Normal Breast Physiology

The Reasons Hormonal Contraceptives and Induced Abortion Increase Breast-Cancer Risk

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Abstract

A woman gains protection from breast cancer by completing a full-term pregnancy. In utero*, her offspring produce hormones that mature 85 percent of the mother's breast tissue into cancer-resistant breast tissue. If the pregnancy ends through an induced abortion or a premature birth before thirty-two weeks, the mother's breasts will have only partially matured, retaining even more cancer-susceptible breast tissue than when the pregnancy began. This increased amount of immature breast tissue will leave the mother with more sites for cancer initiation, thereby increasing her risk of breast cancer. Hormonal contraceptives increase breast-cancer risk by their proliferative effect on breast tissue and their direct carcinogenic effects on DNA. Hormonal contraceptives include estrogen-progestin combination drugs prescribed in any manner of delivery: orally, transdermally, vaginally, or intrauterine. This article provides the detailed physiology and data that elucidate the mechanisms through which induced abortion and hormonal contraceptives increase breast-cancer risk.*

Since 1957, a large number of epidemiological studies have suggested a link between induced abortion and breast cancer,[1] with other studies indi-

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cating the lack of such an association.[2] This author and others have reviewed this literature at length and shown that proper analysis of valid studies indicates an increased risk of breast cancer following induced abortion.[3] It is noteworthy that there is a universally accepted protective effect of full-term pregnancy in decreasing breast-cancer risk,[4] and this protective effect is abrogated by induced abortion. Although the National Cancer Institute's 2003 "Workshop on Early Reproductive Events and Breast Cancer Risk" concluded that there was no association of abortion and breast cancer, this author and a workshop participant have demonstrated error and bias in that conclusion.[5] In addition, the users of hormonal contraceptives are clearly at increased risk for breast cancer, as acknowledged by the World Health Organization.[6] The purpose of this article is to review the biology which underlies these associations. After all, the goal of most epidemiologic studies is to provide association which then provides clues for discovery of the pathophysiology of disease.

In order to understand the reasons why both abortions and hormonal contraceptives cause breast cancer, one must first understand three areas: 1) normal breast development and maturation throughout a woman's life from her conception through the birth of a child, 2) the "susceptibility window" when a woman is most vulnerable to carcinogens, and 3) the carcinogenic effects of the predominant female sex steroids (estrogen and progesterone) upon the breast.

I. Breast Development and Maturation

In the nascent times of a woman's life before birth, two parallel ridges of tissue (the "milk ridge") form on her body about five weeks after conception. In normal embryological and fetal development, the only part of the milk ridge to remain after birth to further develop into breasts overlies the fifth ribs. Cords of ectoderm (the outer skin layer of the embryo) on this ridge burrow into the mesenchyme (the middle layer of the embryo).[7] It is from these cords that development of the milk-producing glands and their ducts will occur in concert with the maturation of its mother's breast. More remarkably, it is the embryo, and later the fetus and placenta through the production of two hormones, hCG and hPL (human chorionic gonadotropin and human placental lactogen), who is largely responsible for the final maturation of its mother's breast into milk-producing breast lobules. With this maturation through a full-term pregnancy, a mother reduces her future breast-cancer risk.

A mother's breasts enlarge very soon after conception, making sore and tender breasts one of the first signs of pregnancy. Even before the embryo (or blastocyst) implants in its mother's womb, a chemical signal, hCG,

produced by the embryo causes its mother's ovaries to increase production of estrogen and progesterone in order to sustain the pregnancy.[8] After about eleven weeks, it is the fetus and placenta and not the mother which produced most of the needed estrogen and progesterone to sustain the pregnancy. Fetal developmental abnormalities that prevent adequate production of those hormones cause miscarriage (spontaneous abortion) in the first trimester.[9] The inadequate levels of the pregnancy hormones (estrogen, progesterone, and hCG) during an abnormal pregnancy that result in a first trimester spontaneous abortion do not suffice for stimulating breast development and leave the mother's breasts unchanged. Therefore, following a first-trimester spontaneous abortion, the mother typically has no change in breast-cancer risk as her breasts were never stimulated to grow. Often a mother who spontaneously aborts (miscarries) in the first trimester will often remark that she never "felt" pregnant before she miscarried; she had no morning sickness nor sore and tender breasts that she may have experienced in prior pregnancies. Thirty-one percent of all conceptions will end in a spontaneous abortion.[10]

Pregnancy Outcomes, Breast Structure, and Cancer Risk

Pregnancy outcomes other than a full-term birth can increase breast-cancer risk. If the mother ends her normal pregnancy with an induced abortion, her breasts will have already started to enlarge and grow by increasing the numbers of Type 1 and 2 lobules that developed in her breasts during puberty, leaving her breast with more sites for cancers to initiate.[11] Lobules are units of breast tissue comprised of a milk duct with surrounding mammary (milk) glands, which are in turn composed of individual breast cells. Each breast cell contains a nucleus—a center space that contains DNA, the coded complete blue print of genetic information that every cell in the body contains. The source of any cancer that develops in a body is the result of a mutation or damage done to a cell's DNA, the blueprint. The damage may be the result of a chemical, such a benzopyrene in cigarette smoke; a virus, such as human papilloma virus that causes cervical cancer; or even a naturally occurring hormone such as estrogen (see below).

There is recent literature regarding stem cells in the breast that are believed to be the site for some cancers to form. At a microscopic, pathologic level, analysis of the types of cytokeratin (a protein) that these stem cells produce reveals that breast cells do not fully mature until they undergo lactation,[12] thereby becoming cancer resistant. In other words, they are changed through pregnancy and lactation. There is also literature which reveals the changes in gene expression (this is not a mutation), i.e., the genes which are up and down regulated (turned on and off), which occur with a full-term pregnancy.[13] This is a molecular basis for breast-cancer risk.

At a microscopic pathologic level, Type 1 lobules are the sites where about 85 percent of all breast cancers arise, named ductal cancers because they arise in the milk ducts. The cells in Type 1 lobules have greater numbers of estrogen and progesterone receptors in their cells' nuclei than Type 2 lobules. Type 2 lobules are more mature yet still are the sites where 10 to 15 percent of all breast cancers start (called lobular cancers because they arise in the milk-secreting mammary glands).[14] The longer a mother is pregnant before the induced abortion, the greater the numbers of Type 1 and 2 lobules she will have formed, providing more cells which are at risk of developing into breast-cancer cells. There will be more sites for cancers to start, following an induced abortion. There is about a 3 percent increased risk in her chance of cancer for each week of gestation before the induced abortion.[15]

If the pregnancy is a normal, healthy one that goes to forty weeks or "full-term," there will be near complete (about 85 percent) maturation of the mother's mammary glands into Type 4 lobules. Type 4 lobules have progressed through a complete maturation process.[16] This is why there is a known protective effect against breast cancer when a woman has a full-term pregnancy. Each successive pregnancy causes more of the mother's mammary glands to mature which further reduces her risk by 10 percent with each pregnancy.[17] Pregnancy causes Type 1 lobules to increase the number of ductules (which become mammary glands) from an average of eleven ductules per lobule to forty-seven, becoming Type 2 lobules. Type 2 lobules mature still more fully into Type 3 lobules when there is an average of eighty ductules in each lobule. Type 3 lobules have very few estrogen/progesterone receptors and do not quickly copy their DNA, thereby decreasing the possibility of mutations and carcinogenesis.[18] By 32 weeks these Type 3 lobules start to produce colostrum, the first milk, thereby becoming Type 4 and resistant to cancer. Studies have been done which show exactly which genes have been turned off and on (down regulated and up regulated) through a full-term pregnancy.[19] During this time of maternal breast maturation, in the womb at 32 weeks gestation, the solid cords of epithelial cells on the fetal chest wall become canaliculized (become hollow), thereby developing the milk ducts and glands of the newly forming breast.[20]

The maturation process that protects a woman from breast cancer happens only because the child in her womb produces the hormones hCG and hPL which prepare the mother to breast feed. In the first half of pregnancy, hCG stimulates estrogen and progesterone levels which cause the breast to enlarge with increased numbers of Type 1 and Type 2 lobules. In the later half, hPL, which rises three times higher than the mother's prolactin levels by the end of pregnancy, enables full differentiation to Type 4 lobules which produce colostrum.

This is why women who have had a full-term pregnancy have a lower breast-cancer incidence than those who remain childless.

Additional Benefits of Pregnancy and Childbirth in Reduction of Breast-Cancer Risk

Breast feeding after birth further reduces the mother's risk of breast cancer in proportion to the length of breast feeding.[21] The mammary glands remain in a state of near-complete differentiation. Breast feeding results in the mother's temporary loss of her menstrual cycles. Menstrual cycles cause monthly elevations of estrogen and progesterone. Exposure to estrogen during menstrual cycles is a known risk factor for breast cancer that increases in proportion to the number of lifetime menstrual cycles women have in their reproductive lives.[22] She may also have anovulatory cycles that lack the pre-ovulatory estrogen elevation needed for the release of an ovum (egg) from the ovary, again reducing her exposure to estrogen. After the baby is weaned and milk production ends, morphologically the Type 4 lobules appear to regress to Type 3. However, there are permanent gene-expression changes (expression refers to normal, not mutated, genes) in the cells of these lobules that permanently make them resistant to cancer formation. Even after menopause when they morphologically regress further to Type 1 lobules the gene-expression changes remain.[23] This accounts for the life-long protection a woman gains after a full-term pregnancy.

Premature Births: Before and After 32 Weeks

Hormonally normal pregnancies that end prematurely *before* 32 weeks and which are not first trimester spontaneous abortions (miscarriages) increase breast-cancer risk because they have left the mother's breast with more places for cancer to initiate.[24] The breasts enlarge and double in volume by mid-second trimester by producing more vulnerable Type 1 and 2 lobules. A pregnancy that ends before maturation into cancer resistant lobules will result in breasts that have more incompletely differentiated mammary tissue than before pregnancy, thereby increasing the number of cells susceptible to carcinogenesis. This is especially true for a woman's first pregnancy. It does not matter if the pregnancy is ended prematurely through an induced abortion or by a premature delivery, because the hormonal effects on the mother's breast are not changed by the intent of the pregnancy's end. For example, a woman may be faced with the option of an induced premature delivery before 32 weeks because her baby has severe developmental abnormalities that are not compatible with life outside the womb. By choosing induction, she would have increased her breast-cancer risk because of the loss of the protective effect of a term delivery, and she will have increased the number of susceptible cells in which cancer could initiate. This increased

risk due to the increased numbers of lobules where cancers can arise is referred to as the "independent effect" of abortion and breast cancer.

If a pregnancy ends prematurely between 32 and 37 weeks, the mother still gains some of the protection she would have gotten if she were able to carry to term. The gain in protection is proportional to the number of weeks after 32 weeks up until term at 40 weeks.[25]

Secondary Causes for Induced Abortion Increasing Breast-Cancer Risk

In addition to the "independent effect," induced abortion may increase the mother's risk of breast cancer by another effect. Induced abortion is a recognized cause of premature birth often due to cervical incompetence, uterine infection, and scarring post-abortion. The cervix is the mouth of the uterus, and its muscle tightly holds the fetus and placenta inside during pregnancy. If the cervix is damaged during forced dilatation during an abortion, the situation becomes a vicious cycle in which induced abortion is a cause of prematurity, and prematurity more than doubles breast-cancer risk if it is before 32 weeks. The greater the number of previous abortions a woman has, the higher her risk of premature births in future pregnancies.[26]

Sadly, premature birth not only affects the health of the mother, but that of any future children as well. Prematurity increases the chance those children will suffer from cerebral palsy and other ailments related to prematurity.[27] Induced abortion causes the death of her child and risks the health of children subsequent to her abortion.

A mother who is pregnant and chooses abortion loses the protective effect she would have gained by carrying that pregnancy to term. If after an abortion of her first pregnancy. a mother chooses to have a completed pregnancy, it means that she has delayed her first full-term pregnancy by a varying length of time. This delay lengthens her "susceptibility window" (as described below) which also increases her breast-cancer risk. A woman who has a full-term pregnancy at eighteen years of age has a 50 percent reduction in breast-cancer risk than if she waits until age 30.

II. The "Susceptibility Window"

During the time after puberty and before a full pregnancy, called "susceptibility window," a woman's breast has a relatively much smaller amount of breast tissue than after a pregnancy.[28] A pregnancy of any length that has normal levels of estrogen and progesterone increases the number of breast lobules in proportion to the length of the pregnancy. This accounts for the fact that the later in pregnancy an abortion is done, the higher is the mother's risk for breast cancer, as the pregnancy has left her with more susceptible cells in which cancer could initiate. This fact makes teenagers who have

second trimester abortions especially vulnerable to breast cancer. There is data that suggests that a woman who has a complete pregnancy and lactates within five years of an abortion has a lower risk of breast cancer than if a woman waits more than ten years before her first child is born.[29] It is important for women to be aware of this fact, because many women will become pregnant again within a year of an induced abortion. If that next pregnancy is carried to term and she lactates within five years of the abortion, her risk of subsequent breast cancer will be lower.[30]

The aforementioned facts illustrate the significance of the "susceptibility window" concerning breast development and breast-cancer risk. The susceptibility window is that period following puberty, which causes the growth of immature breast tissue, and before the first full-term pregnancy that induces breast tissue maturation making it resistant to cancer. For example, after the Hiroshima atomic bomb exposed women to high doses of radiation, it was young, nulliparous women who later developed breast cancer while the older parous women did not.[31] Childless women who take estrogen-progestin combination drugs (hormonal contraceptives) are at higher risk for breast cancer than women who take those same drugs after having children.[32] The breast-cancer risk of the benzopyrenes in cigarette smoke is much greater in childless women than those that have given birth.[33] The longer a woman's susceptibility window is, the greater her risk of breast cancer.

Pregnancy after a Long Susceptibility Window Increases Breast-Cancer Risk

The effect of the susceptibility window also accounts for the transient rise in breast-cancer incidence in those who postpone childbirth until late in their reproductive lives.[34] A woman who gives birth at the age of 18 has at least a 50 percent in reduction in risk compared to a woman who delays her first childbirth to age 30. When a woman delays child bearing and exposes her cancer-vulnerable immature breast cells and lobules to the estrogen elevations of her regular menstrual cycles or the estrogen in hormonal contraceptives, she increases the risk that a cancer cell may form. This breast-cancer cell will either be killed by her immune system, start to grow, or remain dormant until it is "provoked" to grow. One such provocation is the extremely high elevations of estrogen and progesterone during pregnancy. By the end of the first trimester, estrogen levels are elevated by 2000 percent. If the cancer cells have estrogen and progesterone receptors, they may quickly grow to create a tumor large enough to become detectable soon after or even during pregnancy. In fact, if a woman takes oral contraceptives prior to a first full-term pregnancy, her breast-cancer risk is higher than if she took birth control pills[35] and never got pregnant.

The longer the susceptibility window, the longer this transient elevation will remain until the woman is afforded the benefits of near-complete breast maturation and risk reduction. A completed pregnancy at 20 years old carries no increased breast-cancer risk, but a first pregnancy completed through at least 32 weeks at age 30 elevates breast-cancer risk for as long as 15 years before its risk reduction effects become manifest. However, no matter how late in a woman's life she completes her first pregnancy, so long as it lasts at least 32 weeks, she will eventually enjoy the beneficial risk-reduction effects.[36]

Breast Cancer during Pregnancy

The development of breast cancer detected during pregnancy is relatively uncommon but is of great concern. This situation seemingly might pit the needs of the mother for treatment against the well-being of her child in the womb. However, in one study it was shown that the only long-term survivors of breast cancer found during pregnancy are those women who delivered to term.[37] Those women who spontaneously aborted had slightly shorter survivals, but those who underwent induced abortion in the hopes that they might be able to get better treatments when they were no longer pregnant had the shortest survivals. What was not considered and known when induced abortion was recommended to these patients was the fact that the hormone hCG produced by the fetus not only stimulates the mother's breast tissue to grow but also stimulates the mother's ovaries and breast tissue to produce a protein, inhibin.[38] Inhibin inhibits the growth of cancer cells. Experimental studies in women who were not pregnant but had newly diagnosed breast cancers showed that the cancers would get smaller when the women were injected with hCG.[39]After the first trimester, the chemotherapy given to the mother to fight her breast cancer is not harmful to the fetus because the fetal organs are already formed.[40] Surgery with general anesthesia can be safely done after the first trimester.

III. Carcinogenic Effects of Estrogen

Carcinogenesis

The root cause of the formation of all cancers is damage of a cell's normal DNA. A person's body is made of individual cells organized into tissues and organs that have different functions. Every cell's DNA is in the nucleus. The nucleus contains the chromosomes that are made of long, specific DNA sequences, the genes. Genes control the life and function of the cell. So even though the DNA is the same in each cell, the cells function differently because of which genes are up and down regulated (turned on and off).

In order to grow, cells must replicate their DNA so that each new cell will have a complete copy of all genes. During the process of replication, errors (mutations) may occur resulting in mutated genes. If the mutations accumulate or if a critical mutation occurs, a cancer cell may form which then goes on to uncontrolled growth. Anything that directly damages DNA, such as a virus, a chemical, or radiation, may induce cancer cells to form. Anything that stimulates a cell to replicate itself may also cause mutations and cancer cells to form because in the process of copying its DNA errors can occur, such as copying errors resulting in deletions or additions to the cell's DNA. One way to understand the process of cancer cells forming is to think of DNA being like a book of instructions that is copied for each new cell formed. If a minor error in a sentence of instructions is made, such as a single "the" being deleted or added, most of the sense of that sentence is still intelligible to the reader. However, if lots of "thes" and nouns are added or deleted in the sentence, the instructions become useless. In addition, even just one critical error in a sentence, such as leaving out the word "no," may make the instruction wrong.

Estrogen Increases Breast-Cancer Risk

Breast cancer that is not attributable to DNA mutations that were inherited from a parent, such as the BRCA genes, are largely due to the effects of the natural, female hormone, estrogen.

The age specific incidence curve, which is the incidence of breast cancer plotted against the age of women, shows breast-cancer rates start to rise about eight to ten years after the average age of the first menstrual cycle (menarche) when a woman is first exposed to increasing levels of estrogenic hormones. The incidence curve rises sharply until the approach of menopause when the incidence of breast cancer rises more slowly as her estrogen levels drop.

Estrogen has long been known to be associated with breast cancers. Before there were chemotherapy drugs, physicians would remove a breast-cancer patient's ovaries, reducing the patient's estrogen levels, slowing the growth of her cancer or causing regression. Now drugs such as Tamoxifen that block estrogen receptors or Arimidex that decrease a patient's production of estrogen are used to treat breast cancer.

The carcinogenic effects of estrogen are due to two actions of estrogen:

1) as a mitogen acting in concert with progesterone;

2) as a direct carcinogen through the formation of metabolites.

Mitogens cause breast cells to multiply through division of one cell into two cells, mitosis. Before a cell can divide into two, its DNA must be copied

so that after division each cell will have a complete set of genes, which are segments of DNA that control a particular cell function. When the DNA is copied, errors can be made which result in mutations. These mutated cells can mutate further; and when multiple mutations occur, a cancer cell may result. Breast-cancer cells that form can also have estrogen and progesterone receptors that stimulate them to grow. Therefore, estrogen and progesterone are not only cancer initiators but also promoters.

Estrogen alone and its metabolites can also be directly carcinogenic. For example, a particular metabolite of estrogen, 4-hydroxy catechol estrogen quinone, can directly damage DNA, resulting in mutations. Studies have shown that breast-cancer patients have higher levels of 4-hydroxy catechol estrogen quinone[41] as well has higher levels of the most potent estrogens, such as 17-β estradiol, compared with the least potent ones, such as estriol.

These two mechanisms which promote the formation of breast cancer through estrogen exposure are the reason that hormonal contraceptives and combination hormone replacement therapy cause breast cancer.

In 2005, the International Agency for Research on Cancer (IARC), part of the UN's World Health Organization classified hormonal contraceptives as Group 1 carcinogens for breast, cervical, and liver cancers after reviewing the world's literature on estrogen-progestin combination drugs. This was done after the scientists had gathered in France and reviewed the extant world's literature on the carcinogenicity of estrogen-progestin combination drugs.[42]

In Conclusion

There is a well-known and documented physiology supporting both induced abortion and hormonal contraceptives as risk factors for breast cancer. Yet these risks are largely unknown to women seeking family planning services. Without this knowledge, women cannot make informed choices when they are faced with the choice of an induced abortion or life for their child and the use of hormonal contraceptives. By choosing abortion, a woman increases her risk in four ways: she creates in her breasts more places for cancers to start, which is the "independent effect"; she loses the protective effect that a full-term pregnancy would have afforded her; she increases the risk of premature delivery of future pregnancies; and she lengthens her susceptibility window. Contraceptives containing estrogen-progestin drugs increase breast-cancer risks by causing breast cells to proliferate increasing the chance of mutations leading to cancer cells, and by acting as direct carcinogens.

This knowledge is especially important for teenagers who are most vulnerable and negatively impacted by abortion and hormonal contracep-

tives. At a time when their breasts are already growing under the influence of their own heightened hormonal milieu, induced abortion alters their physiology in a way that results in a much higher risk of subsequent breast cancer. A common occurrence is a teenager unaware ofwho hides her pregnancy. until she starts showing in the second trimester. The pregnancy is not revealed to others until she starts showing in the second trimester. This circumstance quite frequently results in a late-term abortion, which is made worse in most circumstances by the addition of carcinogenic, contraceptive hormones post-abortion, elevating her risk of breast cancer even more. Knowledge of her risk factors and the benefits of carrying the pregnancy to term with subsequent birth and adoption could prevent this from occurring with great frequency.

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