PILLS FOR PREVENTION

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INTRODUCTION

Since our founding in 1990, Breast Cancer Action (BCAction) has emphasized the ongoing importance of identifying the root causes of breast cancer so that we can focus on the prevention of this disease. There is a growing body of evidence that the genesis of many cases of breast cancer lies in our toxic environment. Yet the focus of national resources devoted to breast cancer prevention has been on the development of drugs to lower the incidence of or treat breast cancer rather than finding the environmental triggers of the disease.

This fact sheet describes the efforts to bring drugs to the market to reduce breast cancer incidence in healthy people, as well as the problems created by this approach, and explains why BCAction opposes a pills-based approach to breast cancer prevention.

THE TAMOXIFEN FOR PREVENTION TRIAL — BCPT P-1

In the early 1990s, the National Cancer Institute (NCI) undertook a long-term study of tamoxifen (trade name Nolvadex), a hormonal treatment that had been shown to reduce the risk of recurrence in people with breast cancer, to see if it lowered breast cancer incidence in healthy people with a high risk of developing the disease.[1] The Breast Cancer Prevention Trial P-1 (BCPT P-1), which started in 1992, was halted before its planned conclusion because of the significant reduction in breast cancer incidence found in those treated with tamoxifen compared to the placebo control group. Participants were informed of the findings and which group they had been randomized to, and those in the placebo group were offered the opportunity to either begin taking tamoxifen or enter a new trial that was comparing tamoxifen with another drug, raloxifene, that showed potential to reduce breast cancer incidence as well.

Soon after BCPT P-1's termination in 1998, the Food and Drug Administration (FDA) approved tamoxifen for use in high-risk healthy people to lower the risk of breast cancer. Manufacturers and other proponents of tamoxifen at the FDA hearings lobbied strongly to have the drug described as "preventing" breast cancer. Prevention refers to protecting individuals or populations from the development of disease. Because a portion of those taking tamoxifen develop breast cancer, even if at lower rates, public health advocates, including BCAction, argued successfully that it could not be labeled as preventing breast cancer, but rather as lowering risk.

TREATING RISK AS DISEASE—TAMOXIFEN AND DISEASE SUBSTITUTION

Tamoxifen has significant side effects. Milder effects include hot flashes and vaginal dryness. The more severe risks include endometrial cancer, pulmonary emboli (blood clots in the lung), stroke, deep vein thrombosis, and cataracts. After many years of study, the drug was found to significantly increase the risk of uterine sarcoma, an uncommon and dangerous form of cancer of the uterus.[2]

Despite years of direct-to-consumer advertising by AstraZeneca, tamoxifen's manufacturer, use of tamoxifen by healthy people to reduce breast cancer risk remained relatively low.[3]

In preventive medicine, only very minimal risks are considered acceptable—such as those from vaccination or vitamins. The prevalence and severity of tamoxifen's side effects led to coining the term "disease substitution."

STUDY OF TAMOXIFEN AND RALOXIFENE—STAR TRIAL (BCPT P-2)

Since the FDA approved tamoxifen's use by healthy people, a number of other drugs have been and continue to be studied as possibly safer alternatives to tamoxifen. Raloxifene (trade name Evista), in the same class of drugs as tamoxifen, has been compared to tamoxifen in a clinical trial ("STAR" or BCPT P-2) of healthy women at high risk for breast cancer.

Raloxifene's manufacturer, Eli Lilly, hoped that its product would prove more popular as a "prevention" pill than tamoxifen, since many post-menopausal women were already taking it for its approved use to increase bone density (even though it is ineffective in reducing hip fractures, and marginally effective in reducing spinal fractures).[4]

For many years now, raloxifene has been widely prescribed to healthy people to lower breast cancer risk, even though it was not FDA-approved for this purpose until 2007. The manufacturer of raloxifene was fined $36 million for illegally promoting the drug to doctors as a breast cancer preventative.

Results from the STAR trial found that the two drugs are equivalent in reducing invasive breast cancer risk. Raloxifene is portrayed by the NCI as being safer than tamoxifen, but the published results show that the differences between most of their side effects are not statistically significant.[5] The exceptions were that raloxifene users had fewer deep-vein blood clots and cataracts than tamoxifen users. Study participants had taken the treatments for an average of only three years at the time the study was ended.

AROMATASE INHIBITORS

Aromatase Inhibitors (AIs) are the other main class of drugs being tested to lower breast cancer risk in post-menopausal people. There are three AIs currently approved by the FDA for treating breast cancer, and they are listed in the accompanying chart (see below). These drugs block aromatase—an enzyme that converts the hormone androgen into estrogen—which is the primary source of estrogen for post-menopausal women.[6] AIs have been shown to lower breast cancer risk in post-menopausal people who have a high risk of the disease. According to a publication released by the University of Texas's MD Anderson Cancer Center, aromatase inhibitors are among the most effective medications today for treating or preventing the recurrence of estrogen-fueled breast cancers in post-menopausal women.[7]

In the early 2000s, there was limited research on AIs in post-menopausal people with early stage, estrogen-positive breast cancer. By 2023, AIs have been extensively studied in this population. These studies have consistently shown that AIs are effective in reducing the risk of reoccurrence[8] and are now commonly used as adjuvant therapy.[9]

Side effects of these drugs still exist for some people, which include hot flashes, vaginal dryness, nausea, increased risk of osteoporosis and bone fractures, joint and muscle pain, elevated cholesterol, and cognitive problems. Recent studies find that the addition of a bisphosphonate, such as zoledronic acid or alendronate, has demonstrated efficacy in preventing and managing osteoporosis in postmenopausal women with breast cancer who are being treated with an AI.[10] The combination of bisphosphonates with AIs has been shown to preserve bone mineral density in post-menopausal women undergoing hormonal therapy for breast cancer, as well as in some subgroups of individuals living with breast cancer.[11,12,13]

HORMONAL TREATMENTS STUDIED FOR REDUCING BREAST CANCER RISK

SELECTIVE ESTROGEN-RECEPTOR MODULATORS (SERMS):

Generic name:	Brand name:	Manufacturer:
Tamoxifen	Nolvadex	AstraZeneca
Raloxifene	Evista	Eli Lilly

AROMATASE INHIBITORS:

Generic name:	Brand name:	Manufacturer:
Anastrozole	Arimidex	AstraZeneca
Exemestane	Aromasin	Pfizer
Letrozole	Femara	Novartis

CHEMOPREVENTION—A BAD IDEA FOR PUBLIC HEALTH

Chemoprevention,[14] or the idea of using drugs to "prevent" breast cancer as described in this fact sheet, is troublesome. Research on the so-called breast cancer "prevention" medications[15] has been problematic in four major areas: comparative studies that do not include a placebo group; the misleading reporting of findings; the widespread increase of screenings that expose people to harmful radiation; and the lack of diversity in clinical trials that assumes "one size fits all." These studies appear to be designed to promote sales of expensive drugs to large populations of people living with and at risk of breast cancer, without clear evidence of safety, and little to no concrete data on overall survival rates and quality of life.

THE COMPLEXITY OF ANALYZING LONG-TERM SURVIVAL BENEFITS

Studies of breast cancer "prevention" medications have focused on the specific goal of achieving lower rates of breast cancer incidence. The long-term survival benefits of these breast cancer "prevention" drugs still depend on various factors, including the individual's risk profile, the specific characteristics of the breast cancer, and how well the treatment is tolerated. For example, for people diagnosed with hormone receptor-positive breast cancer, adjuvant therapy with drugs like tamoxifen or aromatase inhibitors have been shown to significantly reduce the risk of cancer recurrence, leading to improved long-term survival. Also, in some high-risk individuals without a breast cancer diagnosis, these drugs have been shown to reduce the risk of developing breast cancer in the first place, potentially contributing to long-term survival benefits.

The duration of treatment with breast cancer prevention drugs seems to also impact their long-term effectiveness. Studies have explored the optimal duration of treatment, and decisions about the duration are often individualized based on factors such as the type of drug, patient characteristics, and potential side effects. Responses to these drugs also vary among individuals.[16] Some people experience significant benefits, some are unable to tolerate the side effects, and others may not respond well for other reasons.

The absence of a definite, clear answer on whether these medicines are truly preventive, or whether they simple delay a person's cancer diagnosis, is why we continue to prioritize and advocate for individualized treatment plans. Also, while these drugs may provide substantial long-term survival benefits, they are also associated with side effects, and the decision to use them should be based on a thorough evaluation of individual risk and benefit factors.[17]

ABSENCE OF PLACEBO CONTROLS

The STAR Trial compared raloxifene directly to tamoxifen, without use of a placebo group. The decision to not include a placebo control group was heavily criticized at the beginning of the trial and eliminated the possibility of knowing how taking either drug compares to taking no drug at all. The practice of running studies that compare one drug to another—without providing a control group to determine whether no treatment is as good as the treatment being evaluated—is prevalent in chemotherapy trials. This practice assumes that one of the drugs is a highly regarded treatment, and that denying that treatment would be unethical.

MISLEADING STATISTICS

Another concern with "prevention" medication studies was the misleading reporting of results. It had become the practice to make public announcements of results prior to peer-reviewed publication. Such announcements, and even journal articles, often couch statistical findings in the most positive manner, and create a media outpouring that is almost always exaggerated and misleading. BCAction is not in favor of "medicine by press release!"

Breast cancer is not considered to have a relatively rare occurrence in people assigned female sex at birth. It is one of the most common cancers among people in this category, globally. However, the differences in incidence portrayed using "relative risk" tend to appear much larger than absolute risk differences. We are interested in absolute risk, which is essential to understanding outcomes. But more often, relative risk is what gets reported. Emily Kaplan, writing for the Broken Science Initiative, provides a simple example of absolute risk:

"Let's say that we have two groups, that we each have a thousand people that we're going to study. One group exercises a lot. One group doesn't exercise at all. We want to know if the likelihood that you get hit by lightning is greater increased or decreased based on how often you exercise.

"So, let's just say we have a group of a thousand people who work out regularly, and out of that group five of them get struck by lightning in the course of our experiment. In our other cohort, or group, we have four people who are hit by lightning who never work out.

"So, we can compare these two groups, and we can say what is the absolute difference between these two groups? The answer is one: 5 minus 4 is 1, so that's our absolute difference.

"If we're looking at that statistically it's simply 0.1 percent. That's the difference. That's a teeny, tiny difference. No one would really ever think there was anything to report on that because obviously your rate of exposure to lightning is probably not at all impacted by working out or not work working out."

Another example of this comes from the preliminary findings from the STAR trial, which found both raloxifene and tamoxifen reduced breast cancer incidence by 50%. Maryann Napoli, of the Center for Medical Consumers[18], explains what this means:

"Of the 9,700-plus women in each drug group, about 167 got breast cancer. This translates to 1.7%; whereas, 3.4% would be expected to develop breast cancer had they not taken a drug. (Hence the 50% reduction in breast cancer incidence). Another way of saying the same thing is: 98.3% of women will not get cancer if they take raloxifene or tamoxifen; whereas, if they take no drug, 96.6% of women will not get cancer [an absolute difference of 1.7%]. Obviously, much more research is needed to determine who is at high risk for breast cancer."

PREVENTION CREEP—DANGER AHEAD

Most of the so-called breast cancer prevention pills were initially used as treatments for advanced breast cancer, then later to treat people with early-stage breast cancer, and finally considered to lower risk in people without symptoms. Eric Schneider, a medical and public health professor at Harvard, has referred to this process as "prevention creep."[19]

In 1999, there was a concerted campaign in the medical community to boost the number of people taking drugs to lower their risk for cancer. The American Association for Cancer Research's (AACR) Chemoprevention Working Group proposed the promotion of a broad educational drive to be directed at physicians and "society as a whole" to accomplish this.[20] **The centerpiece of this educational campaign was to correct the "misperception" that healthy people should not be treated with potentially harmful drugs.**

According to the AACR's working group, we need an intensive educational effort to convince people that absence of clinical symptoms may not guarantee that one is "healthy," and that a more sophisticated understanding of risk factors can be used constructively to develop interventions that have the potential to provide better health.[21]

The AACR chemoprevention campaign was particularly troubling in an era when the FDA was led by people who favor accelerated approval of chemoprevention drugs, had close relationships with drug manufacturers, and supported product liability changes that would protect drug companies from suits initiated by injured patients.[22]

People deserve to be fully informed about the benefits and risks of breast cancer "prevention" drugs prior to making a decision about whether or not to take them. Individuals should not have to make these important decisions under conditions of uncertainty.

Breast Cancer Action, while clearly understanding the large numbers of people at risk for developing breast cancer, does not advocate using drugs to treat risk. At the moment, each of the drugs currently marketed for cancer prevention has serious side effects. Moreover, the focus on pills for prevention diverts resources from finding and eradicating environmental causes of, as well as effective treatments for, breast cancer.

A NOTE ABOUT GENDERED LANGUAGE

Breast Cancer Action prefers to use specific gender identities, such as cis-woman, trans-woman, non-binary, or gender expansive person, instead of gendered categories like "man" and "woman," which can erase or exclude the entirety of our identities. But when citing studies that use this type of gendered language, we do not alter the original language employed by the authors.

ABOUT BREAST CANCER ACTION

The mission of Breast Cancer Action (BCAction) is to achieve health justice for all people at risk of and living with breast cancer by focusing on systemic interventions, which includes policies, institutions, and practices, and by centering people with the furthest relationships to power.

REFERENCES

[1] Tamoxifen is one of a class of drugs called selective estrogen receptor modulators (SERMs) that inhibit cancer growth. By attaching themselves to estrogen receptors in cells, SERMs prevent natural estrogens from entering those cells. SERMs are termed "selective" because in some receptors they block estrogen, and in others they act as estrogens.

[2] Tamoxifen is officially listed as a cancer-causing agent on the list of carcinogens reported by the US Department of Health and Human Services.

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[13] Ibid

[14] Gu, K. J., & Li, G. (2020). An Overview of Cancer Prevention: Chemoprevention and Immunoprevention. Journal of cancer prevention, 25(3), 127–135. https://doi.org/10.15430/JCP.2020.25.3.127

[15] Other drugs have been mentioned as candidates for prevention pills. For some time, aspirin and other pain-killers, particularly COX-2 inhibitors (such as Vioxx and Celebrex), were thought about as possible breast cancer prevention pills, but the revelation that Vioxx and related drugs caused deaths from cardiovascular events removed them from further consideration. Statins, a class of cholesterol lowering drugs, have been studied as a potential chemoprevention pill, but there is no evidence to substantiate their effectiveness in lowering breast cancer risk.

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[17] Ibid

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