

# Breast Cancer Risks and Prevention

## Fourth Edition

*This booklet is written to help women understand what their risk factors are for the development of breast cancer and how they can reduce their risk.*

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## Contents

About the Authors	2
Preface to the Third Edition	3
Preface to the Fourth Edition	3
1 Introduction	4
2 Understanding What Risk Means	4
3 Understanding Breast Cancer, Carcinogens and Promoters	5
4 Exposure to Estrogen & Breast Cancer Risk	6
5 Breast Maturity & Breast Cancer Risk	8
6 Age and Length of Carcinogen Exposure & Breast Cancer Risk	10
7 Reproductive History & Breast Cancer Risk	10
8 Pregnancy & Breast Cancer Risk	11
9 Radiation & Breast Cancer Risk	11
10 Genetics & Breast Cancer Risk	12
11 Hormonal Birth Control and Hormone Replacement Therapy & Breast Cancer Risk	12
12 Breast Feeding & Breast Cancer Risk	13
13 Metabolism & Breast Cancer Risk	13
14 Diet and Life Style & Breast Cancer Risk	13
15 Factors Which Increase and Decrease Breast Cancer Risk	15
16 Strategies for Lowering Your Breast Cancer Risk	17
Summary	18
Glossary	19
References	21

Page references refer only to the pages in this PDF file, **NOT** to the 29-page printed and bound booklet which is available for purchase. Printing this 22-page document to double-sided pages will produce an 11-page document.

## About the Authors

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## Preface to the 3<sup>rd</sup> Edition

Over the last thirty years, while most major cancers have started to decline, breast cancer incidence in the US has increased by an alarming 40%. Most of this increase has occurred in the authors' generation, the generation of "Women's Lib."

This generation has lived with marked changes in lifestyle compared to their mothers. For example, they pursued careers and delayed childbearing with the help of contraceptive pills or decided to forego childbearing altogether. Such changes in reproductive patterns as well as other lifestyle changes can account for most, if not all of the increase in breast cancer. "You've come a long way baby," said one ad encouraging women to smoke, causing not only an increase in lung cancer but in breast and other cancers as well.

Publication of the first edition of this booklet was prompted by the authors' knowledge that much of the recent surge in breast cancer was attributable to avoidable risks, and the fact that other sources of information on breast cancer risk tended not to offer complete information on avoidable risks. It has been the authors' hope that, armed with full and accurate information, women can make healthier choices that will minimize their risk of breast cancer.

In this effort, the third edition has been greatly expanded, with particular emphasis on dietary and lifestyle factors, such as alternatives to hormone use for contraception and postmenopausal medication. The reference list has also been updated and expanded.

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Joel Brind, Ph.D.  
July 18, 2005

## Preface to the 4th Edition

Although the 3<sup>rd</sup> Edition of Breast Cancer Risks and Prevention was published less than two years ago, recent dramatic events have necessitated the updating and expansion of the information and references, resulting in the 4<sup>th</sup> edition.

In 2002, a major clinical trial of combination hormone replacement therapy (HRT) was halted due to unexpected negative results. While HRT was supposed to decrease the risk of heart attack, by the time the 5-year study was half way done, it was clear that the risk of heart attack went up. That negative surprise required the early termination of the study, which garnered wide publicity.

Yet the most significant result of that event had to do not with cardiovascular disease, but with breast cancer. Although researchers had known for years that long-term use of HRT increased the risk of breast cancer, this was news to the general public—to American women and even many of their doctors. The result was a breathtaking drop in HRT use: Between 2002 and 2005, the annual number of HRT prescriptions for American women plummeted from 61 million to 18 million.

Late last year, the cancer incidence results were compiled for 2003. A decrease in the number of new breast cancer diagnoses was evident almost immediately after the WHI study's termination in 2002. The steep decline continued until it leveled off in 2004, when the reduced number of HRT prescriptions had also leveled off. Moreover, the decline in breast cancer incidence was confined to women over age 50 (the only age groups with significant HRT use) in which groups breast cancer incidence dropped by 11.5%! In addition, the preponderance of the drop was in estrogen receptor-positive tumors, the type most likely to be stimulated to progress from occult, pre-clinical cancer to clinically apparent cancer, by the growth-stimulating action of HRT.

Although the HRT story caused a sea-change in the breast cancer field, the changes in the 4th Edition are relatively minor, since the 3<sup>rd</sup> Edition had already kept readers ahead of the curve. For example, non-cancer-causing alternatives to contraceptive steroids and HRT were encouraged. The 4th edition also has new references documenting increased public acknowledgment by medical journals and public health agencies, including the National Cancer Institute and the World Health Organization, of the carcinogenic effects of 'the pill'.

Breast cancer advocacy organizations often seem interested only in research for cures, even making erroneous claims, such as that “a majority” of breast cancer patients “have no known risk factors outside of their gender.” However, we always endeavor to provide practical guidance for **preventing** breast cancer.

Prevention is paramount because even early detection and a high cure rate don’t spare a woman the trials of surgery, chemotherapy and the emotional toll on her and her loved ones. Hence, we rededicate our commitment to prevention with our 4<sup>th</sup> Edition of Breast Cancer Risks and Prevention.

Angela Lanfranchi, M.D., F.A.C.S.  
Joel Brind, Ph.D.  
July 6, 2007

## 1 Introduction

This booklet is written to help women understand what their risk factors are for the development of breast cancer and how they can reduce their risk.

Sometimes women are made to feel helpless and hopeless when it comes to their risk of developing breast cancer. After all, they cannot change the fact that they are women, are getting older, and have already inherited a certain set of genes from their parents. These are well-established risks for breast cancer. However, there are factors you **can** control to minimize your risk, including the amount of estrogen to which you are exposed and your reproductive history. Even if you have inherited either of the BRCA genes, which are well known to increase the risk of cancer, you can control other aspects of your life to decrease your risk.

In order to understand and control your risk factors for breast cancer, you must first understand how **risk** is expressed in numbers, how exposure to estrogen relates to most known risk factors, and how the maturity of breast lobules from Type 1 & 2 to Type 3 & 4 lobules decreases the risk of breast cancer. This booklet will also inform you about risk reduction strategies.

## 2 Understanding What Risk Means

- ◇ ***Cumulative lifetime risk***
- ◇ ***Incidence***
- ◇ ***Relative risk***

**1. Cumulative lifetime risk** of breast cancer is a statistically derived number assuming all women live to be a certain age. If all women alive in the year 2007 were to reach the age of 85, then one in seven (14%) will have developed breast cancer.

### **2. Incidence**

This is the number of women who get breast cancer in a defined number of women in the population during a given time period. For example, during 1991-1995, the incidence of breast cancer of women aged 30 to 34 years old was 25 per 100,000 women.

### **3. Relative Risk**

This is a number used to compare the impact of different risk factors associated with the likelihood of developing breast cancer.

It is a number commonly used to tell women what their risk is when comparing them to women without that particular factor.

Relative risk (RR) is a number used in epidemiological studies and is the one most often used in risk tables.

### Examples:

#### (Relative Risk is abbreviated RR)

*RR 1.0 means there is no increase or decrease in risk.*

*RR 1.5 means there is a 50% increase in risk.*

*RR 2.0 means there is a 100% increase in risk.*

*RR 0.5 means there is a 50% decrease in risk.*

If a relative risk is greater than 1, the factor can be called a risk factor. If the relative risk is less than 1, the factor can be called a protective factor.

In general, most breast cancer risk factors, other than inherited genes and chemical or radiation injury to cells, are related to how much estrogen a woman is exposed to in her lifetime and how early she matures her breast lobules to Type 3.

For example, women are exposed to elevations of estrogen levels with each menstrual cycle, so the more menstrual cycles a woman has, the higher her risk. This is why going through menarche at a very young age and menopause at a very old age will increase that woman's breast cancer risk. Women are also exposed to high levels of estrogen in hormone replacement therapy and birth control pills, injections or patches. Many new drugs devised to prevent or treat breast cancer act by blocking estrogen receptor sites in breast cells (e.g. Tamoxifen), or cause our bodies to produce less estrogen (e.g. Arimidex).

Having a full-term pregnancy matures a woman's breast lobules from Type 1 (where ductal breast cancers start) and Type 2 (where lobular breast cancers start) to Type 4, which are resistant to carcinogens. Type 4 lobules are those that contain colostrum or milk. Type 4 later regress to Type 3 lobules after weaning but remain cancer resistant. Women who have never been pregnant have approximately 75% of their breast lobules as Type 1, while women who have had a full-term pregnancy have 85% Type 3 lobules. This is why women who have children have a lower breast cancer risk than women who never had a full-term pregnancy. They have fewer places for cancers to start.

Remember, a "risk" is just that, and not a certainty. You may have many risk factors mentioned in this booklet and never develop breast cancer, especially if you also practice risk reduction strategies.

## 3 Understanding Breast Cancer: Carcinogens and Promoters

Breast cancer is characterized by abnormal breast cells, whose growth (cell proliferation or multiplication), is unresponsive to normal cell control mechanisms. A cell's genes are made of DNA, and that information is stored in the cell's nucleus. A normal cell is controlled by its genes to have limited proliferation or growth, and to have regulated differentiation from immature to mature cells that can produce milk. Normal cells also have a "life span" that does not allow them to continue to multiply without limit. Normal cells are "programmed" to die after a finite number of multiplications. The abnormal genes, which cause cancer to form, can be inherited from parents or formed after birth. For example, women can inherit abnormal genes, such as the BRCA genes, which make breast cancer more likely to form. Another way for a woman to get abnormal genes is to be exposed to carcinogens.

Approximately 85% of all breast cancers start in the milk ducts. Breast cancers where the cancer cells remain in the milk duct are called ductal carcinomas in situ (DCIS). These cancers are virtually all curable because they have not invaded the duct wall. When these cancer cells invade through the wall of the milk duct, they are referred to as invasive or infiltrating ductal cancers. These cancers can metastasize or spread to other body parts. They are often curable if they are found when they are small.

### *Carcinogens:*

In order for abnormal or cancer cells to form after birth, the cells from which they arise have had their DNA damaged by a carcinogen, i.e. a cancer initiator. These initiators cause genetic changes (mutations), which cause cancer cells to form and grow. An initiator can be a virus as in the case of human papilloma virus, which causes cervical cancer. It can be a chemical such as benzopyrene in cigarette smoke, which causes breast, lung and other cancers. It can be a breakdown product or metabolite of estrogen such as 4-hydroxy-catechol estrogen quinone, which can damage DNA and cause breast cancer. Radiation is another cancer initiator that can damage DNA if the amount is great enough or over an extended period of time.

It often takes many repeated exposures to carcinogens before the DNA sustains enough damage that a cancer cell is formed. Many cigarettes over many years are necessary before the benzopyrenes in cigarette smoke cause a cancer to be formed.

Our bodies have repair mechanisms to correct abnormal DNA that is formed when exposed to initiators. Sometimes people who are more susceptible to cancers have inherited faulty genes that control these repair mechanisms. Although we may form cancer cells many times during our life, our body's immune system can keep these cells from reproducing, and destroy them without our ever being aware of them. It is only when a large number of cancer cells have reproduced that we are even aware of these cells. On average it takes 8-10 years before one breast cancer cell multiplies enough times to cause a cancerous tumor ½ inch in diameter to form.

### *Promoters (Mitogens):*

Cancer cells are also influenced by cancer promoters. Promoters or mitogens are substances that do not damage DNA, but which stimulate cells to multiply. For example, cancers that have estrogen receptors can be stimulated to grow faster when elevated levels of estrogen are present. Women taking hormone replacement therapy containing estrogen may develop a breast cancer caused by the hormones. Or the hormone replacement therapy may simply cause the breast cancer cells that have estrogen receptors in them to grow faster.

Cancer cells that form in our bodies may also remain dormant and inactive. That is one reason why, after being exposed to a carcinogen, a cancer may not become apparent for many years. For example, workers exposed to asbestos do not typically develop cancer for over 20 years.

## **4 Exposure to Estrogen & Breast Cancer Risk**

Estrogen is a normal female hormone made in your ovaries and to a lesser extent in your fat (adipose) tissue. It is the hormone that causes women to be “womanly.” For example, estrogen causes your breasts to develop. Estrogen acts in concert with progesterone, another female sex hormone made primarily in the ovaries. Progesterone and estrogen enable you to get pregnant and to maintain the pregnancy.

Estrogen can cause cancers in two ways. First, estrogen acts as a “mitogen.” Estrogen stimulates your breast tissue to increase cell divisions (mitoses). This sometimes results in cancers due to errors in cell division (mutations). Second, certain metabolites of estrogen also act as carcinogens or genotoxins, by directly damaging DNA, thereby causing cancer cells to form.

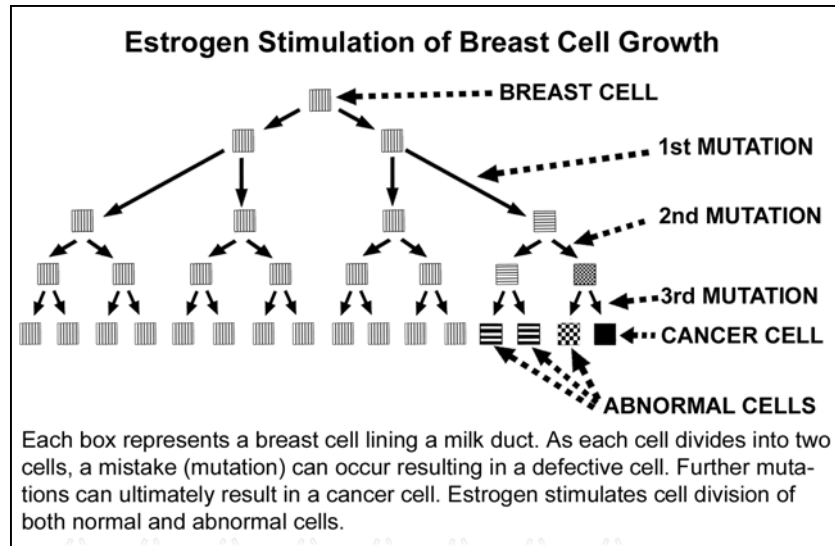
Estrogen is also recognized as a carcinogen in your body for certain types of cancer including breast cancer. Other substances (carcinogens) or exposures (e.g., high dose radiation) can also result in cancer.

Drugs which block estrogen from attaching to breast cell receptors, such as Tamoxifen, or prevent estrogen from forming in our fat cells, such as Arimidex, are widely used to treat breast cancer.

### *Estrogen As a Mitogen (Promoter)*

Estrogen is a “mitogen,” causing breast cells to multiply through division (one cell divides to form two cells). (This effect depends upon the presence of some progesterone, which plays what is known as a permissive role.)

The diagram below illustrates the effect of estrogen as a mitogen:

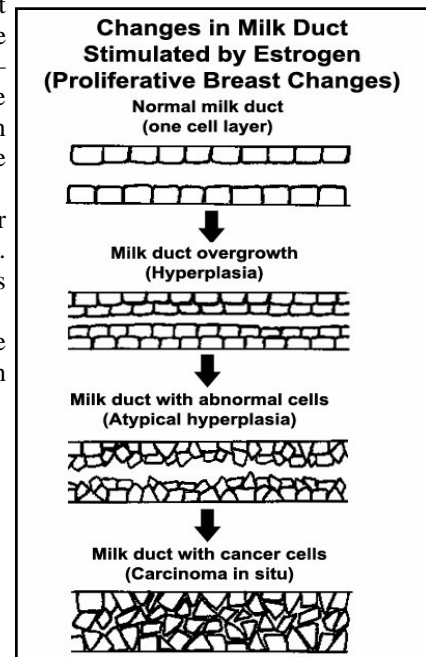


The time it takes to go from one cancer cell to two, from two to four, four to eight, etc., is referred to as the **doubling time**. To go from one cancer cell to a group of cells about ½" inch in diameter takes approximately 8-10 years, if that cancer has an average doubling time. One-half inch is about the size at which a cancer can be found by physical examination. Mammograms can find tumors ¼" in diameter. (A ½" diameter tumor is eight times the size of a ¼" diameter tumor in volume or number of cells.) Small tumors are generally more differentiated and less likely to have metastasized to lymph nodes, and are therefore more curable than large tumors. That is why early detection with mammography results in increased survival.

The doubling time is why, after being exposed to a risk factor, it may take 8-10 years before a cancer can be detected, even if the exposure has caused a cancer to develop. Sometimes prolonged estrogen exposure—such as with estrogen therapy in postmenopausal women—can cause the very rapid growth of dormant cancer cells that may already be present. In some cases, cancer may become clinically detectable within months (see Chapter 11).

Prolonged and increased estrogen exposure also may cause your breast cells to progress from hyperplasia to atypical hyperplasia to cancer. Hyperplasia refers to the overgrowth of cells; for example, in multiple layers instead of one layer in a milk duct. (see diagram on right).

Proliferative breast disease found on biopsy indicates an exposure to increased levels of estrogen. An increased risk of breast cancer is found in women who have proliferative breast disease.



### *Estrogen As a Carcinogen*

Certain estrogen metabolites (or breakdown products) can directly damage DNA. For example, one metabolite, 4-hydroxy-catechol estrogen quinone, directly damages DNA. Women with breast cancer have higher levels of this metabolite than women without breast cancer.



## Factors which Affect Estrogen Exposure

During each monthly menstrual cycle, a woman is exposed to increased estrogen levels, especially just before an egg is produced by her ovaries (ovulation). During pregnancy, women have prolonged exposure to high levels of estrogens. If a woman gives birth before 32 weeks, or has an induced abortion, she will have an increased risk of breast cancer because of increased estrogen exposure without the protective effect of lobule differentiation. Her breasts are left with more places for breast cancers to start (see illustration in chapter 5).

Both early age at the start of menstrual cycles (menarche) and late menopause **increase** breast cancer risk through increased exposure to estrogen during menstrual cycles. Similarly, late age at menarche and early age at menopause **decrease** breast cancer risk. Birth control pills, injections, vaginal rings and patches, and hormone replacement therapy **increase** breast cancer risk through increased exposure to estrogen. The more alcoholic beverages you drink, the more impaired your liver becomes in its ability to eliminate (metabolize) estrogen in your body. That is why regular alcohol consumption **increases** breast cancer risk in direct proportion to the amount of alcohol you drink. DES, a potent synthetic estrogen, when taken by mothers to prevent miscarriages, increased breast cancer risk in mothers and their daughters. Clomid, a drug chemically related to DES, is a commonly used fertility drug.

After menopause, obesity **increases** breast cancer risk by increasing your level of estrogen. This is because fat tissue produces small amounts of estrogen. The more fat you have, the higher your estrogen level.

Before menopause, obesity causes hormonal changes, which **decrease** estrogen production by the ovaries and can even result in infertility. Therefore, premenopausal obesity does not increase breast cancer risk.

Women sometimes will undergo surgical removal of their ovaries before menopause due to different diseases. This surgery will result in decreased breast cancer risk if the woman is not given replacement therapy, as she will be exposed to less estrogen in her lifetime.

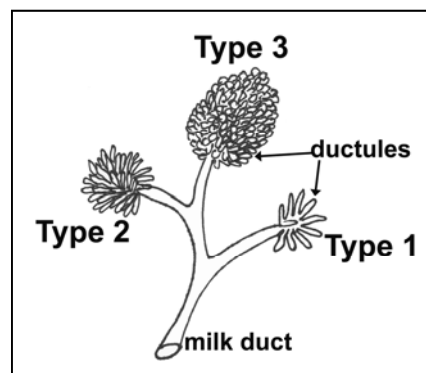
### Summary

In short, women can be at increased risk for breast cancer when they are exposed to higher levels of estrogen. This may occur through increased number of menstrual cycles or particular patterns of estrogen metabolism which allow for elevated levels or more potent estrogens to be formed. Higher estrogen exposure may also be induced artificially, with hormonal drugs in the form of birth control pills, injections, vaginal rings, IUDs and patches, or hormone replacement therapy (HRT). Surgical removal of a woman's ovaries before menopause lowers her exposure to estrogen and decreases her risk.

## 5

### Breast Maturity & Breast Cancer Risk

Another aspect of breast development affecting breast cancer risk is the maturation of breast lobules from Type 1 lobules to Type 4 lobules. Breasts are composed of units of breast tissue called lobules and are surrounded by supportive tissue made of fat and stromal (connective) tissue. A lobule is composed of a milk duct with surrounding ductules which are the glands that make the milk. Lobules are in turn composed of individual breast cells.



Schematic of breast lobules

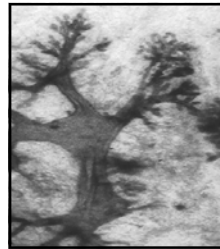


At birth, you have a small amount of breast tissue, Type 1 lobules, which are very immature and are known as TDLUs (terminal ductal lobular units). Ductal cancers which account for 85% of all breast cancers are known to arise in Type 1 lobules. An infant's breast tissue may be stimulated by the mother's hormones present in the infant at birth. This can cause a milky secretion called "witch's milk" for a short time after birth. At puberty, in response to the cyclic elevations of estrogen and progesterone, the breasts start to develop further, and some Type 1 lobules are matured into Type 2 lobules, which have more ductules per lobular unit. 2 lobules are where up to 15% of all breast cancers start. By the end of puberty, about 75% of breast tissue is Type 1 lobules and 25% are Type 2.

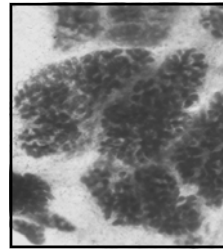
Full maturation and cancer resistant Type 4 lobules are not formed until late in pregnancy when the breast is under the influence of the pheromones hCG and hPL which are made by the fetus and placenta in the womb. Type 4 lobules contain colostrum, the first milk. By mid 2nd trimester 70% of the breast tissue is Type 4 lobules, and at 40 weeks (full-term), 85% is Type 4 and cancer resistant. After weaning, the Type 4 lobules regress to Type 3, but remain cancer resistant due to permanent genetic changes which have made them cancer resistant. Each subsequent pregnancy after the first matures more of the breast tissue resulting in a further decrease in breast cancer risk of 10%.

Not only do these lobules look different anatomically, but they grow differently. For example, Type 1 and 2 lobules copy their DNA faster than Type 3 lobules. The faster DNA is copied, the higher the risk of mutations or cancer cells forming.

Actual photomicrographs of human breast lobules:



Lobule Type 1



Lobule Type 3

The principle of breast cancer risk relating to lobule maturity can explain other well-documented breast cancer risks as well.

If a woman does not have a full-term pregnancy (meaning she is childless or nulliparous), she has **increased** risk for breast cancer, since she never develops Type 4 lobules. If she has children later in life (after age 30), she has **increased** risk, because, for most of her menstrual life, her estrogen has been stimulating immature Type 1 and 2 breast lobules. If she has children as a teenager, she has **decreased** risk of breast cancer, since her breast tissue matures very early in her reproductive life to Type 4 lobules.

If a woman breast-feeds, she often has anovulatory cycles (in which estrogen is low) or misses menstrual cycles altogether. She has **decreased** risk due to two factors: less exposure to estrogen and breast tissue maturity to Type 4 lobules. Risk decreases in proportion to duration of breastfeeding.

The risk factors of estrogen exposure and breast immaturity can also act in concert with one another, causing greater risk. For example, if a teenager, who has not had a full-term pregnancy (she is nulliparous), takes birth control pills, her risk of breast cancer is much higher than it is for a woman who has had several children and then takes birth control pills. A woman who gets pregnant increases her estrogen level 2,000 percent by the end of the first trimester. If her pregnancy goes to full term, she will have lower breast cancer risk by developing full breast maturity. If it ends before 32 weeks, by very premature birth or induced abortion, she will have increased risk as she will not get the benefit of full breast maturation, but instead be left with more places for breast cancer to start. Spontaneous abortions (miscarriages) in the first trimester do not increase breast cancer risk because they are associated with low estrogen levels.

Cigarette smoking before a full-term pregnancy can **increase** a teenager's breast cancer risk substantially, because her breast lobules are immature and rapidly growing.

## 6

### Age and Length of Carcinogen Exposure & Breast Cancer Risk

The age at which a woman is exposed to carcinogens or cancer promoters also greatly affects the risk of cancer cells forming. When cells are actively growing and rapidly copying DNA, as breast cells do during puberty, the more likely cancers are to form. For example, when teenagers take birth control pills before a full-term pregnancy, their risk is more substantially increased, compared to the risk increase in women in their twenties, whose breasts are no longer growing.

The length of exposure also varies the risk of cancers forming. Studies show the longer women take birth control pills, the higher their risk of breast cancer. For example, women taking birth control pills for two years may only have a small increase in breast cancer risk but taken for more than 4 years, the risk is significantly greater.

The longer your exposure to increased levels of estrogen, the higher your risk will be. Taking hormone replacement therapy after menopause for 1 to 2 years does not significantly increase breast cancer risk. However, a woman who has taken hormone replacement for many years, especially if she had not had a full-term pregnancy and had taken birth control pills most of her life, will have significantly **increased** breast cancer risk.

Women who are exposed to known carcinogens such as benzopyrenes in cigarette smoke or estrogens in birth control pills are more likely to develop cancer if they have not matured their breast lobules from Type 1 and 2 lobules to mature Type 4 lobules. When Type 4 lobules regress after weaning, they become mature cancer resistant Type 3 lobules. This maturation substantially occurs after 32 weeks during a full term pregnancy. This is because Type 1 and 2 lobules more rapidly replicate their DNA and multiply through division of their cells than matured Type 3 lobules. The faster cells divide and the faster they replicate DNA the more chance there is that a mutation or cancer cell will form.

There is a critical time in a women's life between menarche, when she has her first period, and when she has her first full-term pregnancy, that she is most susceptible to carcinogens. This is called the **susceptibility window**. This is because she has a higher percentage of immature breast lobules. The shorter this time period, the lower her risk; the longer this period, the higher her risk.

## 7

### Reproductive History & Breast Cancer Risk

During a normal pregnancy, estrogen levels rise 2,000% by the end of the 1<sup>st</sup> trimester. During the first half of pregnancy, the breasts grow and double in volume by producing more Type 1 and 2 lobules where ductal and lobular cancers are known to start respectively. During the latter half of pregnancy, the breasts fully mature into Type 4 lobules so that by 32 weeks a sufficient amount of breast tissue is matured so that the mother's risk of breast cancer will continue to decrease until 40 weeks, full-term. If a pregnancy ends early between 32 and 37 weeks, she achieves about 90% of the risk reduction afforded through a 40-week pregnancy. During the growth phase of pregnancy, the breast becomes sore and tender.

Sometimes, a woman will miscarry during the first trimester. These miscarriages (spontaneous abortions) **do not increase** breast cancer risk, since they are associated with low estrogen levels that do not cause breast growth. Approximately 23% of all conceptions end in spontaneous abortions and approximately 90% of spontaneous abortions occur in the first trimester. Many times women who miscarry will say they never felt pregnant because their breasts did not change and they did not get nauseous from high estrogen levels. However, miscarriages in the 2<sup>nd</sup> trimester can increase risk.

A first trimester miscarriage is quite a different situation from induced abortion of a normal pregnancy in its effect on the woman's breasts. The longer a woman is pregnant before an induced abortion, the higher her risk of breast cancer. This is because high estrogen levels of the 1<sup>st</sup> and 2<sup>nd</sup> trimesters cause breast growth of Type 1 & 2 lobules. When her pregnancy is terminated **before most** of the breast lobules reach full maturity around 32 weeks, she is left with more places for cancer to start than when her pregnancy began. Therefore, she is at increased risk. Her breasts do not mature to Type 4 lobules, which would have occurred in the 3<sup>rd</sup> trimester and would have lowered her risk. This risk is especially high for teenagers who have an abortion in the late 1<sup>st</sup> or 2<sup>nd</sup> trimester and for those women who have never have a child, since their breasts never mature. Women who have had an induced abortion or premature birth before 32 weeks can therefore substantially reduce risk by subsequently completing a pregnancy of

at least 32 weeks, especially when they are young. Premature births before 32 weeks are known to double breast cancer risk, again because they leave these mothers with more places for breast cancers to start.

Induced abortion—especially in teenagers—also increases the risk of very premature delivery in subsequent pregnancies. This further **increases** the breast cancer risk of the mother, as well as the risk of cerebral palsy in the prematurely born child. In one prominent study, if a teenager also had a family history of breast cancer, her relative risk was reported as infinity because all 12 such women in this study developed breast cancer by the age of 45. This does **not** mean every teenager that has an abortion and a family history of breast cancer will get breast cancer by the age of 45. However, it does show a high risk.



## 8 Pregnancy & Breast Cancer Risk

A woman may become pregnant after a cancer cell has formed in her breast, a cell which may have been dormant for many years. Early in pregnancy, even before the embryo has implanted in the womb, the woman's estrogen levels rise, and this may stimulate the dormant cancer cell to grow into a clinically detectable cancer. This accounts for the slight, **temporary** increase in breast cancer risk in the post-partum woman over age 25.

But sometimes the dormant cancer may grow into detectable cancer while the woman is still pregnant, a situation known as gestational breast cancer. Often, doctors recommend “therapeutic abortion” so that, by terminating the pregnancy as soon as possible, the most aggressive cancer therapy can be given to maximize the woman's chances of survival. However, many decades of clinical data have shown the reverse to be true: A woman's chances of survival are maximized if she carries the pregnancy to term. Strong doses of chemotherapy can even be given without harm to the baby, as long as the pregnancy has gone beyond the first trimester. Even in cases where a premenopausal woman has previously been treated for breast cancer, having a full-term pregnancy decreases the risk of recurrence of the cancer.

Sometimes, a pregnant woman learns that the child she is carrying has a developmental problem that will not allow him or her to survive long after birth, and abortion or premature induction of labor will be recommended. However, carrying that child to term will decrease the mother's future risk of breast cancer, while abortion will increase her risk. There are perinatal hospice programs, organizations that specialize in adoption services for children with such disabilities as Down's Syndrome, and organizations which support the families of these infants.

## 9 Radiation & Breast Cancer Risk

High doses of radiation are known to **increase** breast cancer risk. Exposure to radiation from the atomic bomb at Hiroshima caused **increased** breast cancer incidence, especially in women exposed as teenagers, when their breast cells were very immature. Repeated x-ray exposure for treatment of tuberculosis, postpartum mastitis, chest acne and monitoring treatment for scoliosis **increases** risk. Life saving radiation treatment to the chest of young women with Hodgkin's disease **increases** breast cancer risk.

The amount of radiation needed to cause breast cancer is from 100 to 450 rads, (a rad is a radiation dosage measurement). Fortunately, with today's screening mammograms, breasts are exposed to only 0.25 rads. Therefore, it is estimated that a woman would need at least 400 mammograms to **increase** her breast cancer risk at all.

# 10

## Genetics & Breast Cancer Risk

Only 5-10% of all breast cancer cases are felt to be truly genetic and caused by a breast cancer gene. For example, BRCA 1 or 2 genes are passed from a parent to a child. Usually these genes cause breast cancers before menopause in mothers and daughters and also in men. There are about 1,200 cases of male breast cancer a year.

It is also possible to have a family history of breast cancer without inheriting one of these faulty genes. However, other inherited characteristics, such as how early you go through menarche, or how your liver processes estrogen, may make you at higher risk.

Having any type of family history may increase the effect of other known risk factors. For example, if you have a benign proliferative breast disease, you have increased risk. If you also have a family history of breast cancer, your risk is even higher.

# 11

## Hormonal Birth Control and Hormone Replacement Therapy & Breast Cancer Risk

Two very common ways women are exposed to hormonal therapy are through contraceptive medications and hormone replacement therapy (HRT) after the menopause.

It is now well established that birth control medications (contraceptive steroids) increase breast cancer risk, especially if they are taken before the first full-term pregnancy, when breast cells are still immature. Birth control pills are very commonly used by young women. In one study, women who took birth control pills before the age of 20 had a more than ten-fold increased risk of breast cancer. The longer the pill is used, the higher the risk. Contraceptive steroids increase risk whether they are given orally (i.e., ‘the pill’), by injection (e.g., Depo-Provera), implantation, through the skin with a patch, intravaginally with a ring (e.g., Nuva Ring) or with an intrauterine device (IUD). Even ‘low dose’ estrogen pills have been associated with higher breast cancer risk.

The so called “emergency contraceptives” or “morning after pills” (e.g., “Plan B”) consist of a very high dose of the same synthetic progestational steroid as found in ordinary oral contraceptives. Although “progestin only” contraceptives (e.g., Depo Provera) are associated with increased breast cancer risk, “emergency contraceptives” are intended to be taken only on rare occasions. It is unlikely that such occasional use would result in any significant increase in breast cancer risk. Even though these pills can act by inducing very early abortions, estrogens do not rise to very high levels until after the second week of pregnancy. Therefore, abortions induced by “emergency contraceptives” also would not be expected to add significantly to a woman’s breast cancer risk.

The effect of hormone replacement therapy (HRT) on the risk of breast cancer depends on the type of formulation. Remember (Chapter 4) that estrogen’s effect as a mitogen depends upon the presence of some progesterone. After the menopause, when the ovaries stop making estrogen and progesterone, if a woman takes an ‘estrogen only’ form of HRT (usually a mixture of naturally derived estrogens), the absence of progesterone from her ovaries means there is little or no increase in breast cancer risk. However, estrogen alone acts as a mitogen in the uterus and increases the risk of uterine cancer, which is why it is typically prescribed for women who have had a hysterectomy. When the uterus is still present, most doctors have prescribed combination HRT (e.g., the “Prem-Pro” regimen), which also contains a synthetic progestin. Combination HRT decreases the risk of uterine cancer, but increases the risk of breast cancer, as do contraceptive steroids. Importantly, the effects of estrogen acting as a mitogen are apparent much sooner among older women, who may have undetectable, precancerous abnormalities in their breasts. Use of HRT can stimulate such abnormal cells to grow into clinically apparent cancer, sometimes within a matter of months. This was recently demonstrated on a massive scale with a substantial drop in breast cancer incidence among postmenopausal American women in 2003-4, following a sharp decline in combination HRT use in 2002-2003. Such dramatic effects with even the natural estrogens of HRT echo earlier findings of the risk-increasing effect of the potent synthetic estrogen DES. DES has even been found to increase the breast cancer risk of women whose mothers took the medication during their pregnancy, as well as that of the mothers themselves.

Like other patient medications, estrogenic hormones and drugs, used judiciously and for short periods, can be beneficial. With long term use, they can significantly increase breast cancer risk. There are effective alternatives to the use of these medications which do not increase breast cancer risk. These are discussed in Chapter 14.

## 12 Breast-Feeding & Breast Cancer Risk

Breast-feeding **decreases** risk of breast cancer, because it results in some menstrual cycles without an estrogen peak before ovulation and missed menstrual periods. Therefore, a woman is exposed to less estrogen and has **decreased** breast cancer risk. Breast-feeding also keeps breast tissue matured into Type 4 lobules that **decrease** cancer risk. Breast feeding is known to decrease breast cancer risk in proportion to the total duration of breast feeding of all infants.

## 13 Metabolism & Breast Cancer Risk

Metabolism refers to the way the body changes and processes hormones and other chemicals. This process also involves elimination of these chemicals from the body. Most of the active estrogen made by the ovaries is changed by the liver into an inactive form, which does not cause the breast cells to divide (mitoses). But some estrogen is transformed into a long-acting estrogen that continues to stimulate the breast cells to divide. Some women's bodies produce higher levels of this long-acting estrogen, and therefore have a higher breast cancer risk.

However, some things we eat can affect estrogen metabolism. For example, indole-3-carbinol, a substance found in cruciferous vegetables, is converted to DIM (diindolylmethane) in the stomach. This causes greater production of the inactive metabolite of estrogen, decreasing the risk of breast cancer.

By inhibiting liver function, alcohol decreases the body's ability to change estrogen into the inactive form and therefore, increases risk.

Women have increased risk when their bodies create more of the active metabolite of estrogen.

## 14 Diet and Life Style & Breast Cancer Risk

How we live our lives and the choices we make concerning what we consume, what habits we keep, how we control our fertility and decide if and when to have children, how much we exercise, and even how long we stay in school and our career choices all influence our risk of breast cancer.

### *Diet*

Diets that are high in phytoestrogens, especially as teenagers, can lower breast cancer risk. Phytoestrogens are plant estrogens that can block our estrogen receptors. These phytoestrogens do not stimulate our breast cells to proliferate as much as our own body's estrogens do. Teenagers who eat soy products have lower breast cancer rates. Phytoestrogens are found in many vegetables.

Indole-3-carbinol is found in cruciferous vegetables such as cauliflower and broccoli. This chemical is converted by the stomach to DIM, which causes estrogen to be metabolized into an inactive estrogen that does not stimulate breast tissue to proliferate and thereby reduces breast cancer risk. DIM is also widely available in pill form, as a nutritional supplement.

Countries which have diets high in omega-3 fatty acids, such as those found in deep water fish oils, have populations which develop breast cancer at an older age than countries with diets low in these oils. Olive oil has been found to decrease breast cancer risk in postmenopausal women. Canola, flax seed and walnut oils are also rich in omega-3 fatty acids.

A diet too high in calories, which leads to obesity, increases breast cancer risk. Postmenopausal obesity increases breast cancer risk because the aromatase enzyme system in fat cells causes more estrogen to be formed. Children who are obese develop menstrual cycles at an early age, also increasing breast cancer risk.

Drinking alcohol in any form, beer, wine or spirits, increases breast cancer risk through its effect upon the liver. The liver metabolizes estrogen and can change it into an inactive form. A liver impaired by alcohol lets estrogen build to higher levels, thereby stimulating the breast. For example, men who are alcoholics develop increased breast tissue, called gynecomastia, from elevated estrogen levels.

## *Lifestyle habits*

Recent studies suggest that cigarette smoking before having children—especially among teenagers—also **increases premenopausal** breast cancer risk substantially. Benzopyrenes in cigarette smoke act as direct carcinogens to cells lining the milk ducts.

Exercise is also important in **reducing** breast cancer risk. Overall, moderate exercise can **reduce** breast cancer risk by 30%. Exercise also can prevent obesity, which **increases** breast cancer risk. Exercise can delay the onset of a woman’s first menstrual cycle, menarche, which also **decreases** breast cancer risk. Exercise may result in anovulatory, and therefore, low-estrogen menstrual cycles, thus **decreasing** risk.

The method a woman chooses to control her fertility also greatly affects her breast cancer risk. While synthetic steroid drugs in the form of birth control pills, patches, vaginal rings, IUDs or injectable progestins can increase breast cancer risk by up to 1,000%, as one study showed, the use of natural family planning (NFP) will not cause any increase in breast cancer risk. Natural family planning teaches a woman to reliably determine her fertile days by recognizing her own bodily changes during her fertile and infertile days of her menstrual cycle. Studies have shown efficacy rates similar to those of “the pill” without the cost and side effects. NFP is **NOT** the “rhythm method” and can be used effectively by women with regular or irregular menstrual cycles. There are several NFP methods in wide use, including the Billings Ovulatory Method, and NaProTechnology, which is based on the Creighton model. These methods are also used by women to overcome infertility, thus avoiding the use of synthetic fertility drugs such as Clomid.

The age at which a woman chooses to have children also determines breast cancer risk. Compared to a woman who gives birth at 30, a woman who has a full-term pregnancy before age 20 has only one-third the risk of breast cancer. By having children early in their reproductive life, women can greatly reduce their breast cancer risk. Women also avoid the risk of infertility, which advancing age brings, by having children when they are young. By avoiding infertility, a woman avoids exposure to hormonal fertility drugs. Choosing to end a pregnancy through an induced abortion, especially the first pregnancy as a teenager, significantly increases breast cancer risk.

Breast feeding your children will also decrease breast cancer risk. Breast feeding fully matures the breast and often results in anovulatory or missed cycles.

High socioeconomic status and a high level of education are also presently associated with higher breast cancer risk. Women, who have high socioeconomic status, more commonly have children late in their reproductive life or remain childless, well established risks for breast cancer. Women who achieve high levels of education through college and postgraduate levels also tend to delay childbearing or remain childless. They commonly accomplish this through hormonal birth control (contraceptive steroids in pill, patch or injectable form). In 1975 only 10% of women between 40 and 45 were childless, now it is 18% according to the US 2000 census data.

## *Making informed health care choices*

Don’t take hormones for conditions which are not necessarily abnormal, such as irregular menstrual cycles in teenagers. In fact, teenagers who do not experience regular menstrual cycles until 5 years after menarche, have a **decreased** breast cancer risk compared to those who cycle regularly right after menarche.

Don’t take hormones for disease treatments for which other non-hormonal treatments are equally effective. Actonel, Fosamax, calcium supplements and exercise can reduce osteoporosis without the need for estrogen. DHEA (dehydroepiandrosterone), a normal metabolic intermediate substance produced by the adrenal gland, but which declines with age, is widely available as a nutritional supplement. While not itself an active hormone, DHEA can be converted to active hormones by certain tissues. For example, it can be converted to estrogen by bone and vaginal lining, but not uterine lining. Thus it does not increase the risk of uterine cancer, but it can prevent or reverse bone loss and other menopausal symptoms. (DHEA cannot be converted to testosterone by muscle tissue or cause an increase in muscle mass.) Acne can be treated with antibiotics. There are effective methods of birth control (such as NFP) that do not rely on hormones. Menstrual cramps can be treated with non-steroidal anti-inflammatory drugs such as ibuprofen.



# 15 Factors Which Increase and Decrease Breast Cancer Risk

## Factors Which **INCREASE** Breast Cancer Risk

<b>Factor</b>	<b>Mechanism</b>
Alcohol	Increases estrogen exposure by impairing liver function
Benign proliferative breast disease	Result of increased estrogen exposure
BRCA genes	Inherited defects in cancer defense genes
Cigarette smoking	Benzopyrenes damage DNA
Contraceptive steroids (in pills, patches, vaginal rings, IUDs or injectable forms)	Increases estrogen exposure
Early menarche	Increases estrogen exposure
Female sex	Increased estrogen exposure
High socio-economic group	Delayed childbearing
Higher education	Delayed childbearing
Hormone replacement therapy (HRT)	Increases estrogen exposure
Increasing age	Premenopausal: Increases estrogen exposure Postmenopausal: Impairs immune function
Induced abortion	Leaves increased number of immature breast lobules and increases risk of premature births Increases estrogen exposure
Late childbirth (over 30 years old)	Increases exposure of Type 1 & 2 lobules to estrogen before first birth; long susceptibility window
Late menopause	Increases estrogen exposure
Nulliparity (never bearing children)	Maturity of breast lobules does not occur
Premature birth before 32 weeks	Leaves increased number of immature breast lobules Increases estrogen exposure
Postmenopausal obesity	Increases estrogen exposure
Radiation	Damages DNA
2nd trimester miscarriage	Leaves increased number of immature breast lobules



## Factors Which **DECREASE** Breast Cancer Risk

Factor	Mechanism
Breast feeding	Decreases estrogen by decreasing number of menstrual cycles and/or ovulation
Cruciferous vegetables (e.g., broccoli, Brussels sprouts or DIM supplements)	Indole-3-carbinol decreases estrogen exposure by causing estrogen to be changed to an inactive metabolite of estrogen
Early menopause	Decreases estrogen exposure
Exercise	Decreases estrogen exposure
Having children (especially starting at a young age)	Decreases number of immature breast lobules
Late menarche	Decreases estrogen exposure
Omega-3 fatty acids (e.g., olive, flax seed, walnut oils)	Unknown
Oophorectomy (removal of ovaries) before menopause	Decreases estrogen production
Soy isoflavonoids(phytoestrogens)	May block estrogen receptors

## Factors Which **HAVE NO EFFECT** on Breast Cancer Risk

Factor	Reason
Saturated fat	Saturated fat intake not related to obesity
Spontaneous abortions (miscarriages) in the first trimester	No increased levels of estrogen as found in healthy pregnancies

# 16

## Strategies for Lowering Your Breast Cancer Risk

### Dietary Strategies

#### *Eat cruciferous vegetables*

The cruciferous vegetables (e.g., broccoli, Brussels sprouts, cauliflower, watercress, kale and cabbage) contain high levels of indole-3-carbinol. This chemical, which is changed to DIM in the stomach, causes the liver to form more of the inactive metabolite of estrogen, thereby reducing estrogen exposure. DIM can also be taken as a nutritional supplement.

#### *Eat Omega-3 fatty acids*

These essential fatty acids are found in fish and many vegetable oils. Postmenopausal women who eat olive oil daily reduce their risk of breast cancer by 25%. Vegetable oils rich in omega-3 fatty acids include canola, flax seed, walnut and olive oils.

#### *Eat soy products and vegetables with phytoestrogens*

One study suggests that teenage girls who eat soy products may lower their risk of breast cancer later in life. Soybeans contain “phytoestrogens” which decrease the activity of estrogen produced by the ovaries. Other vegetables also contain phytoestrogens.

#### *Limit alcoholic beverages*

The more alcohol you drink, the higher your risk of breast cancer. Occasional alcoholic drinks will not increase your risk; however, regularly drinking alcohol every day will.

### Life Style Strategies

#### *Reduce your exposure to estrogen*

Avoid steroidal hormone therapies for contraception to minimize breast cancer risk. These include birth control pills and patches, and injectable or implantable hormones. Methods of fertility regulation that do not increase breast cancer risks can be used; for example, natural family planning (NFP).

Avoid prolonged hormone replacement therapy (HRT) for perimenopausal (around menopause) and postmenopausal symptoms to minimize breast cancer risk. There is no **proven** benefit to the heart with HRT. In fact, there is very strong recent evidence that HRT actually increases the risk of heart disease, stroke and dementia. There are other medications available, such as Fosomax and Actonel which can increase bone density for the treatment and prevention of osteoporosis. The nutritional supplement DHEA can also increase bone density and ameliorate other menopausal symptoms.

#### *Don't smoke!*

Benzopyrenes—the known carcinogens in tobacco smoke—damage DNA and **increase** the risk of breast, bladder, cervical and lung cancer.

#### *Exercise*

One to three hours of exercise a week can reduce your breast cancer risk by 30%. Women who train strenuously may lose their menstrual cycle or become anovulatory, and therefore be exposed to far less estrogen. Exercise can also delay the onset of menarche.

### *Maintain normal body weight*

Obesity after menopause increases breast cancer risk because fat (adipose) cells manufacture estrogen. Obesity may cause early menarche.

### *Have children earlier in life*

Having children in the early twenties or as a teenager decreases risk. Delaying child bearing until after 30 increases the risk of breast cancer substantially.

### *Breast feed your children*

Breast feeding is known to decrease breast cancer risk in proportion to the total duration of breast feeding of all infants.

### *Avoid induced abortions*

Having an induced abortion, especially as a teenager or before you have a full-term pregnancy, increases risk. If you do have an abortion, taking contraceptive steroids (e.g., “the pill”) after an abortion will increase risk further. However, subsequently having children and breast-feeding them will reduce the risk. Induced abortions also increase the risk of premature delivery and very premature delivery (before 32 weeks) in subsequent pregnancies. Since most breast lobules are not matured until after 32 weeks gestation, very premature delivery also increases breast cancer risk, as well increasing the risk of cerebral palsy in the newborn. There are organizations which specialize in the placement of Down’s Syndrome babies with families that welcome these infants if the mother is not able to care for a special needs child herself.

### *Avoid induced premature deliveries*

Sometimes women are counseled to end the pregnancy when there is a fetal abnormality not compatible with life after birth by having her labor induced prematurely. However, by carrying that child to term, such as an anencephalic infant, the mother will gain protection against breast cancer. There are perinatal hospices for the child after birth.

### *Make informed health care choices*

Use non-hormonal therapies when available to treat osteoporosis, acne or painful periods. Use natural family planning (NFP) for birth control instead of birth control pills, patches or injections.

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### *In summary,*

There are many ways women can reduce their risk of breast cancer through the avoidance of unnecessary hormones and drugs and through dietary and lifestyle changes.

Finding breast cancers by mammogram when they are small *does* increase breast cancer survival. Smaller tumors are usually more differentiated and are less likely to have spread to lymph nodes.

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## Glossary

Anovulatory menstrual cycle	A menstrual cycle that does not produce an egg, thereby producing lower estrogen levels in a woman's body.
Arimidex	Example of a drug which blocks the aromatase enzyme.
Aromatase	The enzyme responsible for estrogen production present in the ovaries and also in fat tissue.
Atypical ductal hyperplasia	Overgrowth of abnormal cells within a milk duct (see diagram on page 7).
BRCA gene	A defective gene which can be inherited from a parent, increasing the risk of breast cancer.
Cancer promoter	A mitogen which stimulates cancer cells to grow faster.
Carcinogen or cancer initiator	An agent which causes a normal cell to transform into a cancer cell.
DHEA	Dehydroepiandrosterone, an inactive adrenal product which declines with age. It can be converted to estrogen in bone and vaginal lining, and can be used to treat menopausal symptoms.
Differentiation	The maturing of cells from immature cancer susceptible cells to mature cancer resistant cells.
DIM	Diindolylmethane, a metabolite of indole-3-carbinol (from cruciferous vegetables) which aids in the inactivation of estrogen.
Estrogen	The main type of female sex steroid hormone primarily responsible for breast growth.
Estrogen receptor	Place in cell where estrogen can attach, thereby stimulating the cell to grow or change.
Gene	A portion of DNA in the nucleus of a cell which controls an inheritable trait.
Hyperplasia	Overgrowth of normal cells (see diagram on page 7).
Induced abortion	Termination of pregnancy by surgery or medication.
Lobule	A milk duct with its surrounding ductules; the glands that make the milk.
Mammogram	A soft-tissue x-ray of the breast used to detect breast cancers.
Maturation of breast lobules	The development of lobules from primitive, immature cell structures present at birth, which are incapable of producing milk and are most susceptible to carcinogens, <b>into</b> advanced, mature cells which are capable of producing milk and are most resistant to carcinogens.
Menarche	Age at which menstrual periods start.

Menopause	Age when menstrual periods have stopped for 12 consecutive months due to the cessation of ovarian activity.
Metabolism	Mechanism by which the body changes, processes and eliminates hormones and other body chemical substances; i.e., turns them into metabolites.
Miscarriage	The spontaneous, natural loss of a pregnancy.
Mitogen	An agent that causes mitosis.
Mitosis	The process of cell division causing one cell to become two cells.
Natural Family Planning (NFP)	Any of several methods whereby a woman learns to recognize her own bodily changes so that she recognizes the few days of fertility in her menstrual cycle (e.g., type of cervical mucus and basal temperature). NFP is <b>not</b> the “rhythm method.”
Nulliparous	Never bearing children.
Perimenopause	Years immediately preceding menopause, when menstrual periods can be irregular.
Progesterone	The steroid hormone which enables and maintains pregnancy, and permits the mitogenic effect of estrogen.
Progestin	Any substance that acts like progesterone.
Proliferation	The multiplication of cells through mitosis.
Proliferative breast disease	Breast tissue which has “overgrown,” e.g., ductal hyperplasia which has multiple layers of cells instead of a single layer.
Spontaneous abortion	A miscarriage.
Tamoxifen	Example of a drug which blocks estrogen receptors.

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