Commentary

Prevention of breast cancer by recapitulation of pregnancy hormone levels

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Abstract

At the present time, the only approved method of breast cancer prevention is use of the selective estrogen receptor modulator (SERM) tamoxifen. Many breast cancers are driven to grow by estrogen, and tamoxifen exploits this by blocking estrogen action at the estrogen receptor. A counter-intuitive and controversial approach to breast cancer prevention is administration of estrogen and progestin at an early age to achieve pregnancy levels. This approach is supported by the fact that breast cancer incidence is halved by early (≤ 20 years of age) full-term pregnancy. Moreover, it has been demonstrated in rodent models that mimicking the hormonal milieu can effectively prevent carcinogen-induced mammary cancer. In this issue of *Breast Cancer Research* Rajkumar and colleagues use the rodent model to further define the timing and type of hormonal therapy that is effective in preventing mammary carcinogenesis. Clearly, application of this approach in humans may be difficult, but the potential benefit is intriguing.

Keywords: breast cancer, estrogen, pregnancy, prevention, progesterone

Introduction

Numerous epidemiologic studies have demonstrated the protective effect of a full-term pregnancy before age 20 years on the risk for developing breast cancer, as compared with women who have never had a full-term pregnancy. Rodent models can replicate the protective effect of pregnancy against the development of carcinogen-induced mammary cancer. Most intriguing is the ability to prevent mammary cancers in these rodent models by recreating the hormonal milieu of pregnancy by providing estradiol and progesterone to achieve pregnancy levels, either before or after the carcinogenic insult. In this issue of *Breast Cancer Research*, Rajkumar and coworkers [1] take a step further in recapitulating the protective effect of pregnancy. They demonstrate that both natural and synthetic estrogens in combination with progestins at lower doses and with shorter durations of treatment are capable of providing the protective effect. These studies are compelling because this hormonal regimen may be applicable to the prevention of human breast cancer. However, this approach, despite impressive preclinical studies, may be difficult to translate into a clinical trial.

Pregnancy and the protective effect on breast cancer in humans and rodent models

The protective effect afforded by full-term pregnancy in women who are 20 years old or younger, as compared with nulliparous women, is recognized among all ethnic groups, but the mechanism of this effect is not fully understood. Rodent models have been extensively utilized to demonstrate the role of pregnancy [2,3] and hormones simulating pregnancy [4,5] in preventing mammary carcinogenesis. Actually, two separate models have been used to demonstrate the protective effects of parity: a pretreatment model and a post-treatment model [6]. In the pretreatment model the hormonal treatment is given before the carcinogen, whereas in the post-treatment model the carcinogen is given first, followed by the hormone treatment. The latter is the model used by Rajkumar and coworkers [1]. The fact that the timing of hormonal

SERM = selective estrogen receptor modulator.

treatment – before or after the carcinogenic insult – is irrelevant to the protective effect is an important consideration when devising the first clinical trial. However, the mechanism of protection is likely to be quite different in the two rodent models. Several hypotheses for the cellular and molecular mechanisms underlying this protective effect have been proposed; induction of differentiation [7], decreased proliferation, upregulation of p53 [8], and greater DNA repair capacity are but a few of the hypotheses offered. Whatever the mechanism of protection, based on the epidemiologic findings this protective effect lasts throughout a woman's lifetime and makes hormonal mimicry of pregnancy such an attractive approach.

From rodents to teenagers: translation to the clinic

Rodent models have been invaluable in the preclinical evaluation of selective estrogen receptor modulators (SERMs) and aromatase inhibitors. Indeed, had it been known that tamoxifen caused rat liver tumors and endometrial cancer, it is unlikely clinical trials would have proceeded so rapidly. It is not possible to extrapolate all possible ramifications of applying hormonal manipulation to simulate full-term pregnancy. The difference between the translation of SERMs into the clinic for both breast cancer treatment and prevention, and hormonal prevention strategies that simulate a full-term pregnancy is the age of the target patient population. Because the hormonal treatment must be administered during the teenage years, clinical trials of such a treatment will probably attract more scrutiny. The findings of Rajkumar and coworkers [1] are likely to alleviate some of these concerns. Notably, treatment with synthetic hormones such as ethynyl estradiol plus norethindrone for only 1 week was shown to reduce mammary cancer incidence from 75% to 25%. These synthetic hormones are already used in oral contraceptive preparations, and therefore safety issues will be less of a concern. However, one must remember that the hormone level that must be achieved is that of the last trimester of pregnancy. This level is considerably higher than is found in oral contraceptives, and this is a considerable obstacle that must be overcome when considering treatment of very young women. The shorter duration of treatment is advantageous and may offset some of the drawbacks, although the optimal duration of treatment will be difficult to ascertain in humans.

Conclusion

The findings of Rajkumar and coworkers [1] have fascinating implications for the prevention of breast cancer in the future. Although tamoxifen is a truly remarkable chemopreventive drug, it has certain drawbacks. Tamoxifen does not prevent the emergence of estrogen receptor negative breast cancer [9], whereas it was recently reported that administration of hormones to achieve pregnancy levels does not alter the spectrum of estrogen receptor status in resulting tumors [10]. Tamoxifen does not prevent breast cancer in women with *BRCA1* mutations [11], and unfortunately it appears that an early pregnancy does not afford protection for *BRCA1* and *BRCA2* mutation carriers either [12]. Finally, tamoxifen increases the incidence of endometrial cancer – a problem that may be solved following publication of the results of the STAR (Study of Tamoxifen and Raloxifene) trial, which will compare tamoxifen with the newer SERM raloxifene [13]. It is unknown what potential side effects may result from recapitulating the pregnancy hormonal status in young women. Several obstacles will have to be overcome before translation of this strategy into the clinic. However, the potential benefit is enormous.

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