Hormonal approaches to the chemoprevention of endocrine-dependent tumors

A Manni
Section of Endocrinology, Diabetes, and Metabolism, Department of Medicine, The Milton S. Hershey Medical Center, The Pennsylvania State University College of Medicine, 500 University Drive, Hershey, Pennsylvania 17033, USA

Abstract
The estrogen dependency of human breast cancer has been successfully exploited in the treatment of early and advanced diseases and provides a unique opportunity for chemoprevention of this common malignancy. Preliminary results with the antiestrogens Tamoxifen and Raloxifene show an encouraging reduction in the incidence of breast cancer. Alternative approaches include the use of highly selective and non-toxic aromatase inhibitors and, in premenopausal women, the use of LHRH agonists in conjunction with the administration of small doses of estrogen and progesterone. The rationale for these chemopreventive strategies and their possible limitations are briefly discussed.

The importance of ovarian hormones in the development of most, if not all, human breast cancers is widely appreciated. The increased risk of breast cancer conferred by early menarche and late menopause points to the importance of cumulative exposure to ovarian hormones as a determinant of mammary carcinogenesis. Among ovarian hormones, estradiol has clearly emerged as the predominant one involved in human breast cancer. In the author’s opinion, the role of progesterone, while possibly important, is less clearly defined. Both proliferative and antiproliferative effects of progesterone have been reported in breast epithelial cells (Meyer 1977, Masters et al. 1977, Barrat et al. 1990, Chang et al. 1995). Furthermore, progesterone has a clear role in inducing alveolar differentiation which, at least in rodents, has been shown to have a protective effect on experimentally induced mammary carcinogenesis (Segaloff 1973). The role of estrogens, on the other hand, appears to be more straightforward. A recently published meta-analysis has shown a positive association between serum estradiol concentration and breast cancer risk in postmenopausal women (Thomas et al. 1997). Furthermore, local estrogen production in the breast tissue itself has received increasing attention as a major contributor to breast cancer risk in postmenopausal women (Thomas et al. 1997). These observations indicate that estrogens contribute to mammary carcinogenesis both in an endocrine and paracrine fashion. There are at least two mechanisms by which estrogens could promote breast cancer formation (Santen et al. 1999). The prevailing theory is that estrogens increase the number of mutations as a result of their receptor-mediated, growth-promoting effect. An alternative, not mutually exclusive, possibility is that estrogens are metabolized to genotoxic products which cause direct DNA damage independently of the presence of the estrogen receptor.

The estrogen dependency of human breast cancer has been successfully exploited therapeutically in the treatment of both advanced and early disease. Therefore, it is not surprising that effective interference with estrogen action or biosynthesis is being actively pursued in the chemoprevention of breast cancer. Encouraging preliminary results have already started to emerge with the use of Tamoxifen in the NSABP-P1 trial involving 13 388 high-risk women, where a 45% reduction in the incidence of invasive breast cancer was observed in the treated compared with the placebo group (Fisher 1998). Similar results have been reported with the selective estrogen receptor modulator, Raloxifene, in the multiple outcomes of Raloxifene evaluation (MORE) trial involving 7704 postmenopausal women with osteoporosis (i.e. not at increased risk of breast cancer) (Cummings et al. 1998). These findings need to be interpreted with caution because of the short duration of follow-up. Furthermore, two smaller European studies, the Royal Marsden Hospital Chemoprevention Trial (Powles et al. 1998) and the Italian Tamoxifen Prevention Study (Veronesi et al. 1998), have failed to demonstrate any reduction in breast cancer incidence with Tamoxifen.
Highly selective and non-toxic aromatase inhibitors are also being considered for breast cancer chemoprevention (Santen et al. 1999). They may offer a few theoretical advantages over antiestrogens within this context. In premenopausal women, they may selectively deplete local estrogen production in the breast tissue without affecting systemic estrogen levels, since the ovary is resistant to the action of aromatase inhibitors. If, indeed, local estrogen production is the major determinant of mammary carcinogenesis, aromatase inhibitors would offer protection from breast cancer while preserving the beneficial effects of circulating estrogens on the host. An additional theoretical advantage of aromatase inhibitors is their potential ability to counteract both receptor-mediated and direct genotoxic effects of estrogens, while only the former would be expected to be influenced by antiestrogen therapy. At present, however, the role of aromatase inhibitors in breast cancer chemoprevention remains theoretical, since no clinical data are yet available.

Dr Malcolm Pike has pioneered a different endocrine approach to the chemoprevention of hormone-dependent tumors. He and his co-workers propose to suppress ovarian function with GnRH analogue therapy and to add back low doses of estrogen and progesterone which would be insufficient to promote mammary and uterine carcinogenesis but would be high enough to provide beneficial effects such as cardiac protection and bone preservation (Spicer & Pike 1994). A significant potential advantage of this approach over those discussed above is that it would reduce the risk, not only of breast cancer, but also of ovarian and endometrial cancer. According to Dr Pike's estimate, this contraceptive regimen, applied for five years, would reduce breast cancer risk by 30%, ovarian cancer risk by 40%, and endometrial cancer risk by 20%. In a pilot study involving 21 young women (14 assigned to the contraceptive regimen and 7 to no treatment), Dr Pike reported a significant reduction in mammographic densities at 1 year in hormonally treated women compared with the control group (Spicer et al. 1994). It is hoped that a reduction in mammographic densities will translate into reduced breast cancer risk, although there is no direct evidence to support this assumption. Reduction in mammographic densities will also be the end point of a multi-center, 12-month study including a small group of high-risk premenopausal women (mostly with BRCA-1 mutations) who will be placed on a similar contraceptive regimen with additional administration of low doses of testosterone (Weitzel 1999).

Every attempt at endocrine chemoprevention of breast cancer (and other endocrine-related tumors) faces the same challenge, i.e. eliminating the adverse hormonal effects on carcinogenesis while preserving their multiple beneficial actions, such as those on bones, heart, sexuality and possibly brain. The development and introduction of SERMs represent a logical approach to address this issue which is based upon improved understanding of the molecular mechanisms of estrogen action. It should be recognized, however, that both Tamoxifen andRaloxifene, the only two SERMS currently available in clinical practice, are still in their infancy as chemopreventive agents. First of all, the still relatively short duration of follow-up of both the NSABP-P1 and MORE trials does not allow us to categorically distinguish between true chemoprevention and a suppressive effect on already established tumors. Secondly, Tamoxifen use has been found to be associated with increased risks of endometrial cancer and thromboembolic events. These side effects need to be taken into serious consideration since normal women, not patients with breast cancer, are being considered for long-term treatment. The approach proposed by Dr Pike has a sound biological rationale, but still remains theoretical at this point. Data beyond reduction in mammographic densities will need to be generated to prove the efficacy of this regimen. Furthermore, the safety of long-term administration of GnRH analogue therapy in young women needs to be demonstrated. In addition, this protocol is quite complex and its practical applicability on a large scale could be questioned.

Finally, all protocols still face many unresolved issues such as definition of the optimal demographic characteristics of the target populations (e.g. age, risk factor profiles), as well as the identification of optimal duration of treatment. In sum, chemoprevention of hormone-dependent cancers is truly a multi-disciplinary effort which will require improved understanding of the molecular biology of hormone action on neoplastic and normal tissues and a more clear definition of the genetic changes leading to carcinogenesis, as well as a better appreciation of their interaction with epigenetic events.

References


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