

## ***Overview: Breast Cancer and the Pill***

### ***Q-A: What is an oral contraceptive pill?***

An oral contraceptive pill is usually a combination of a synthetic estrogen and progestin (ie, the two major types of female hormones) which women take for 21 days out of a 28-day cycle. These hormones work by suppressing, but not eliminating ovulation, thickening cervical mucus, and by changing the lining of the uterus.

### ***Q-B: Is there any evidence that OCP (oral contraceptive pill) use 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 group of six female rhesus monkeys [1]. This was especially worrisome because 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: 2, 3, 4, 5, 6].

### ***Q-C: How might OCP use cause breast cancer in humans?***

In 1989, Anderson et al [7] published a classic paper regarding the influence of OCP use 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 because it is known that in general, cells that divide more rapidly are more vulnerable to carcinogens (ie, cancer producing agents) and thus more likely to become cancerous.

### ***Q-D: Does OCP use cause an early abortion and if so, could this also be playing a role in the increased risk of breast cancer?***

Both pro-life and pro-abortion groups openly admit that OCP use causes early abortions, with the latter doing so publicly in testimony before the Supreme Court in 1989 [8]. Induced abortion before a woman’s first full-term pregnancy (FFTP) has been noted to increase a woman’s risk of breast cancer by 50% [9]. Could an abortion (defined to be the death of the zygote, embryo or fetus after conception has occurred) within the first week after conception have a deleterious effect as concerns breast cancer? The hormonal physiology of early pregnancy is difficult to measure but Stewart et al [10] and Norman et al [11] have shown that estradiol and progesterone levels (ie, the female hormones) start to rise above baseline levels within 4 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.

***Q-E: Can you give a brief history of the studies that showed a link between OCP use prior to a first full-term pregnancy (FFTP) and the increased risk of breast cancer?***

In 1981, Pike et al [12] found that women who took OCPs for 4 years before their first full-term pregnancy (FFTP) had at least a 2.25-fold (125%) increased risk of developing breast cancer before the age of 32. This startled the research world and led to additional studies, including a very large American trial called the CASH study (ie, Cancer And Steroid Hormone study). In 1993, the CASH study showed that women who took OCPs prior to their FFTP and were under 44 years of age had a 40% increased risk of breast cancer, which reached statistical significance in the 35 to 44 year-old age group [13].

Later in England, Chilvers et al [14] 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 FFTP had at least a 44% increased risk in breast cancer. The last large study was performed in 1995 by Brinton et al [15]. It showed a 42% increased risk for women who used OCPs for more than 6 months prior to their FFTP.

***Q-F: 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], the 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 people have to rely on what “the experts” tell them.

A good example of this occurred recently in the Oxford study reported in a condensed version in *The Lancet* [16] and in complete form in *Contraception* [17]. 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.

***Q-G: 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 [17, p.5S].

A woman's breast is especially sensitive to carcinogenic influence (ie, cancer producing influence) *before* she has her first child because the breast undergoes a maturing process throughout a woman's first pregnancy. By failing to measure the effect of OCP use *before* a premenopausal woman's first full-term pregnancy (FFTP), 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 FFTP (eg, many teenagers and women in their 20s).

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 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 U.S. 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.

***Q-H: Why is it important to study women who are under the age of 45?***

Women who are under the age of 45 are more likely to have used OCPs prior to having a child than woman over the age of 45. For example a 55-year old woman 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 because OCPs were just coming to the U.S. in the early 1960s when the cited woman would have been in her late 20s.

***Q-I: What do the four largest studies, which take the bulk of their data after 1980, state regarding women who used OCPs prior to their first full-term pregnancy (FFTP)?***

**Table 3A: RISK OF BREAST CANCER TO WOMEN WITH OCP USE PRIOR TO THEIR FFTP**

AUTHOR	YEARS STUDIED	SIZE OF STUDY	FINDINGS
Wingo [13]	12/80-82	2089 less than age 45	40% increase; ages 20-44
Rosenberg [18]	1977-1992	1427 less than age 45	88% increase*
White [19]	1983-1990	747 less than age 45	50% increase: use 5 years of menarche
Brinton [15]	5/90-12/92	1648 less than age 45	42% increased risk*

\*Computed from data from study, increase reflects the odds ratio.

The four largest retrospective studies\*\* of parous women under the age of 45 all show *at least a 40%* increased risk for women who took OCPs prior to their FFTP or

within 5 years of menarche. Two studies (Rosenberg and Brinton) did not list a formal risk but it was calculated from the data in their paper.

**\*\***An example of a retrospective study is one in which women with breast cancer would be interviewed and asked questions about their risk factors such as family history, OCP use, induced abortion, etc.

***Q-J: Has anyone done a meta-analysis of retrospective studies that examined the question of risk to women under the age of 45 who had taken OCPs prior to their FFTP?***

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 their FFTP had a 44% increased risk [ $RR=1.44$  (1.23-1.69)] [20]. 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 the age of 45 who had taken OCPs for 4 or more years prior to their FFTP had a 72% increased incidence [ $RR=1.72$  (1.36-2.19)] of breast cancer [21].

***Q-K: Can you comment on why a recent large study published by researchers at Harvard claimed to show no increased risk of developing breast cancer in women who had taken OCPs for 5 years or more prior to their FFTP?***

In 1997, a group of researchers at Harvard Medical School led by Dr. Hankinson published a study in *Cancer Causes and Control* [22]. It based its conclusions on data taken from the Nurses' Health Study and *claimed* to show that women who took oral contraceptive pills for 5 years or more prior to their FFTP had no increased risk of developing breast cancer compared to women who never took OCPs [ $RR=0.57$  (0.24-1.31)]. The study's conclusions appear to have been based on a flawed analysis.

***Q-L: Can you describe the problems with the study?***

Yes. The researchers compared women with breast cancer who took OCPs for 5 years or more prior to their FFTP [let's refer to these women as Group A] to women with breast cancer who never took OCPs [Group B].

It is known that women took OCPs *for longer periods of time and earlier in their reproductive lives* in the 1980s and 1990s than in the 1960s and 1970s as was clearly noted in the Oxford study [17, p.9S; Tables 14, 15]. So any group of women who had taken OCPs for 5 years or more prior to their FFTP (ie, Group A) *would have been more likely to have done so while in their late teens and 20s in the 1980s or 1990s*, whereas women in Group B (who never took OCPs) *would be more likely to contain a distribution of women who would have been in their late teens and 20s in either the 1960s, 1970s, 1980s or 1990s. But this strongly supports the contention that women in Group A would have a lower average age and a shorter follow-up time than the women in Group B, which would of course invalidate the study's conclusions.*

It is frightening to note that the Harvard team presented **no data** on *either the average age of women in the noted groups or their respective lengths of follow-up time. The research team instead chose to follow the noted groups in "person-years" as their measure of follow-up time.* This is the length of a follow-up period derived from the number of women followed, multiplied by the average number of years they were followed. For example, if group A had 100 women who were followed for 10 years, the total amount of follow-up time would be  $100 \times 10 = 1,000$  person-years. But if group A had 250 women who were followed for 4 years it would also have 1,000

person-years of follow-up. This is totally inadequate because the measure of “person-years” gives no data on the length of follow-up time *in actual years* and without this information the study must remain suspect *because it was noted that women in group A most likely had both a younger average age and were followed for a shorter period of time than the women in group B.*

***Q-M: Is there any way that the public will ever have access to the necessary data that was not presented in the Harvard study?***

I am not sure. This author tried in vain to obtain the answers to three basic questions over a 6 month period of time from three different researchers involved in the Harvard study via e-mail, phone calls and certified mail. It is ironic that one cannot access data from these researchers especially because their study obtained its data from the Nurses’ Health Study, *a study which was funded by citizen tax dollars through a grant via the NCI (National Cancer Institute).* The essential questions that need to be answered are presented at the end of this chapter. If the Harvard team had answered these questions the average age and follow-up time period for both Group A and Group B’s women could have been easily calculated. Until the noted researchers at Harvard make their data available *for all* to see, the study’s conclusions must remain suspect.

***Q-N: Have any other recent studies had methodological problems?***

Yes, a large prospective study conducted in England by Beral et al [23] claimed that a “cohort” (ie, the group being examined in a prospective study) of 23,000 women who took the OCP had no greater risk of developing breast cancer than 23,000 women who did not take it. The main problem with the study is that women entered it from 1968 to 1969. But many of these women were taking OCPs *after* they had a FFTP because as we noted earlier, women took OCPs *for shorter periods of time and later in their reproductive lives* in the 1960s and 1970s than in the 1980s and 1990s [17]. The study’s claim that OCP use had no long-term risk of increasing breast cancer cannot be applied to the subset of women who took (or currently take) OCPs for longer periods of time prior to their FFTP.

***Q-O: Can you give an overall statement regarding early OCP use and breast cancer?***

Yes. If a woman takes the oral contraceptive pill before her FFTP, she suffers a 40% increased risk of developing breast cancer compared to women who do not take OCPs. If she takes OCPs for 4 years or more prior to her FFTP, she may have an even higher risk, as noted by Dr. Romieu earlier.

***Q-P: Are any other groups of women at high risk?***

Yes. Women who take OCPs for *long periods of time* (ie, 4 years or more) [14,24,25], are at increased risk for developing breast cancer. Other women at risk are *those who use them after the age of 25* [26,27,28] and *nulliparous women* who use them for a long time (ie, 4 or more years) [14,29]. 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 [15] is significant in that it allowed a longer latent period to pass and found a 210% increased risk of developing breast cancer in young women (ie, under the age of*

35) who took OCPs for more than 10 years, if they began taking them before the age of 18 [RR=3.1 (1.4-6.7)].

**Q-Q: *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 use did not increase the risk of breast cancer in women who took it. Finally, in the 1980s, it was discovered that DES use increased breast cancer risk by about 35% — especially in older women [30]. A similar phenomenon may be occurring with OCPs. The truth is, no one knows how dangerous OCP use will be for women as they grow older.

**Q-R: *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 [31, 32, 33]. For example the largest study to date, performed by the World Health Organization, examined over 2,300 women and found that use of OCPs before the age of 25 increased the risk of invasive cervical cancer by 45% [34]. In addition, more women get breast cancer in the U.S. 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 are prevalent* [34, 35, 36].

**Q-S: *Often women who have painful menstrual cycles are placed on OCPs. Are there medical alternatives with less risks than OCPs?***

Menstrual cramps can be controlled by less harmful drugs than OCPs. For example, taking 1,000 mg of Calcium and 399 mg of Magnesium around the time of a woman's onset of menstrual bleeding appears to help with menstrual cramps and migraine headaches. In addition, taking high dose anti-inflammatory agents (eg, ibuprofen) *after* one's menstrual flow has started (and under a doctor's care) will often give relief. Also, 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 *after* her menstrual cramps had begun [37]. Nicardipine is a type of calcium channel blocker that is used for treating hypertension.

**Q-T: *What about the risk of "low dose" progestin containing contraceptives such as "the minipill," or long-acting progestins such as Norplant or Depo-Provera?***

Skegg et al [38] pooled the data from the World Health Organization (WHO) and New Zealand studies, *the two largest studies that looked at women who took Depo-Provera* (active ingredient is DMPA: depot-medroxyprogesterone acetate) for long periods of time. He found that women who had taken DMPA for between 2 and 3 years before the age of 25 had a *310% statistically significant risk* of getting breast cancer [RR=4.1 (1.6-10.90)] whereas women who had taken DMPA for more than 3 years prior to the age of 25 had at least a *190% increased risk*, that was also significant [RR=2.9 (1.2-7.1)]. The risks for long-term Norplant use in young women could be just as high as for Depo-Provera users, although widespread tests have not

been done because Norplant was developed later than Depo-Provera. In regard to the progestin containing “minipill,” the Oxford study noted an overall increased risk of 19% (ie,  $RR=1.19$  [0.89-1.49]) in women who had taken minipills for 4 or more years, but they said nothing about extended use in young women, especially women who took them prior to their FFTP [17, p.98S]. The latter group of women might be at an especially increased risk.

***Q-U: How do the natural means of regulating birth compare to the artificial means?***

Several well-designed trials by the World Health Organization have shown that Natural Family Planning (NFP) (ie, methods for determining when a woman is most fertile or infertile, based on qualitative observations of cervical mucus and, for some NFP methods, measuring basal body temperature) has had an effectiveness rate when used correctly that is better than OCPs, that is, less than a 3% rate of pregnancies per year. These trials have been done in both modern and less advanced countries and have shown low annual pregnancy rates: the United Kingdom — 2.7% [39], Germany — 2.3% [40], Belgium — 1.7% [41], and India — 2.0% [42]. *One of the largest trials (of 19,843 women performed by the World Health Organization in India) showed the failure rate to be 0.2 pregnancies per 100 women yearly — a rate that is significantly better than almost all artificial methods of contraception [43].* (For more information regarding NFP see end of bibliography).

***Q-V: How can the above noted information be verified?***

Go to the nearest medical library — nearly every hospital has one — and ask the librarian to help look up the medical references of interest.

***Q-W: What are the three questions never answered by the Harvard study?***

The researchers at Harvard have never answered the following simple questions:

- 1) How many women were there in the group who were under the age of 45 and who used OCPs for 5 years or more prior to their first full-term pregnancy (FFTP) (see page 69, Table 3 of your paper [ie, the women who were followed for 9,741 person-years]). What was the mean age for the women in this group?
- 2) How many women were there in the group who were under the age of 45 and never used OCPs? (see Table 2 page 68, these women were followed for 176,306 person-years). What was their mean age?
- 3) How many women were in the group who were under the age of 45 and had used OCPs for 10 years or more of total duration? (see Table 2, p. 68, the group that had 21,760 person-years of follow-up)

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For more information on NFP call or write to:

The Couple to Couple League	1-513-471-2000
Pope Paul VI Institute	1-402-390-6600
Family of the Americas	1-800-443-3395
Billings Ovulation Method Association	1-888-637-6371
The St. Augustine Foundation	1-877-554-4637
NW Family Services	1-503-215-6377