AAPLOG 2015
Reproductive Breast Cancer Risks

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Robert Wood Johnson Medical School

President
Breast Cancer Prevention Institute

American Medical Association 2003

ORIGINAL CONTRIBUTION

Incidence of Breast Cancer With Distant Involvement Among Women in the United States, 1976 to 2009

Rebecca H. Johnson, MD
Franklin L. Chien, BA
Archie Bleyer, MD

Importance Evidence from the US National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database suggests that the incidence of advanced breast cancer in young women is increasing.

Conclusion and Relevance Based on SEER data, there was a small but statistically significant increase in the incidence of breast cancer with distant involvement in the United States between 1976 and 2009 for women aged 25 to 39 years, without a corresponding increase in older women.

JAMA. 2013;309(8):800-805

www.jama.com

Young women with breast cancer tend to experience more aggressive disease than older women and have lower survival rates.[2,3] Given the effect of the dis-

2.21) per 100 000 in 1976 to 2.90 (95% CI, 2.31 to 3.59) per 100 000 in 2009. This is an absolute difference of 1.37 per 100 000, representing an average compounded increase of 2.07% per year (95% CI, 1.57% to 2.58%; $P<.001$) over the 34-year interval. No other age group or extent-of-disease subgroup of the same age range

SINCE 1976

- There has been a 400% increase risk of in-situ breast cancer in women under 50 by SEER data
- There has been a 2% per year increase in metastatic breast cancer in women under 40

Objectives

1. Understand biologic basis of all breast cancer risks
2. Learn about the “susceptibility window” when the breast is most susceptible to cancer formation
3. Learn the breast cancer risks associated with reproduction
4. Understand the pathophysiology of breast maturation during pregnancy which accounts for these known risks including the association with induce abortion and preterm birth

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THREE
Major Influences of Breast Cancer Risk

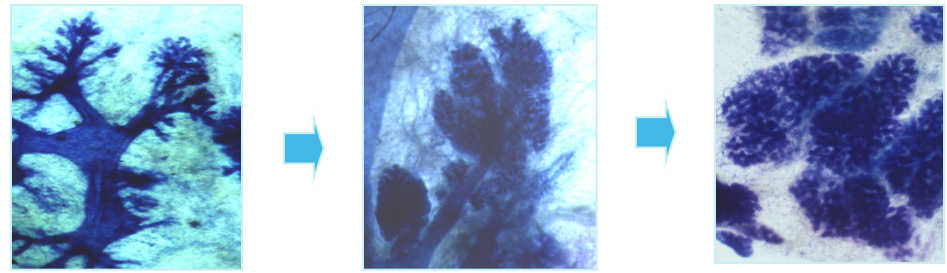
1. Mutated genes which account for approximately10% of all breast cancers (e.g. inherited BRCA genes 1 & 2 or radiation, virus or chemically induced injury)
2. Cumulative lifetime exposure to estrogen both as a mitogen and genotoxin
3. Breast differentiation from Type 1 lobules, the most primitive type to Type 4 lobules, the most differentiated

Therefore 90% of breast cancer risk factors are based on an interplay of these 2 major influences

1. **Cumulative lifetime exposure to estrogen both as a mitogen and genotoxin**
2. **Breast differentiation from Type 1 lobules, the most primitive type to Type 4 lobules, the most differentiated**

Principle of Reproductive Risks

- The **more estrogen** a woman is exposed to in her lifetime, the **higher her risk** for breast cancer
- The **sooner a woman differentiates** her breast lobules, from Type 1 and 2 to Type 3 and 4, the **lower her risk** of breast cancer.



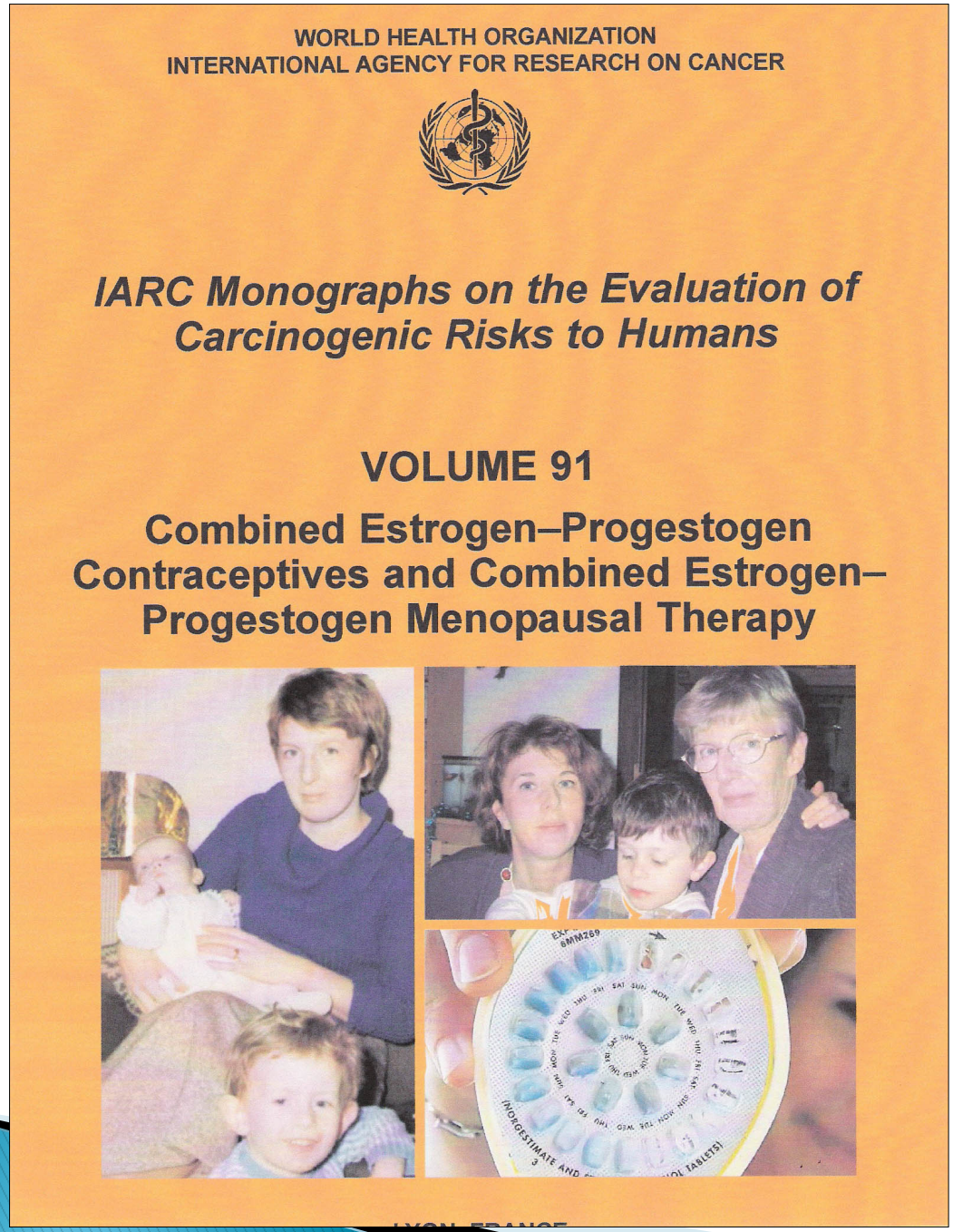
Type 1 lobule Type 2 Lobule Type 3 lobule

Estrogen has 2 effects on breast tissue

1. **Mitogen**
   - **Acts to cause proliferation**
   - **Cancer promoter**
2. Carcinogen
   - Acts as mutagen and genotoxin
   - Cancer initiator

Breast Changes With Menstrual Cycle

Uterus	Breast		Ovary
Endometrial **proliferative** phase	Stroma	No edema Cellular density	Follicular phase Estrogen
	Lobules	Simple No secretions No mitoses	
Endometrial secretory phase differentiated	Stroma	Edema	**Corpus luteal phase** **Estrogen** **Progesterone**
	Lobules	**Increase number and size** Luminal secretions **Increase epithelial mitoses**	
Menstruation	Stroma	Dense with lymphocytic infiltration	
	Lobules	Epithelial cells degenerate & slough Decrease epithelial mitoses	



2005

UN's World Health Organization

International Agency on Research of Cancer (IARC)

Lancet Oncology, August 2005

Policy Watch

Carcinogenicity of combined oestrogen-progestagen contraceptives and menopausal treatment

Vincent Cogliano, Yann Grosse, Robert Baan, Kurt Straif, Béatrice Secretan, and Fatiha El Ghissassi
WHO International Agency for Research on Cancer

Upcoming meetings

Oct 11–18, 2005
Polycyclic aromatic hydrocarbons

Feb 7–14, 2006
Carbon black, titanium dioxide, non-asbestiform talc

In June, 2005, 21 scientists from eight countries met at the International Agency for Research on Cancer (IARC) in Lyon, France, to assess the carcinogenicity of combined (oestrogen progestagen) contraceptives and hormone therapy to humans. Their assessment will be reported as volume 91 of the IARC Monographs,[1] updating previous assessments of these agents.[2]

Worldwide, more than 100 million women—about 10% of all women of reproductive age—use combined contraceptives. Use varies substantially between countries, but is generally higher in more-developed countries (16%) than in less-developed (6%) countries. Rates of ever-use are much higher than are those of present users, exceeding 80% in some more-developed countries and amounting to about 200 million women

for human papillomavirus. Data from in-vitro studies and animal studies suggest that oestrogens and progestagens could enhance expression of certain human-papillomavirus genes and stimulate cell proliferation in the human cervix through hormone-response elements in the viral genome and through receptor-mediated mechanisms, although other mechanisms could also be involved.

The risk of hepatocellular carcinoma is heightened in long-term users of combined oral contraceptives in populations with low frequencies of hepatitis-B infection and chronic liver disease, two of the main causes of human liver cancer. Increases in the occurrence of hepatocellular carcinoma were also noted in analyses that excluded women with such infections. Three case-control

International Agency for Research on Cancer (IARC) June 2005

GROUP 1 CARCINOGEN

(In same group as cigarettes for lung cancer)

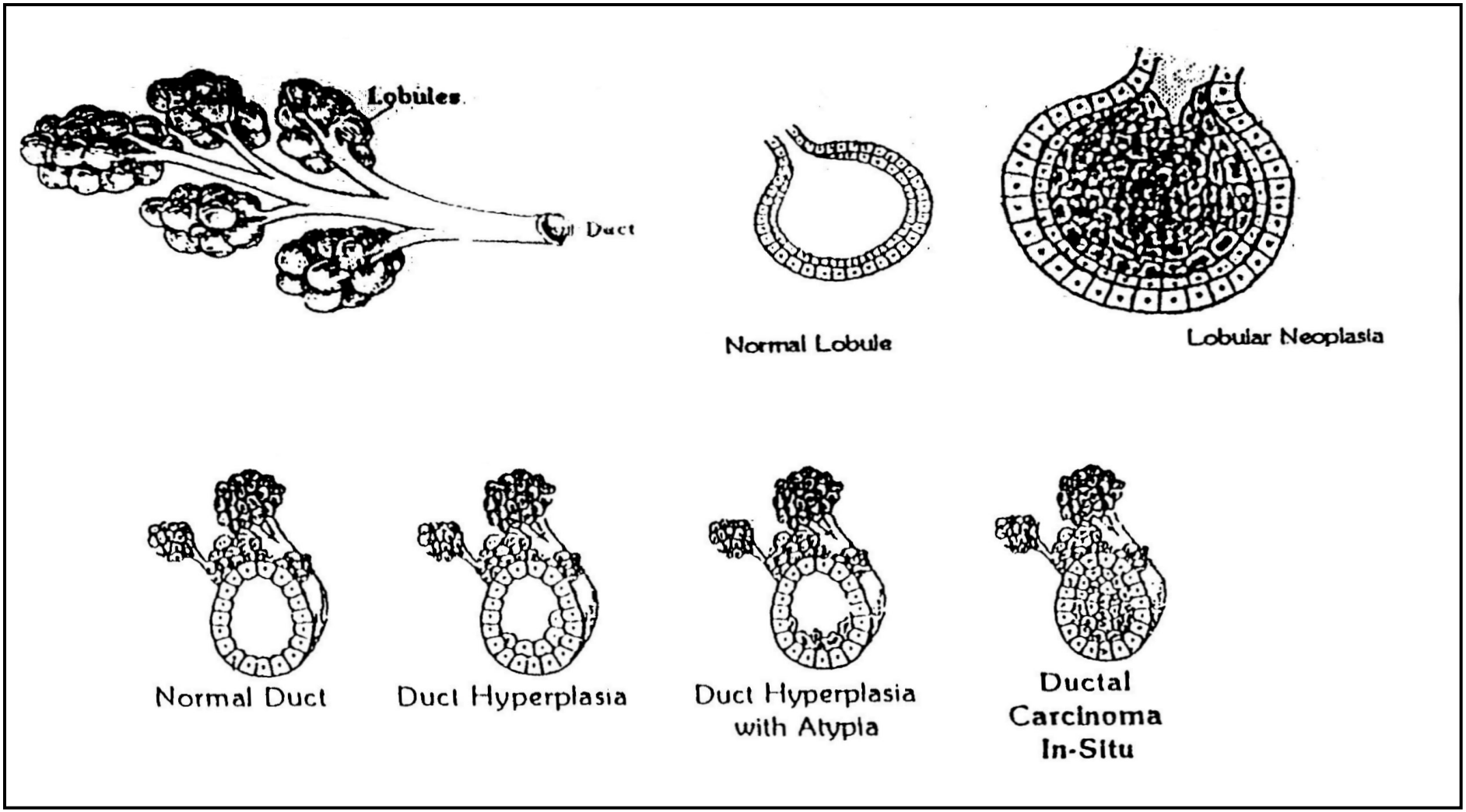
Estrogen – progestin combination drugs used in oral contraceptives and hormone replacement

- Carcinogenic for
  - Breast cancer
  - Cervical cancer
  - Liver cancer
- Protective of
  - Endometrial cancer
  - Ovarian cancer

The response of breast tissue to ESTROGEN *is* PROLIFERATION

There is a progression of:

- Normal growth (menstrual cycle)
- Hyperplasia (ductal epithelial hyperplasia)
- Neoplasia (cancer without needing initiator such as radiation)



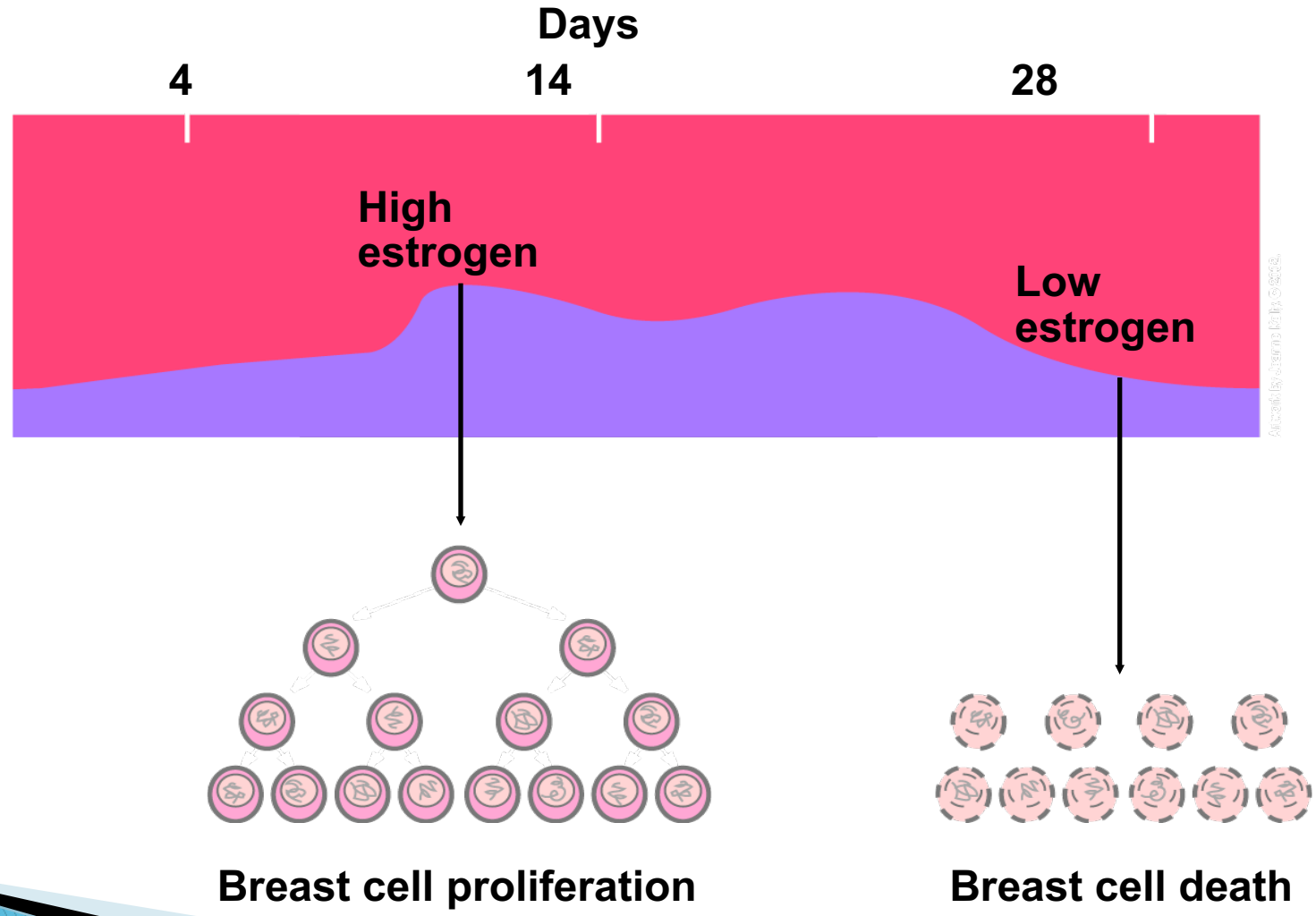
Hyperplasia to Neoplasia

Relative risk for invasive breast cancer in patients with benign disease

Risk	Disease type
No increased risk	Mild hyperplasia Duct ectasia Apocrine metaplasia Simple fibroadenoma Microcysts Periductal mastitis Adenosis
Slight increased risk 1.5-2 times	Gross cysts Moderate and florid hyperplasia Papilloma Sclerosing adenosis Complex fibroadenoma
Moderately increased risk 4-5 times	Atypical hyperplasia

Estrogen as a Mitogen

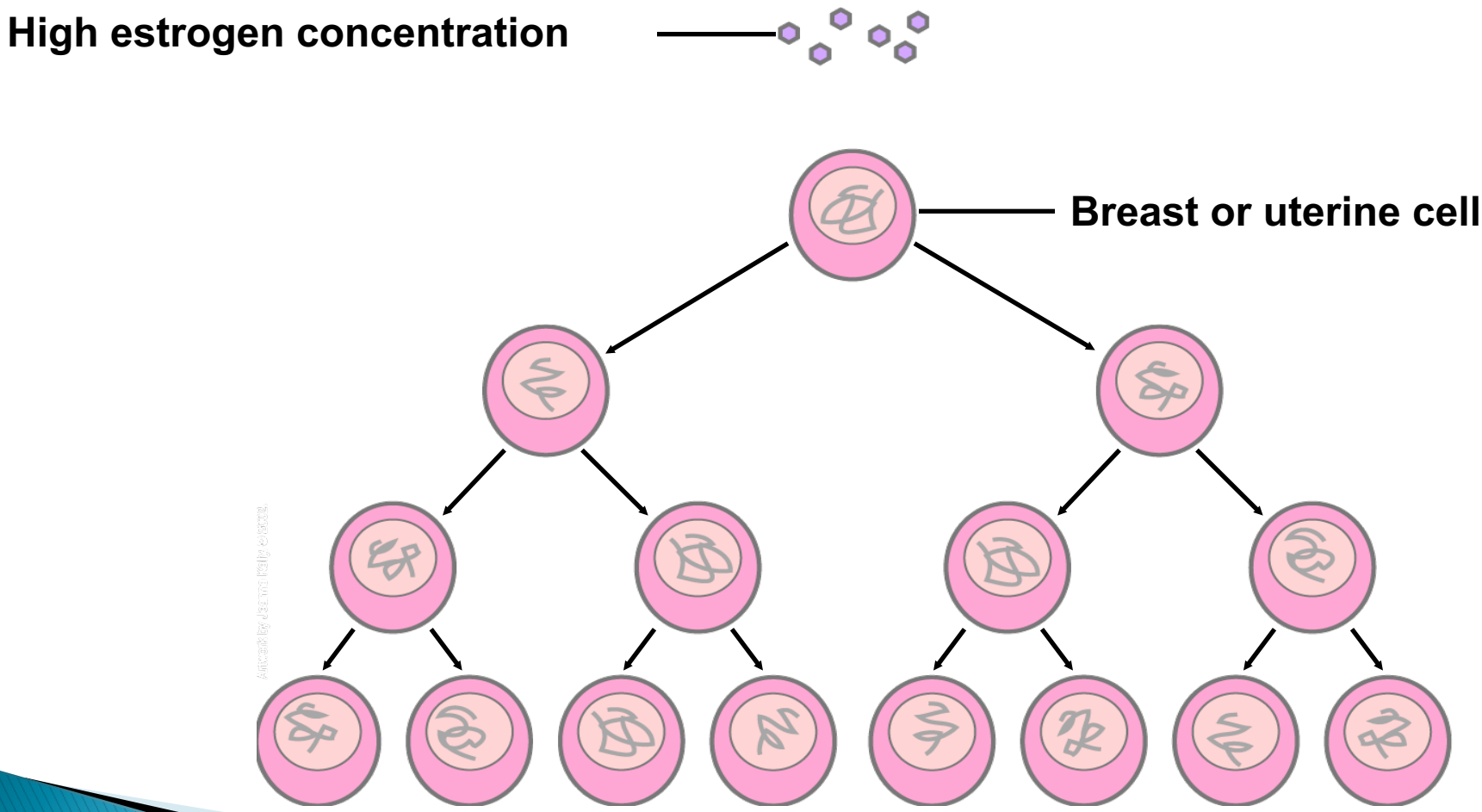
The Menstrual Cycle



Estrogen as a mitogen

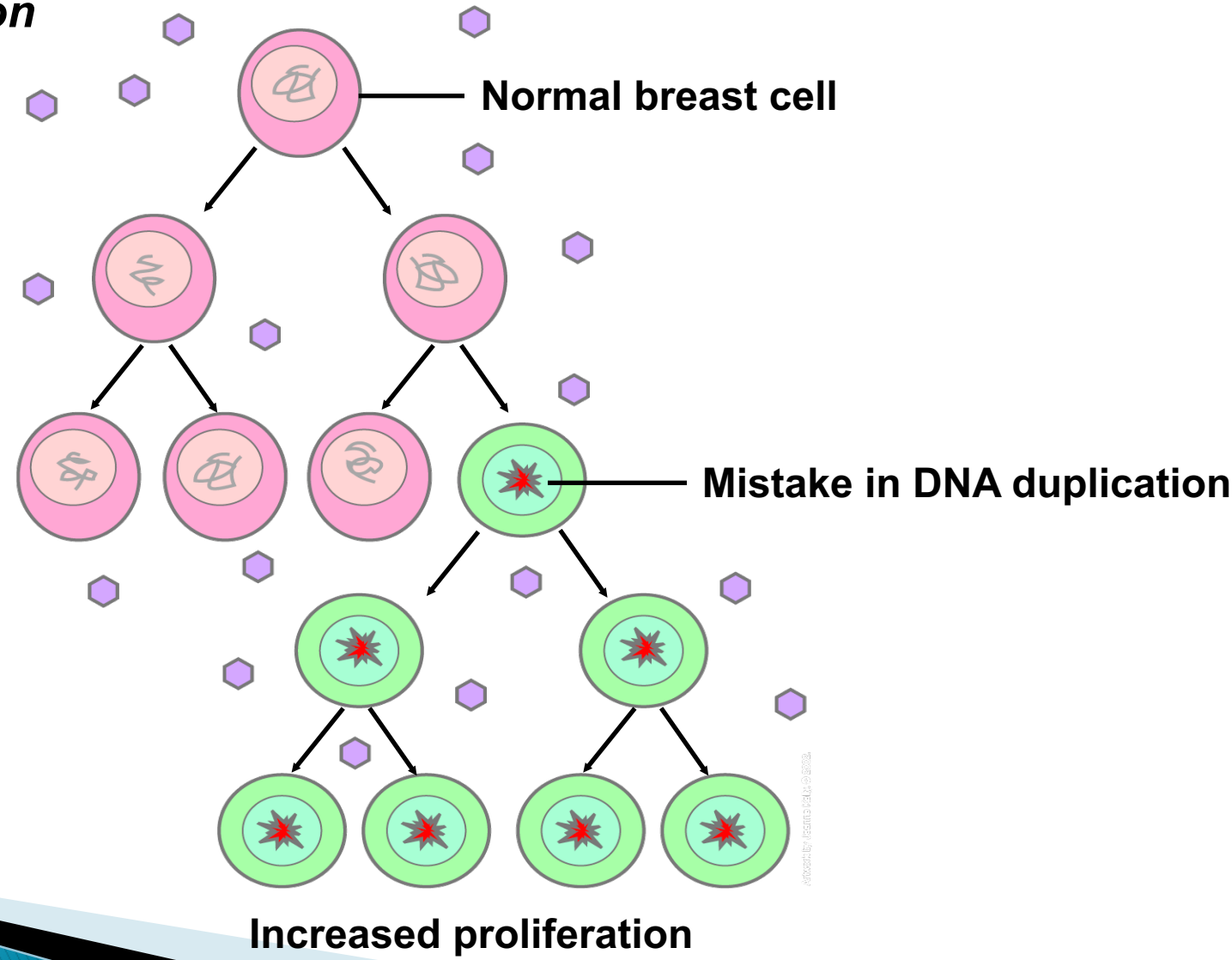
- Estrogens (in the presence of progesterone) stimulate breast cells to proliferate, i.e., multiply through division (mitosis)
- This sometimes results in errors in cell division (mutations) which can result in malignancy

Estrogen-Induced Stimulation of Cell Proliferation



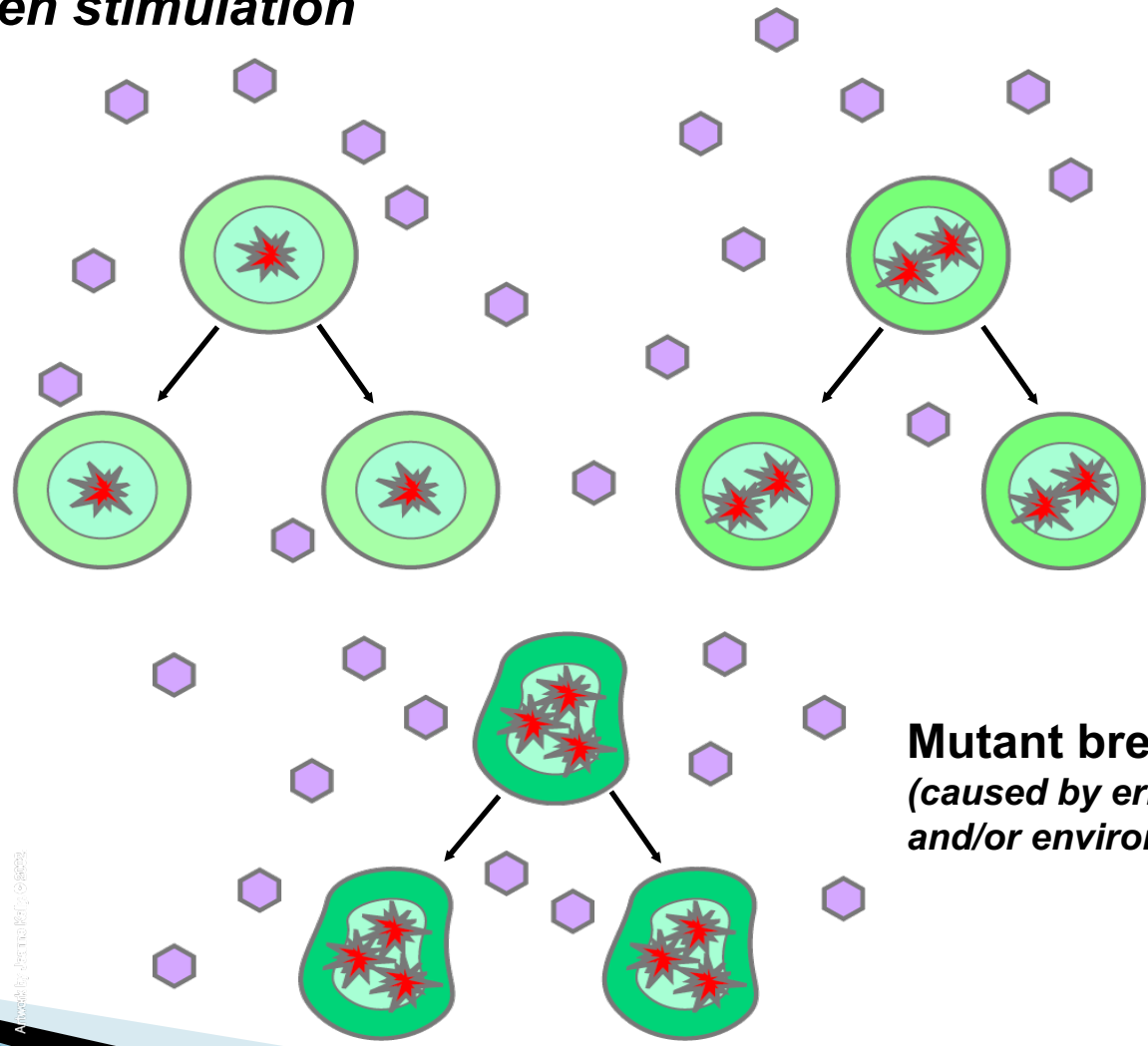
Estrogen-Induced Proliferation and Spontaneous New Mutations

Estrogen stimulation



Estrogen-Induced Proliferation of Existing Mutant Cells

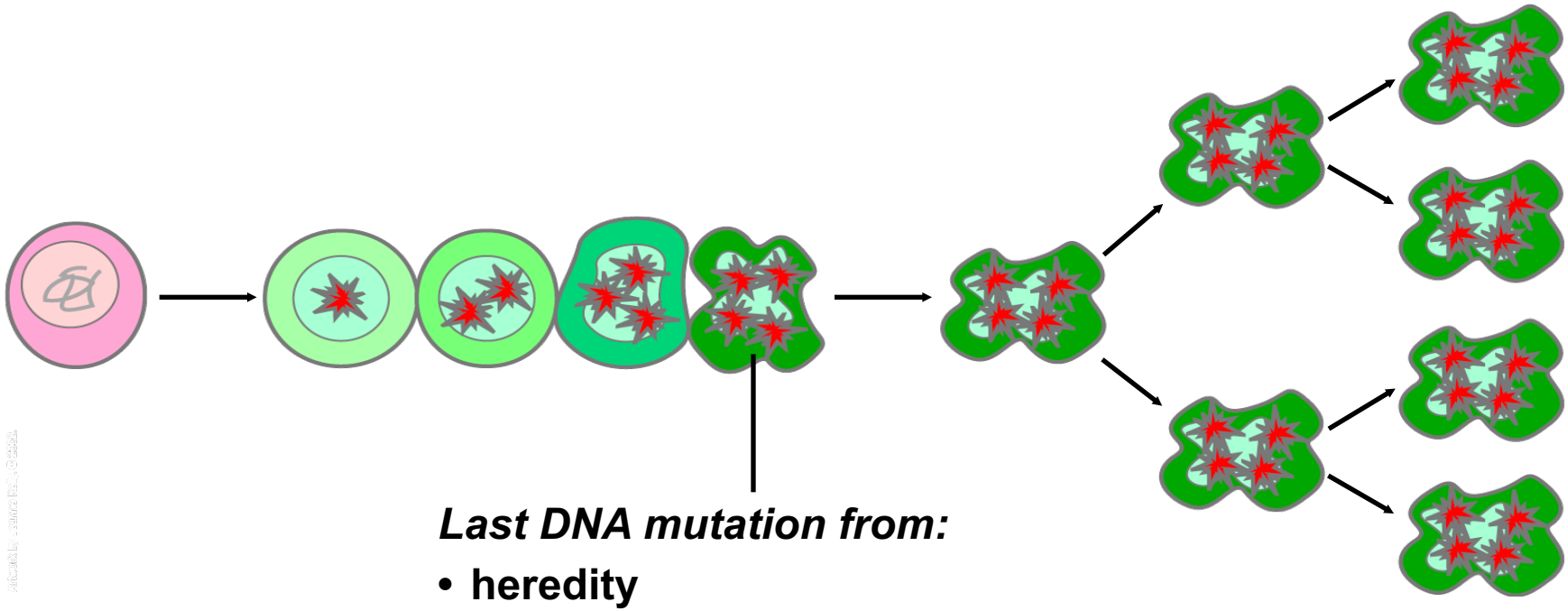
Estrogen stimulation



Mutant breast cells
(caused by error, inheritance, and/or environmental factors)

Cancer Arises From DNA Mutations in Cells

Normal cell **DNA mutations** **Uncontrolled proliferation**



Last DNA mutation from:

- **heredity**
  or
- **radiation or chemicals**
  or
- **spontaneous errors during DNA duplication**

Estrogen has 2 effects on breast tissue

1. Mitogen
   - Acts to cause proliferation
   - Cancer promoter
2. **Carcinogen**
   - **Acts as mutagen and genotoxin**
   - **Cancer initiator**

Cancer Research 48, 246-253, January 15, 1988

[CANCER RESEARCH 48, 246-253, January 15,

Special Lecture

Estrogens as a Cause of Human Cancer: The Richard and Hinda Rosenthal Foundation Award Lecture[1]

B. E. Henderson,[2] R. Ross, and L. Bernstein

University of Southern California School of Medicine, Los Angeles, California 90033-0800

The concept that hormones can cause, *i.e.*, increase the incidence of, neoplasia was first developed by Bittner *et al.* (1), based on experimental studies of estrogens and mammary cancer in mice. We have refined that concept into a hypothesis for a major role of estrogen and other hormones in the etiology of several human cancers (2). A key element of this hypothesis is that neoplasia is the consequence of excessive hormonal stimulation of a particular target organ, the normal growth and function of which are under hormonal control. The response of this end organ (*e.g.*, endometrium, breast) to the proliferative effects of the hormone is a progression from normal growth to hyperplasia to neoplasia. In this model, hormones increase the incidence of neoplasia in the absence of outside initiators such as chemicals or ionizing radiation.

We have hypothesized three specific circumstances in which estrogen plays a role in this model of hormone-induced neoplasia. In the first two circumstances, which relate to the breast and the endometrium, estrogens themselves act as the stimulatory hormones, increasing the frequency of mitotic activity in the target organ. As rare consequences of this estrogen-induced proliferation, malignant phenotypes develop due to errors in the mechanics of cell division (*e.g.*, DNA copying errors, chromosomal translocations, etc.) (Fig. 1).

We believe that breast cancer risk is determined primarily by (3), with estrogen serving as the "initiator" and gonadotropins serving as the second stage "promoters."

Estrogen can be derived from both endogenous and exogenous sources. Endogenous sources in women include direct secretion of estrogens from the ovary, operative only during menstrual life, and peripheral conversion of adrenal-derived androgens to estrogen in fat cells. The primary exogenous source of estrogen during reproductive years is OCs,[3] with hormone replacement therapy becoming the primary source thereafter. Until the 1970s, the use of DES in pregnancy provided a third important exogenous estrogen source during the childbearing years. Exposure to estrogens from exogenous sources can be measured directly in epidemiological studies, either through careful interviewing or by examination of medical and pharmaceutical records. Measurement of endogenous estrogen exposure often must be done indirectly. Ovarian activity is usually measured by evaluating the onset, cessation, timing, and regularity of menstruation and the timing and frequency of pregnancy and lactation. Adipose tissue sources are measured primarily by evaluating physical characteristics and dietary habits.

In the discussion which follows, we attempt to establish estrogen as a cause of several human cancers by describing the epidemiological evidence linking estrogen exposure from endogenous and exogenous sources to endometrial, breast, and

Philadelphia Inquirer
Dec. 16, 2001

Scientists vote to list estrogen as carcinogen despite benefits

By Randolph E. Schmid
ASSOCIATED PRESS

WASHINGTON — While stressing the value of estrogen treatments for women, a governme entific advisory panel recom ed yesterday that the chemi added to the nation's list of c causing agents.

Maybe, one scientist said step might encourage doct talk with their patients abou the risks and the benefits.

There was no suggestion t trogen use be restricted or banned.

"Physicians never discuss any of these risks when they are prescribing hormone therapy," Michelle Me-

The listing should not frighten women, said Susan Wysocki, a Washington nurse-practitioner who was not a part of the panel. "Women

Michelle Medinsky, National Toxicology Program Advisory Committee. "They only discuss the benefits. Listing might force it on the table."

control pills. The amount of estrogen in those pills has dropped dramatically in recent years.

The advisory panel acted after looking at studies showing that estrogen was associated with an increase in endometrial cancer and, to a lesser extent, breast cancer.

Doctors already know about the cancer link. That is why postmeno-

But panel member Sheila H. Zahm of the National Cancer Institute noted that NCI researchers, in a paper published in January, had found a slight increase in breast cancer in women treated with the estrogen-progestin combination.

The committee, chaired by toxicologist Clay Frederick of Rohm &

use, Pa., advises
ology Program, a
onal Institutes of
two years up-
dates the federal list of proven and suspected cancer-causing substances.

Also yesterday, the panel voted unanimously to recommend adding wood dust to the list. It has been associated with cancer of the nose and sinuses in workers in furniture factories and cabinetmaking shops.

Journal of the National Cancer Institute, Vol. 95, No. 2, 100–102, January 15, 2003

JNCI Journal of the National Cancer Institute

Journal of the National Cancer Institute, Vol. 95, No. 2, 100-102, January 15, 2003
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NEWS

Estrogen and DNA Damage: The Silent Source of Breast Cancer?

Katharine Miller

"It has been an uphill battle to convince the mainstream that estrogen initiates cancer by damaging DNA, said David Longfellow, Ph.D., chief of the Chemical and Physical Carcinogenesis Branch at the National Cancer Institute."

medicine has been on a different vector."

Estrogen Metabolism

Carcinogenesis vol.24 no.4 pp.697–702, 2003
DOI: 10.1093/carcin/bgg004

Carcinogenesis vol.24 no.4 pp.697–702, 2003
DOI: 10.1093/carcin/bgg004

Relative imbalances in estrogen metabolism and conjugation in breast tissue of women with carcinoma: potential biomarkers of susceptibility to cancer

Eleanor G.Rogan[1,6], Alaa F.Badawi[2], Prabu D.Devanesan[1], Jane L.Meza[3], James A.Edney[4],

ultimate carcinogens that react with DNA to cause the mutations leading to initiation of cancer (5–7).

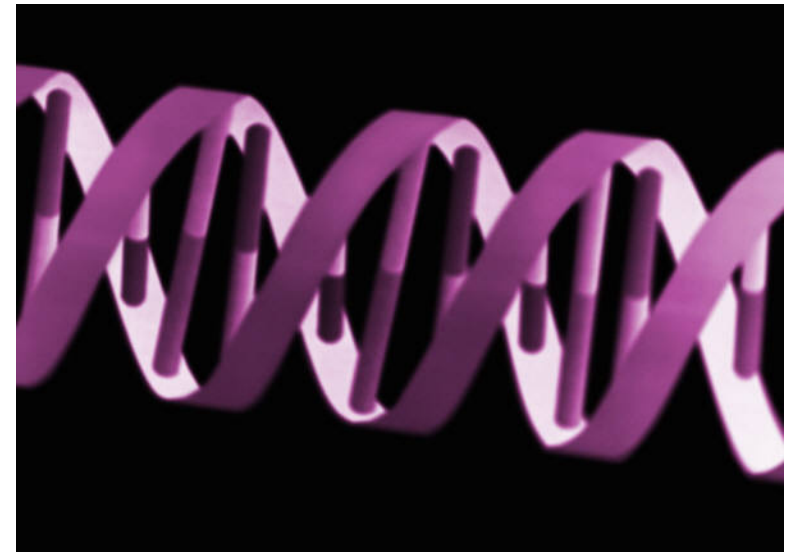
Article explains the metabolism and metabolites of the forms of estrogen (estradiol, estriol, and estrone) associated with breast cancer formation

Exposure to estrogens has been associated with an increased risk of developing breast cancer. Breast biopsy tissues from 49 women without breast cancer (controls) and 28 with breast carcinoma (cases) were analyzed by HPLC with electrochemical detection for 31 estrogen

thesized that estrogens, E_1 and E_2, initiate breast cancer by reaction of their electrophilic metabolites, catechol estrogen-3,4-quinones [$E_1(E_2)$-3,4-Q], with DNA to form depurinating adducts (4–6). These adducts generate apurinic sites leading to mutations that may initiate breast, prostate and other human

Estrogen as a carcinogen

- Estrogen → metabolized in 4 steps to catechol estrogen quinone (CE-quinone)
- 4 OH-CE Quinone pulls purine bases out of DNA strands directly damaging DNA
- 185delAG is a common mutation of the BRCA genes



Estrogen as a carcinogen

Women with breast cancer have higher levels of 4 hydoxy catechol estrogen quinone than women without breast cancer.

Rogan, Ph.D., University of Nebraska,
San Antonio Breast Cancer Symposium 2002

NEJM January 16, 2006

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

MECHANISMS OF DISEASE

Estrogen Carcinogenesis in Breast Cancer

James D. Yager, Ph.D., and Nancy E. Davidson, M.D.

From the Bloomberg School of Public Health, Department of Environmental Health Sciences (J.D.Y.), and the Sidney Kimmel Comprehensive Cancer Center (N.E.D.), Johns Hopkins University, Baltimore. Address reprint requests to Dr. Yager at the Johns Hopkins Bloomberg School of Public Health, Rm. 1033, 615 N. Wolfe St., Baltimore, MD 21205, or at jyager@jhsph.edu.

N Engl J Med 2006;354:270-82.

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IN THIS ARTICLE, WE REVIEW RECENT FINDINGS RELATED TO ESTROGEN EXposure and the risk of breast cancer, the mechanisms that may be involved, and the clinical implications of these findings. The weight of evidence indicates that exposure to estrogen is an important determinant of the risk of breast cancer. The mechanisms of carcinogenesis in the breast caused by estrogen include the metabolism of estrogen to genotoxic, mutagenic metabolites and the stimulation of tissue growth. Together, these processes cause initiation, promotion, and progression of carcinogenesis. Insight into the mechanisms of the causation of cancer by estrogen will identify determinants of susceptibility to breast cancer and new targets for prevention and therapeutic intervention.

NEJM January 16, 2006

CONCLUSIONS

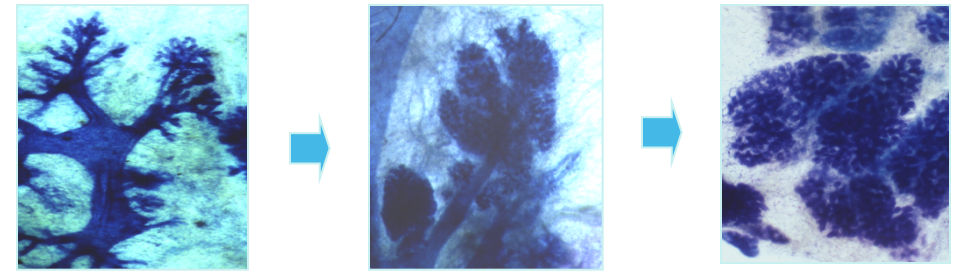
Studies of breast cancer have consistently found an increased risk associated with elevated blood levels of endogenous estrogen, clinical indicators of per-

Studies of breast cancer have consistently found an increased risk associated with …the use of exogenous estrogen plus progestin … and use of oral contraceptives.

tumors. Together, these observations support the hypothesis that estrogen is a mammary-gland carcinogen.

Principle of Reproductive Risks

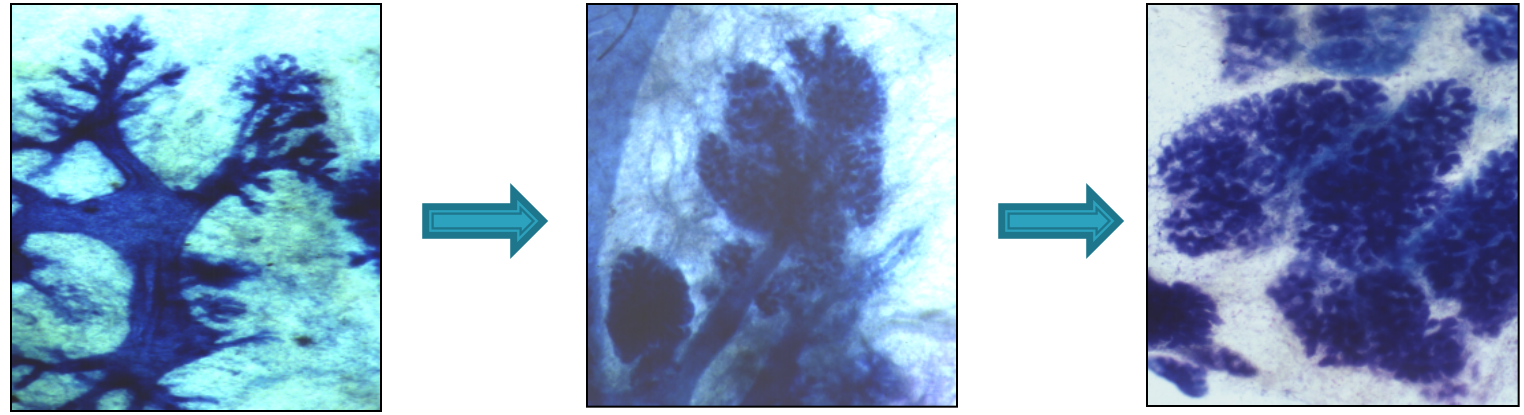
- The **more estrogen** a woman is exposed to in her lifetime, the **higher her risk** for breast cancer
- The **sooner a woman differentiates** her breast lobules, from Type 1 and 2 to Type 3 and 4, the **lower her risk** of breast cancer.



Type 1 lobule Type 2 Lobule Type 3 lobule

Biology of the abortion breast cancer link

It is the biology of the breast lobule maturation that occurs during pregnancy which accounts for the abortion breast cancer link.



Before pregnancy

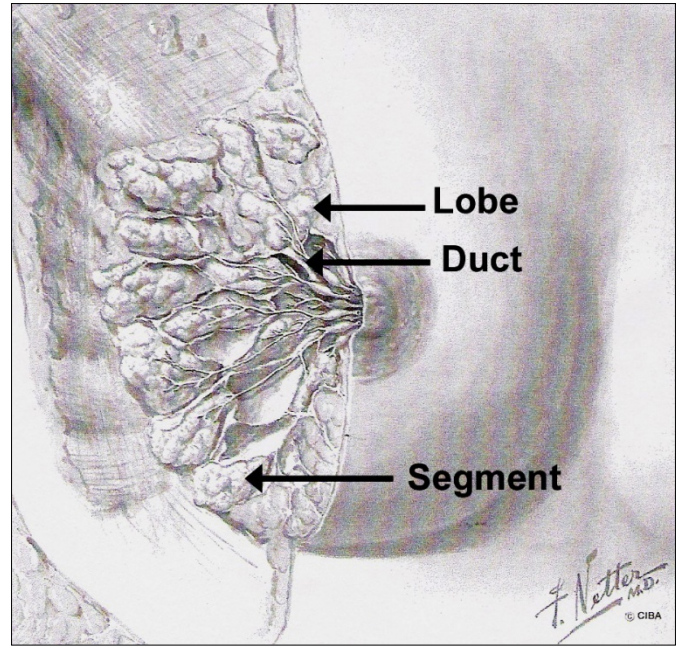
After a full-term pregnancy

Breast maturation with pregnancy

Breast Changes with Pregnancy		
1st half of pregnancy	Stroma	Increase fat and connective tissue
1st half of pregnancy	Lobules	Breast volume doubles by increasing the number of Type 1 and 2 lobules **Proliferation**
2nd half of pregnancy	Lobules	Maturation to Type 4 lobules **Differentiation**
		placental hormones from lactating)

Reproductive breast cancer risks & breast lobule maturation

- At full development, the breast is comprised of 15–25 lobes which are in turn comprised of lobules.
- Lobules in turn are composed of breast cells.



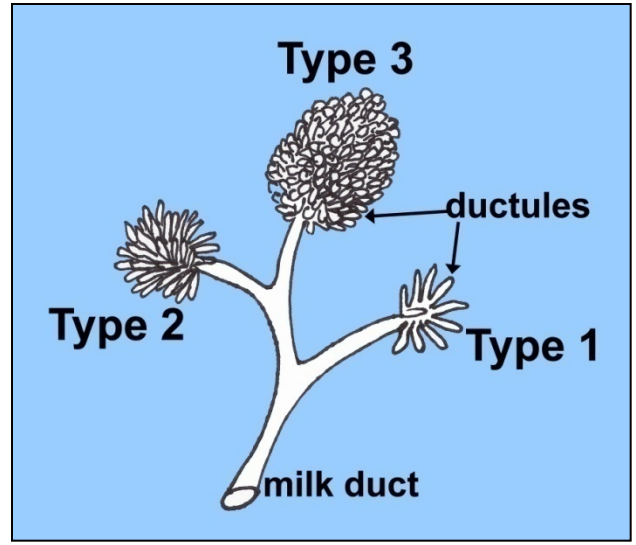
Lobes → lobules → cells

There are 4 types of lobules whose structural differences appear under the microscope

Type 1, 2 & 3 lobules are differentiated by the *average number of ductules per lobular unit*:

Type 1 has *11*
Type 2 has *47*
Type 3 has *80*

Type 4 lobules are fully matured and contain colostrum or milk.



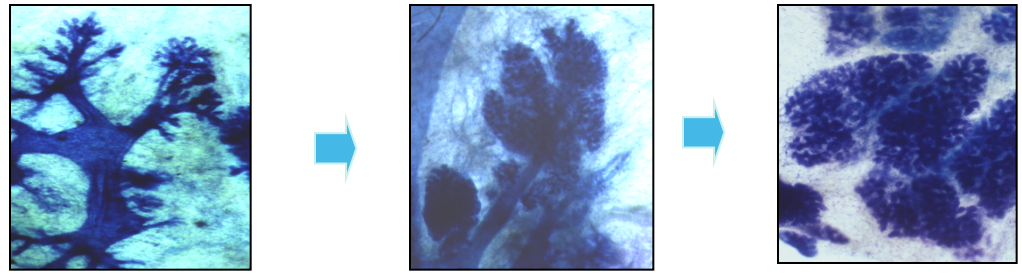
Ductules become the milk glands

Table 2: Lobular Morphology, Cancer Vulnerability, and Structure

Type of lobule	Morphology of lobules	Type of cancer that forms from lobules	Structural and metabolic differences of lobules
Type 1	Average 11 ductules per lobular unit	Ductal cancers (which are approximately 85 percent of all breast cancers), arising in milk ducts[34]	• Highest number of estrogen and progesterone receptors in the cells • Highest rate of cell proliferation (marked by Ki67 protein) • Shortest DNA doubling time
Type 2	Average 47 ductules per lobular unit	Lobular cancers (which are approximately 15 percent of all breast cancers), arising in milk glands	• Approximately half the number of estrogen and progesterone receptors as Type 1 lobules • One third of the cell proliferation marker Ki67 protein of Type 1 lobules • A shorter DNA doubling time than Type 3 lobules
Type 3	Average 81 ductules per lobular unit	Cancer-resistant	• Negligible numbers of estrogen and progesterone receptors • Less than one tenth of the cell proliferation marker Ki67 protein of Type 1 and Type 2 lobules

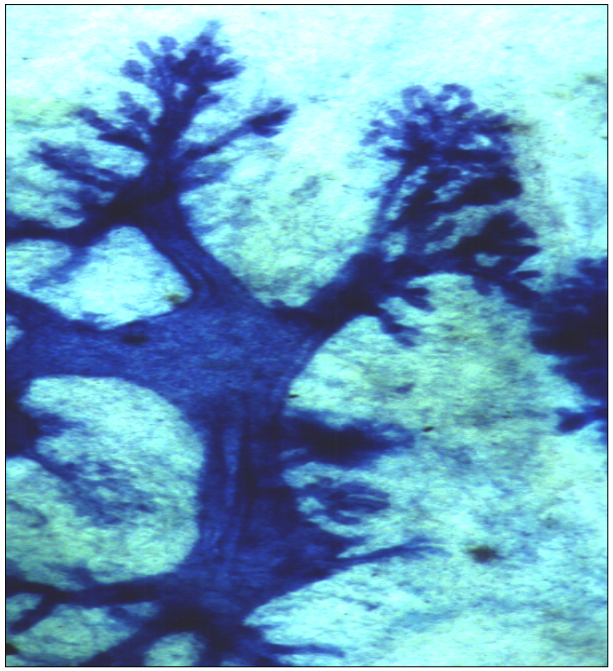
Breast maturation with pregnancy

- Type 1 lobules mature into Type 2 lobules under the cyclic influence of the female hormones, estrogen and progesterone, during menstrual cycles.
- Type 2 lobules only become fully mature into Type 4 lobules under the influence of the hormonal changes of a full-term pregnancy.
- Type 4 regress to Type 3 after weaning.



Type 1 lobule Type 2 Lobule Type 3 lobule

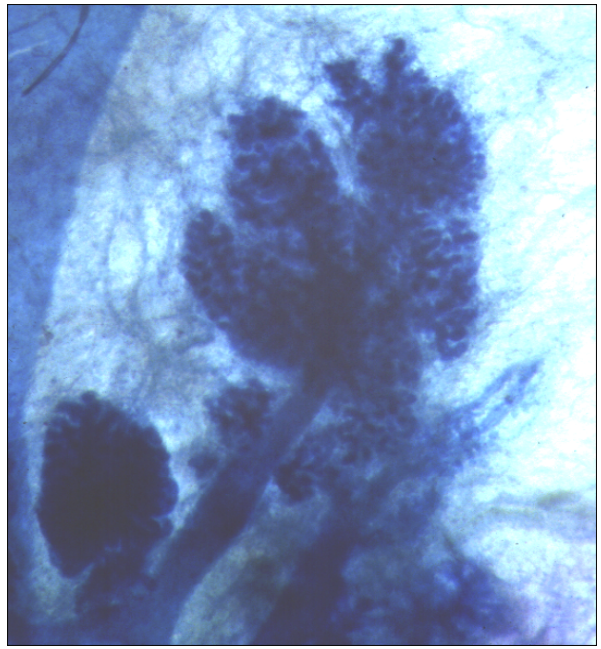
Types of Breast Lobules



Type 1 Lobule

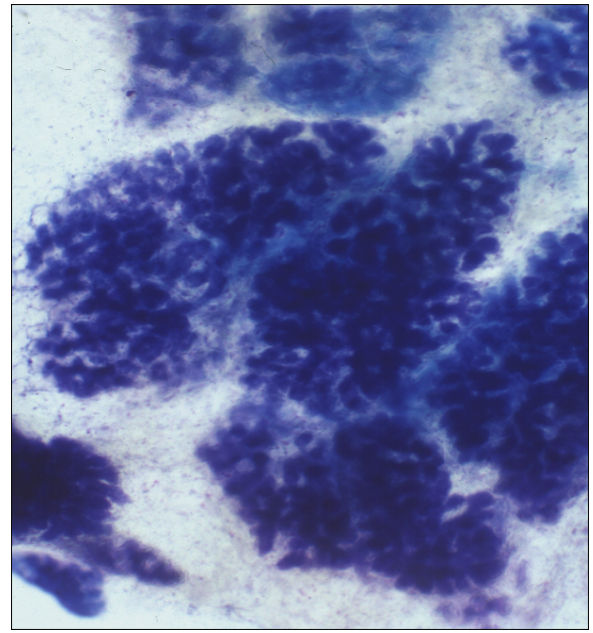
(TDLUs)

85% of all breast cancers arise in Type 1 Lobules (Ductal cancer)



Type 2 Lobule

10-15% of all breast cancers arise in Type 2 Lobules (Lobular cancer)



Type 3 Lobule

Cancer resistant

Breast maturation with pregnancy

Breast Changes with Pregnancy		
1st half of pregnancy	Stroma	Increase fat and connective tissue
1st half of pregnancy	Lobules	Breast volume doubles by increasing the number of Type 1 and 2 lobules **Proliferation**
2nd half of pregnancy	Lobules	Maturation to Type 4 lobules **Differentiation**
		placental hormones from lactating)

Hormonal changes during pregnancy

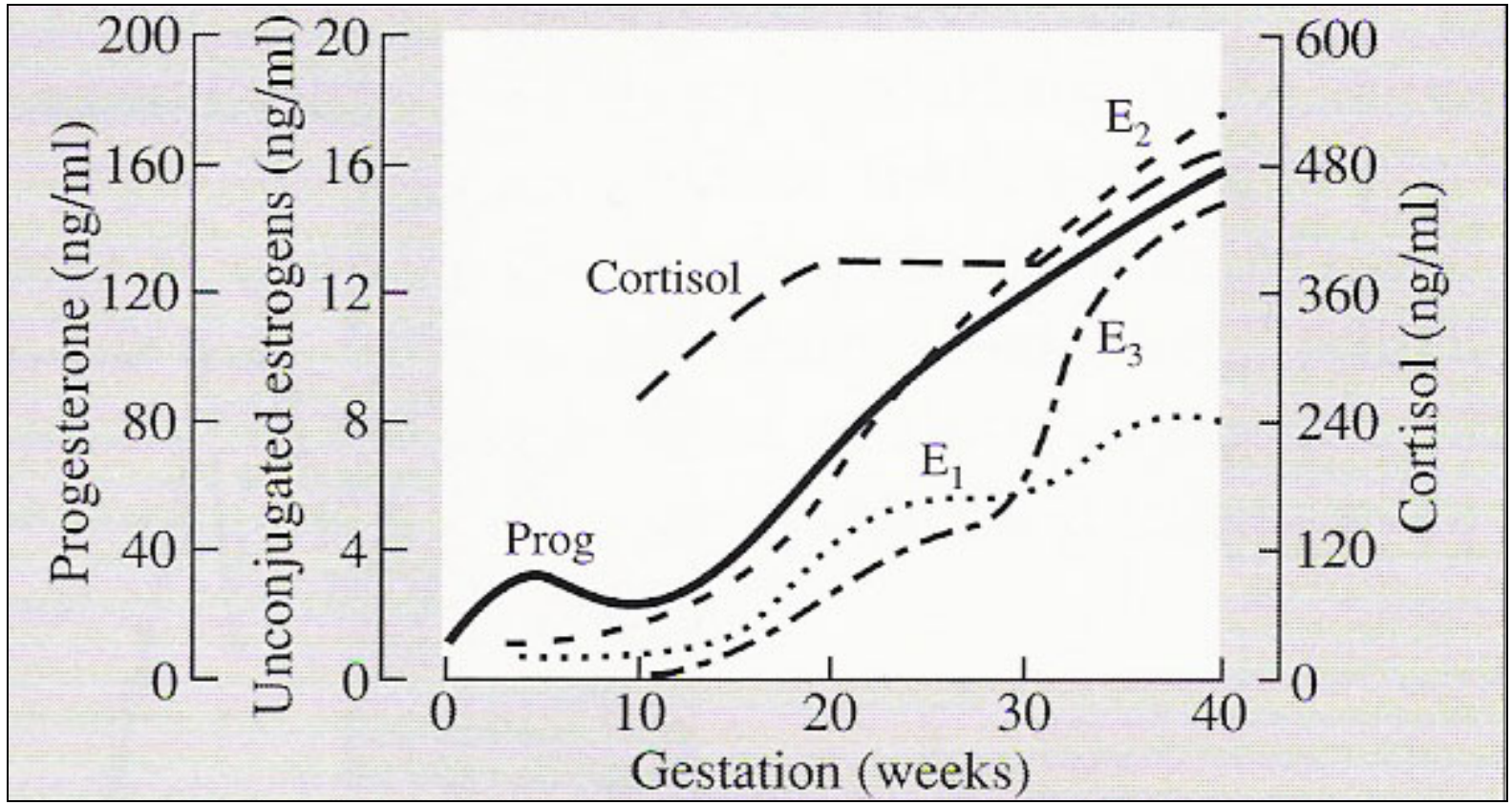
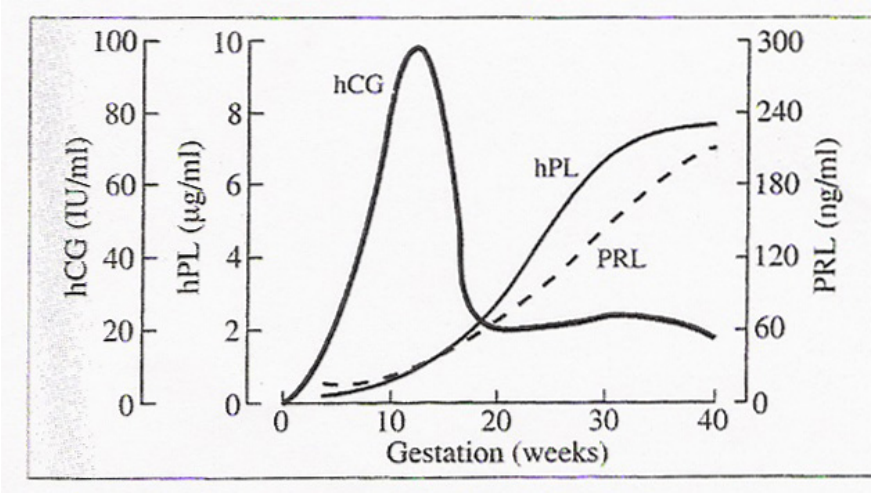


Figure 2.2. Serum concentrations of prolactin, human chorionic gonadotropin (hCG), human placental lactogen (hPL), cortisol, progesterone, and unconjugated estrogens during pregnancy. The values have been obtained from several sources in the literature (E_1 = estrone; E_2 = estradiol; E_3 = estriol). Reprinted by permission from Rebar RW. Gestational changes of the reproductive tract and breasts. Philadelphia: WB Saunders, 1991.

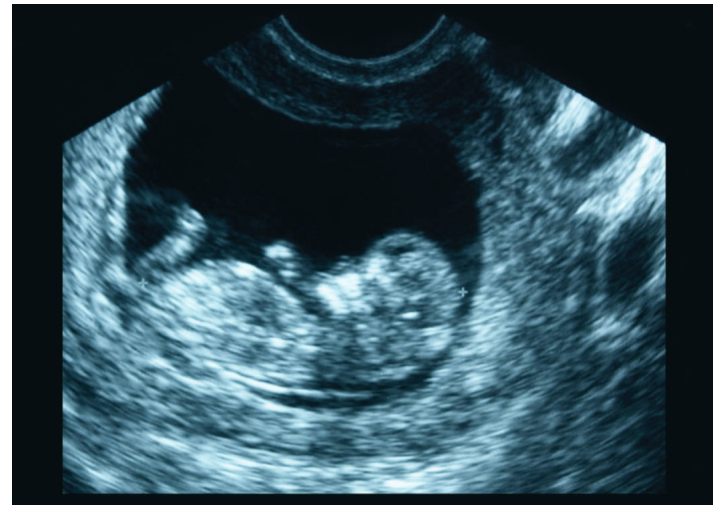
Hormonal influences of breast lobule development

- Human chorionic gonadotropin (hCG) which stimulates the ovaries to produce estrogen and progesterone within a few days after conception (PROLIFERATION)
- A major influence in this final stage of maturation into Type 4 lobules is human placental lactogen (hPL) which sharply rises during the second half of pregnancy. (DIFFERENTIATION)
- HCG and hPL are made by the fetus in the mother's womb during pregnancy.

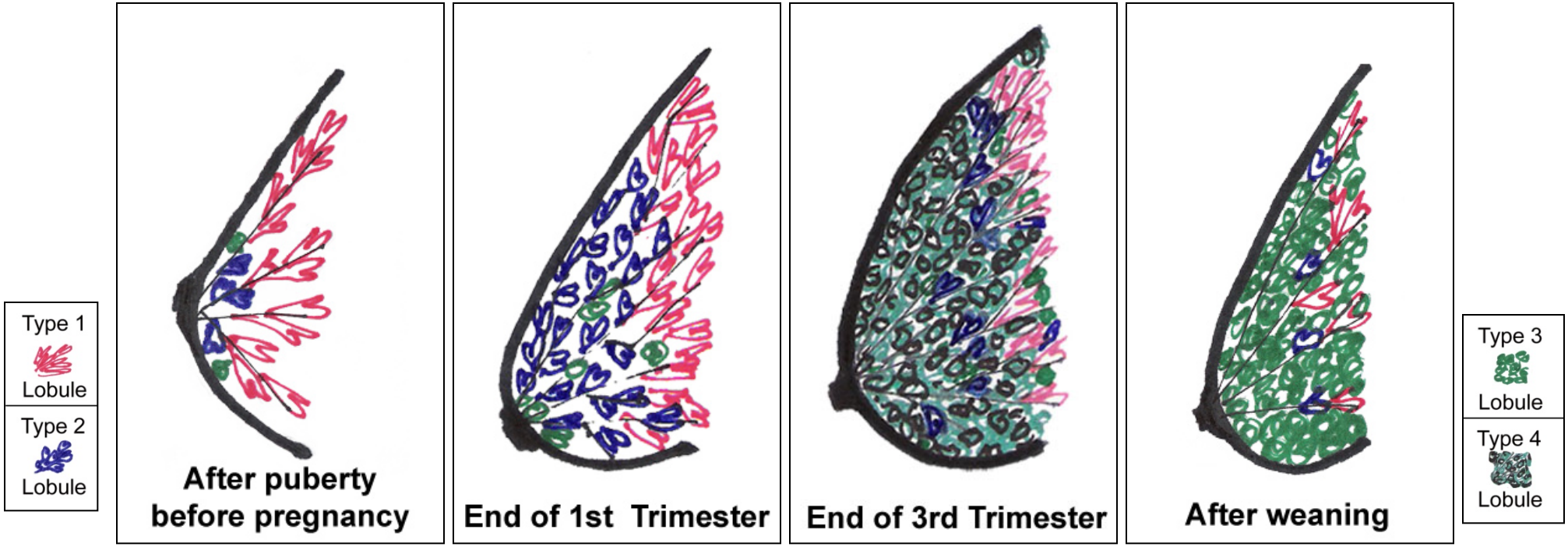


Hormonal influences of breast lobule development

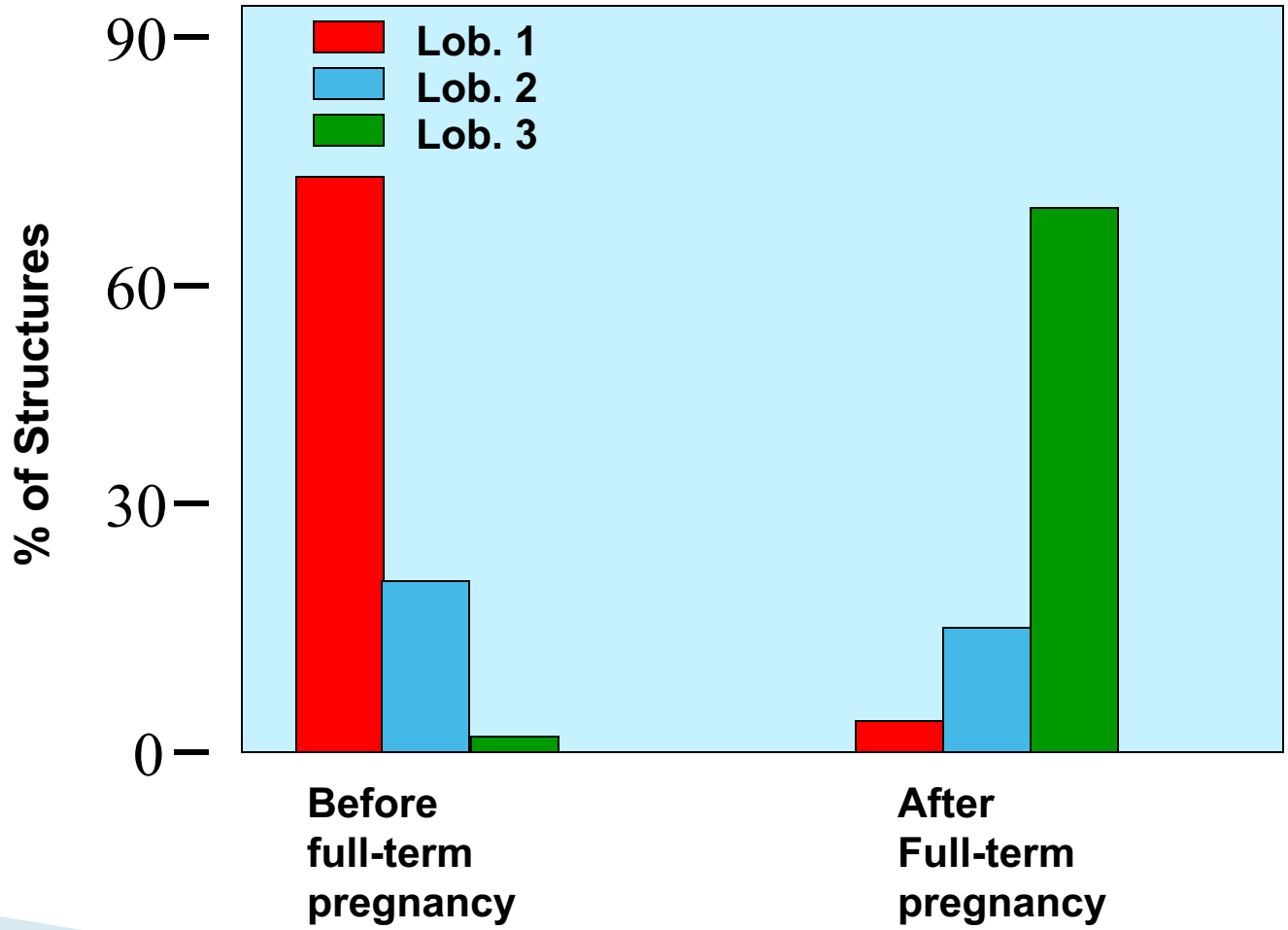
- HPL made by the fetal-placental unit during pregnancy induces full differentiation of breast tissue to Type 4 lobules, which are cancer resistant
- When Type 4 lobules regress to Type 3 post-weaning, Type 3 lobules are cancer resistant
- HCG also stimulates the ovary to produce inhibin, a cancer suppressing hormone, protection of the mother even more



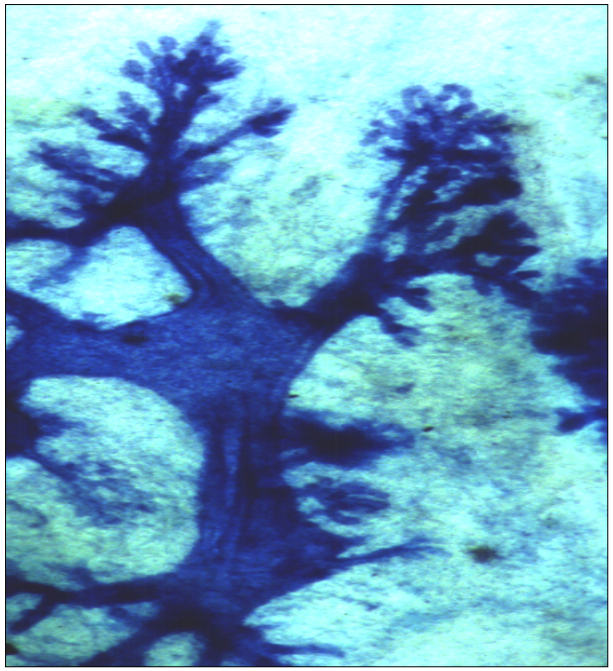
Breast lobule maturation before and after first pregnancy



Lobular Structures in the Human Breast



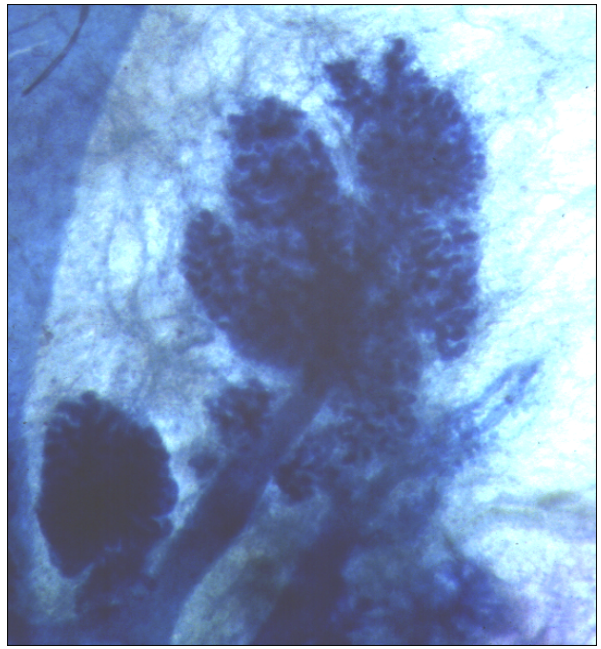
Types of Breast Lobules



Type 1 Lobule

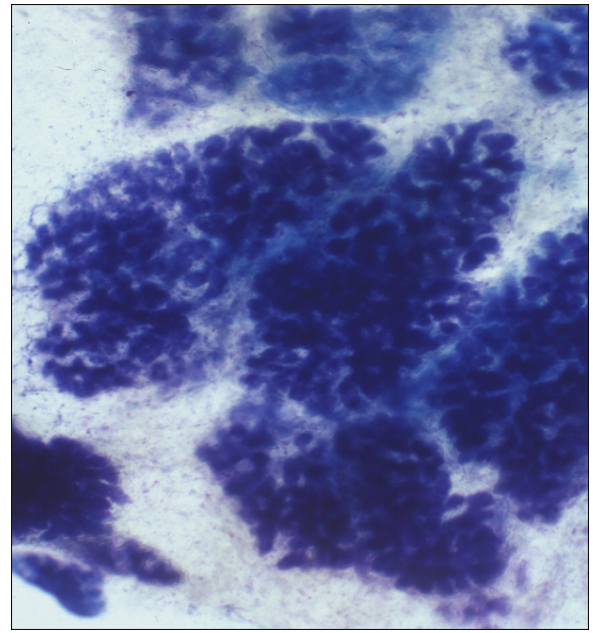
(TDLUs)

85% of all breast cancers arise in Type 1 Lobules (Ductal cancer)



Type 2 Lobule

10-15% of all breast cancers arise in Type 2 Lobules (Lobular cancer)



Type 3 Lobule

Cancer resistant

Objectives

1. Understand biologic basis of all breast cancer risks
2. **Learn about the "susceptibility window" when the breast is most susceptible to cancer formation**
3. Learn the breast cancer risks associated with reproduction
4. Understand the pathophysiology of breast maturation during pregnancy which accounts for these known risks including the association with induce abortion and preterm birth

These facts of the breast maturation process account for the following known facts about breast cancer risk:

- The longer a woman waits before having her first child, the higher her risk because she has a longer **"susceptibility window."**
  - For example, a woman who gives birth at 18 has a 50–75% lower risk of breast cancer than a woman who waits until she is 30.

Susan Love's Breast Book

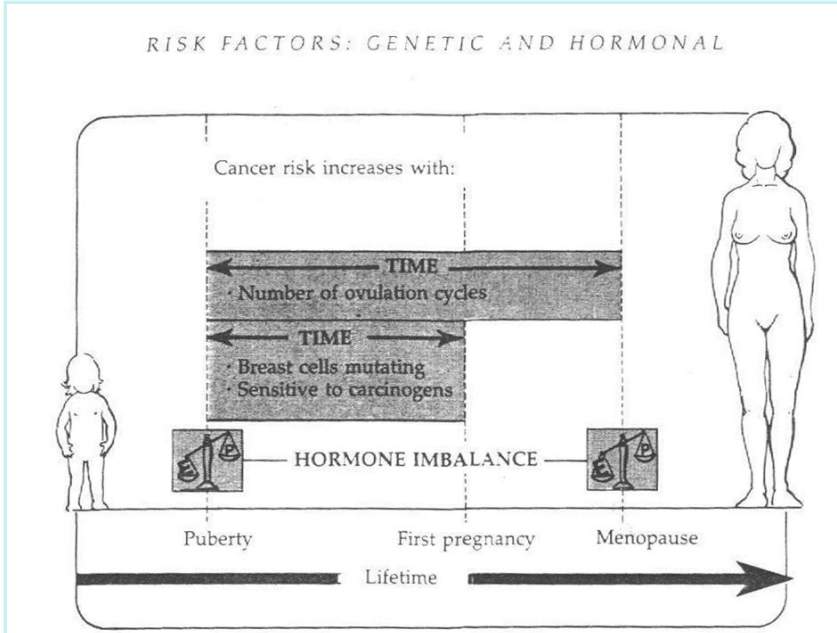


FIGURE 14-3

Lancet, Vol 360, October 2002

ARTICLES

Carcinogenic and endocrine disrupting effects of cigarette smoke and risk of breast cancer

Parous women smoking within 5 yrs of menarche	**RR 1.69**
Nulliparous women smoking 1 pack a day	**RR 7.08**
Nulliparous women smoking 20 pack years	**RR 7.48**
Parous postmenopausal women, started smoking after FFTP	**RR .49**

Objectives

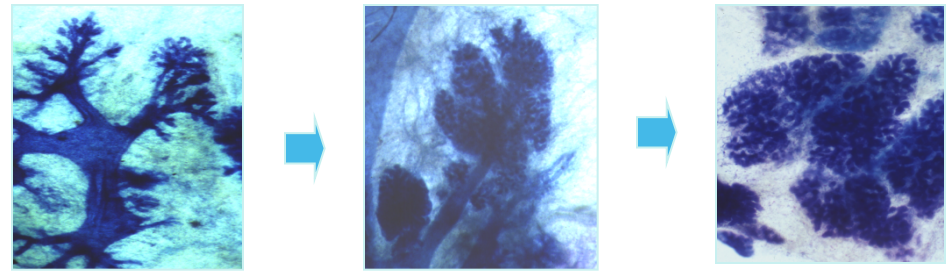
1. Understand biologic basis of all breast cancer risks
2. Learn about the “susceptibility window” when the breast is most susceptible to cancer formation
3. **Learn the breast cancer risks associated with reproduction**
4. Understand the pathophysiology of breast maturation during pregnancy which accounts for these known risks including the association with induce abortion and preterm birth

Reproductive risks

- **Control of fertility**
  - Hormonal methods: OCP's, injections, implanted, intravaginal intrauterine and transdermal
  - Induced abortion
  - Abortifacients: IUDs, RU-486, morning after pill
  - Fertility drugs: Clomid, Perganol
- **Menstrual cycles**
  - Number of lifetime cycles (age at menarche, age at menopause)
  - Number of anovulatory cycles
  - Length of time to develop regular cycles post menarche

Reproductive risks

- **Breast maturation**
  - Nulliparity
  - Parity
  - Multiparity
  - Pregnancy Outcomes:
    - spontaneous abortions, induced abortions, premature delivery, still birth, and ectopic pregnancies
  - Age at 1st birth (FFTP): Length of "susceptibility window"
  - Lactation/breast feeding



Type 1 lobule Type 2 Lobule Type 3 lobule

We know as established medical facts we can agree upon:

Risk of Breast Cancer	
Decreases Risk	Increases Risk
Late menarche (age at 1st period)	Early menarche
Early menopause	Late menopause
Early first full-term pregnancy	■ Nulliparity (no children) ■ Late child bearing
Oophorectomy (removal of ovaries)	■ Hormone replacement therapy ■ Birth control pills
	Benign proliferative breast disease

Established and probable risk factors for breast cancer

Risk factor	Comparison category	Risk category	Typical relative risk
Age at menarche	16 years	11-14 years	1.3
		15 years	1.1
Age at menopause	45-54 years	After 55 years	1.5
		Before 45 years	0.7
		Oophorectomy before 35 years	0.4
Age at birth of first child	Before 20 years	20-24 years	1.3
		25-29 years	1.6
		30 years	**1.9**
		Nulliparous	1.9
Family history of breast cancer	No first-degree relatives affected	Mother affected before age of 60	2.0
		Mother affected after age of 60	**1.4**
		Two first-degree relatives affected	4.0-6.0
Benign breast disease	**No evidence of proliferation**	Proliferation only	2.0
		Atypical hyperplasia	**4.5**

Established and probable risk factors for breast cancer

Risk factor	Comparison category	Risk category	Typical relative risk
Alcohol use	Non-drinker	**1 drink/day** 2 drinks/day **3 drinks/day**	**1.4** 1.7 **2.0**
Radiation	No special exposure	Atomic bomb (100 rad) Repeated fluoroscopy	3.0 1.5-2.0
Oral contraceptive	Never used	Current use* **Prolonged use before first pregnancy** Past use	1.5 **2.0** 1.0
Postmenopausal oestrogen replacement therapy	Never used	<5 years use 10 years use **15 years use**	1.04 1.13 **1.27**

*Relative risks may be higher for women with diagnosis of breast cancer before the age of 40

- Handbook of Diseases of the Breast, 2nd ed, 1998;97.

Objectives

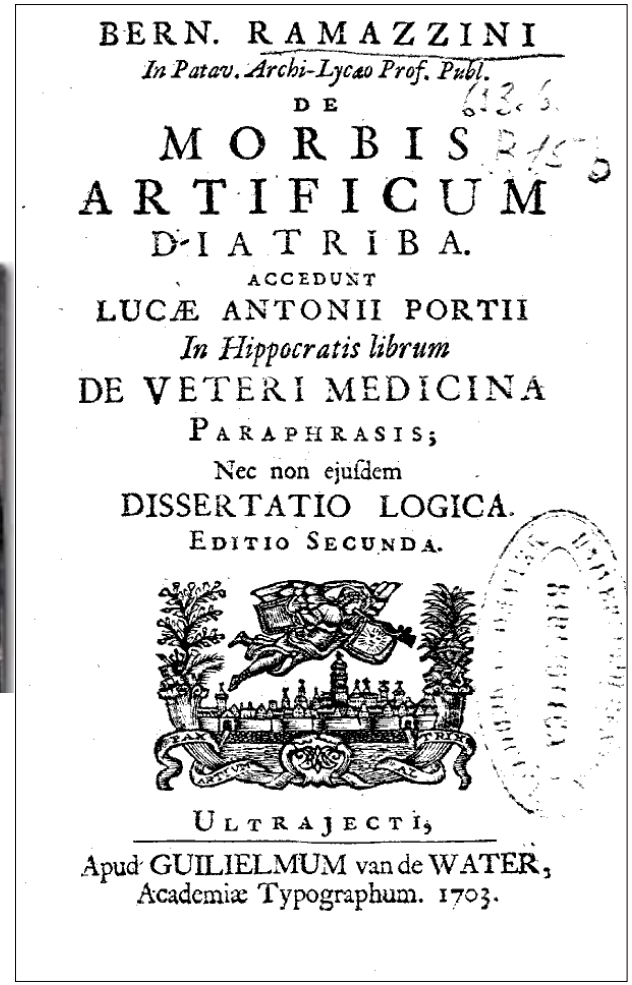
1. Understand biologic basis of all breast cancer risks
2. Learn about the “susceptibility window” when the breast is most susceptible to cancer formation
3. Learn the breast cancer risks associated with reproduction
4. **Understand the pathophysiology of breast maturation during pregnancy which accounts for these known risks including the association with induce abortion and preterm birth**

Biology of the abortion breast cancer link

The protective effect of a full-term pregnancy on breast cancer risk has been known since the Middle Ages when it was noted that nuns had a higher risk of breast cancer than women with children.

Biology of the abortion breast cancer link

- In the18th century the protective effect was observed and published by Ramazzini of Padua in 1743.


BERN. RAMAZZINI
In Patav. Archi-Lycæo Prof. Publ.
DE
MORBIS
ARTIFICUM
DIATRIBA.
ACCEDUNT
LUCÆ ANTONII PORTII
In Hippocratis librum
DE VETERI MEDICINA
PARAPHRASIS;
Nec non ejuſdem
DISSERTATIO LOGICA.
EDITIO SECUNDA.
ULTRAJECTI,
Apud GUILIELMUM van de WATER,
Academiæ Typographum. 1703.

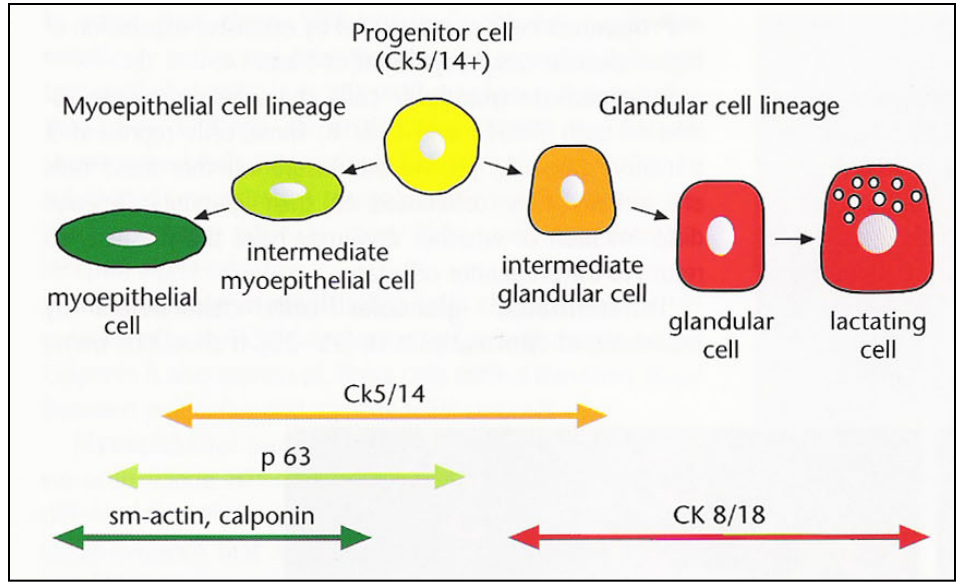
- Today we know the molecular basis of the protective effect of a full-term pregnancy.

Biology of the abortion breast cancer link

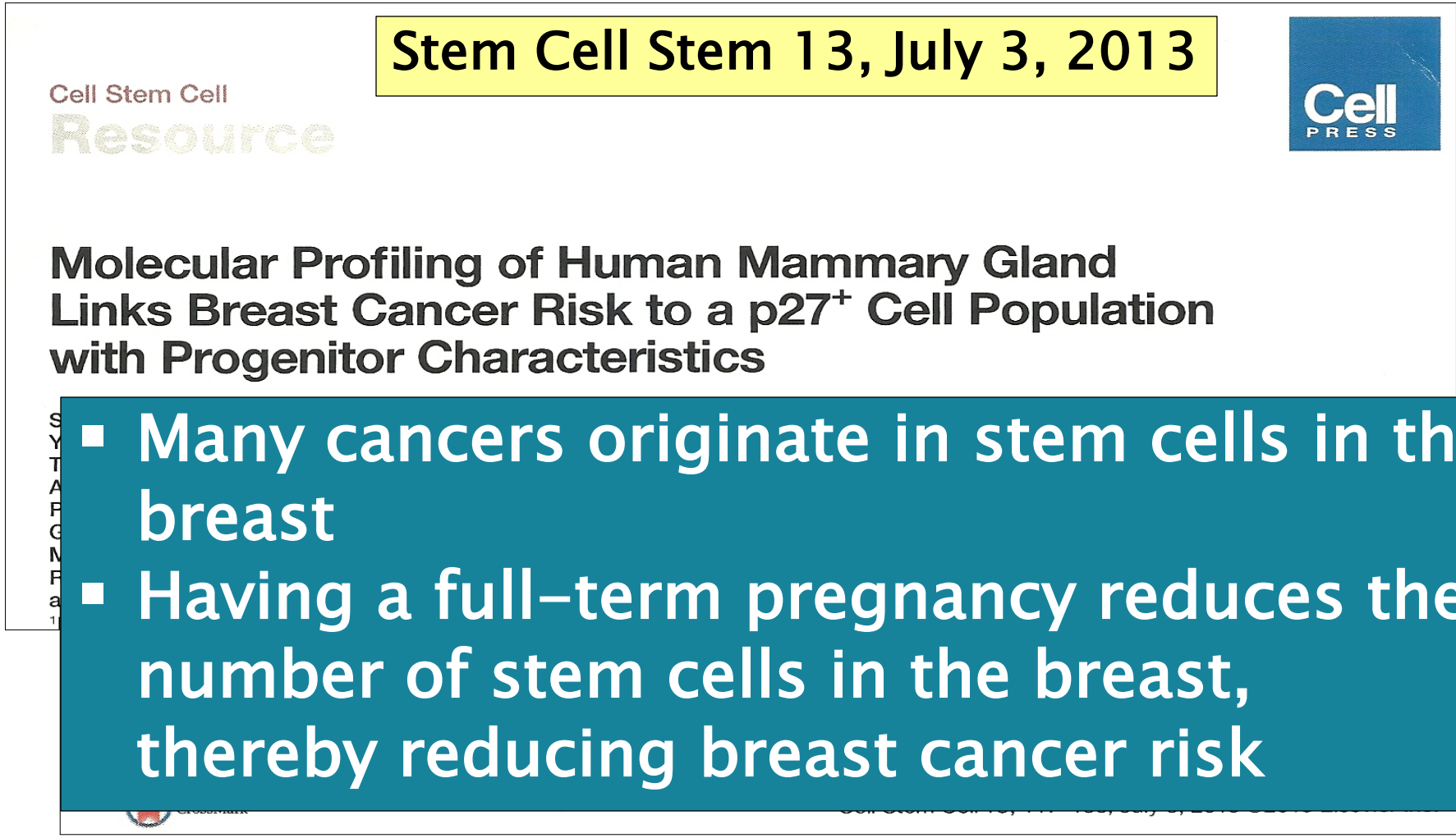
Stem cell paradigm for breast cancer

Preneoplasia of the Breast (2006) Boecker, W.

"It is not until Pregnancy and lactation that they (CK8/18) undergo terminal differentiation to become secretory end cells."

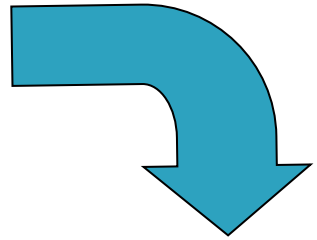


Biology of the abortion breast cancer link



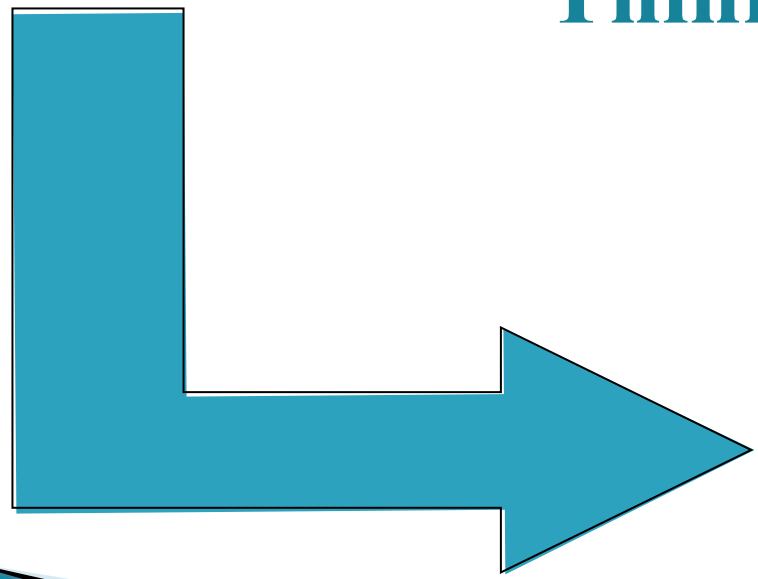
Breast Cancer Research

Jose Russo, MD
And Irma H. Russo, MD
Fox Chase Cancer Center
Philadelphia, PA, USA



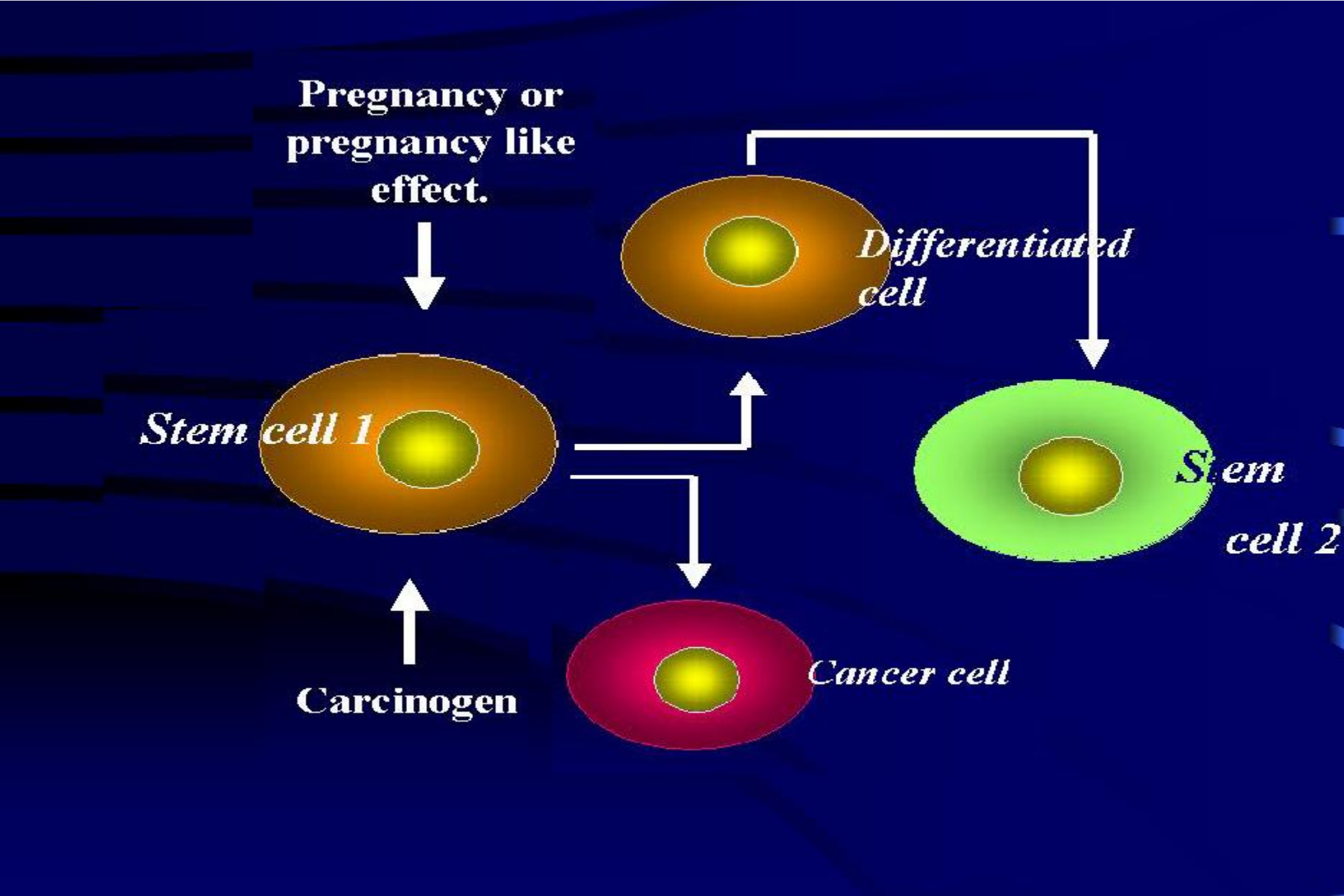
Conventional Thinking

- Diet
- Life style
- Hormonal Control
- SERMs
- Aromatase Inhibitors

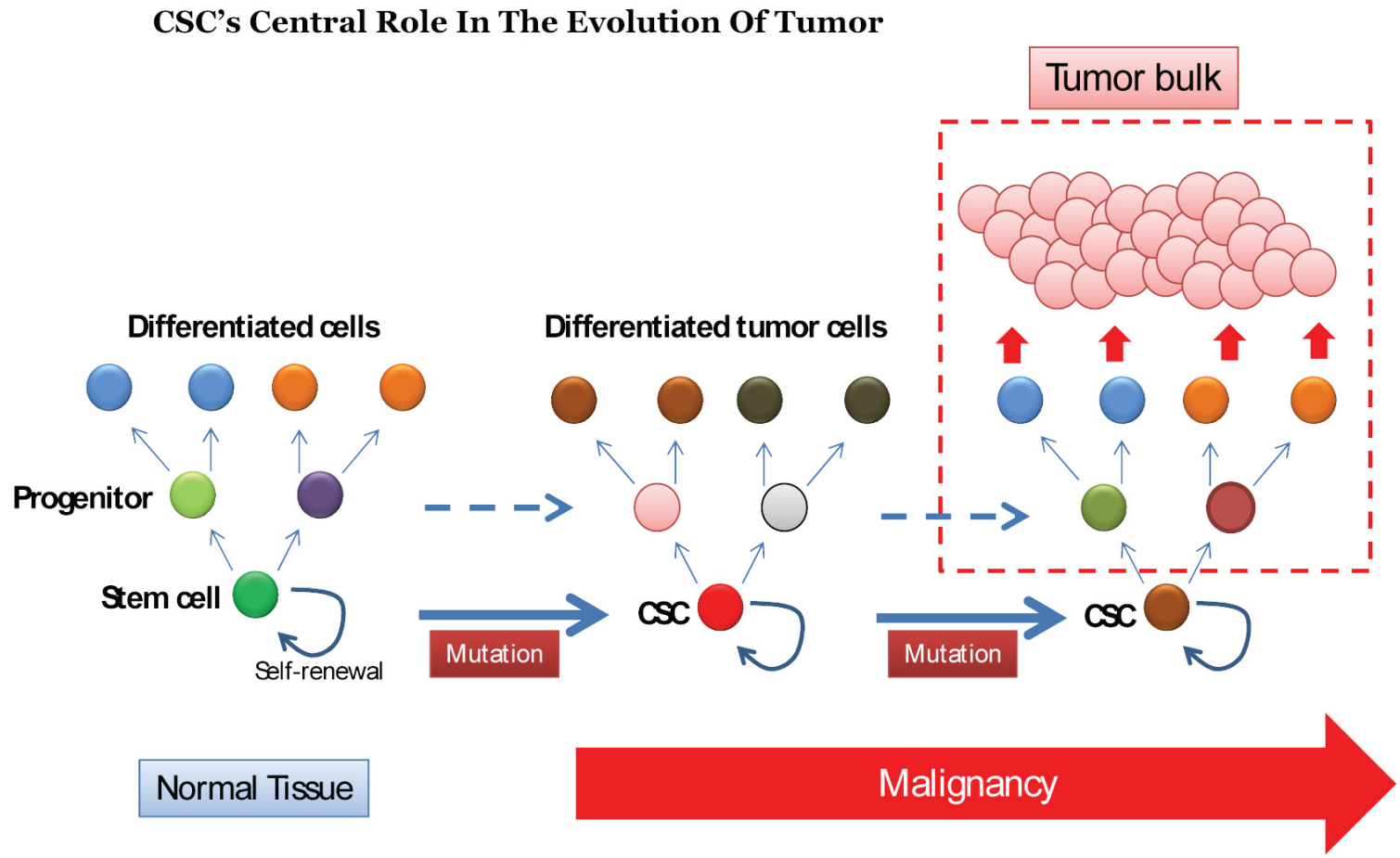


New Paradigm

From: Russo et al., Eur. J. cancer 2002

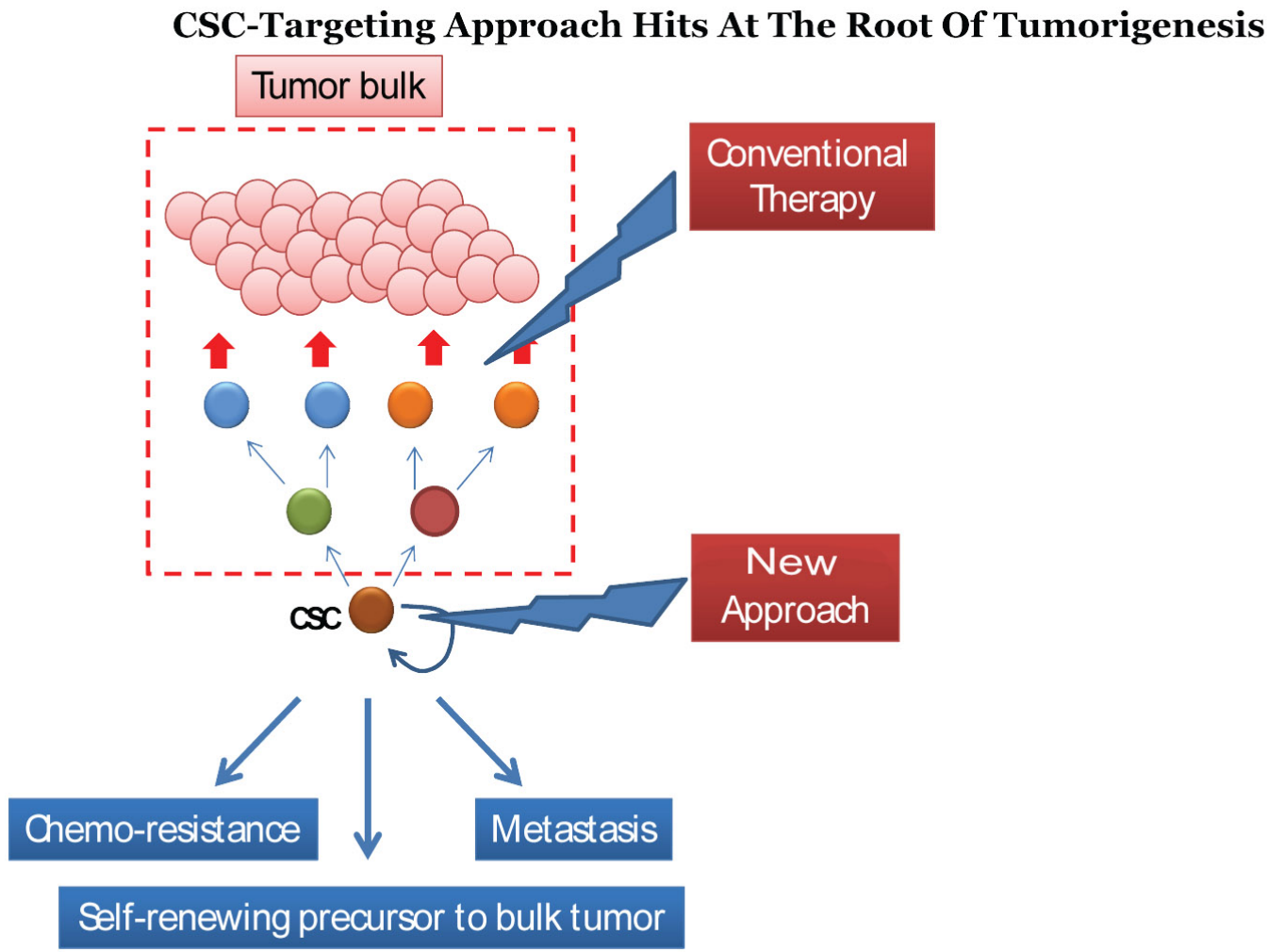

Pregnancy or pregnancy like effect.
Differentiated cell
Stem cell 1
Stem cell 2
Cancer cell
Carcinogen

Cancer Stem Cell Directed Therapies



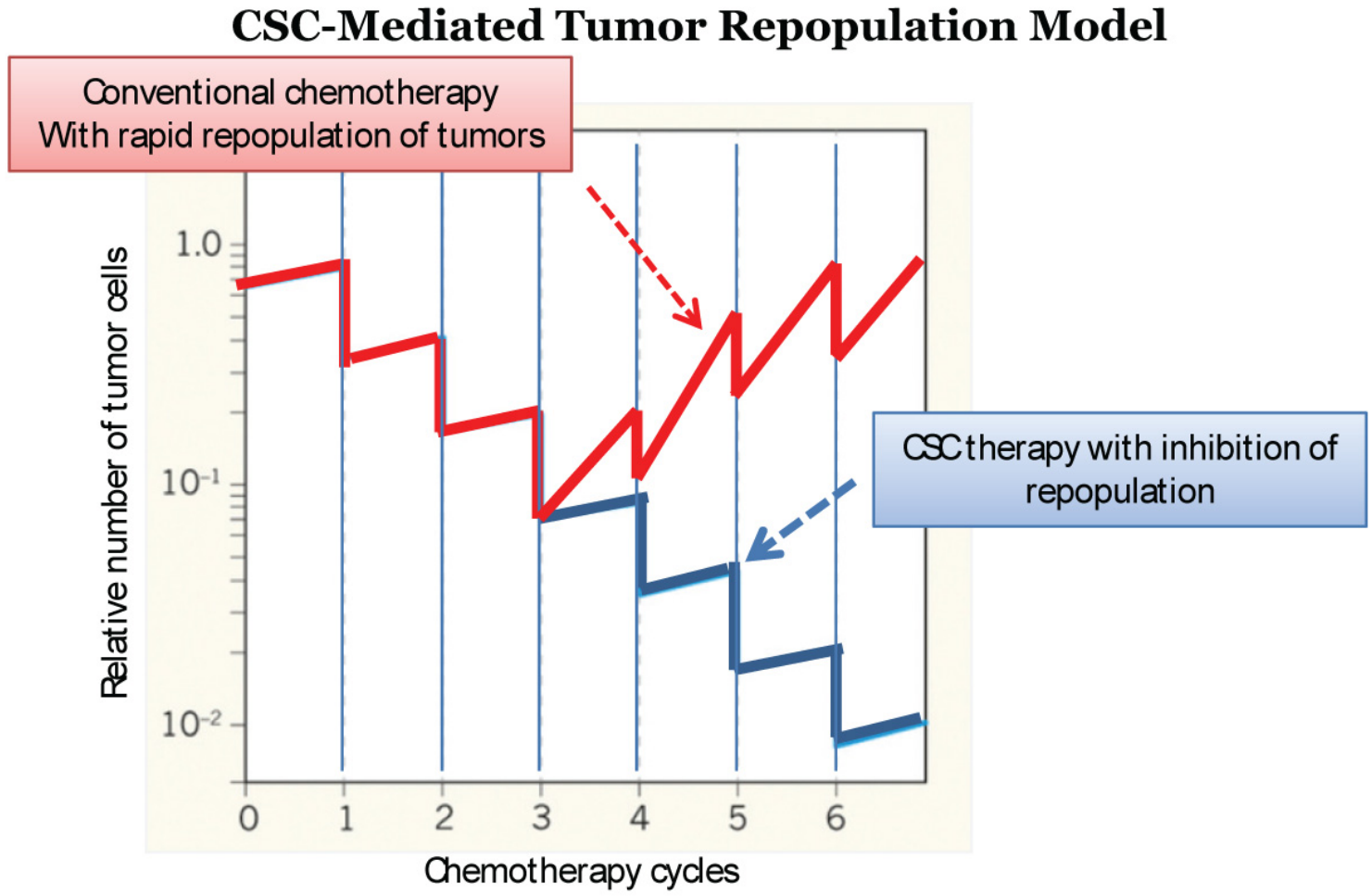
Source: Wells Fargo Securities, LLC

Cancer Stem Cell Directed Therapies



Source: Wells Fargo Securities, LLC

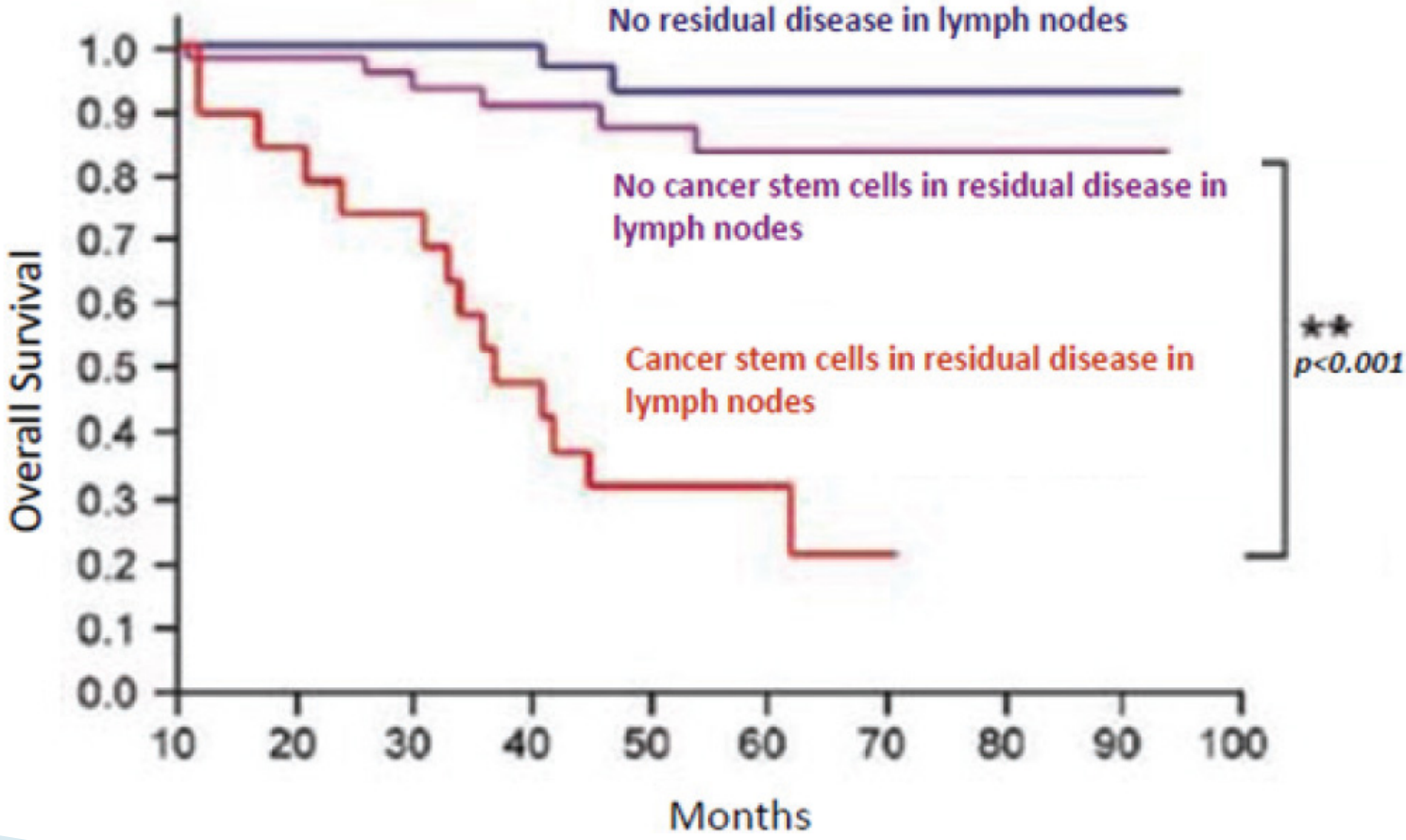
Cancer Stem Cell Directed Therapies Relapse Risk Due to Persistent CSCs



Source: Adapted from Nature 12/2014 and Wells Fargo Securities, LLC

Cancer Stem Cell Directed Therapies

Strong Correlation Between Presence Of Cancer Stem Cells And Breast Cancer Patient Survival



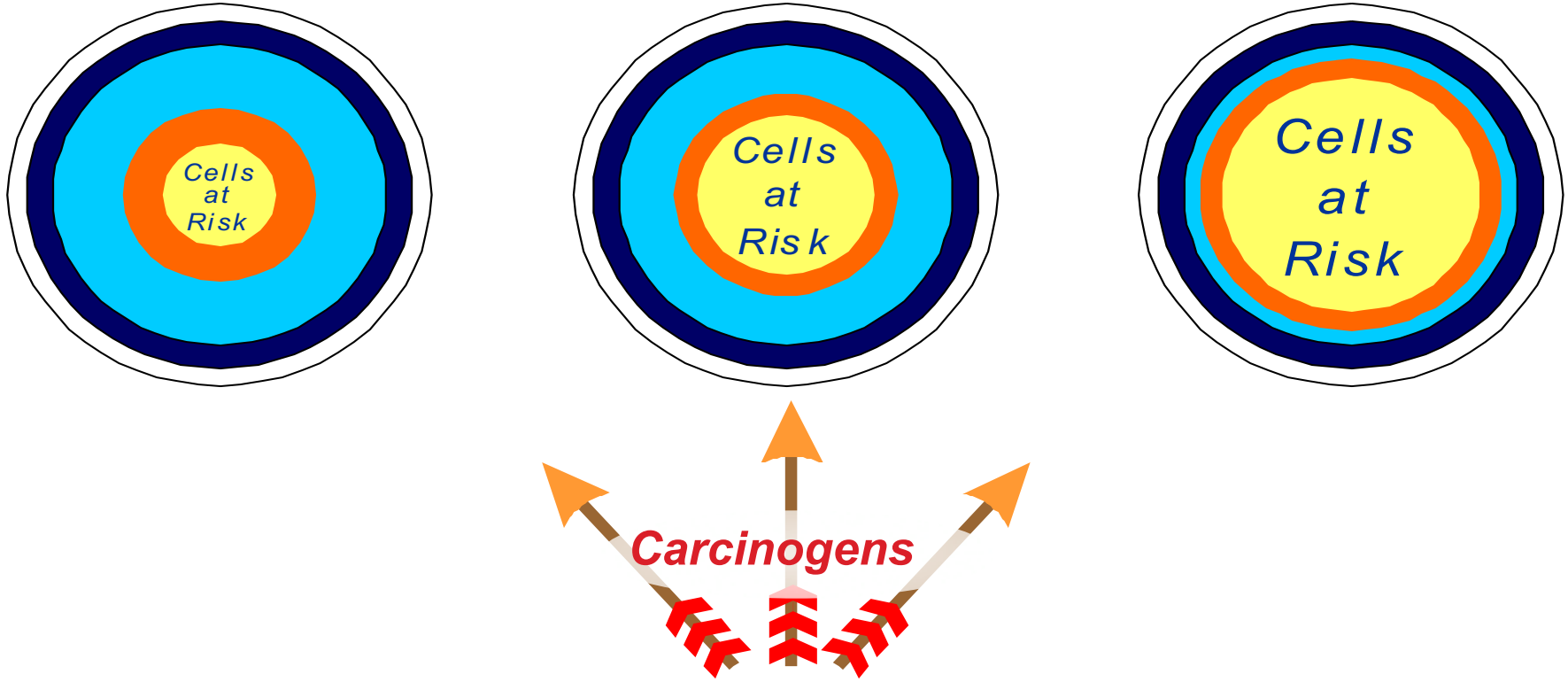
Source: Company reports and Wells Fargo Securities, LLC

Diet, Lifestyle and Breast Cancer Risk

Barbour S Warren, PhD
Program on Breast Cancer & Environmental Risk Factors
Sprecher Institute for Comparative Cancer Research

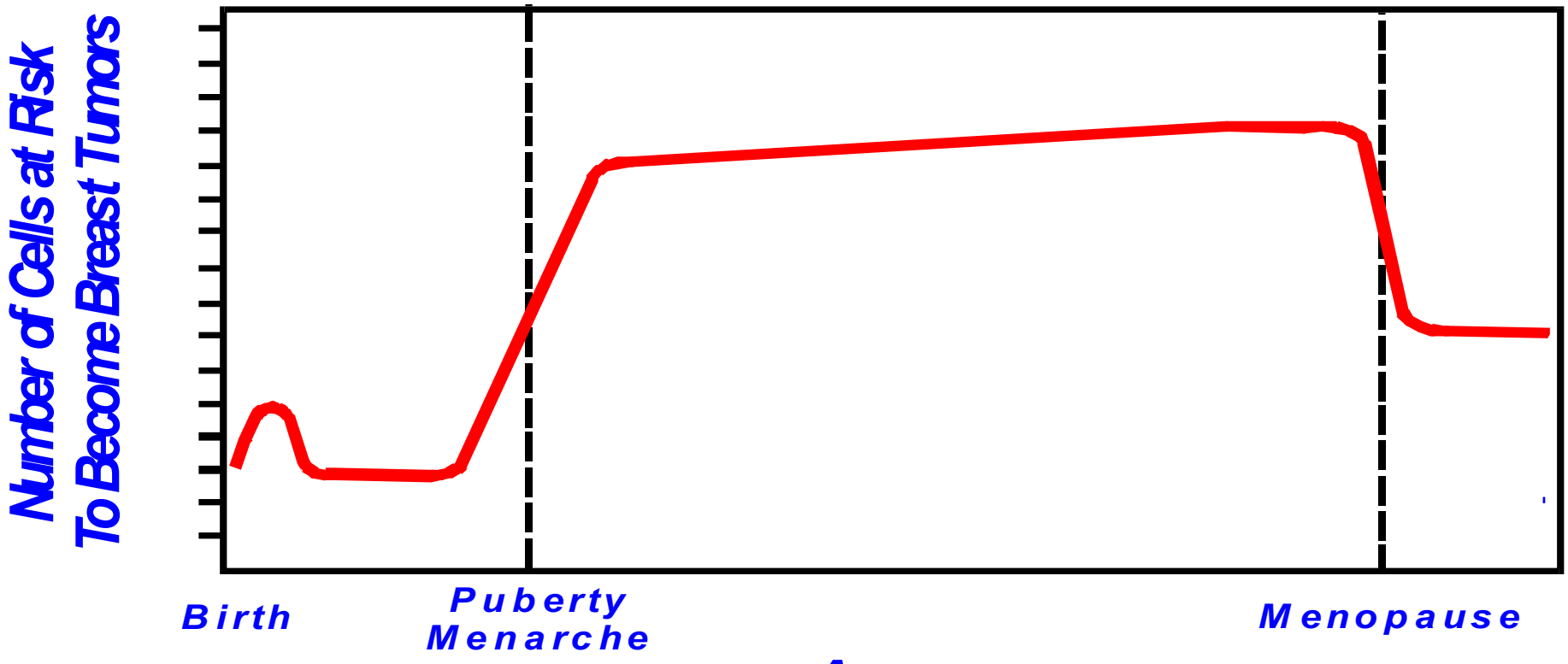
CORNELL

Cells at Risk Are Analogous to a Target's Bull's-eye

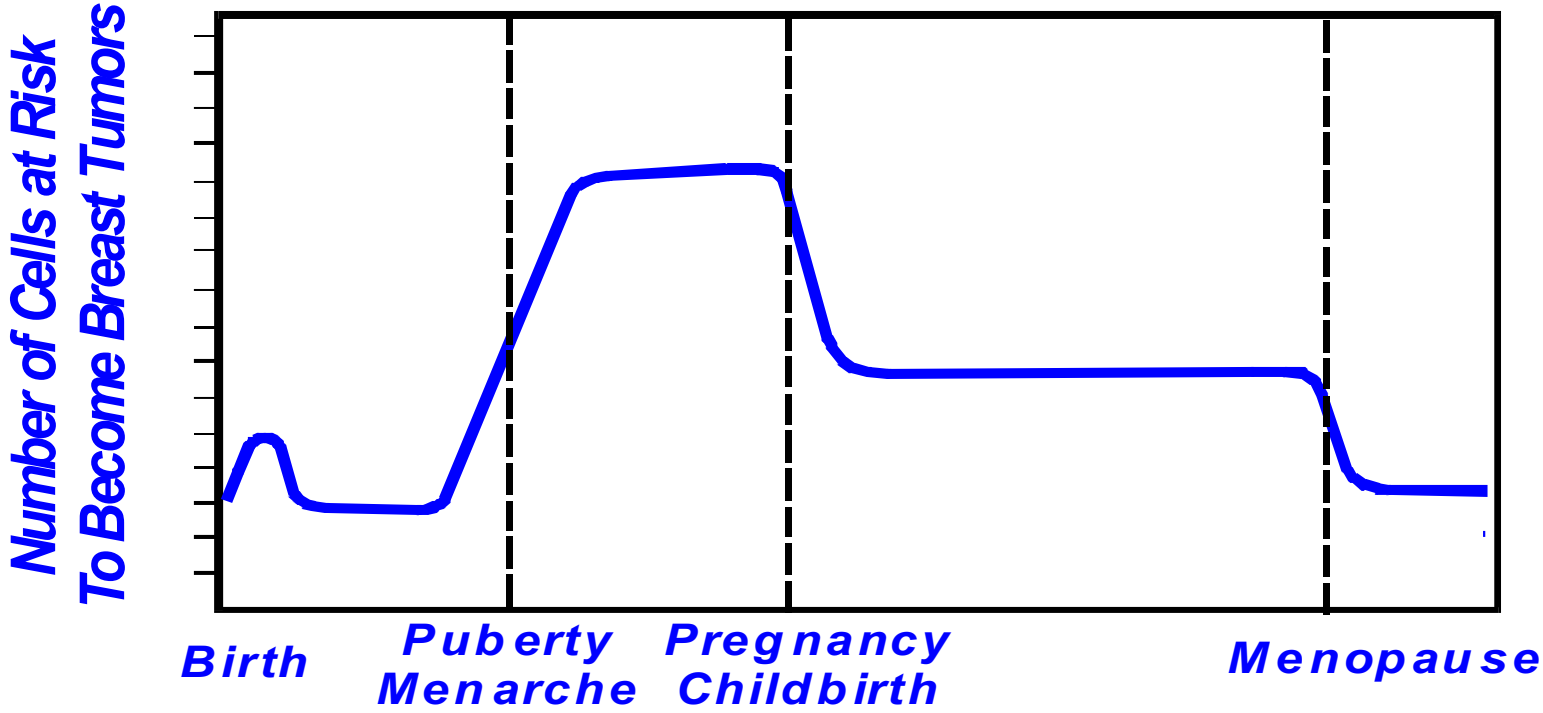


- A larger number of cells at risk produces a larger (and easier to hit) bull's-eye.

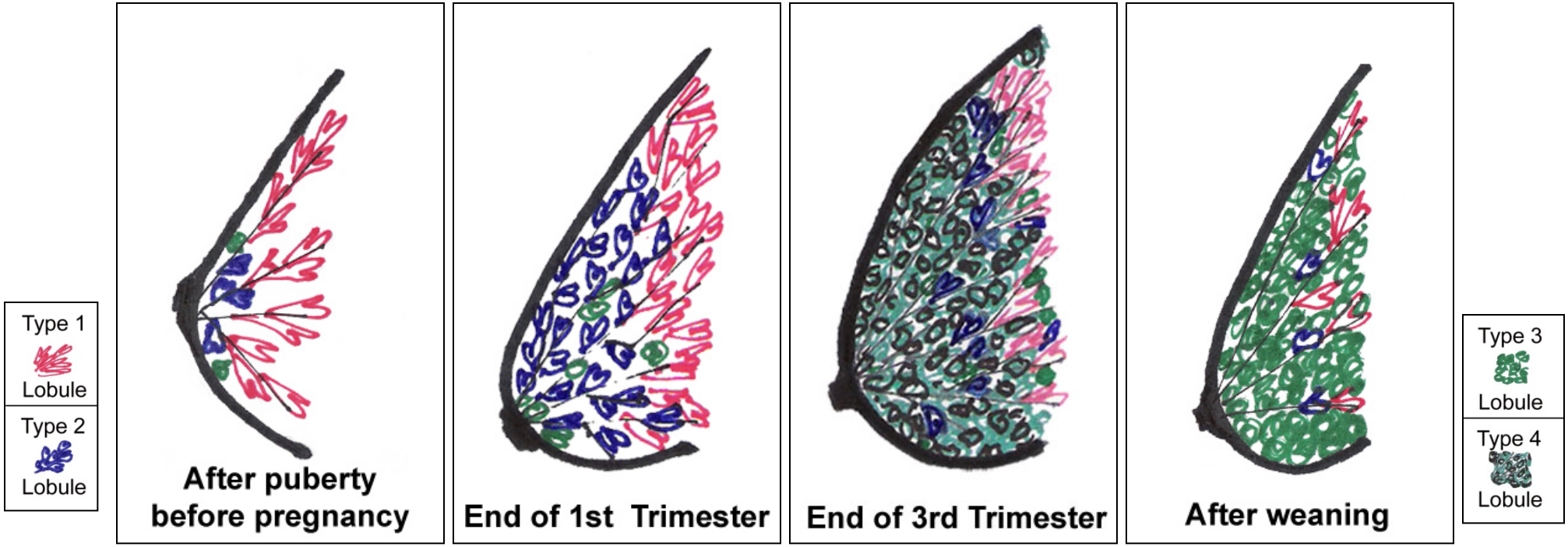
Lifetime Changes in Number of Cells at Risk to Become Breast Tumors in a Theoretical Childless Woman



Lifetime Changes in Number of Cells at Risk to Become Breast Tumors in a Theoretical Childbearing Woman

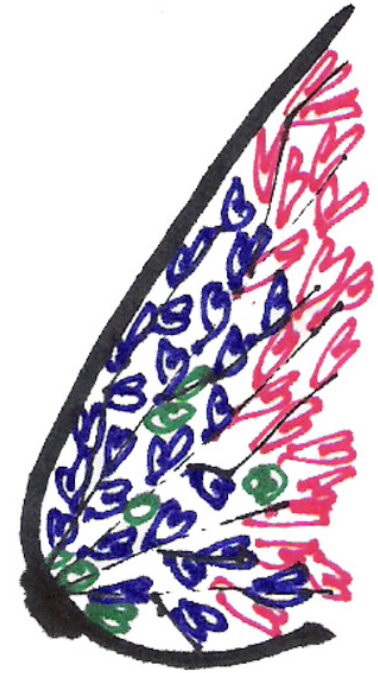


Breast lobule maturation before and after first pregnancy



Before & After Induced Abortion

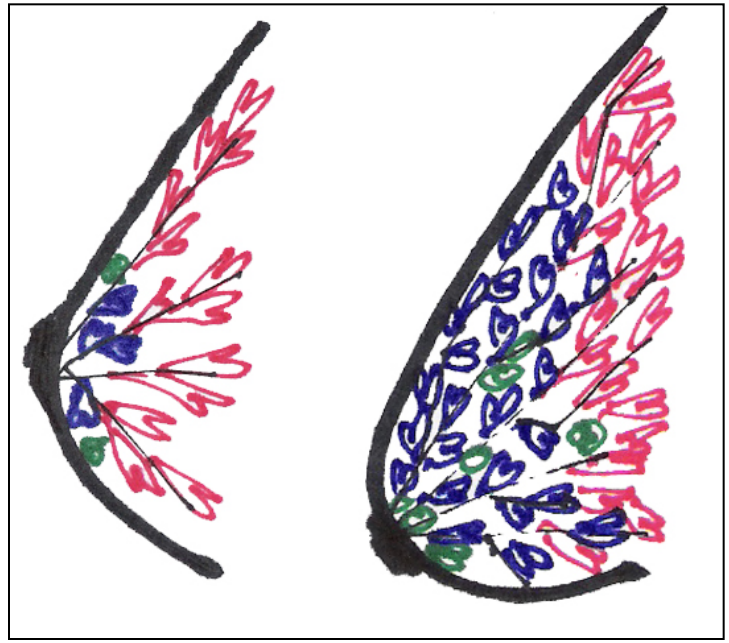
Before 1st Pregnancy



After Induced Abortion

The longer the pregnancy proceeds before abortion, the greater the number of undifferentiated lobules are left and the higher the risk.

(Melbye's 1997 and Daling's 1994)



Spontaneous abortion and hormone levels

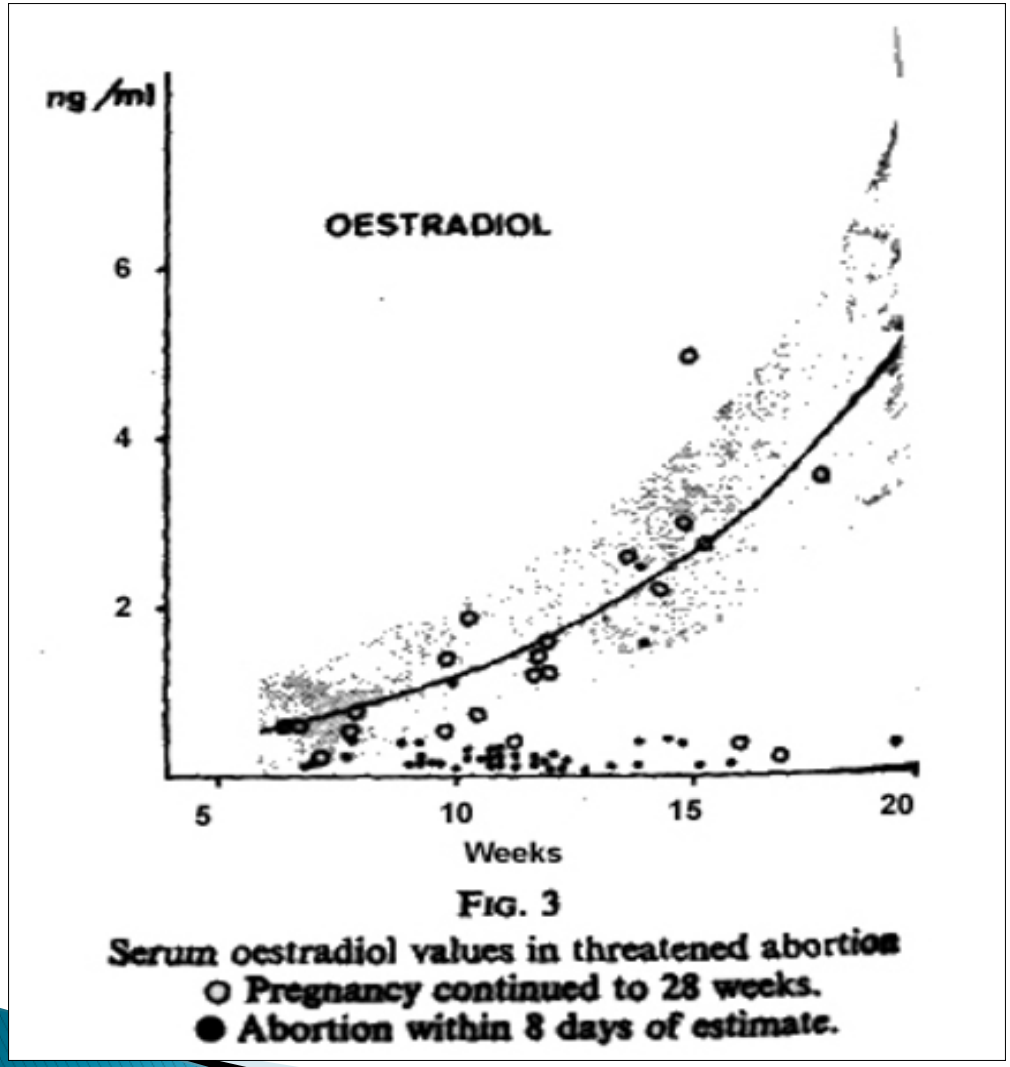


FIG. 3

Serum oestradiol values in threatened abortion
○ Pregnancy continued to 28 weeks.
● Abortion within 8 days of estimate.

British Journal of Obstetrics and Gynaecology August 1976. Vol 83

J. KUNZ and P.J. KELLER
Department of Gynaecology and Obstetrics
University of Zurich, Switzerland

Women who spotted blood while pregnant had spontaneous abortions if their estrogen levels were found to be low.

If their estrogen levels were normal, they did not spontaneously abort.

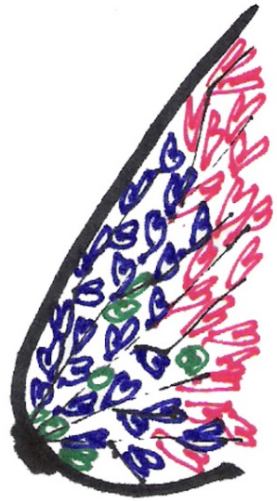
Before and After Spontaneous Abortion/ Miscarriage

Before 1st Pregnancy

After Spontaneous Abortion/Miscarriage

Before & After Induced Abortion

Before 1st Pregnancy



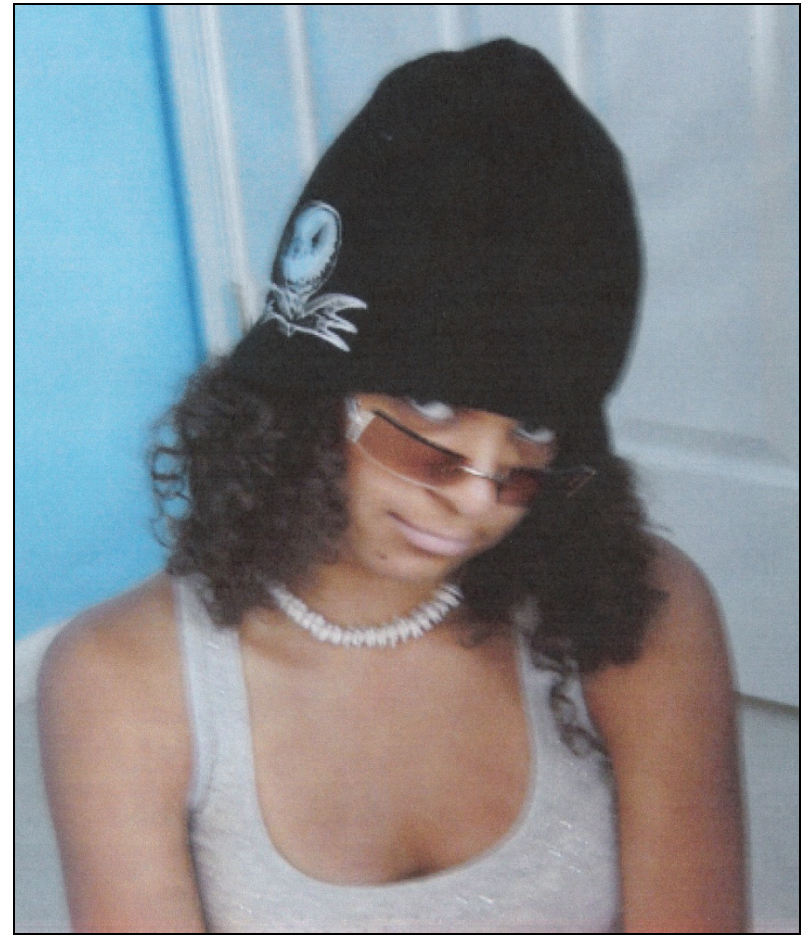
After Induced Abortion

Before and After Spontaneous Abortion/ Miscarriage

Before 1st Pregnancy

After Spontaneous Abortion/Miscarriage

Pregnancy – A Double Edged Sword



Pregnancy – A Double Edged Sword

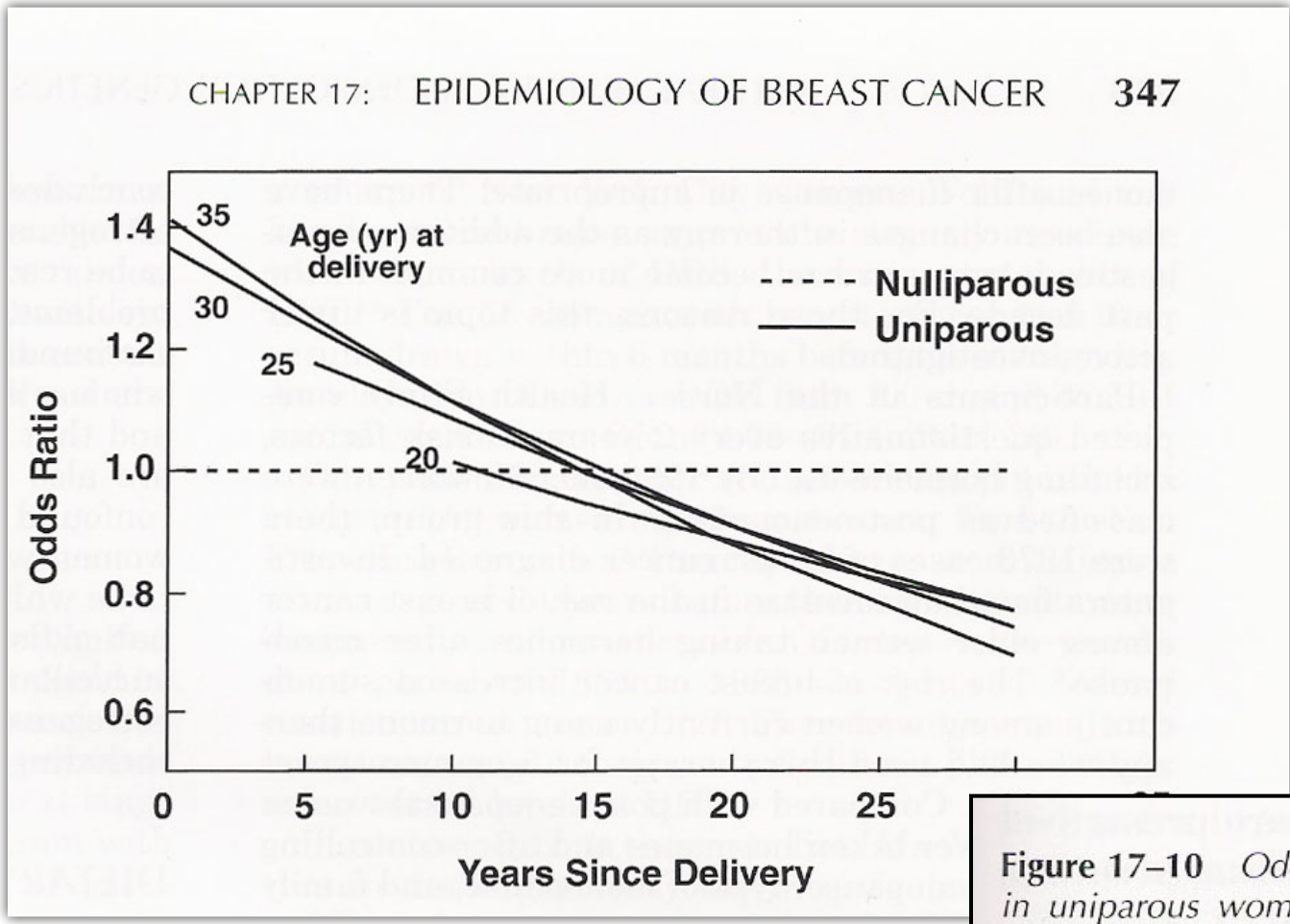


Figure 17–10 *Odds ratios for the risk of breast cancer in uniparous women of various ages at delivery, according to the number of years since delivery. (Lambe M, Hsieh C-C, Trichopoulos D, et al: Transient increase in the risk of breast cancer after giving birth. N Engl J Med 331:5–9, 1994.)*

Pregnancy – A Double Edged Sword

For each year a woman delays her pregnancy after age 20:
she increases her risk of
premenopausal breast cancer 5%
per year
post menopausal breast cancer 3%
per year.

These facts of the breast maturation process account for the following known facts about breast cancer risk:

- **Each additional birth results in a further 10% risk reduction.**

Lambe M, et al. Parity, Age at First and Last Birth, and Risk of Breast Cancer: A population based study in Sweden. *Breast Cancer Res Treat* 1996;39:305-11.

These facts of the breast maturation process account for the following known facts about breast cancer risk:

Breast feeding reduces risk in proportion to the cumulative length of lactation.

Lancet, Vol 360, July 2002

Articles

Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50 302 women with breast cancer and 96 973 women without the disease

*Collaborative Group on Hormonal Factors in Breast Cancer**

The longer lifetime breast feeding, the lower risk of cancer

1 yr	RR	.94	3 yr	RR	.89
2 yr	RR	.89	<6 yr	RR	.73

Pre-term delivery and risk of breast cancer

Melbye M, *et al… Brit J Cancer* 1999;80:609

Premature births before 32 weeks more than doubled the risk of breast cancer. The breast tissue has not gone through differentiation into Type 3 & 4 lobules

Melbye M, *et al. Brit J Cancer* 1999;80:609

Table 2 Adjusted relative risk of breast cancer in 474, 158 parous women According to gestational age at delivery

Gestational Age (weeks	No of cases	Person-years (in thousands)	RR (95% CI)
<29	7	9	2.11 (1.00-4.45)
29-31	13	17	2.08 (1.20-3.50)
32-33	11	26	1.12 (0.62-2.04)
36-37	82	214	1.04 (0.83-1.32)
38-39	350	949	1.02 (0.89-1.17)
40	552	1526	1
➢ 40	326	985	1.03 (0.90-1.18)

*Adjusted for age, calendar period, parity and age at first childbirth.

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July 2006

INSTITUTE OF

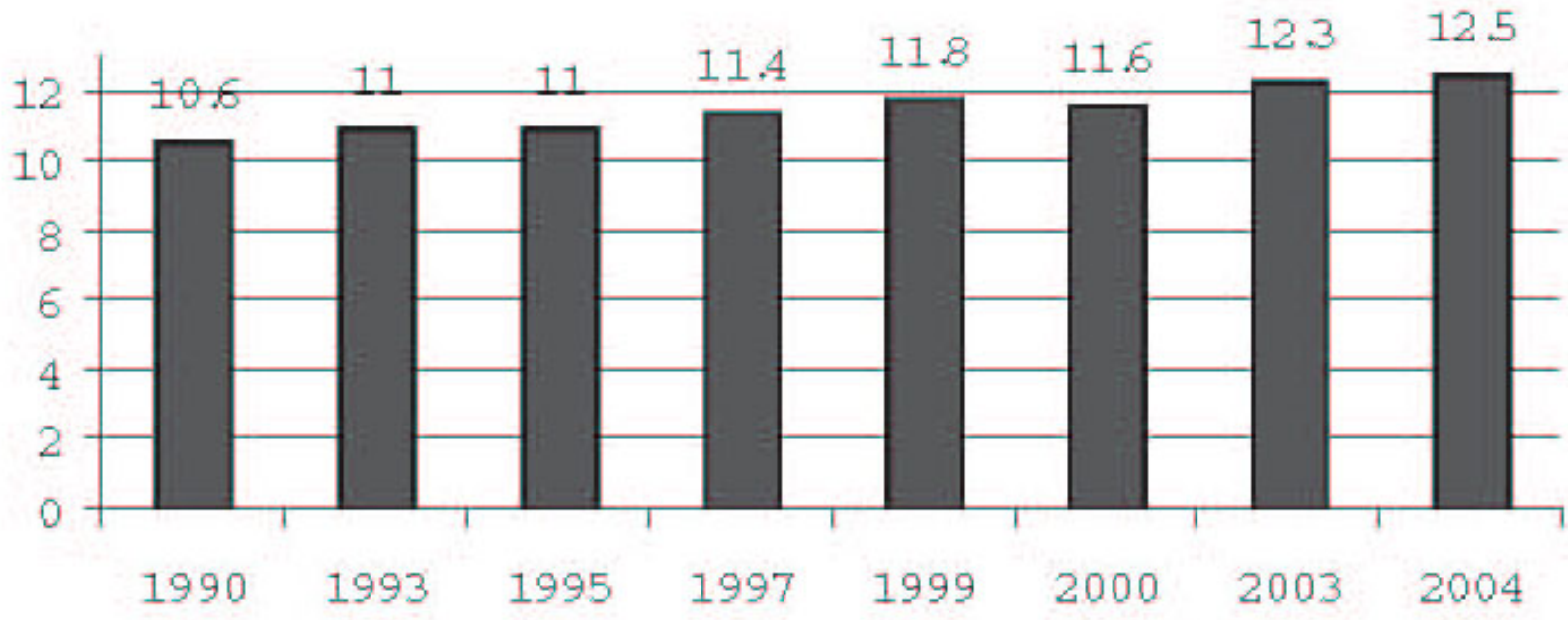

FIGURE 1. Preterm births as a percentage of live births in the United States, 1990 to 2004.
SOURCES: CDC (2001, 2002, 2004a, 2005a).

economic consequences of preterm birth, and establishes a framework for action in addressing a range of priority issues, including a research and policy agenda for the future.

of 12.5 percent of all births in the United States...

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Advising the Nation. Improving Health.

July 2006

TABLE B-5 Immutable Medical Risk Factors Associated with Preterm Birth

Previous low birth weight or preterm delivery
Multiple 2nd trimester spontaneous abortion

Prior first trimester induced abortion

Placental abnormalities
Cervical and uterine anomalies
Gestational bleeding
Intrauterine growth restriction
In utero diethylstilbestrol exposure
Multiple gestations
Infant sex
Short stature
Low prepregnancy weight/low body mass index
Urogenital infections
Preeclampsia

Journal of American Physicians and Surgeons, Vol 8, No 2, Summer 2003

Induced Abortion and Risk of Later Premature Births

	Number of prior IAs		
	1	2	3 or more
Gestational age	RR	RR	RR
20-27 weeks (XPBs)	1.6	2.5	5.6
28-31 weeks	1.6	1.1	2.6
32-36 weeks	1.1	1.6	2.4

[RR = relative risk]

Table 1: Premature birth risk by number of prior induced abortions (IAs) compared with outcome of first pregnancies, Victoria, 1986-1990[12]

minations by courts.

Premature delivery, the delivery of a live infant,

is **NO** different physiologically in its effect on the mother's breast than

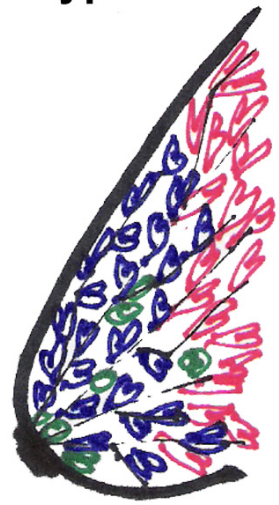
Induced abortion, the delivery of a dead infant

Breast Tissue After Abortion

Types 1 & 2

Before Pregnancy

Types 1 & 2



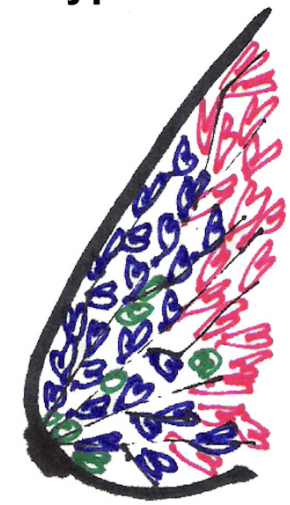
After Induced Abortion

Breast Tissue After Premature Delivery

Types 1 & 2

Before Pregnancy

Types 1 & 2



After Premature Delivery

BREAST CANCER Prevention INSTITUTE

1-866-622-6237

(1-86 NO CANCER)

www.bcpinstitute.org

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