Breast Cancer and the Pill

C. Kahlenborn, MD

April, 2007

In the United States…

- In 2006, 212,920 women developed breast cancer and 40,970 died from it.

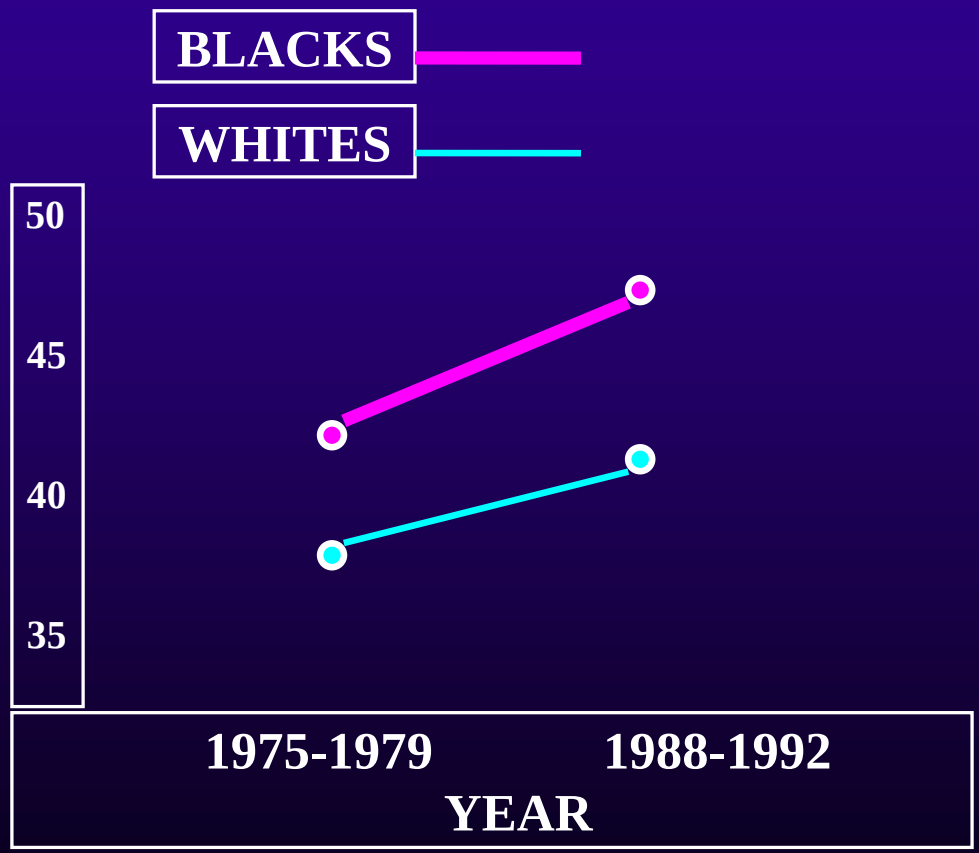
- Today, over one in eight women will develop breast cancer in her lifetime.

American Cancer Society, 2006.

Over 20% (ie, 47,000) of women with breast cancer develop it prior to age 50

Ghafoor A et al. Breast Cancer Facts & Figures 2003-2004. *American Cancer Society*. 2003.

RISING RATES OF BREAST CANCER (Ages 20-44)

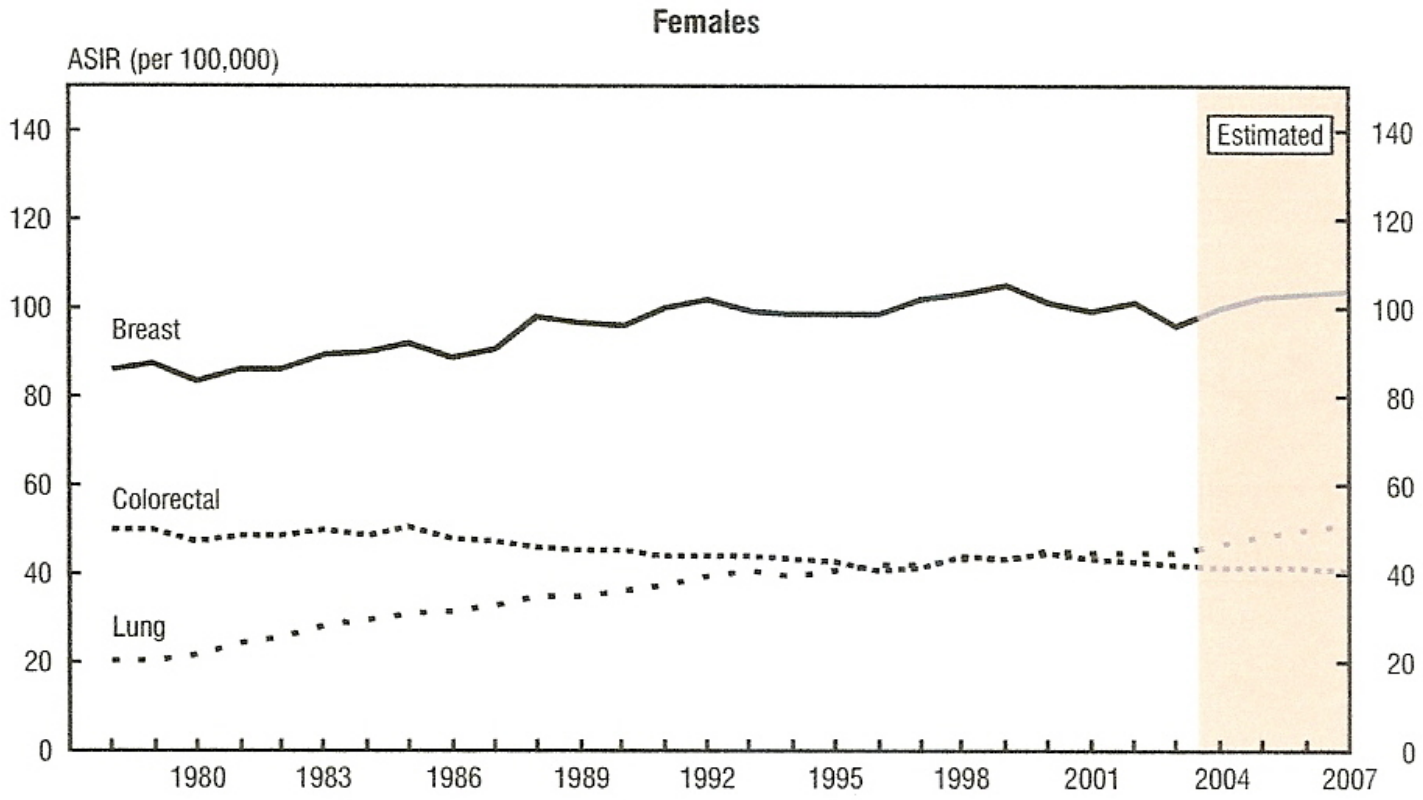


data from NCI

Breast Cancer Rates in Canada

Figure 6.1

Age-Standardized Incidence Rates (ASIR) for Selected Cancers, Females, Canada, 1978-2007



Canadian Cancer Society/National Cancer Institute of Canada: *Canadian Cancer Statistics 2007*

AGE AND SEX DISTRIBUTION OF CANCER

Table 11

Distribution by Selected Cancers, Age Group and Sex, Canada, 2007

Age Group	Lung			Colorectal			Prostate	Breast
	Total	M	F	Total	M	F	M	F
New Cases								
0-19	10	5	5	10	5	5	–	5
20-29	25	15	10	40	20	20	–	70
30-39	120	50	70	210	110	100	5	840
40-49	1,050	410	660	1,050	550	520	340	3,500
50-59	3,500	1,650	1,800	3,200	1,850	1,350	3,500	6,200
60-69	6,700	3,600	3,100	5,200	3,200	1,950	8,000	5,300
70-79	7,600	4,300	3,200	6,100	3,500	2,600	7,000	3,800
80+	4,400	2,300	2,100	5,000	2,200	2,900	3,400	2,600
All Ages	**23,300**	**12,400**	**10,900**	**20,800**	**11,400**	**9,400**	**22,300**	**22,300**

Canadian Cancer Society/National Cancer Institute of Canada: *Canadian Cancer Statistics 2007*

Risk Factors for Breast Cancer

- Positive family history
- Age
- Nulliparity
- Hormone Exposure
- Late menopause
- Early Menarche

Risk Factors

- Age at first birth
- Some types of fibrocystic breast disease
- Previous History of breast cancer
- Postmenopausal hormone use
- Defective BRCA1 or BRCA2 gene

Risk Factors

- Alcohol consumption
- Obesity in postmenopausal women
- Radiation exposure
- Diethylstilbestrol (DES).
- History of Other Cancers
- Early miscarriage/abortion?

Why have breast cancer rates risen?

- Fewer children
- Less breast feeding
- More (induced) abortion
- More hormonal contraceptive use

The History of Oral Contraceptives

Discovery of Hormones

In 1905, physiologist Ernest Starling identified “glandular secretions” which “stimulated the action of cells when carried through the blood stream.”

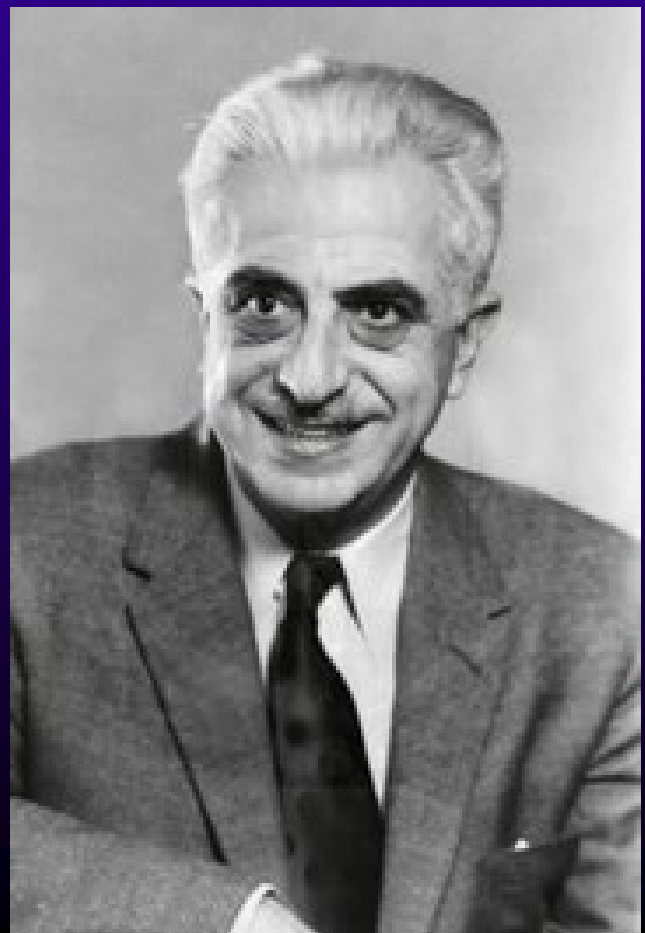
This soon led to the discovery of two major female hormones:

Estradiol and Progesterone

Several prominent figures played roles in the development of the first oral contraceptive.

Gregory Pincus, PhD:

Pioneer of the Birth Control Pill



In 1943, Dr. Russell Marker, discovered a way to extract progesterone from Yams. (ie, "Marker Degradation.”)

In the early 1950s, Pincus injected rabbits with progesterone and it stopped ovulation.

- In 1951, Dr. Pincus met with feminist Margaret Sanger

- Sanger formally asked Pincus to develop the first birth control pill

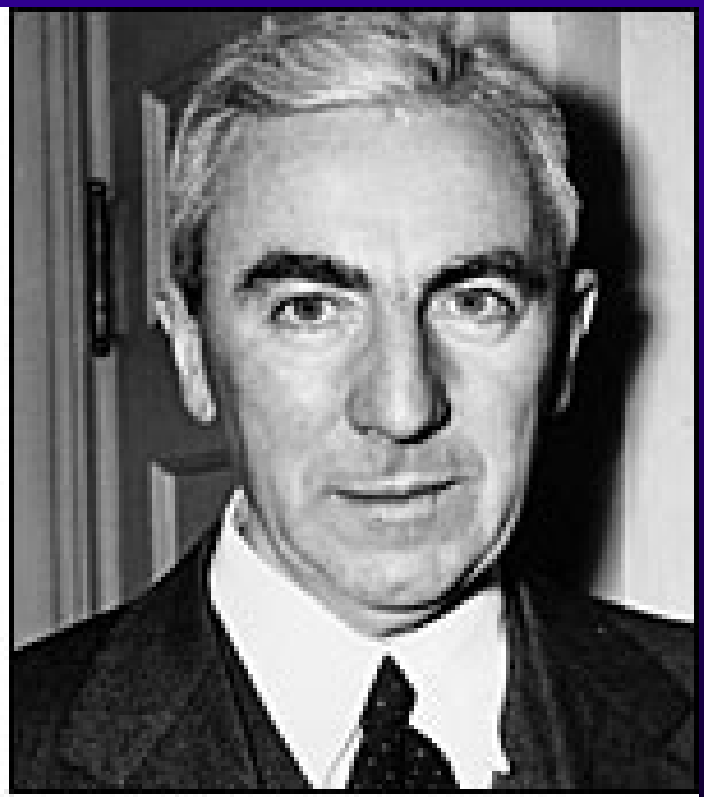
Margaret Sanger
(1879-1966)

In 1952…

Pincus received money, through the contacts of Sanger, from wealthy widow Katharine McCormick.

Pincus also was funded via the Population Council (JD Rockefeller)

John Rock, MD (Ob/Gyn)



- Infertility Expert
- Harvard Trained
- Roman Catholic

The First Experiment: *The Worcester Trial*

Performed on fifteen hospitalized schizophrenics patients at Worcester State Hospital

The Second Experiment: *The Puerto Rican Trial*

Chosen due to lack of Comstock laws

Pincus and Rock enrolled 300 women in trial

Puerto Rican Trial

- Women were given Enovid:

- 162 women dropped out second to nausea, dizziness and headaches

On May 11, 1960 the FDA officially approved Enovid, for the purpose of contraception in the United States.

What is an oral contraceptive?

Usually a combination of a synthetic estrogen and progestin

Mechanism of Action?

- Suppresses ovulation
- Thickens cervical mucus
- Changes the endometrium

Animal Data?

In 1972 an oral contraceptive containing mestranol and norethynodrel appeared to cause a case of metastatic breast cancer in a female rhesus monkey.

Kirschstein RL et al. *JNCI*; 1972

Worrisome?

Yes, because until that time, only three cases of breast cancer were reported in rhesus monkeys.

Concern grew further when it was noted that both **beagles** and **rodents** developed breast cancer when exposed to the hormones contained in today's OCs.

Geil et al. J Tox. Env. Health 1979; Shubik P. IARC Sci. Publ. 1985:

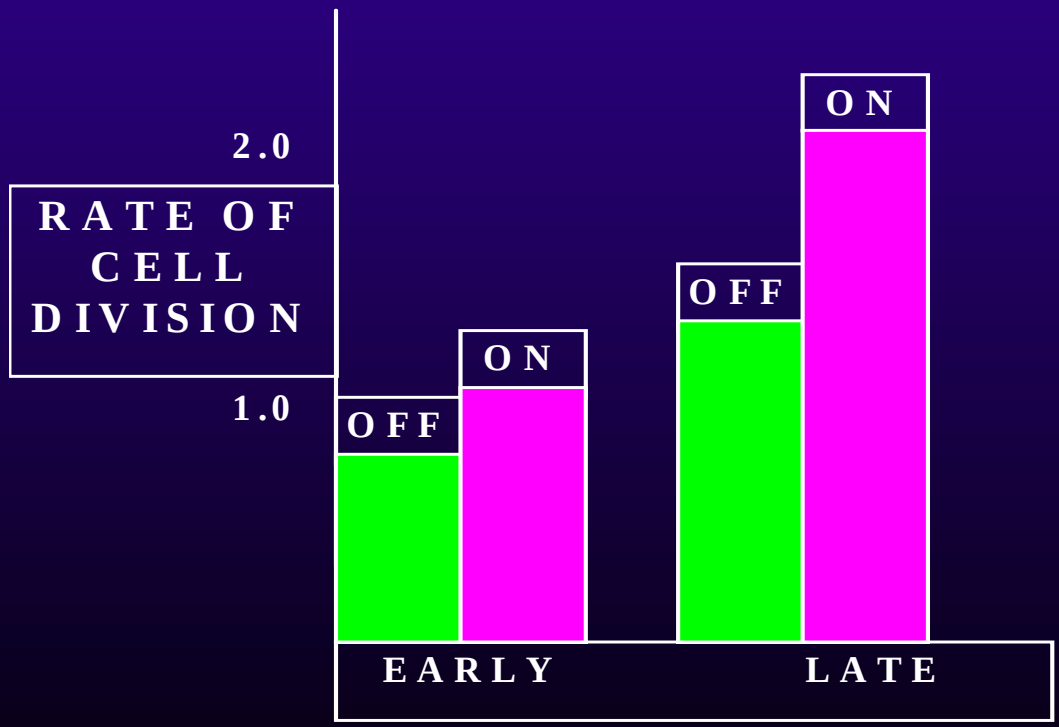
Kahn RH et al. *Endocrinology*. 1969; Weisburger JH et al. *Life Sci.* 1968;
Welsch CW et al. *British J. of Cancer*. 1977

How might OCs cause breast cancer in humans?

In 1989, Anderson et al published a classic paper in which he noted that nulliparous women who took OCs had a significantly higher rate of breast cell division than nulliparous women who did not take them.

Anderson et al, *Human Pathology*, 1989

RATE OF BREAST CELL DIVISION IN NULLIPAROUS WOMEN WHO TAKE THE PILL

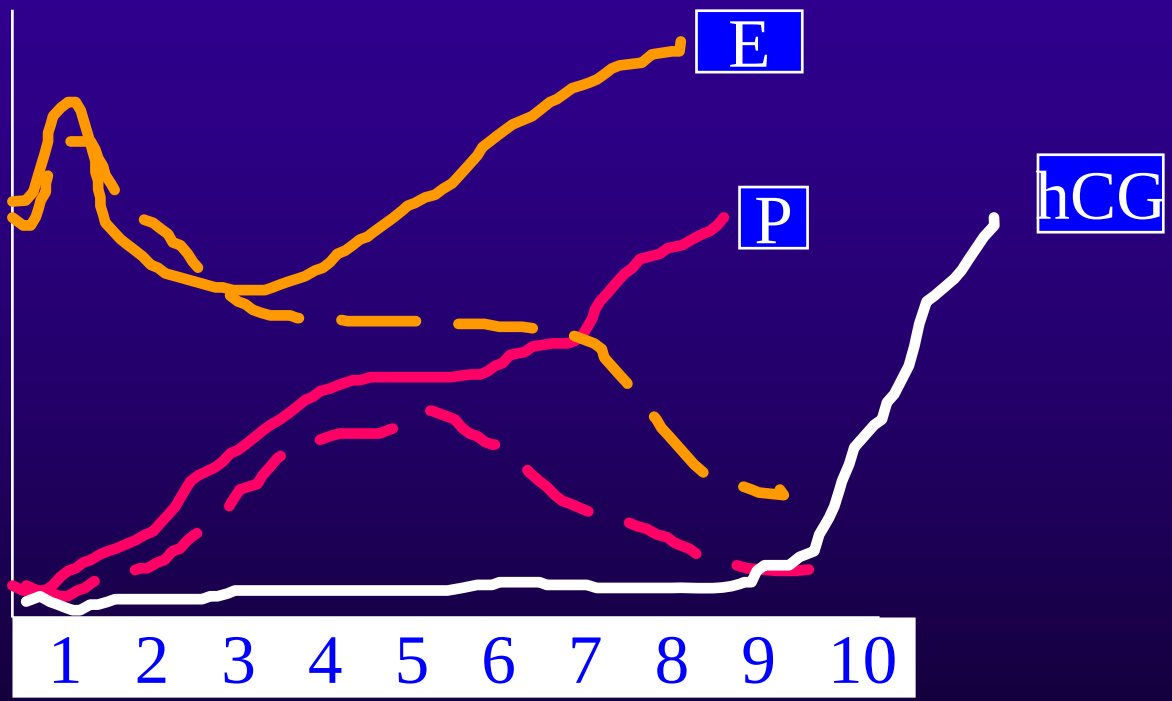


Is there another way in which OCs may be causing breast cancer?

Larimore and Stanford, in an exhaustive review, showed that the Pill works at times by causing a "post-fertilization" effect.

Larimore and Stanford, *Archives of Family Medicine*, 2/2000

Hormone Levels in Early Pregnancy



Stewart et al. *J. of Clin End and Met.*, 1993

HISTORY

- **1981: Pike et al:**

  -125% increased risk

- **1993: the CASH study:**

  -40% increased risk

Pike et al. *British J of Ca*., 1994;

Wingo AP et al, *Cancer*, 1993

- **1989: Chilvers (United Kingdom Study)**.
  - 44% increased risk

- **1995: Brinton et al.**
  - 42% increased risk

Chilvers et al. *The Lancet*, May 6, 1989;
Brinton et al, *JNCI*, 6/7/95

If the major studies showed increased risks, then why have women failed to hear about it?

The Oxford Pooled Analysis:

- Published in 1996 in *The Lancet* it included over 53,000 women, 54 studies, 25 countries

The Lancet, 1996 (V347); *Contraception*, 1996 (V34)

Conclusion:

"Women who are currently using combined oral contraceptives or have used them in the past 10 years are at a slightly increased risk of having breast cancer diagnosed, although the additional cancers tend to be localized to the breast...

…There is no evidence of an increase in the risk of having breast cancer diagnosed 10 or more years after cessation of use...”

Four Defects of the Oxford Analysis:

Defect # 1

Oxford study used data from older studies which took some of their data from the 1960s and the early 1970s.

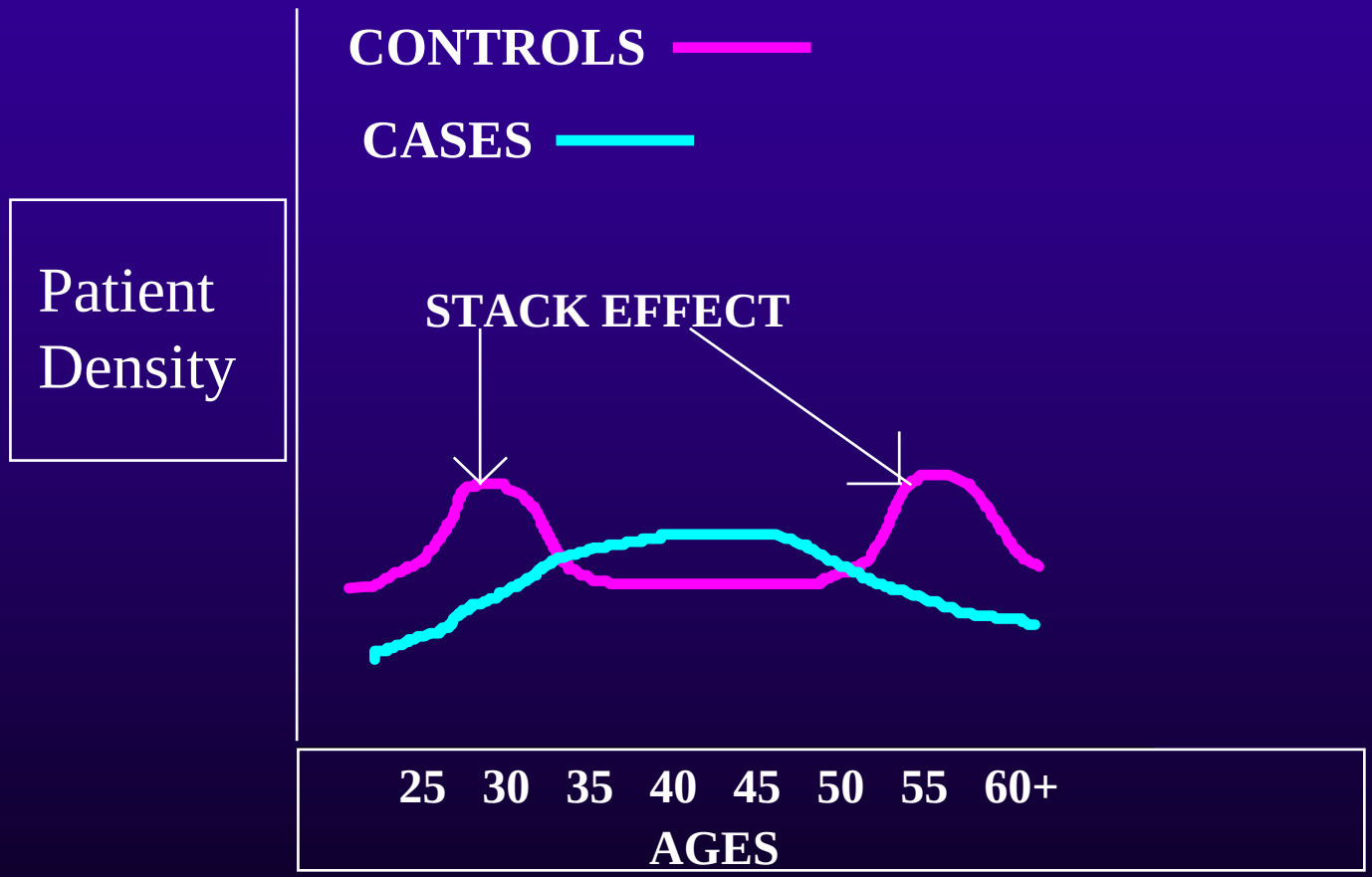
Defect #2

Failure to examine the risk in premenopausal women who used OCs prior to their first-term pregnancy.

Defect # 3

The Stack Effect…

STACK EFFECT



…so did the Oxford pooled-analysis suffer from the stack effect?

… 12% of the "controls" (women without breast cancer) and 9% of the "cases" (women with breast cancer) were less than 34 years old, and that 2% of the "controls" and 1% of the "cases" were less than 25 years old.

Defect # 4

Inclusion of ten prospective studies…

Often in research prospective studies are the preferred method of study, however…

…the prospective studies used in the Oxford analysis had several problems…

One study* never examined women who had breast cancer.

Much of the data of the other nine studies included postmenopausal women who had little access to OC use early in their lives.

*Wang DY et al. *Eur J Clin Oncol.* 1987; 1541-48.

Conclusion:

The Oxford study suffers from four glaring defects which serve to greatly reduce its credibility.

In light of these criticisms, their conclusion that “Women who are currently using combined oral contraceptives or have used them in the past 10 years are at a slightly increased risk of having breast cancer diagnosed" cannot be accepted.

Recent News:

July 29, 2005 Press Release…

THE IARC* (a branch of the World Health Organization) declared oral contraceptives to be a Group 1 carcinogen!

*International Agency for Research on Cancer

Definition of a Group 1 Carcinogen:

"The agent (mixture) is carcinogenic to humans. The exposure circumstance entails exposures that are carcinogenic to humans."

“There is sufficient evidence in humans for the carcinogenicity of combined oral contraceptives. This evaluation was made on the basis of increased risks for cancer of the breast among current and recent users only.”

The vol. 91 of the Monograph series, on Combined Oral Contraceptives and Menopausal Therapy is Available: See http://monographs.iarc.fr/ for more details.

EVIDENCE?

Previous meta-analysis that examined women under age 45 who had taken OCs prior to first birth

- Thomas: 1991: 42% increased risk
- Romieu: 1990: 4 years pFFTP = 72% increased risk

Thomas et al. *Contraception*. 1991

Romieu et al. *Cancer*. 1990

What do today's studies show?

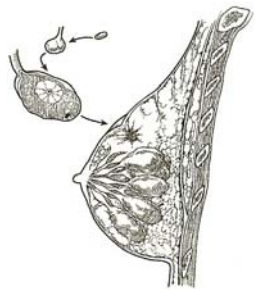
MAYO CLINIC
College of Medicine

October 2006
Volume 81
Number 10

Mayo Clinic Proceedings

A Peer-Reviewed Medical Journal Sponsored by Mayo Clinic College of Medicine and Authored by Physicians Worldwide

THIS MONTH'S FEATURES



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ORIGINAL ARTICLE

Oral Contraceptive Use as a Risk Factor for Premenopausal Breast Cancer: A Meta-analysis

CHRIS KAHLENBORN, MD; FRANCESMARY MODUGNO, PHD, MPH; DOUGLAS M. POTTER, PHD; AND WALTER B. SEVERS, PHD

OBJECTIVE: **To perform a meta-analysis of case-control studies that addressed whether prior oral contraceptive (OC) use is associated with premenopausal breast cancer.**

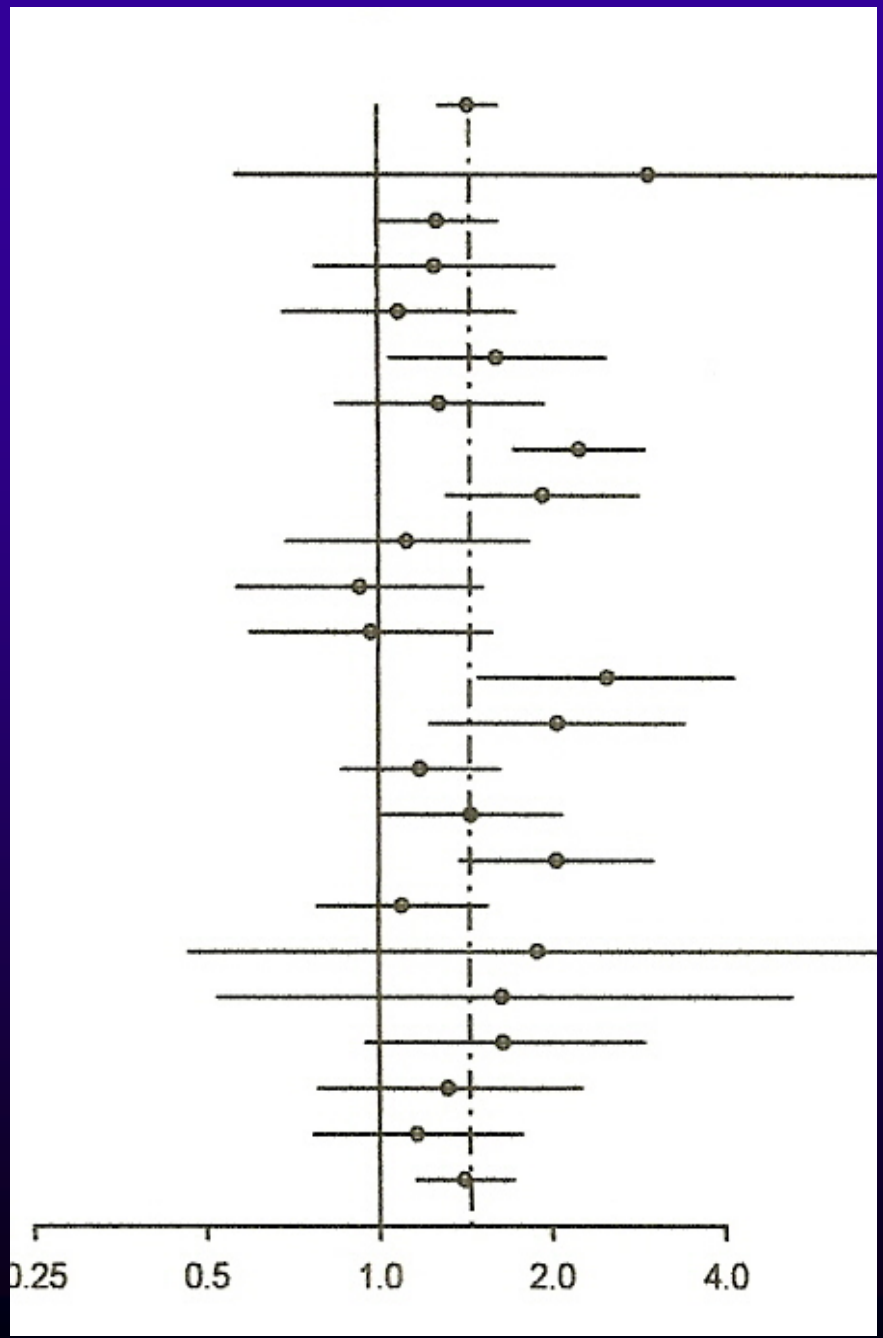
METHODS: **We searched the MEDLINE and PubMed databases and bibliography reviews to identify case-control studies of OCs and premenopausal breast cancer published in or after 1980. Search terms used included *breast neoplasms, oral contraceptives, contraceptive agents,* and *case-control studies.* Studies reported in all languages were included. Thirty-four studies were identified that met inclusion criteria. Two reviewers extracted data from original research articles or additional data provided by study**

population) and by 26.4% in African American women younger than 50 years (ie, 34.8 per 100,000 population to 44.0 per 100,000 population).[3]

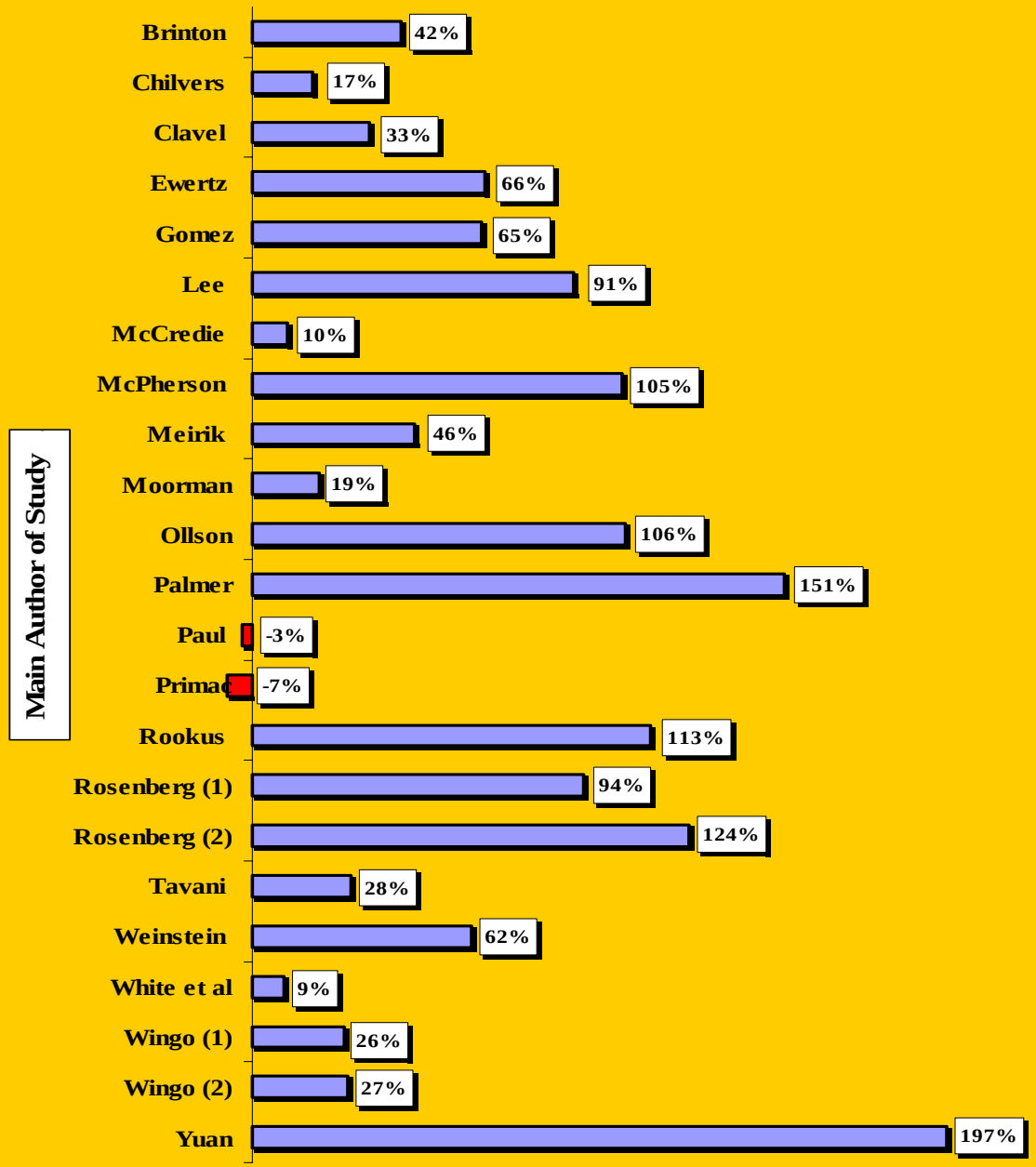
Although the medical research community has long recognized breast cancer risk factors such as a positive family history of breast cancer, early menarche, late menopause, nulliparity, and lack of breastfeeding,[4-7] concordance is lacking regarding the carcinogenic potential of female hormones. The Women's Health Initiative Clinical Trial re-

Twenty-one out of twenty-three retrospective studies, the bulk of whose data comes after 1980, show a notable increased risk of breast cancer from OC use prior to FFTP.

ODDS RATIOS FOR USE PRIOR TO FIRST PREGNANCY



Increased Risk of Breast Cancer in Studies of Pre-menopausal Women Who Took Oral Contraceptives Prior to Their First-Term Pregnancy*



The overall risk comes to:

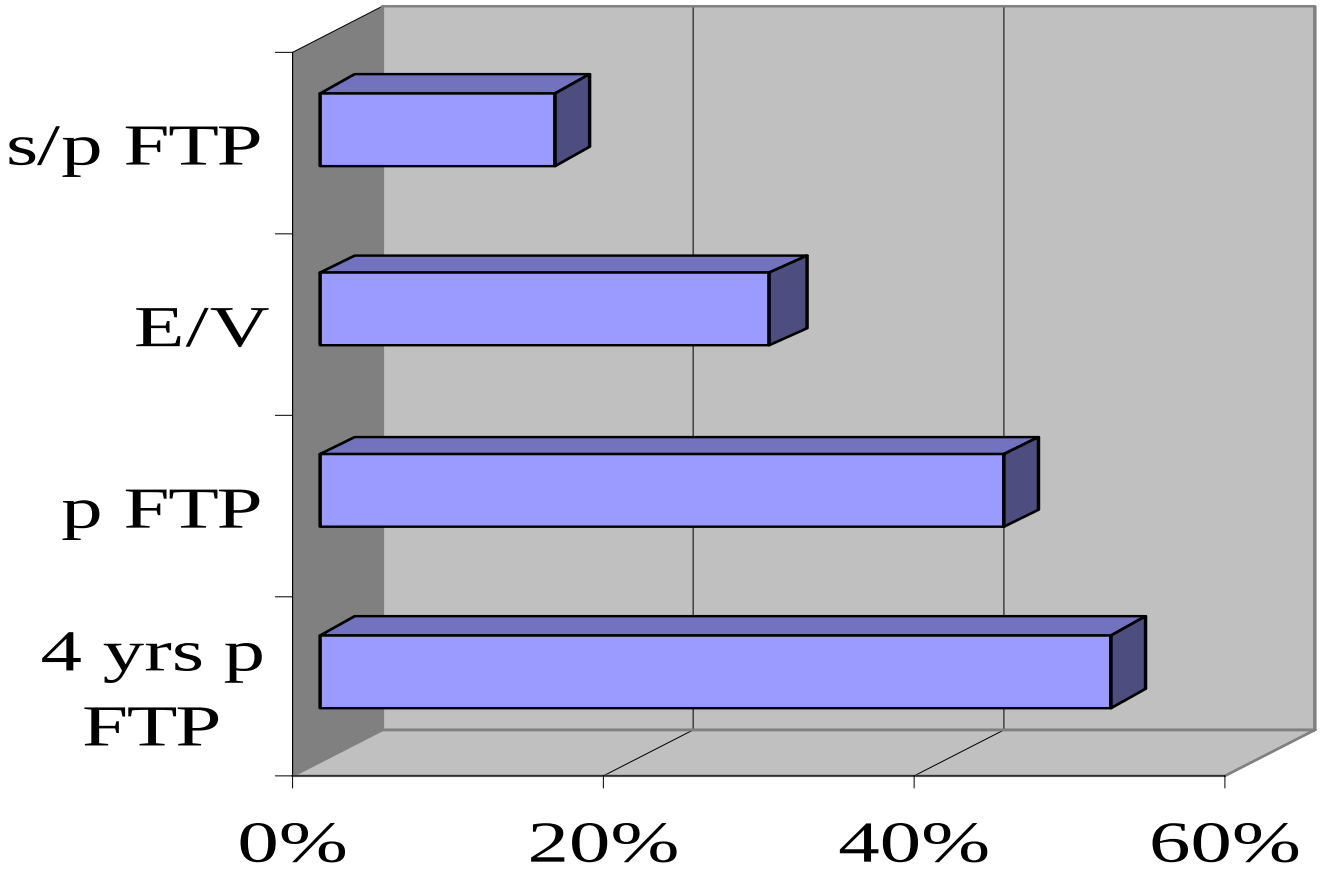
1.44 (1.24-1.68)

…at the 99% CI

PAROUS WOMEN

OC use	Number of Studies	Pooled Odds Ratio
Ever versus Never	14/14	1.29
Prior to FFTP	21/23	1.44
After FFTP	14/14	1.15
4 or more years prior to FFTP	9/10	1.52

Percent Increased Risk in Parous women



Nulliparous Women

OC use	Number of Studies	Pooled Odds Ratio
Ever vs. Never	8/12	1.24
Four or more years	5/8	1.29

Critiques?

- “Premenopausal breast cancer is rare”
- “Oxford said the risk of breast cancer falls to normal after ten years”
- “A pooled analysis needs to be done”

What is the overall cancer risk of oral contraceptives?

Oral contraceptives are known to increase the risk of breast, cervical (and liver cancer), while they protect against uterine and ovarian cancer. So what is the net effect in regard to the overall risk for cancer?

Statistics for the United States

TYPE OF CANCER	NUMBER OF CASES	NUMBER OF DEATHS
BREAST CANCER	**212, 920**	**4 0,970**
CERVICAL CANCER	**9,710**	**3,700**
UTERINE CANCER	**41,200**	**7,350**
OVARIAN CANCER	**20,180**	**15,310**

Statistics from the American Cancer Society, 2006

CUMULATIVE MORBIDITY OF OCP USE PRIOR TO FTP

BREAST CANCER	40% increase	**+85,168**
CERVICAL CANCER	40% increase	**+ 3,884**
OVARIAN CANCER	50% decrease	**- 10,090**
UTERINE CANCER	50% decrease	**- 20,600**
TOTAL		**+58,362**

CUMULATIVE MORTALITY OF OCP USE PRIOR TO FTP

BREAST CANCER	40% increase	**+16,388**
CERVICAL CANCER	40% increase	**+ 1,480**
OVARIAN CANCER	50% decrease	**- 7,655**
UTERINE CANCER	50% decrease	**- 3,675**
TOTAL		**+6,538**

Statistics for Canada

TYPE OF CANCER	NUMBER OF CASES	NUMBER OF DEATHS
BREAST CANCER	22,300	5,300
CERVICAL CANCER	1,350	390
OVARIAN CANCER	2,400	1,700
UTERINE CANCER	4,100	740

Statistics from the Canadian Cancer Society, 2007

CUMULATIVE MORBIDITY OF OCP USE PRIOR TO FTP

BREAST CANCER	40% increase	**+8,920**
CERVICAL CANCER	40% increase	**+ 540**
OVARIAN CANCER	50% decrease	**- 1,200**
UTERINE CANCER	50% decrease	**- 2,050**
TOTAL		**+6,210**

CUMULATIVE MORTALITY OF OCP USE PRIOR TO FTP

BREAST CANCER	40% increase	**+2,120**
CERVICAL CANCER	40% increase	**+ 156**
OVARIAN CANCER	50% decrease	**- 850**
UTERINE CANCER	50% decrease	**- 370**
TOTAL		**+1,056**

Conclusion:

Use of oral contraceptives, especially at an early age is contributing to an increased risk of cancer in women, which may increase as the latent period increases. Doctors need to become aware of this data and women are entitled to it.

To access entire Mayo Clinic article go to:

MayoClinicProceedings.com

(October, 2006)

THANK YOU!