

Reducing Breast Cancer Risk with Drugs

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Executive Summary

1. Researchers have found that some drugs indicated for breast cancer treatment—aromatase inhibitors (AIs) and selective estrogen receptor modulators (SERMs)—may also be effective for reducing the risk of developing breast cancer among high-risk women, with some studies showing upwards of a 50 percent decrease in cancer risk. The U.S. Food and Drug Administration (FDA) approved tamoxifen for this purpose years ago, and now raloxifene (a SERM) has also been approved. The AIs anastrozole, letrozole, and exemestane are not FDA-approved for preventive use. The AIs have only been studied in postmenopausal women, and are likely to be effective only in postmenopausal women.
2. SERMs block estrogen activity in certain tissues, whereas AIs block estrogen production in the adrenal glands and in fatty tissue. High-risk women who consider using these drugs for chemoprevention should take all of the potential side effects into account before starting a drug regimen, as they will need to be on the drug for years in most cases. Tamoxifen has a side effect of increasing the chances of developing endometrial cancer in postmenopausal women. Raloxifene and AIs do not carry that side effect but can only be used in postmenopausal women. Both SERMs can increase the risk of venous thrombosis and pulmonary emboli (blood clots that travel from the leg veins to the lungs), although raloxifene appears to be safer than tamoxifen for this problem. The AIs can lead to thinning of the bones (osteoporosis) and have undergone a shorter period of scrutiny for other side effects than SERMs.
3. Tamoxifen and the AIs have been shown to reduce recurrence of breast cancer among those who already have the disease, making them effective drugs for secondary chemoprevention. This indication has not yet been established for raloxifene.
4. Physicians should discuss breast cancer chemoprevention with all high-risk women. Women who are considering chemoprevention need to be aware of all of the potential benefits and risks and should carefully weigh those factors before making a decision. This requires a precise analytical tool to quantify, as accurately as possible, her real risk of developing breast cancer. Since those choosing chemoprevention will be healthy at the time of this decision and are expected to be taking the medication for a long period, the patient and her doctor must be fairly sure that she is a member of a significantly higher risk group before initiating this therapy.
5. Future research goals include the development of safer effective drugs, better risk models, and progress in preventing estrogen-receptor-negative tumors.

Introduction

Thirteen percent of women in the United States are expected to be diagnosed with breast cancer at some point in their lives, and more than 178,000 new cases are projected to be diagnosed in 2007. Excluding non-melanoma skin cancers, breast cancer is the most common cancer among American women, and more than two million survivors currently live in the United States. Approximately one-tenth of newly-diagnosed breast cancer patients will have metastases at the time of diagnosis. Even after successful initial treatment, recurrences will occur in more than 25 percent of patients. The disease kills more than 40,000 women in this country each year and is the second deadliest cancer among women, second only to lung cancer.¹

Earlier detection due to improvements in breast cancer screening technology and increased awareness and utilization of these modalities, along with better treatments, has significantly curbed fatality rates. Chemotherapy regimens are constantly improving; women diagnosed with breast cancer have a wider array of options for battling the disease.

But among the most significant advances are those efforts to actually prevent breast cancer from ever arising, a preventive tactic aimed particularly at high-risk women. Although this strategy—*chemoprevention*—has been intensively studied recently, it has not gotten its fair share of media and public health attention.

Chemoprevention involves the administration of medication(s) to prevent the development of a cancer in the initial absence of cancer, or to prevent a known pre-cancerous condition or lesion from progressing to actual cancer.

Preventing breast cancer is not an easy task. Unlike some other cancers, where modification of lifestyle factors reduces risk substantially (e.g., lung cancer risk being markedly reduced by not smoking), the effect of the known risk factors for breast cancer is relatively small. Furthermore, with the exception of a few risk factors (obesity after middle age, for example), most factors that contribute to risk of breast cancer, such as age, family history of the disease, and age at menarche and menopause, don't change with lifestyle modifications. Because of practical limitations, researchers have searched for other ways to stop the disease before it starts.

One such method is reducing the risk of breast cancer with medication, known as chemoprevention, which is geared toward women who have never had breast cancer but are considered to be at a higher than average risk. This report presents a snapshot of the risk factors for breast cancer and examines some of the most promising chemoprevention drugs: aromatase inhibitors (AIs), specifically anastrozole, letrozole, and exemestane; and selective estrogen receptor modulators (SERMs), specifically tamoxifen and raloxifene. At present, tamoxifen and the AIs are used primarily in women already diag-

nosed with breast cancer to reduce the incidence of recurrence. But evidence has shown that all these drugs dramatically cut the risk among women who have the greatest likelihood of developing breast cancer. Of the five drugs this report focuses on, only tamoxifen and raloxifene have been approved by the Food and Drug Administration (FDA) for chemoprevention of breast cancer. Doctors, however, can prescribe any of them for breast cancer prevention, as long as the patient understands and accepts that these drugs (with the exception of tamoxifen and raloxifene) are not FDA-approved for that indication.

Risk Factors for Breast Cancer

“Risk factors” are specific characteristics, predispositions, or exposures that are believed to increase the chance of developing a disease. And as with most cancers, breast cancer causation can’t be ascribed to a single risk factor; rather, a range of factors affect a woman’s chances.²

Risk factors for one cancer do not necessarily have any role in the development of other cancers. For example, although sun exposure increases the likelihood of developing skin cancer (and thus is considered a risk factor for the disease), it does nothing to change one’s chances of getting stomach or lung cancer. And just because a person has a risk factor (or several) does not mean he or she will develop the disease; rather, it means that they are part of a group having a higher than average risk for that cancer. Vigilance and risk-reduction strategies in higher-risk groups can provide sensible and cost-effective approaches to cancer prevention.

As the names imply, modifiable risk factors include characteristics and exposures that a person can change, whereas non-modifiable risk factors are predetermined or out of a person’s control. The following list shows that the majority of risk factors for breast cancer are non-modifiable, minimizing their value for risk modification. The limited number of modifiable risk factors underscores the need for identification of preventive approaches for breast cancer.

The principal risk factors for breast cancer are:³

Gender (non-modifiable) – Fewer than 1 percent of breast cancer cases occur in men, so it is primarily considered a women’s disease. The much larger amount of breast tissue in women and their unique hormone profile make them more susceptible to the disease.

Age (non-modifiable) – The risk of developing breast cancer, like most cancers, increases with age: nearly four out of five breast cancer cases occur among women aged 50 and older, and only about 15 percent of breast cancer cases occur in women less than 40 years old.¹

Family History (non-modifiable) – Having one or more first-degree relatives—specifically a mother, sister, or daughter—with breast cancer approximately doubles a woman’s chances of developing the disease.² Other familial risk factors include having several generations of family members with breast or ovarian cancer, having a relative with cancer in both breasts, and having a relative diagnosed with breast cancer at a young age. In fact, a review of risk factors for breast cancer concluded that women who had a first-degree relative who developed cancer in both breasts before the age of 50 had an eight-fold increased risk of breast cancer.³ The increased risk involved in having a close relative develop breast cancer after age 50 is not as great as it is if the relative is younger.

Genetic Risk Factors (non-modifiable) – In about 10 percent of breast cancer cases, the disease is considered hereditary because of gene mutations, and the BRCA1 and BRCA2 gene mutations have received particular attention. About one in 500 women in the general population is estimated to have a mutation in one or both of the BRCA genes; among those who do, the risk of developing breast cancer is markedly increased. Women who inherit the BRCA1 mutation are estimated to have a 65 to 85 percent chance of developing breast cancer by age 70, and those who inherit the BRCA2 gene mutation are estimated to have about a 45 percent chance.^{4,5} Both mutations increase the likelihood of developing breast cancer at a younger age. The BRCA-1 mutation also confers an increased risk of ovarian cancer, but such an increase is not seen with BRCA-2 carriers.

Other single gene mutations, such as *p53*, ATM, and CHEK-2 also have been shown to increase breast cancer risk. And in May 2007, researchers with the human genome project reported that they had found six new sites of gene mutations that are believed to increase the risk of breast cancer. The researchers said more than 60 percent of U.S. women probably carry at least one of the mutations in one of these genes.⁶ It is likely that, in the foreseeable future, we will be able to diagnose these carriers early on, leading to both more widespread and more targeted chemoprevention modalities, with a resultant lowering of the toll of breast cancer.

Personal Medical History (non-modifiable) – Women who have already had breast cancer have a three- to four-fold increased risk of developing a new cancer¹, either in the other breast or in a different part of the same breast (this is not a recurrence of the original cancer). Other breast conditions, such as lobular carcinoma *in situ* (LCIS), ductal carcinoma *in situ* (DCIS), and atypical ductal hyperplasia, may increase risk as well.

Reproductive History (semi-modifiable) – Women who started menstruating before age 12 or who went through menopause after age 55 have a slightly elevated risk of breast cancer. Women who never had a full-term pregnancy or gave birth for the first time after age 35 also have a slightly higher risk. The factors related to menstruation are noted in the “semi-modifiable” area above. Reproductive factors influencing breast cancer risk are likely to be related to a woman’s lifetime exposure to estrogen, a female hormone that fluctuates with a woman’s menstrual cycle and reproductive history.

Lifestyle Factors (modifiable) – Obesity among postmenopausal women has been found to increase breast cancer risk.¹ Regular exercise and sensible, balanced dietary regimes can prevent obesity. Although obesity has not been shown to be a risk factor in young women, participation in regular and vigorous exercise reduces risk of breast cancer in young women as well. Long-term hormone-replacement therapy has been linked to an elevated breast cancer risk, especially in older women.⁷ Some studies have linked other factors to breast cancer, such as breastfeeding (one shows that breast feeding for 1.5 to 2 years slightly lowers the risk¹), but many are inconclusive. Alcohol consumption has been shown to be fairly clearly linked to increased risk of breast cancer—and smoking and oral contraceptive use have also been labeled as risk factors, but the evidence remains inconclusive. There are a large number of hypothetical, unsupported (but often highly publicized) causes of breast cancer, such as trace chemicals in the environment, the use of antiperspirants, or wearing certain clothing, which have no scientific basis.

Chemoprevention

Most people have probably heard the word *chemotherapy*, which occurs when doctors use medicines to treat patients who have cancer. *Chemoprevention*, on the other hand, is the use of medications to reduce the risk of getting cancer in the first place. The term can be somewhat misleading, as cancer chemoprevention doesn't eliminate the risk of getting cancer completely (unlike a vaccine, which can provide close to 100 percent protection). But to varying degrees, chemoprevention can substantially decrease the risk of developing cancer, in much the same way that cholesterol-lowering drugs can help prevent heart disease or bone-strengthening pills can help prevent osteoporosis.

The topic of chemoprevention is riddled with difficult questions, and anyone considering it has to consult with a physician and balance the risks and the benefits before moving forward. Any agent that has the power to reduce the risk of cancer is likely to also have other consequences for the body, including undesirable side effects. The thought of giving healthy people strong medication is distressing for some, but it is not unprecedented. Some people at risk of a heart attack will take aspirin, for example, and others take blood pressure-lowering medication to reduce the risk of a stroke. Those medication regimens—even aspirin—aren't without some risk of harmful effects. But when healthy people are at a higher risk of getting a disease, they have to weigh the options, and decide if the (generally less severe) risks associated with preventive medicine are worth reducing the possibility of getting a more severe disease or condition.

Those who don't have a significantly elevated chance of developing an illness have less to gain with chemoprevention because they are less likely to get the disease anyway. In such a case, the small chance of a benefit almost certainly would be outweighed by the negative side effects. For example, doctors often recommend that 60-year-old patients take a small dose of aspirin every day to reduce their risk of a heart attack. They will

almost never recommend this to their 20-year-old patients, because heart attacks are common in 60-year-olds and rare in 20-year-olds. Both younger and older people are at risk of developing side effects—such as stomach bleeding—from aspirin therapy. The benefits of aspirin outweigh the risks for the 60-year-old but not for the 20-year-old. Researchers are also looking into medications that can reduce the risk of developing other cancers, such as colorectal cancer. Indeed, the concept of chemoprevention extends beyond cancer itself. The current recommended approach to treating elevated cholesterol with statins to prevent a heart attack can also be termed chemoprevention.

The Use of Aromatase Inhibitors and Selective Estrogen Receptor Modulators to Reduce Breast Cancer Risk

Aromatase Inhibitors (AIs)

There are currently three AIs available to decrease risk in women at high risk of getting breast cancer: anastrozole (Arimidex, made by AstraZeneca Pharmaceuticals), letrozole (Femara, made by Novartis), and exemestane (Aromasin, made by Pfizer). They are approved for use for women already diagnosed with breast cancer to help stop the growth of tumors and prevent recurrences (secondary prevention), but some studies have shown AIs to be an effective means of primary prevention—preventing the initial appearance of breast cancer—as well.^{8 9} It should be noted that these studies were all done in women who already had a diagnosis of breast cancer. Some studies suggest that there may be differences in the degree of estrogen suppression among the AIs, but the nature of those differences thus far hasn't been sufficiently explored.¹⁰

Seventy-five percent of breast cancer patients have cancer that is estrogen-receptor-positive, meaning it uses estrogen to grow. AIs are thought to be effective as a preventive tool because they stop 97 to 99 percent of a postmenopausal woman's estrogen production by inhibiting aromatase, an enzyme that catalyzes the conversion of testosterone (an androgen) to estradiol (an estrogen) in tissues such as the adrenal glands, placenta, fat tissue, and brain. Because they do not stop estrogen production in the ovaries (where most estrogen is produced during childbearing years), these drugs can generally only be taken by women who are postmenopausal because that is when they are most effective, and safe.

None of these AIs has been approved by the FDA for patients who don't already have breast cancer, but all three have been shown to reduce cancer recurrence and the development of new cancers in women who have the disease. In fact, studies have shown the success rate in blocking new cancers to be upwards of 50 percent.⁸ Currently, researchers are studying women at high risk of developing breast cancer to more accurately measure the preventive effects of AIs in women with no personal history of the disease.

Selective Estrogen Receptor Modulators (SERMs)

Tamoxifen (formerly made by AstraZeneca in the U.S., now only generic) and raloxifene (Evista, made by Lilly) are SERMs, which block estrogen activity in certain tissues and enhance it in others. (SERMs have been called “designer estrogens” by some, but they are non-hormonal, and they are certainly not estrogens. They do have estrogen-like effects in some tissues.) Tamoxifen has been used to treat breast cancer since 1977. In the Breast Cancer Prevention Trial (BCPT), which took place from 1992 to 1997 and included 13,000 women at high risk of getting breast cancer, those who took the drug developed only half as many breast cancers as those taking a placebo.¹¹ But because it has estrogen-like effects in the uterus, tamoxifen comes with an increased risk of endometrial cancer, and for that reason, doctors are hesitant to prescribe it for healthy women. In the BCPT, however, five women developed breast cancer for every one who developed endometrial cancer, indicating that breast cancer is a much more common threat. Tamoxifen use also increases the risk of developing blood clots and cataracts.

Raloxifene was FDA approved as an osteoporosis drug in 1997, and it was secondarily found to decrease breast cancer incidence. When it was studied with breast cancer as a focus, researchers found that women were 66 percent less likely to develop breast cancer if they were taking raloxifene rather than a placebo for eight years.¹² Long-term use of raloxifene, like tamoxifen, comes with an increased risk of developing blood clots. But use of raloxifene in breast cancer prevention might be more widely accepted in those women who are at high risk for both breast cancer and osteoporosis, since the drug has been shown to help prevent both. And because it does not promote estrogen activity in the uterus the way tamoxifen does, raloxifene also does not increase endometrial cancer risk.

Recently, the Study of Tamoxifen and Raloxifene (STAR) in 2006 found that raloxifene worked as well as tamoxifen in reducing the incidence of breast cancer (about a 50 percent reduction in breast cancer risk) with 36 percent fewer uterine cancers and 29 percent fewer blood clots.¹³

In September of this year (2007), Evista was approved by the FDA for use as a chemopreventive agent against invasive breast cancer, as well as for women with osteoporosis.

Comparing the Two Classes of Drugs

AIs may have a better chance of preventing breast cancer because they reduce overall estrogen levels, whereas SERMs only inhibit the function of estrogen receptors. (Some women, however, might prefer SERMs because they preserve some fundamental estrogen-like functions in other tissues.) The side effects of AIs, unlike tamoxifen, do not include an increased risk of endometrial cancer, and they very rarely cause blood clots. There is, however, an increased risk of bone loss with AIs, so women who take them are also encouraged to take calcium, vitamin D, and osteoporosis drugs, as well as have regular bone-density screenings. In addition, there are other reported side effects, such as

night sweats, weight gain, nausea, fatigue, hot flashes, and joint pain. Taking AIs and SERMs simultaneously is not advisable, as they have been found to have antagonistic interactions.

All of these drugs are intended for women who have a high risk of developing breast cancer, and it is important that a woman considering an AI or SERM drug regimen be educated about their potential side effects. Some side effects, such as the increased risk of endometrial cancer, are serious health concerns; others, such as night sweats, mainly affect quality of life.

Another barrier to chemoprevention is the cost of medicines. Unlike medical-trial participants, women who choose to take AIs or SERMs as chemoprevention are likely to face significant prescription costs, which might cause some high-risk healthy women to decide against taking the drugs. Until (and unless) more studies establish the effectiveness of AIs and SERMs for breast cancer chemoprevention—thus encouraging the FDA to approve them for that indication—insurance companies will not help high-risk women cover the cost of the medications for this use.

Secondary Chemoprevention

Chemoprevention can also play a role in fighting recurrence of breast cancer. Secondary chemoprevention differs from primary chemoprevention in that it is intended for women who have (or have had) cancer and are seeking to prevent both the recurrence of the disease and any new cancers. In these cases, some type of chemotherapy (drugs used to kill cancer cells present in the body) may have already been used, but chemoprevention may still serve its purpose of reducing the risk of cancer recurrence or of a new cancer.

By hindering the activity of the hormone estrogen in the breast tissue (SERMs), or reducing the levels of estrogen in the circulation (AIs), aromatase inhibitors and selective estrogen receptor modulators have been found to both slow the growth of cancer and reduce the likelihood of new cancer forming. Indeed, the best data in favor of using AIs and SERMs as chemoprevention come from studies involving women who already have breast cancer, where the medication was shown to reduce the incidence of new cancers.

One study published in 2003 showed that a drug regimen involving one of the AIs—letrozole—significantly improved disease-free survival. In that study, the patients who took letrozole after standard tamoxifen (SERM) treatment were 46 percent less likely to develop a new primary tumor in the other breast than those taking the placebo.⁸ Other studies have found the other AIs to be similarly potent in preventing new cancers.⁹

AIs and SERMs in Secondary Chemoprevention

For women who have had breast cancer, these drugs have been found to be effective for secondary chemoprevention as well. One study among breast cancer patients who took tamoxifen for two years found that those who began taking AIs instead had a 40 percent lower recurrence rate than women who continued to take tamoxifen.¹⁴ Other research concurs: among postmenopausal breast cancer patients who took anastrozole (either alone, or combined with tamoxifen), there was a 58 percent reduction in the odds of developing a new cancer in the other breast compared to those in the tamoxifen-only group.¹⁵ In a study of 5,000 women with early-stage breast cancer who took tamoxifen for five years, Letrozole reduced the recurrence of new cancer by 50 percent.⁸

One limitation of tamoxifen is that it becomes less effective after five years of treatment—a problem researchers say occurs because the cancer cells become resistant to the drug. Also, studies have shown that side effects begin to outweigh benefits after five years. AIs have been shown to be effective in reducing recurrence after the completion of either two or five years of tamoxifen therapy. The optimum sequence and duration of AIs and SERMs remain under evaluation.

SERMs are still an effective means of secondary chemoprevention, however. Some studies showed that tamoxifen produced a 40 to 50 percent reduction in breast cancer risk among women with a history of previous breast cancer or ductal carcinoma *in situ*.¹¹ In light of that, SERMs are commonly prescribed initially, then followed after several years by AIs. However, some breast cancer experts are now prescribing initial treatment with AIs instead. Studies are underway to evaluate whether combinations of SERMs and AIs may be even more effective.

It should be noted, again, that the AIs have only been studied in postmenopausal women, and their mechanism of action suggests that they are likely to be effective only after menopause.

Alternative Remedies

No scientific study has shown alternative remedies involving herbal or dietary supplements to be effective at preventing or treating breast cancer. Additionally, numerous studies suggest that interactions between dietary or herbal supplements and cancer drugs could be dangerous.¹⁶

This does not mean that a woman at high risk of getting breast cancer should not examine every option available to her. Being healthy overall is always helpful in terms of fighting off disease. These alternative methods have not, however, been shown to be an effective replacement for a chemoprevention or chemotherapy regimen. And any complementary effort a woman makes to either prevent or treat breast cancer should be discussed in detail with her physician to ensure no unintended side effects arise.

From a scientific point of view, there are many downsides and risks to so-called “alternative therapies”—especially with regard to cancer—and essentially no proven advantages, so any woman contemplating such an approach should beware of quackery. Delaying effective treatments while employing unproven methods can lead to preventable progression of disease and needless suffering.

Individual Decision-Making

Self-assessment is an initial step a woman should take when it comes to chemoprevention. Along with her doctor, a woman needs to evaluate her personal risk of getting breast cancer based on her family, reproductive, and medical history. Some women will find they overestimated their risk of developing breast cancer, and others may find they underestimated their risk. False and unproven risk factors—such as prior abortions or breast augmentation—or even the idea that local environmental factors cause “cancer clusters”—sometimes lead women to believe they are at greater risk than they actually are.

Even if a woman has an increased risk of developing breast cancer, several other issues should be considered before she decides whether to take an AI or SERM. Some of these issues include:

Age – AIs and SERMs are most effective in postmenopausal women, though younger women who have a particularly high risk may consider chemoprevention with a SERM. Tamoxifen seems to have a lower incidence of side effects in the premenopausal population.

Osteoporosis – Women who have osteoporosis or who are at a high risk for it should take the osteoporosis-promoting effect of AIs into consideration before making a decision on a particular course of treatment. Raloxifene can help to avoid or treat osteoporosis while also lowering the risk of breast cancer.

History of Blood Clots Requiring Medical Treatment – Women who have an increased risk of developing blood clots should be cautious about SERMs, which are known to increase the risk of blood clots.

Use of Anticoagulant (“Blood Thinner”) Medication – The anticoagulant effects of some drugs can be increased when they are taken simultaneously with tamoxifen, so women who are taking medication with blood-thinning effects (e.g., coumadin) should be cautious about taking this drug. Raloxifene, however, has the opposite effect: it inhibits the blood-thinning effects of anticoagulants. The benefits and risks of using AIs and SERMs in combination with these medications must be thoroughly discussed with a doctor.

Previous Hysterectomy – A woman who has had this procedure is not at risk of endometrial cancer, and thus tamoxifen would be safer than it would be for a woman with a uterus.

Plans for Contraception Among Premenopausal Women – Because of the hormonal effects of these chemoprevention drugs and the potential for fetal damage, women should not become pregnant while taking them, and sexually active premenopausal women should use a reliable form of contraception, including a barrier method.

Taking all of this into account, a woman and her physician should be able to determine whether she is a suitable candidate for breast cancer chemoprevention. The decision to move forward with any of these medications can only be made by the informed patient, and her personal concerns about side effects and her fear of breast cancer are likely to have a major influence on the decision. As with any medical decision, it comes down to each patient making a choice based on the likely risks and benefits. If a woman has an above-average chance of developing breast cancer, she needs to determine whether taking steps to reduce that risk are worth the potential side effects of preventive drugs.

There are tools that allow women to assess their own breast cancer risk before going to see a physician. For example, the National Cancer Institute at the U.S. National Institutes of Health has a risk calculator (www.cancer.gov/bcrisktool/) on its website, which allows a woman to enter her personal history and determine whether she needs to be particularly vigilant. This standardized and commonly used risk-assessment tool, also known as the Gail Model, takes the following factors into account: age, race, age at menarche (period onset), age at first live birth, number of close relatives with breast cancer, number of breast lesions requiring biopsy, history of atypical hyperplasia, BMI, and mammographic density of breast tissue.

But self-assessment has its limitations. Any woman in this situation will have doubts and fears, which are best discussed in detail with her doctor. Women have the right to know all of the information necessary to make educated choices in this important area of their personal health.

Some women, at very high risk of developing breast cancer—i.e., those with the BRCA1 or BRCA2 mutations—consider prophylactic (preventive) bilateral mastectomy instead of living with the fear of cancer. The incidence of these mutations in the general population is quite low, in the one in 500 range, but should be evaluated in women with a strong family history of early-onset breast cancer. Ashkenazi Jews have a somewhat higher incidence. Among women with one of these genetic profiles, the risk of breast cancer rises to the 50-85 percent level, explaining why surgery is often considered. Chemopreventive drugs will not lower such a woman's risk sufficiently to rely upon this type of therapy in isolation.

No woman should consider dealing with these mutations on her own: genetic counseling should be done even before undergoing the test, and if the test results come back positive, an expert in this sub-specialty should be consulted.

What the Future Holds

Effective screening for breast cancer—and early steps to combat it—have substantially improved the outlook for those diagnosed with the disease. But more can be done, and as researchers continue to examine the potential for chemoprevention, the number of women with breast cancer in this country can likely be lowered.

A word that is consistently invoked in cancer research is “cure.” Finding a cure for those with breast cancer is a lofty and worthy goal, but if current chemoprevention efforts continue, drugs could prevent the disease from ever forming in most high-risk women. AIs and SERMs are really just the beginning: they’re the first drugs of their kind, and scientists are constantly modifying what they have and exploring new ways to prevent—and fight—breast cancer, with the fewest side effects.

One promising new SERM called arzoxifene is in clinical trials. This drug could provide postmenopausal women a new preventive option without some of the negative side effects (namely the endometrial cancer risk) of tamoxifen.

In addition, researchers are looking into ways to combat estrogen-receptor-negative breast cancer—the type of breast cancer that does not use estrogen to grow. Neither the SERMs nor the AIs have any significant effect on estrogen-receptor-negative growths, even before they are clinically apparent.

The recent discoveries made by the human genome project—that is, the linking of six more gene mutations to an increased risk of breast cancer—will only help refine researchers’ efforts to find pharmaceutical options for those high-risk women. Such advances are likely to further tilt the risk-benefit balance in favor of medical prevention of breast cancer. As this sort of research becomes more sophisticated as a tool to predict risk of certain diseases, more people will see that having an excellent predictor of breast cancer risk will allow us to make better decisions as to who will benefit from chemoprevention drugs.

AIs and SERMs are primarily for postmenopausal women, so there is also a need to further explore premenopausal preventive options. Scientists are studying isoflavones, which can act as estrogens in the body and might result in less potent levels of estrogen or estrogen metabolites, as well as short-course hormonal combinations that mimic pregnancy for women in their twenties and thirties who haven’t given birth.¹⁷

Since only lung cancer results in more cancer deaths among American women, more should be done to promote research into chemoprevention of breast cancer. Some of the best methods of preventing breast cancer have arisen from drugs originally studied to treat breast cancer patients. And when raloxifene was found to be potentially effective in preventing breast cancer—even though it was originally studied as an osteoporosis

drug—the results were encouraging. In September 2007, the FDA approved Lilly's application to market raloxifene as a breast cancer prevention drug, to protect women from invasive cancer (it's also now approved for chemoprevention in women with osteoporosis). Similarly, the AIs are not yet indicated as chemoprevention drugs, although evidence that they help reduce breast cancer risk, particularly in high-risk women, is accumulating.

If the FDA approves these drugs for preventive purposes, one of the most important steps toward breast cancer prevention could be taken. Some doctors presumably already prescribe SERMs and AIs for high-risk patients who do not already have breast cancer. If the FDA makes it easier for doctors to take that step (and for insurance companies to grant coverage), it is likely that many more high-risk women will have a new layer of defense against a disease that currently takes the lives of about 40,000 women in our country each year.

Other types of drugs now being evaluated for chemoprevention include: retinoids, retinoids (a sub-category of retinoids, related to vitamin A), anti-inflammatory drugs such as celecoxib (Celebrex), and statin drugs (usually used to reduce cholesterol levels in the blood). Also, pituitary and hypothalamic hormones that desensitize the ovary to normal stimulation, thereby reducing estrogen production, are being investigated for prevention use. And tyrosine-kinase inhibitors of the same class as the breakthrough drug Gleevec (imatinib) are being studied.

Perhaps the two major challenges for medical researchers in this area in the near-term are (1) increasing the awareness among both women and primary care/gyn physicians about the benefits and nature of chemopreventive agents and (2) finding ways to reduce the risk of breast cancer that is not dependent on estrogen, e.g., estrogen-receptor-negative tumors (approximately 25-30 percent of breast cancers, with a poorer prognosis and less response to all treatments). Many women who might benefit from a risk-lowering agent are not being offered one because their doctors are not fully informed as to their benefit-risk properties, and women are not yet educated enough on the subject to demand consideration of such treatment. Employing the newer techniques in drug discovery and development, including toxicogenomics and pharmacogenetics, will enable researchers to develop preventive agents more specific to an individual woman's real risk, thus improving the benefit-risk equation, as would the elucidation of better, non-invasive biomarkers of increased risk.

One thing is clear: the science of chemoprevention of breast cancer (among other cancers) is in its infancy. Over the next decade, it is safe to say that more, safer, and more effective preventive drugs will become available, furthering lowering the toll of this tragic disease.

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