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Summary Report: Early Reproductive Events and Breast Cancer Workshop

Introduction

The Early Reproductive Events and Breast Cancer Workshop convened February 24-26, 2003, and the outcomes of the meeting were reviewed and discussed at the joint meeting of the NCI Board of Scientific Advisors (BSA) and Board of Scientific Counselors (BSC) held March 3, 2003.

The Workshop was established to provide an integrated scientific assessment of the association between reproductive events and the risk of breast cancer. Participants represented a diversity of breast cancer expertise, including epidemiologists, clinicians, basic scientists and breast cancer advocates. The Workshop evaluated the current strength of evidence of the characteristics of pregnancy related to cancer (epidemiologic studies), the biologic changes resulting from pregnancy that may be involved in modifying breast cancer risk (clinical studies), and the biologic mechanisms identified (animal studies).

This report summarizes the epidemiologic, clinical and animal studies findings related to early reproductive events and breast cancer risk, and each finding is given a Strength of Evidence Rating*. Gaps in research knowledge for each scientific area are identified, and recommendations for future research directions are provided.

Epidemiologic Findings

- Early age at first term birth is related to lifetime decrease in breast cancer risk. (1)
- Increasing parity is associated with a long-term risk reduction, even when controlling for age at first birth. (1)
- The additional long-term protective effect of young age at subsequent term pregnancies is not as strong as for the first term pregnancy. (1)
- A nulliparous woman has approximately the same risk as a woman with a first term birth around age 30. (1)
- Breast cancer risk is transiently increased after a term pregnancy. (1)
- Induced abortion is not associated with an increase in breast cancer risk. (1)
- Recognized spontaneous abortion is not associated with an increase in breast cancer risk. (1)
- Long duration of lactation provides a small additional reduction in breast cancer risk after consideration of age at and number of term pregnancies. (1)
- Pregnancy-induced hypertension is associated with decreased breast cancer risk. (2)
- Maternal DES exposure is associated with an increase in breast cancer risk. (3)

Epidemiologic Gaps

- By what mechanism does pregnancy at an early age protect against breast cancer?
- Do pregnancy and age at pregnancy modify radiation-induced breast cancer risk?
- What are the effects of age at pregnancy on subgroups of women (e.g., those with BRCA-1 and BRCA-2 mutations)?
- What is the mechanism by which lactation affects breast cancer risk?
- What is the temporal pattern of breast cancer risk following lactation?
- What is the effect of lactation on women with BRCA-1 and BRCA-2 mutations?
- Does gender of offspring have an effect?
- Does birth weight of offspring have an effect?
- What is the impact of multiple births in the same pregnancy, with and without assisted reproductive technology?
- What are the breast cancer risk implications of abnormal pregnancies (e.g., spina bifida, late fetal death, fertility treatment-induced pregnancy, preterm delivery, small for gestational age offspring)?
- What is the mechanism by which pre-eclampsia reduces breast cancer risk?
- Is there a distinction between hypertension and pre-eclampsia with respect to breast cancer risk?
- Is gestational diabetes associated with breast cancer risk?

Clinical Findings

- There are long-lasting decreases in mammographic density following pregnancy. (2)
- There may be changes in breast histology that can be correlated with risk in premenopausal women. (3)
- Prolactin, estradiol, and IGF-1 are decreased after pregnancy. (3)

Clinical Gaps

- What are the levels, determinants, and interactions of pregnancy-related mammotrophic factors, ligands, and receptors?
- What is the time course of pregnancy-related hormonal changes?
- Are pregnancy-related hormonal changes influenced by genetic polymorphisms?
- What is the precise nature of pregnancy-related changes in breast histology?
- How is the epithelial/stromal relationship altered in pregnancy?
- Can pregnancy-related changes in breast histology be correlated with ductal lavage findings?
- Can noninvasive procedures for assessing breast composition (e.g., MRI and other imaging techniques, particularly functional imaging) substitute for histology?
- What are the molecular changes in the breast during and after pregnancy?
- What are the histologic and molecular characteristics of breast tumors during and after pregnancy?
- Are there immune system changes that may be relevant to breast cancer risk following pregnancy?
- Are there pregnancy-related, non-hormonal metabolic changes relevant to breast cancer risk?

Animal Model Findings

- Pregnancy protects against subsequent chemical carcinogen-induced breast cancer in rats and mice. (1)
- Estrogen and progesterone combinations and hCG protect against carcinogen-induced cancer in rodents by mimicking pregnancy. (1)
- Short-term estrogen exposure, at levels of estrogen mimicking pregnancy, is protective for carcinogen-induced cancer in rats. (1)

Animal Model Gaps

- What are the mechanisms of hormone action when they are given before or after chemical carcinogen exposure?
- What is the relationship between pregnancy and risk of preneoplastic lesions?
- What are the levels, determinants, and interactions of pregnancy-related mammotrophic factors, ligands, and receptors?

Future Research Directions

- Develop additional animal and treatment models, including further examination of existing models.
- Examine the molecular mechanisms of hormone-induced protection, including epithelial/stromal interactions.
- Integrate the methodology of genomics and proteomics into the study of pregnancy in relation to risk of breast cancer.
- Pursue descriptive studies about human breast development in order to formulate new hypotheses.
- Pursue international studies to develop hypotheses for observed international differences in breast cancer risk.
- Develop surrogate markers to identify risk of breast cancer following pregnancy.
- Translate knowledge about protective effects of pregnancy into intervention trials with human populations.
- Promote interactions among epidemiologists, clinicians, and basic scientists.
- Consider a funding mechanism aimed at interdisciplinary research concerning pregnancy and breast cancer.
- Develop high-throughput technology for hormone measurement.
- Support the collecting, archiving, and sharing of relevant biospecimens.

Boards' Response

The NCI Board of Scientific Advisors and Board of Scientific Counselors reviewed and discussed the results of the Early Reproductive Events and Breast Cancer Workshop, and unanimously approved the Workshop findings. One additional gap in our clinical understanding of breast cancer was identified: Do breast cancers diagnosed during pregnancy have different morphologic or molecular characteristics than those diagnosed at other times? It is hoped that the outcomes of this Workshop will help guide the Institute's future research agenda and public communication materials.

*Strength of Evidence Ratings Key

Strength of Evidence Ratings: Epidemiology

1
= Well established
2
= Weight of evidence favors
3
= Suggested from human population studies, but speculative
4
= Suggested from laboratory or theoretical considerations but essentially unevaluated in human populations

Strength of Evidence Ratings: Biologic Changes

1
= Well established
2
= Weight of evidence favors
3
= Suggested by human evidence, but speculative
4
= Suggested from laboratory findings or theoretical considerations but essentially unevaluated in humans

Strength of Evidence Ratings: Biological Mechanisms from Laboratory Studies

1
= Well established
2
= Weight of evidence favors
3
= Suggested by experimental evidence, but speculative
4
= Not supported by experimental evidence

Minority Dissenting Comment

Participant comment [1] regarding the outcome of the workshop.

Table of Links

[1] http://cancer.gov/cancer_information/doc.aspx?viewid=15e3f2d5-5cdd-4697-a2ba-f3388d732642

Pregnancy and Breast Cancer Risk

Introduction

Every woman's hormone levels change throughout her life for a variety of reasons, and hormone changes can lead to changes in the breasts. Hormone changes that occur during pregnancy may influence a woman's chances of developing breast cancer later in life. Research continues to help us understand reproductive events and breast cancer risk. The National Cancer Institute (NCI) is currently funding research that may lead to discoveries that identify ways to mimic pregnancy's protective effects and translate them into effective prevention strategies.

Pregnancy-Related Factors that Protect Against Breast Cancer

Some factors associated with pregnancy are known to reduce a woman's chance of developing breast cancer later in life:

- The younger a woman has her first child, the lower her risk of developing breast cancer during her lifetime.
- A woman who has her first child after the age of 35 has approximately twice the risk of developing breast cancer as a woman who has a child before age 20.
- A woman who has her first child around age 30 has approximately the same lifetime risk of developing breast cancer as a woman who has never given birth.
- Having more than one child decreases a woman's chances of developing breast cancer. In particular, having more than one child at a younger age decreases a woman's chances of developing breast cancer during her lifetime.
- Although not fully understood, research suggests that pre-eclampsia, a pathologic condition that sometimes develops during pregnancy, is associated with a decrease in breast cancer risk in the offspring, and there is some evidence of a protective effect for the mother.
- After pregnancy, breastfeeding for a long period of time (for example, a year or longer) further reduces breast cancer risk by a small amount.

Pregnancy-Related Factors that Increase Breast Cancer Risk

Some factors associated with pregnancy are known to increase a woman's chances of developing breast cancer:

- After a woman gives birth, her risk of breast cancer is temporarily increased. This temporary increase lasts only for a few years.
- A woman who during pregnancy took DES (diethylstilbesterol), a synthetic form of estrogen that was used between the early 1940s and 1971, has a slightly higher risk of developing breast cancer. (So far, research does not show an increased breast cancer risk for their female offspring who were exposed to DES before birth. Those women are sometimes referred to as "DES daughters.")

Other Breast Cancer Risk Factors Not Related to Pregnancy

At present, other factors known to increase a woman's chance of developing breast cancer include age (a woman's chances of getting breast cancer increase as she gets older), a family history of breast cancer in a first degree relative (mother, sister, or daughter), an early age at first menstrual period (before age 12), a late age at menopause (after age 55), use of menopausal hormone replacement drugs, and certain breast conditions.

Obesity is also a risk factor for breast cancer in postmenopausal women. More information about these and other breast cancer risk factors is found in NCI's publication *What You Need To Know About™ Breast Cancer.*

Misunderstandings About Breast Cancer Risk Factors

There are a number of misconceptions about what can cause breast cancer. These include, but are not limited to, using deodorants or antiperspirants, wearing an underwire bra, having a miscarriage or induced abortion, or bumping or bruising breast tissue. Even though doctors can seldom explain why one person gets cancer and another does not, it is clear that none of these factors increase a woman's risk of breast cancer. In addition, cancer is not contagious; no one can "catch" cancer from another person.

Preventing Breast Cancer

There are some things women can do to reduce their breast cancer risk.

Because some studies suggest that the more alcoholic beverages a woman drinks the greater her risk of breast cancer, it is important to limit alcohol intake. Maintaining a healthy body weight is important because being overweight increases risk of postmenopausal breast cancer. New evidence suggests that being physically active may also reduce risk. Physical activity that is sustained throughout lifetime or, at a minimum, performed after menopause, may be particularly beneficial in reducing breast cancer risk. Eating a diet high in fruits and vegetables, and energy

and fat intake balanced to energy expended in exercise are useful approaches to avoiding weight gain in adult life.

Detecting Breast Cancer

A woman can be an active participant in improving her chances for early detection of breast cancer. NCI recommends that, beginning in their 40s, women have a mammogram every year or two. Women who have a higher than average risk of breast cancer (for example, women with a family history of breast cancer) should seek expert medical advice about whether they should be screened before age 40, and how frequently they should be screened.

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Related National Cancer Institute (NCI) Materials

- National Cancer Institute Fact Sheet 3.75, *Abortion, Miscarriage, and Breast Cancer Risk*
  http://www.cancer.gov/cancertopics/factsheet/Risk/abortion-miscarriage
- *What You Need To Know About™ Breast Cancer*
  http://www.cancer.gov/cancerinfo/wyntk/breast
- General Information About Breast Cancer
  http://www.cancer.gov/cancer_information/cancer_type/breast/
- Summary Report: Early Reproductive Events and Breast Cancer Workshop
  http://www.cancer.gov/cancerinfo/ere-workshop-report

NCI Resources

Cancer Information Service (toll-free)
Telephone: 1–800–4–CANCER (1–800–422–6237)
TTY: 1–800–332–8615

Online
NCI's Web site: http://www.cancer.gov
LiveHelp, NCI's live online assistance:
https://cissecure.nci.nih.gov/livehelp/welcome.asp

This fact sheet was reviewed on 12/30/03

About Breast Cancer

Facts and Figures

Risk factors for breast cancer

There are few well established risk factors for breast cancer and these do not account for the major international differences or allow for practical preventive measures (Table 2). Genetic factors are responsible for only a small percentage of cases.(6) Environmental factors have been speculated as playing a major role since incidence rates vary greatly between countries and rates among migrants moving from both low- and high-risk countries converge to the rate of the destination country.(7) However, the environmental factors responsible for this variation are at present unknown.

Table 2. Established risk factors for breast cancer in women

Factor	High-risk group	Low-risk group
	Relative risk >4.0	Relative risk <1.0
Age	Old	Young
Country of birth	North America, Northern Europe	Asia, Africa
Mother and sister with history of breast cancer, especially if diagnosed at an early age	Yes	No
Biopsy-confirmed atypical hyperplasia and a history of breast cancer in a first degree relative	Yes	No
	Relative risk=2.1B4.0	Relative risk <1.0
Nodular densities on the mammogram	Densities occupying >75% of breast volume	Parenchyma composed entirely of fat
History of cancer in one breast	Yes	No
Mother or sister with history of breast cancer, diagnosed at an early age	Yes	No
Biopsy-confirmed atypical hyperplasia without a family history of breast cancer	Yes	No
Radiation to chest	Yes	No
	Relative risk=1.1B2.0	Relative risk <1.0
Socio-economic status	High	Low

Race/ethnicity breast cancer at >45 years breast cancer at <45 years	 White Black	 Hispanic, Asian Hispanic, Asian
Religion	Jewish	Seventh-day Adventist, Mormon
Oophorectomy before age 40	No	Yes
Nulliparity, breast cancer at >40 years of age	Yes	No
Age at first full-term pregnancy	>30 years	<20 years
Age at menarche	<11 years	>15 years
Age at menopause	>55 years	<45 years
History of primary cancer in endometrium, ovary	Yes	No
Obesity breast cancer at >50 years breast cancer at <50 years	 Obese Thin	 Thin Obese

Demographic factors

Age is the most recognised risk factor for breast cancer, and incidence increases with age. Women of high socio-economic status are at greater risk of breast cancer than women of low socio-economic status with possible reasons including differences in reproductive factors, lifestyle factors, and greater numbers of higher educated women attending mammography screening.

Family history

The risk of breast cancer is doubled among women with a first-degree relative diagnosed with breast cancer before the age of 40 years. (8)

The risk associated with an affected second degree relative is lower, at 1.2- to 1.5-fold. Genetic and familial factors are described in greater detail below.

Medical history

Women with biopsy-confirmed benign breast disease are at increased risk of subsequent breast cancer. The risk of invasive breast cancer depends on the specific type of benign breast disease. High relative risks (RR) are found for benign proliferative disease with atypical hyperplasia (2.5–5.3), particularly if there is a family history of breast cancer, and moderate risks are associated with proliferative disease without atypia (RR 1.6–2.2). Women with lobular carcinoma in situ are also at high risk of developing invasive breast cancer (RR 6.0–12).(9)

Hormonal and reproductive risk factors

Early age at menarche, late age at menopause, late age at first birth and nulliparity are associated with an elevated risk of breast cancer.

Conversely, bilateral oophorectomy before the age of 40 years is protective against breast

The relationship between exogenous hormone use [oral contraceptive pill (OCP), hormone replacement therapy (HRT) and depot-medroxyprogesterone acetate (DMPA)] and risk of breast cancer is not conclusive. A recent meta-analysis of 54 studies relating OCP use to breast cancer found that women who are currently using combined OCP or have used them in the past 10 years are at a slightly increased risk (RR 1.07-1.24) compared to never users.(10) There is continuing debate about the relative effect of long-term HRT use on the risk of breast cancer with conflicting results being reported.(11,12)

Other risk factors

Several other factors implicated in the development of breast cancer include parity, length of menstrual cycle, breast feeding, diethylstilbestrol use during pregnancy, infertility, spontaneous and induced abortion, physical activity, stress, height, alcohol consumption and dietary factors. Current evidence suggests that breast cancer may also be affected by the intra-uterine environment and exposures during adolescence.(13) However, the evidence for these factors is not conclusive because of inconsistency in results or concern that unidentified confounding may explain the association.

Genetic and familial factors

A family history may be due to chance, to non-genetic risk factors shared by relatives, or may be due to the inheritance of a specific germline mutation from either maternal or paternal relatives. Between 5% to 10% of all breast cancers diagnosed in women aged 45 or younger are directly attributable to inherited factors. Inherited breast cancer may be distinguished clinically from sporadic breast cancer by a younger age of onset, a higher prevalence of bilateral breast cancer, and the presence of associated tumors in family members.

Mutations of BRCA1, BRCA2, and the p53 tumor-suppressor gene have been found to markedly increase the risk of breast and ovarian cancer and perhaps colon, rectum and prostate cancer.(14) These genes appear to be transmitted in an autosomal dominant manner.(6,8)

Mutations in BRCA1 are relatively uncommon, being carried by about 1 in 1000 women and explains only 1% or 2% of all breast cancer.(15)

Germline mutations of the BRCA1 gene, located on chromosome 17q21, were initially estimated to be associated with a 50% risk of breast cancer by about age 50 and an 85% lifetime risk in high-risk families.(14,16) A more broad-based survey among a group of Ashkenazi Jews in the Washington DC region showed a lifetime risk of about 50% for women with mutations in either BRCA1 or BRCA2.(17) In addition, the risk of a second primary in the contralateral breast for a woman with BRCA1 mutations appears to be similar to the risk of the first primary (65% for mutated BRCA1 gene carriers who live to age 70).(14)

Preliminary data suggest that the prognosis of patients with BRCA1 mutations may be slightly better than that of women with sporadic tumors (18,19) but this remains to be confirmed.

Over 80 distinct mutations in BRCA1 have been characterised in high-risk families.(20) It is not known whether all mutations on BRCA1 carry the same risk. The implication of mutations that occur in the absence of a strong family history of the disease is also uncertain.

BRCA2 has been located on chromosome 13 and is associated with early-onset breast cancer and breast cancer in males, and to a lesser degree with ovarian cancer.(21) The level of breast cancer risk with mutations of BRCA2 is similar to that of BRCA1.

More common genes, such as the AT gene for ataxia-telangiectasia and the HRAS1 gene have also been implicated in the contribution to familial breast cancer.(22,23) However, the evidence linking these genes with an increased risk of developing cancer is not conclusive.

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Find out about Antibiotics and Breast Cancer

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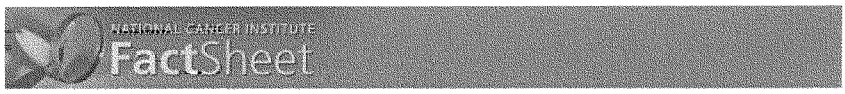
Source: http://www.bci.org.au/public/facts1.htm



Abortion, Miscarriage, and Breast Cancer Risk

Introduction

A woman's hormone levels normally change throughout her life for a variety of reasons, and these hormonal changes can lead to changes in her breasts. Many such hormonal changes occur during pregnancy, changes that may influence a woman's chances of developing breast cancer later in life. As a result, over several decades a considerable amount of research has been and continues to be conducted to determine whether having an induced abortion, or a miscarriage (also known as spontaneous abortion), influences a woman's chances of developing breast cancer later in life.

Current Knowledge

In February 2003, the National Cancer Institute (NCI) convened a workshop of over 100 of the world's leading experts who study pregnancy and breast cancer risk. Workshop participants reviewed existing population-based, clinical, and animal studies on the relationship between pregnancy and breast cancer risk, including studies of induced and spontaneous abortions. They concluded that having an abortion or miscarriage does not increase a woman's subsequent risk of developing breast cancer. A summary of their findings, titled *Summary*

Report: Early Reproductive Events and Breast Cancer Workshop, can be found at http://cancer.gov/cancerinfo/ere-workshop-report.

Related NCI Materials

- National Cancer Institute Fact Sheet 3.77, *Pregnancy and Breast Cancer Risk* http://www.cancer.gov/cancertopics/factsheet/Risk/pregnancy
- *What You Need To Know About™ Breast Cancer* http://cancer.gov/cancerinfo/wyntk/breast

Background

The relationship between induced and spontaneous abortion and breast cancer risk has been the subject of extensive research beginning in the late 1950s. Until the mid-1990s, the evidence was inconsistent. Findings from some studies suggested there was no increase in risk of breast cancer among women who had had an abortion, while findings from other studies suggested there was an increased risk. Most of these studies, however, were flawed in a number of ways that can lead to unreliable results. Only a small number of women were included in many of these studies, and for most, the data were collected only after breast cancer had been diagnosed, and women's histories of miscarriage and abortion were based on their "self-report" rather than on their medical records. Since then, better-designed studies have been conducted. These newer studies examined large numbers of women, collected data before breast cancer was found, and gathered medical history information from medical records rather than simply from self-reports, thereby generating more reliable findings. The newer studies consistently showed no association between induced and spontaneous abortions and breast cancer risk.

Ongoing Research Supported by the National Cancer Institute

Basic, clinical, and population research will continue to be supported which investigate the relationship and the mechanisms of how hormones in general and during pregnancy influence the development of breast cancer.

Important Information About Breast Cancer Risk Factors

At present, the factors known to increase a woman's chance of developing breast cancer include age (a woman's chances of getting breast cancer increase as she gets older), a family history of breast cancer, an early age at first menstrual period, a late age at menopause, a late age at the time of birth of her first full-term baby, and certain breast conditions. Obesity is also a risk factor for breast cancer in postmenopausal women. More information about breast cancer risk factors is found in NCI's publication *What You Need To Know About™ Breast Cancer*.

Important Information About Identifying Breast Cancer

NCI recommends that, beginning in their 40s, women receive mammography screening every year or two. Women who have a higher than average risk of breast cancer (for example, women with a family history of breast cancer) should seek expert medical advice about whether they should be screened before age 40, and how frequently they should be screened.

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Sources of National Cancer Institute Information

Cancer Information Service
Toll-free: 1–800–4–CANCER (1–800–422–6237)
TTY (for deaf and hard of hearing callers): 1–800–332–8615