

OVERVIEW: BREAST CANCER AND THE PILLFDA ProceedingsJune 28, 2000Gaithersburg, MD: Holiday InnC. Kahlenborn, MD

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Q1 Is there any evidence that the OCP (oral contraceptive pill) causes breast cancer in animals?

Yes. Concerns were raised in 1972 when it was noted that an oral contraceptive pill containing the artificial hormones mestranol and norethynodrel appeared to cause a case of metastatic breast cancer in a female rhesus monkey [252]. This was especially worrisome since rhesus monkeys rarely develop breast cancer. Until that time, only three cases of breast cancer in rhesus monkeys were reported. Although some argued that this was simply a "chance finding," concern grew further when it was noted that both beagles and rodents developed breast cancer when exposed to the hormones contained in today's OCPs [sources: 267, 268, 255, 313, 254].

Q2 How might OCPs cause breast cancer in humans?

In 1989, Anderson et al [174] published a classic paper regarding the influence of the OCPs on the rate of breast cell division. They found that nulliparous women (ie, women who have not had children) who took OCPs had a significantly higher rate of breast cell division than nulliparous women who did not take them. This was especially important since it is known that in general, cells which divide more rapidly are more vulnerable to carcinogens (ie, cancer producing agents) and thus more likely to become cancerous.

Q3 Do oral contraceptives cause an early abortion and if so, could this also be playing a role in the increased risk of breast cancer?

It is conservatively estimated that a woman who takes the oral contraceptive pill (OCP) will have at least one abortion for every year that she is on it [251]. Both pro-life and pro-abortion groups openly admit that OCPs cause early abortions, with the latter doing so publicly in testimony before the Supreme Court in 1989 {*The New York Times*} [157]. Induced abortion before a woman's first-term pregnancy has been noted to increase a woman's risk of breast cancer by 50% [98]. Could an abortion within the first week of conception have a deleterious effect as concerns breast cancer? The hormonal physiology of early pregnancy is difficult to measure but Stewart et al [240] and Norman et al [361] have shown that estradiol and progesterone levels (ie, the female hormones) start to rise above baseline levels within four days of conception, thus prior to implantation and before HCG levels begin to rise. An early abortion would cause a sudden fall in the levels of these hormones. Could this early "hormonal blow" be playing a role? To this author's knowledge, no one has asked or studied this question.

Q4 Can you give a brief history of the studies that showed a link between the risk of taking OCPs prior to first term pregnancy and the increased risk of breast cancer?

In 1981, Pike et al [138] found that women who took OCPs for four years before their first term pregnancy had at least a 2.25 fold increased risk of developing breast cancer before age 32. This startled the research world and led to additional studies, including a very large American trial

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called the CASH study (ie, Cancer And Steroid Hormone study). In 1993, the CASH study showed that women who took OCPs prior to first term pregnancy and were under 44 years of age had a 40% increased risk in breast cancer, which reached statistically significance in the 35-44 age group [6].

Later in England, Chilvers et al [8] published the results of another large study called the United Kingdom National Study. She showed that young women under the age of 36 who had used oral contraceptives for at least 4 years before their first term pregnancy had at least a 44% increased risk in breast cancer. The last large study was performed in 1995 by Brinton et al [1]. It showed a 42% (raw relative) increased risk for women who used OCPs for more than 6 months prior to having a full term pregnancy.

Q5: If the major studies showed the risks that have been mentioned, then why do doctors and pharmacists fail to inform their patients of those risks?

That is a good question. Major journals and major medical associations (eg, the AMA {American Medical Association}, ACOG {American College of Obstetricians and Gynecologists}, and the AAP {American Academy of Pediatrics}) have failed to stress or properly note this risk. Part of the problem is that because the OCP/breast cancer debate is complicated, most lay people have to rely on what "the experts" tell them.

A good example of this occurred recently in the Oxford study reported in condensed version in *The Lancet* [257] and in complete form in *Contraception* [258]. This study was and remains the largest meta-analysis (ie, a synthesis of all the major studies done in a particular field, concluding in an overall risk for the pooled studies) regarding the studies of OCPs and breast cancer. Researchers from around the world studied and combined the data from 54 studies, involving 25 countries and 53,297 women who had breast cancer. It concluded 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, 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..." Unfortunately, this study is known more for what it did say, than what it did not say! There were several major weaknesses of the study.

Q6: What are the weaknesses of the Oxford study and what implications do they have?

The main weakness was the failure to report any evidence of what the pooled risk of oral contraceptive use before a first term pregnancy was in women less than 45 years old. Another major weakness is that the Oxford study pooled data from studies which looked at women with breast cancer from the early and mid 1970s [258, p5S].

A woman's breast is especially sensitive to carcinogenic influence (ie, cancer producing influence) *before* she has her first child since the breast undergoes a maturing process throughout a woman's first pregnancy. By failing to measure the effect of OCP use *before* a woman's first term pregnancy (FTP), the Oxford study failed to give data on the one group of women who are most likely to get breast cancer from oral contraceptives, namely, those women who used them before their first term pregnancy (eg, many teenagers and women in their twenties).

The second weakness is that the Oxford study used data from older studies which took some of their data from the mid and early 1970s. This does not leave a long enough latent period. A latent period is the time between exposure to a suspected risk factor (eg, early OCP use) and

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the cancer which it increases (eg, breast cancer). Often the latent period between a risk factor and a cancer is 15 to 20 years or more (eg, cigarettes and lung cancer). Although women in the US began taking OCPs in the 1960s, they only began taking them for longer periods of time at younger ages in the 1970s. Thus, only studies which include data from the 1980s and 1990s or beyond would allow a long enough latent period to pick up the influence of early OCP use.

Q7: Why is it important to study women who are under age 45?

Women who are under age 45 are more likely to have used OCPs prior to having a child than women over 45. For example a 55-year old women who had breast cancer in 1990 would have been very unlikely to have taken the OCP for a significant period of time prior to giving birth since OCPs were just coming to the US in the early 1960s when the cited woman would have been in her late 20s.

Q8: What do the four largest retrospective studies**, which take the bulk of their data after 1980, state regarding women who used OCPs prior to first term pregnancy (FTP)?

Table 2A: RISK OF BREAST CANCER IN WOMEN WITH OCP USE PRIOR TO FIRST BIRTH

AUTHOR	YEARS STUDIED	SIZE OF STUDY	FINDINGS
Wingo [6] CASH Study	12/80-82	2089 less than age 45	40% raw increase; ages 20-44
Rosenberg [28A]	1977-1992	1427 less than age 45	88% raw increase*
White [35]	1983-1990	747 less than age {Parous women}	50% increase: for use within 5 years of menarche
Brinton [1]	5/90-12/92	1648 less than 45 years old	42% increased risk*

*Computed from raw data from study, increase reflects the raw relative risk

The four largest studies of women under the age of 45 all show at least a 40% increased raw relative risk for women who took OCPs prior to their FTP or within five years of menarche. Two studies (Rosenberg and Brinton) did not list a formal risk but it was calculated from the data in their paper.

Q9: Has anyone done a meta-analysis that examined the question of risk in women under age 45 who had taken OCPs prior to full term pregnancy?

Yes. Two different researchers have addressed this question. Thomas et al, in 1991, found that women who took OCPs for extended periods of time prior to FTP had a 42% increased risk [184]. A more refined meta-analysis in 1990 by Romieu et al restricted her analysis to those studies done after 1980. The study showed that women under age 45 who had taken OCPs for

four or more years prior to FTP had a 72% increased incidence [RR=1.72 (1.36-2.19)] of breast cancer [55].

Q10: Can you give an overall statement regarding early OCP use and breast cancer?

Yes. If a woman takes the oral contraceptive pill before her first child is born, she suffers a 40% increased risk of developing breast cancer compared to women who do not take the pill. If she takes OCPs for four years or more prior to her first baby, she suffers at least a 72% increased risk for developing breast cancer.

Q11: Are any other groups of women at high risk?

Yes. Women who take OCPs for a **long periods of time** (ie, four years or more) [8,26,34], are at increased risk for developing breast cancer. Other women at risk are **those who use them after age 25** [18,30,33] and **nulliparous women** who use them for a long time (ie, four or more years) [8,27]. All three categories of women seem to be at increased risk, with individual studies ranging from 40% to over 200% increased risk. Women who took OCPs for longer time periods and started using them at an early age appear to be at an even greater risk. *For example, the Brinton study [1] is significant in that she allowed a longer latent period to pass and found a 210% increased risk of developing breast cancer in young women (ie, under age 35) who took OCPs for more than 10 years, if they began taking them before age 18 [RR=3.1 (1.4-6.7)].*

Q12: The studies you cited involved women who were less than 45 years old from data taken after 1980. What will happen to the risk of developing breast cancer for these women as they grow older?

No one knows. It would be wise to learn from history. In the late 1940s an artificial female hormone named DES (Diethylstilbestrol) was given to women to prevent miscarriages. For more than 25 years researchers maintained that DES did not increase the risk of breast cancer in women who took it. Finally, in the 1980s, it was discovered that DES increased breast cancer by about 35%—especially in older women [85]. The truth is, no one knows how dangerous OCPs will be in women as they grow older.

Q-13: It has been noted that OCPs reduce the rate of uterine and ovarian cancer. Is this true?

Yes, it is true. However it must be noted that OCPs also increase the risk of cervical and liver cancer [215A, 215B, 264]. For example the largest study to date, performed by the World Health Organization, examined over 2,300 women and found that use of the pill before age 25 increased the risk of invasive cervical cancer by 45% [229D]. In addition, more women get breast cancer in the US, than all of the other alluded to cancers combined, making this the most dangerous risk in western countries. Oral contraceptives may be particularly risky in **Asian and African countries where cervical and liver cancer is are prevalent** [224B, 301].

Q14: Often women who have painful menstrual cycles are placed on OCPs. Are there medical alternatives with less risks than the OCP?

Menstrual cramps can be controlled by other less harmful drugs called non-steroidals such as naproxen or ibuprofen, alone, or in combination with acetaminophen.* Other doctors treat cramps by encouraging women to take 1,000 mg of calcium and the RDA (recommended daily allowance) of magnesium directly before and during menstruation. Conversely, *The Journal of Adolescent Medicine* published a case report of a young lady who experienced a 90% reduction in her cramping symptoms when taking nicardipine for relief of her menstrual cramps [344]. Nicardipine is a type of calcium channel blocker that is used for treating hypertension.

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