Tamoxifen or Raloxifene for Breast Cancer Chemoprevention: A Tale of Two Choices—Point

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The stated goal for an investment in cancer research is the eradication of cancer. But this is just talk. A world with no cancer is a noble goal but the problem becomes where to start. In other words, how to put ideas into action and move forward from rhetoric. The task is enormous, but one solution where there has been much talk is cancer prevention. In the case of lung cancer, the solution is simple—stop smoking. But the social engineering that is required to prevent one sector of society from creating a massive health care crisis in another seems to be insoluble. It is now clear that women have been the victims here through a callous campaign to recruit smokers. Lung cancer is the disease that kills more women with cancer than any other. Based on this inconvenient truth of modern society, is there any reason to believe that the cancer research community has made any progress with practical help for people? In contrast to lung cancer, progress is quantifiable in another major killer of women—breast cancer.

In 1971, President Nixon signed the National Cancer Act and declared war on cancer, but there were no serious plans to prevent breast cancer. Nevertheless, the first experiments were being conducted to prevent breast cancer with antihormones but, regrettably, at that time no one cared (1). All efforts were focused on the application of combinations of cytotoxic chemotherapy to treat and cure cancer by killing the last cancer cell. Despite heroic attempts to kill the cancer without killing the patient, progress has been modest but significant improvements in survival did occur in premenopausal patients (2). Unfortunately, this is a hollow victory that on the face of it cannot be applied to cancer prevention; or can it?

We have known for more than a century that there is a link between the growth of breast cancer in patients and sex steroids secreted from the ovary (3) or produced peripherally in a woman’s body fat. Furthermore, we have known for more than 30 years that combination cytotoxic chemotherapy will destroy ovarian function (reviewed in ref. 4) and stop estrogen production. Indeed, we now know that younger women who do not have a premature menopause and who do not take antiestrogen therapy have shorter survival than women who have ovarian failure (5-7). We also know that adjuvant oophorectomy produces disease-free survival comparable with the use of adjuvant cytotoxic chemotherapy in premenopausal women (8, 9). Thus, based on these clinical observations, one would be drawn to the conclusion that preventing hormone action might be a valuable line of future investigation for prevention if one could only work out the mechanism. But research does not travel in straight lines; a parallel universe of knowledge had already developed to address chemoprevention with antihormones.

An ovarian link between spontaneous breast (mammary) cancer in laboratory mice was shown in 1916 (10), but it was Professor Antoine Lassasagne (11) in 1936 who proposed that “a therapeutic antagonist should be sought to prevent the congestion of oestrone in the breast.” In other words, an antiestrogen could be a valuable chemopreventive agent; however, at the time, there was no scientific foundation to support this strategy. The discovery of the estrogen receptor as the putative mechanism of estrogen action in its target tissues (12) opened the door to reinvent tamoxifen from a failed contraceptive (13) to become the first targeted therapy for breast cancer treatment (14). Tamoxifen, a nonsteroidal antiestrogen, was discovered in the 1960s as part of a worldwide effort by the pharmaceutical industry to exploit the serendipitous discovery of the drug group (15). Applications were sought based on in vivo studies and without reference to receptor mechanisms (16). The compounds were excellent postcoital contraceptive in rats but failed in this application because they induced ovulation in women (i.e., it could guarantee pregnancy), exactly the opposite effect that was being sought. As a result, tamoxifen was briefly marketed for the induction of ovulation (17). Although numerous compounds were discovered, only tamoxifen was re-invented as a long-term receptor targeted breast cancer treatment (ref. 18; and potential preventive ref. 19). A decade later, the drugs described as nonsteroidal antiestrogens (20) were recognized as selective estrogen receptor modulators (SERM) that could be estrogen-like at one site (i.e., bone or endometrial cancer) but antiestrogenic at another (i.e., breast; refs. 21-23). This discovery of SERM action (24) led to the proposition that it was plausible to prevent osteoporosis with SERMs in women but prevent breast cancer at the same time (15, 25). Raloxifene, a failed breast cancer drug (26), emerged as the first SERM used
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The SERM raloxifene had been rigorously investigated as a drug to prevent osteoporosis with the beneficial side effect of preventing both breast and endometrial cancer (27-29). This was perfect timing as hormone replacement therapy used to prevent osteoporosis was shown to increase breast cancer incidence (30, 31).

The practical application of using tamoxifen for breast chemoprevention was pioneered by Trevor Powles (32, 33), Bernard Fisher (34, 35), and Umberto Veronesi (36, 37) who created a fundamental change in health care. There were no surprises as the “good, the bad, and the ugly” of laboratory research coupled with the vast resource of clinical experience with tamoxifen that reduced contralateral breast cancer when used as an adjuvant (38-40) were, in the main, predictive for the results in the chemoprevention trials. The “good” news was that tamoxifen reduced the risk of breast cancer in the large trials (34, 35, 41). Cuzick et al. (42) provided additional clinical trials data with the International Breast Intervention Study and did an “overview analysis” of all tamoxifen trials (plus the osteoporosis study with raloxifene; ref. 43). Tamoxifen is currently the only medicine that will reduce breast cancer risk safely and for prolonged periods (5 and probably 10 years) after therapy is stopped (35, 44, 45). This is remarkable and occurs at a time when there are no side effects. The advance with tamoxifen, now Food and Drug Administration–approved for risk reduction in high-risk women for almost a decade, does have problems, but these seem to be overplayed by the media. Concerns about the “bad” side effects of endometrial cancer (generally good grade and curable) or blood clots and stroke are, in the main, associated with use in postmenopausal women. There is, however, a very small concern about uterine sarcomas (46, 47). Obviously, hysterectomized women are an appropriate target population for breast chemoprevention with tamoxifen.

The “bad” for some women is the increased incidence of menopausal symptoms. As it turns out, this may in fact be “good.” Tamoxifen needs to be metabolically activated to endoxifen by the CYP2D6 gene product so patients with a variant CYP2D6 usually have fewer hot flashes but have a higher recurrent rate (48, 49). Ironically, women who use the selective serotonin reuptake inhibitors paroxetine or fluoxetine to suppress hot flashes have a poor response to tamoxifen (48-50). This is because these selective serotonin reuptake inhibitors block tamoxifen metabolism. Venlafaxine is the selective serotonin reuptake inhibitor of choice because it does not block endoxifen production.

The “ugly” concern with tamoxifen was liver cancer induced in rats, but this did not translate to an increased incidence of hepatocellular carcinoma in women. It seemed to be obvious that this property, unique to rats, was not going to affect women, as the drug had already been marketed for 20 years at the time the hepatic toxicity was noted (51). No elevation in hepatocellular carcinoma are currently observed (8). Clinicians, however, do have another choice, raloxifene. This compound does not produce hepatocellular carcinomas in rats.

The SERM raloxifene had been rigorously investigated as a drug to prevent osteoporosis, and translational research predicted that this SERM would reduce the risk of breast cancer (21, 22, 25, 27). Based on this evaluation, the National Surgical Adjuvant Breast and Bowel Project chose to initiate the landmark SERM trial, the study of tamoxifen and raloxifene or STAR (28). The results were clear and predictable: Tamoxifen and raloxifene were equivalent at reducing the risk of invasive breast cancer in high-risk women. There were trivial differences in ductal carcinoma in situ in favor of tamoxifen (probably due to the failure of compliance and the short duration of action of raloxifene when compared with tamoxifen; ref. 52) but the safety profile of the two SERMs favored raloxifene. Tamoxifen-treated women had more blood clots, more endometrial cancer, hysterectomies, and cataract operations compared with raloxifene-treated women. Supportive evidence for the value of raloxifene for the chemoprevention of breast cancer in postmenopausal women without a concern about an elevation of endometrial cancer comes from the trial named Raloxifene Use for the Heart (29). This trial was established to test the worth of raloxifene to prevent deaths from coronary heart disease but did not show an advantage for raloxifene over placebo. However, the trial showed a significant decrease in breast cancer and no elevation in endometrial cancer (52). Raloxifene is now SERM of choice in the clinician’s armamentarium to prevent breast cancer in osteoporotic women as well as postmenopausal women at high risk for breast cancer.

In closing, the question that needs to be addressed is why clinicians and women at high risk chose to avoid using approved medicines for appropriate indications? We have seen a dramatic change in the approach to breast cancer treatment and prevention in the past 30 years. Drugs can now be targeted to specific populations. In the case of prevention, tamoxifen is fully tested and is best used for high-risk premenopausal women with wild-type CYP2D6 gene product, and venlafaxine can be used to control hot flashes. Raloxifene cannot be used in premenopausal women. Raloxifene is the agent of choice in postmenopausal women. Raloxifene is being used by an estimated 500,000 women to prevent osteoporosis, which will also prevent the development of tens of thousands of breast cancers over the next decade (53).

The recent approval of raloxifene to prevent breast cancer in high-risk postmenopausal women will add to a reduction in breast cancer incidence while enhancing bone strength. The SERM concept (15, 25, 54, 55) works in medical practice and agents are available now to help the right patient. Only clinician and patient prejudice, convinced by negative media messages, is preventing progress in chemoprevention.

Returning to my original arguments about lung cancer, it is hard to believe that it is acceptable to smoke cigarettes with the attendant list of known health hazards and the highest death rate for cancer among women, but it is unacceptable to use approved medicines to reduce the risk of breast cancer. Fortunately, research is not static and new ideas will evolve and new SERMs will be developed, but, regretfully, progress will not occur in the near future. This is compounded by a lack of will by the government to support clinical research in chemoprevention and to support the training of a new generation of innovative clinical investigators. In the face of these obstacles, it is essential for the physicians to make the right choices for the appropriate patient. Interventions validated by decades of clinical and laboratory research and approved by the Food and Drug Administration can help reduce the risk of breast cancer now. After all, it’s a once around life.
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