining relates to timing and the duration for such hormonal intervention. In the United Kingdom, women with a high risk of developing breast cancer are now enrolled in a double-blind randomized study using tamoxifen or placebo as the chemoprevention agent. The duration of tamoxifen use at a dose of 20 mg daily is set for 3 years. The results of a pilot study in 435 women aged 30-69 years showed that this project would be feasible (15). It is estimated that 10 000-15 000 women, with a 10- to 15-year followup, would be required if a 25% prevention effect is to be detected. Although the study is under way, the question remains whether the timing and duration of tamoxifen use are optimal, especially for premenopausal women.

Study results have suggested that premenopausal and post-menopausal disease may have different biological characteristics (16). While premenopausal breast cancers are closely related to genetic factors, early menarche, and late childbirth, postmenopausal breast cancers are associated with late natural menopause, obesity, and an increased weight-to-height ratio (17). The issue of timing and duration of hormonal chemoprevention for these two types of breast cancer may have to be dealt with separately.

Determination of the time in starting chemoprevention is the first critical issue. For patients with documented breast cancer, the time for adjuvant therapy is more or less defined—immediately following lumpectomy or mastectomy. For women with a high risk of developing breast cancer, the optimal time for chemoprevention is somewhat arbitrary. Timing is more important for premenopausal women than for postmenopausal women, because many premenopausal women have years of reproductive life ahead of them.

The critical period for mammary carcinogenesis is before full development of the breasts (18), a process usually completed at the end of the first pregnancy. Once the terminal end buds of the mammary gland fully differentiate into alveolar buds or lobules after pregnancy, they become less susceptible to carcinogens (18). The best timing for chemoprevention is also at the time of breast development. Studies in most rodent mammary tumor models have demonstrated that chemoprevention during breast development results in a long-lasting protective effect. Evidence from epidemiological studies also supports this theory. Pregnancy before the age of 18 years has a protective effect against the development of breast cancer (19). The rising breast cancer incidence among young women in the 1980s may be due, at least in part, to the trend of delayed childbearing in this cohort (4).

Furthermore, castration before age 35 can reduce the breast cancer risk by one third (20,21). Thus, both rodent experiments and epidemiological findings support the concept that the key element for successful chemoprevention hinges on early hormonal intervention.

Such early timing in use of tamoxifen may be deemed impractical in young women because it would disrupt their normal family life. Human chorionic gonadotropin (hCG) appears to be a promising alternative to circumvent this problem. When hCG was given to rats at the age of 50 days and continued for 21 days, it caused pseudopregnancy with concomitant full development of the mammary gland and subsequent marked reduction in the incidence of chemically induced mammary carcinoma. This result was accomplished without obvious side effects, which was determined by measurement of total body weight and weight of internal endocrine organs (22,23). Although hCG has been used in therapy to stimulate ovulation and to maintain the luteal phase of the menstrual cycle, further research is necessary before its use can be considered for prevention of human breast cancer.
Determination of the optimal duration is the second critical issue in chemoprevention. The long-term use of tamoxifen for up to 10 years as adjuvant therapy has caused no detrimental effect (24), and it may be beneficial, at least in terms of bone mineral density and serum lipid components (25,26). In the mouse mammary tumor system, Jordan et al (13) found that 6 months of tamoxifen therapy was adequate to prevent breast cancer development. These findings must be deemed an important contribution to our understanding of chemoprevention; yet they should be viewed cautiously because the pharmacological effects of tamoxifen in mice and humans are not totally equivalent. Furthermore, unlike the hormonal dependency in rodent models, which is generally uniform, hormonal dependency varies in human breast cancers; only about one third of these human tumors can be classified as hormonally dependent and responsive to hormonal therapy.

Based on recent advances in our current understanding, mammary tumorigenesis is likely a multistep process. In addition to the hormonal and growth factors, which play a major role, other genetic and environmental factors are also intimately involved. In N-nitrosomethylurea-induced rat mammary cancers, both estrogens and mutated ras oncogene are essential for tumor development (27). In human breast cancers, the scenario would be more complex. Changes in the retinoblastoma gene and in the genes p53, HER-2/neu, and int-2 have been described in human breast cancers (28-31). Some of these mutations and deletions are genetically inherited; others may be epigenetic in origin.

Until these genetic factors that affect tumorigenesis are better characterized and new agents or methods are developed to remedy their aberrant functions, hormonal intervention is an appropriate and effective avenue to reduce the incidence of breast cancer. Most importantly, this goal is achievable, especially in postmenopausal women with high risk of breast cancer. Yes, we should be viewed cautiously because the pharmacological effects of tamoxifen in mice and humans are not totally equivalent. Furthermore, unlike the hormonal dependency in rodent models, which is generally uniform, hormonal dependency varies in human breast cancers; only about one third of these human tumors can be classified as hormonally dependent and responsive to hormonal therapy.

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References