

FEATURE ARTICLE

Hormonal Contraception and Breast Cancer: Convincing New Conclusions

There have been suspicions for many years that use of hormonal contraception is linked to an increased risk of breast cancer. These suspicions have been fueled by the fact that widespread use of hormonal contraceptives, particularly oral contraceptives (OCs), has paralleled an increased incidence of breast cancer in many countries. Increasing evidence that breast cancer is hormonally mediated has heightened concern about a possible link.

Yet the numerous investigations of possible OC/breast cancer associations that have been carried out around the world have not provided conclusive answers. In general, these studies have been characterized by weak, sometimes conflicting associations. Some studies have shown an increased risk of breast cancer with OC use before first pregnancy and with long duration of use, but other studies have not shown these increased risks. The inconsistent results have been linked to a variety of factors, including the changing regimens and patterns of OC use over the past 30 years, different methodologies and subject populations among various studies, and other factors.

This article summarizes the results of the Collaborative Group on Hormonal Factors in Breast Cancer study that aimed to answer some of the questions raised by previous studies. The collaborative analysis involved data from multiple studies that together represented about 90 percent of the epidemiological information on the topic. The size of the study allowed for a broad range of analyses, including analyses of specific subgroups (for example women who used OCs for a few years at a relatively young age) that have not been possible in most previous studies.^{1, 2}

TABLE 1

Relative Risks of Breast Cancer and Years Since Last OC Use

Years Since Last Use	Relative Risk	99% Confidence Interval
Current use	1.24	1.20 - 1.28
1-4 years	1.15	1.12 - 1.18
5-9 years	1.07	1.05 - 1.09
10-15 years	0.98	0.96 - 1.00
15-19 years	1.01	0.98 - 1.04

Source: Collaborative Group on Hormonal Factors in Breast Cancer, 1996.¹

Overall, the collaborative study found that women who had ever used OCs had a very slight increased risk of breast cancer compared with never-users. The risk was confined to current users and those who had used hormonal contraceptives within 10 years. The only subgroup that appeared to be at a somewhat higher risk than others was women who started using hormonals at a very young age—before age 20. The majority of excess risk appeared to be associated with tumors that had not spread beyond the breast, rather than metastasized cancers.

The Collaborative Study

The collaborative study involved a compilation of individual data on 53,297 women with breast cancer and 100,239 controls from 54 studies in 25 countries. Most of the studies were from Europe and North America, but Asia, Africa, and Latin America also were represented. All analyses were stratified by study, age at diagnosis, parity, and other factors as appropriate. The median age of diagnosis was 49 years. The vast majority of cases and controls used combined OCs. Progestin-only OCs were used by only 0.8 percent of study population (1,253); progestin-only injectables by 1.5 percent (2,274).

The collaborative study found an overall relative risk of cancer associated with ever use of OCs of 1.07 (all relative risks cited were statistically significant unless stated otherwise). Current users and those who had used hormonal contraceptives within 10 years were at slightly increased risk, though risk declined progressively with time since last use and disappeared after 10 years (see Table 1). No significant variations in risk were found among women with different background risks, including women from different countries or ethnic groups and women with different reproductive histories.

Women who started using OCs before age 20 had a higher relative risk of breast cancer within five years of use than those who started later (see Table 2).

Even among women who use OCs throughout their 20s, however, models suggest little difference in breast cancer incidence compared with non-users because of the low background incidence of breast cancer in this group. Among women who use OCs from age 25 to 29, for example, the incidence of breast cancer is very similar to that of non-users through age 40 (see Figure 1).

Among women who use OCs until their 30s or 40s, the incidence of breast cancer could be slightly elevated compared with non-users in the same age groups (even though the relative risk of breast cancer is lower among women who used OCs at older ages compared with women who used OCs in their 20s). This is because the baseline incidence of breast cancer in older women is higher, particularly in developed countries. In developed countries, the excess number of cases among women who used OCs until age 40 was estimated to be 19 per 10,000 at age 50 and 14 per 10,000 at age 60. In developing countries, the excess number of cases among the same group was estimated to be 8 per 10,000 at age 50 and 5 per 10,000 at age 60.

The collaborative study found that the increased risk of breast cancer associated with current or recent use of OCs was primarily for localized tumors. In fact OC use was associated with a decreased risk of tumors that spread beyond the breast to auxiliary lymph nodes (relative risk 0.89) and to more distant sites (relative risk 0.70). This effect extended up to 20 years after discontinuation of OCs. One possible explanation for this finding is that breast cancer may be more frequently diagnosed early in OC users. Another possibility is that OCs may promote the growth of existing tumors, rather than their likelihood to metastasize.

Although there were few data for hormonal methods other than OCs, the collaborative study results suggest that breast cancer risks also are very low for progestin-only pill and injectable users (no

TABLE 2

Relative Risk of Breast Cancer Among Young Women According to Years Since Last OC Use

Years Since Last Use	Age at First Use			
	≤17	18	19	20
Current Use	1.6*	1.39*	1.81*	1.27*
1-4 years	1.88*	1.33*	1.38*	1.09
5-9 years	0.97	1.11	1.09	1.03

* Statistically significant, p<0.01.

Source: Collaborative Group on Hormonal Factors in Breast Cancer, 1996.¹

What Are the Risks?

The Collaborative Group on Hormonal Factors in Breast Cancer study is being viewed by many experts as a landmark study with broadly applicable results.³ Seven key questions about hormonal contraception and breast cancer are answered below based on results of the study.

Are hormonal methods associated with an increased risk of breast cancer?

Women currently using OCs and those who had used OCs within the past 10 years were at a very small increased risk of breast cancer—relative risks ranged from 1.25 for current use to 1.07 for use within 10 years.

Are hormonal methods associated with a long-term or permanently increased risk of breast cancer?

No, the increased risk of breast cancer associated with OC use disappeared 10 years after last use.

Are specific hormones or formulations linked to breast cancer risk?

No, there appeared to be no specific risk with estrogen or progestin type, formulation, or dose.

Are any specific delivery systems for hormonal methods linked to breast cancer risk?

No, oral contraceptives (combined and progestin-only) and injectable contraceptives appeared to have similar risk patterns.

Is duration of use a significant factor?

No, there appeared to be no specific link between cancer risk and duration of use.

Are particular women or patterns of use linked to risk?

Women who used OCs before age 20 were at a somewhat increased risk of breast cancer compared with older users, but this excess risk disappeared within 5 years of last use. No other subgroup of women or use pattern was linked to increased risk.

What types of breast cancer are associated with OC use?

The excess of breast cancer among hormonal users appeared to be limited to localized tumors, which generally have a better prognosis for cure than tumors that have spread beyond the breast. The association between OC use and localized tumors extends up to 20 years beyond last use.

Is OC use associated with an increased incidence of breast cancer?

This depends upon the average age of last use of OCs among a population. If most women use OCs in their 20s, very few excess cases of cancer will occur among users because of the low baseline incidence of breast cancer. If more women in their 30s or 40s use OCs, more excess cases will occur because the baseline incidence of breast cancer is higher.

data were available for implants or for combined injectables). In summary:

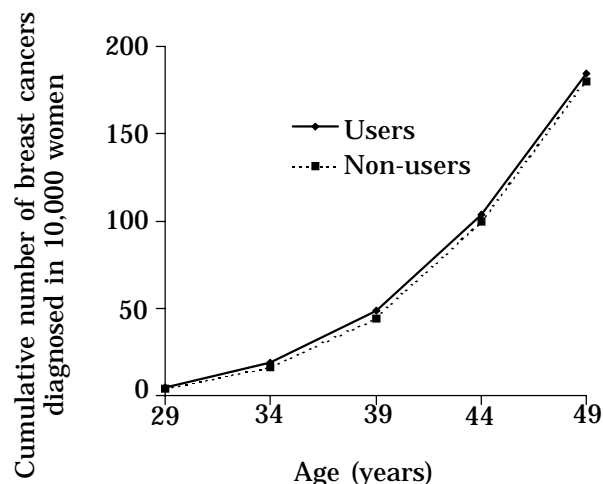
- progestin-only pills were associated with a relative risk of breast cancer of 1.17 within 5 years of use; within 10 years of use there was no increased risk (relative risk 0.99).
- progestin-only injectables were not associated with an increased risk of breast cancer within five years of use (non-statistically significant relative risk 1.17) or within 10 years of use (relative risk 0.94).

Program Implications

What are the implications of the collaborative study for health policy makers and program managers? In short, the very slight association between OC use and breast cancer must be viewed in the context of the significant health advantages of OCs—including effective pregnancy prevention, protection against ovarian and endometrial cancer (users have as much as a 50 percent reduction in risk), and protection against other women's health concerns (dysmenorrhea, ectopic pregnancy, ovarian cysts, anemia), as well as some of the cardiovascular risks associated with OC use (see *Outlook*, Volume 11, Number 3). For most women, the benefits far outweigh the risks. In developing countries, where pregnancy-related health risks are often high, the benefits of OC use are even more clear.⁴

FIGURE 1

Estimated Cumulative Number of Breast Cancers Diagnosed in Never-Users and in Women Who Used OCs from Age 25 to 29: Data from Europe and North America



Source: Collaborative Group on Hormonal Factors in Breast Cancer, 1996.²

At the same time, it is important that key groups—providers, potential clients, women’s groups, and others—be accurately informed about the study results, highlighting that (1) the study suggests that OCs are associated with a very slight increased risk among current users of OCs and those who have used the method within the past 10 years; (2) the increase in risk results in a very small number of excess breast cancer cases, even among women in developed countries where breast cancer incidence is high; and (3) the tumors found to be associated with OC use tend to be localized, more readily treatable tumors.

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SAFETY

Hormonal Contraception and Cervical Cancer

Does use of hormonal contraceptives affect a woman’s risk of cervical cancer? While studies addressing this question have produced varying results, several relatively recent studies confirm that there may be a slight association between use of some hormonal contraceptives and cervical cancer, but the link appears to be small and reversible. Evaluating results of research on this issue is challenging because numerous factors may influence development of cervical cancer, and the disease develops over a long time period. Furthermore, in some settings, hormonal contraceptive users are more likely to have Pap smears, resulting in detection bias (see *Outlook*, Volume 6, Number 2).

Cervical cancer is the leading cause of death from cancer among women in developing countries. The disease generally progresses slowly, starting with mild cervical dysplasia (a precancerous condition that regresses in about 60 percent of cases). In some

cases, it advances to severe dysplasia or carcinoma *in situ* (CIS)—treatable precursors of invasive disease—and eventually to invasive carcinoma. The primary underlying cause of cervical cancer is human papilloma virus (HPV), a sexually transmitted infection. Other factors that may influence whether a woman is likely to develop cervical cancer include tobacco use, nutritional status, and some hormonal factors, such as parity. Most other factors identified as associated with cervical cancer—for example, age at first intercourse and number of sexual partners—are most likely indicators of risk of HPV exposure rather than independent risk factors. Cervical cancer can be largely prevented by periodic Pap smear screening and treatment of precancerous lesions.¹

Risk Among Oral Contraceptive Users

Results of two recent long-term studies suggest that OC users may have a slightly elevated risk of cervical cancer or its precursors, adding support to earlier studies suggesting an association.

The WHO Collaborative Study of Neoplasia and Steroid Contraceptives analyzed data gathered between 1979 and 1988 on two types of cervical cancer from 11 hospitals in 9 countries. The analysis of squamous cell cervical carcinoma—the most common form of cervical cancer—involved 2,311 cases and 13,644 controls and was adjusted for various confounding variables. The study found a statistically significant increased relative risk of invasive squamous cell cervical cancer of 1.31 among ever-users of OCs. Risk was highest among women who had used OCs for four or more years and declined in the eight years after last use to that of non-users² (see Table 1). A second analysis evaluated possible links between OC use and adenomatous cervical cancer—a rarer cancer of the glandular epithelial cells; the relative risk among ever-users of OCs was 1.5 (95% confidence interval [CI] 1.1-1.9). Risk increased with duration of OC use and young age (< age 25) at first use. Risk was highest in recent and current users, and declined with time since last use.³ Another analysis of the WHO study data evaluated the link between OC use and carcinoma *in situ*—the precursor of invasive cancer. The analysis found an increased risk of CIS among OC users, but could not rule out detection bias as a factor in the result.⁴

An analysis of data from the Oxford Family Planning Association contraceptive study, which has followed a cohort of 17,032 women recruited at family planning clinics in England and Scotland between 1968 and 1974, found a possible effect of OC use on the later stages of cervical carcinogenesis among recent, long-term users.⁵ Some 310 cases diagnosed before age 45 were compared with almost

TABLE 1

**Relative Risk of Invasive Cervical Cancer
and Time Since Last OC Use**

Months Since Last Use	Relative Risk	95% Confidence Interval
Current	1.04	0.83-1.31
2-12	3.34	2.69-4.13
13-36	1.55	1.22-1.97
37-96	1.21	1.02-1.44
97-156	1.11	0.94-1.31
≥157	1.14	0.97-1.34

Source: WHO, 1993.²

3,000 controls. After adjusting for social class, smoking, age at first birth, and ever use of a diaphragm and condom, ever-users of OCs had a slightly higher overall risk of cervical cancer compared with never-users (odds ratio [OR] 1.40, CI 1.00-1.96). Odds ratios were highest for invasive carcinoma (OR 4.44, CI 1.04-31.6). Total duration of OC use was not a strong independent risk factor and cancer risk decreased with increasing time since last use. Highest risks were observed for current or recent users of OCs (last use within 24 months) who had used OCs for a total of 49 months or more. While the authors believe the results are unlikely to be affected by detection bias, they could not rule out confounding due to some other factors, including HPV infection.

Adding further support to a possible association, a study of 197 cases of confirmed cancer found that women who had used OCs were more likely to test positive for HPV DNA.⁶ Although based on a small number of women, the results hint at a possible interaction between HPV infection, cervical cancer development, and OC use. The possibility that OC use enhanced HPV detection could not be ruled out.

Injectable Contraceptives

The WHO Collaborative Study also analyzed data on use of the progestin-only injectable DMPA and cervical cancer risk. Overall, the study found no association between use of DMPA and risk of invasive cervical cancer.^{7, 8} Data were from three hospitals in Thailand, one in Mexico, and one in Kenya. A separate analysis of data from the study, however, found that DMPA users may have a slightly increased risk of CIS, the precursor to invasive cancer.⁹ After adjusting for various confounding variables, DMPA users had a relative risk of CIS of 1.43 (CI 1.22-1.67) compared to non-users; the risk appeared to decline with time since last use. The researchers concluded that the increased risk of CIS found in this analysis could be

Does Use of Barrier Methods Protect Against Cervical Cancer?

While condoms, diaphragms, and spermicides protect users against some STDs (see *Outlook*, Volume 12, Number 4 and Volume 11, Number 4), results of studies on their effect on cervical cancer risk and HPV infection have been mixed. Some studies suggest a protective effect. For instance, a US case-control study of moderate to severe dysplasia found an adjusted odds ratio of 0.5 (CI 0.2-0.9) for ever-use of barrier methods (condom, diaphragm, or spermicide). When the methods were analyzed separately (but not adjusted for number of partners), only condoms and diaphragms were protective.¹⁰ An Italian case-control study found that ever-use of condoms or diaphragms was protective against invasive cancer (relative risk 0.4, CI 0.2-0.9) and against dysplasia (relative risk 0.6, CI 0.4-1.02) when adjusted for confounding factors. Neither effect was significant if duration of use was less than two years.¹¹ The WHO Collaborative Study found that, in Thailand, women's risk of cervical cancer was associated with their husbands' lack of use of condoms with prostitutes.³

In contrast, a case-control study in Mexico, Costa Rica, Panama, and Colombia found no association between invasive cervical cancer and condom use.¹² A nested case-control study within a population-based study of 1,247 women in Greenland and Denmark found that ever-use of barrier methods offered no protective effect against infection with two types of HPV.¹³ The Oxford Family Planning Association study described on page 4 found no protective effect of condoms, although diaphragm use was associated with a protective effect.⁵

These conflicting results are not surprising given that HPV is a very common infection that is not curable; inconsistent short-term use of barrier methods would likely provide little protection. Furthermore, the virus can infect anogenital tissue not covered by condoms.

an artifact due to uncontrolled confounding or unidentified sources of bias or could represent the induction of a condition that is reversible or does not proceed to invasive disease. Nevertheless, they recommend that DMPA users receive periodic Pap smears, where available. There currently are no data on any association between use of combined injectable contraceptives and cervical cancer. Analysis of limited data from Mexico and Chile did not reveal a link between use of monthly estrogen/progestin injectables and risk of cervical cancer.¹⁴ The study

authors noted that additional data were required to confirm this finding, however.

Program implications

Given the possible small increased risk of cervical cancer or its precursor conditions among OC users and the increased risk of CIS among women using DMPA, wherever possible, women using these methods should be screened using a Pap smear. Because cervical cancer develops slowly, screening strategies should focus on achieving a wide coverage rather than on a high frequency of screening. Screening at-risk women at least once in their lifetime would be a good initial goal for programs with limited resources. In low-resource settings, treatment should focus on high-grade dysplasia, with follow-up mechanisms in place for women with lower-grade lesions.¹ In addition, because risk of cervical cancer is so strongly linked to infection with HPV, all women should be advised to limit their exposure to the virus by limiting the number of their sexual partners and choosing a partner who has limited the number of his sexual partners. Correct, consistent use of barrier methods of contraception may provide some protection.

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Abortion and Breast Cancer

Although it has been the subject of extensive research, there is no convincing evidence of a direct relationship between breast cancer and either induced or spontaneous abortion. Available data are inconsistent and inconclusive, with some studies indicating small elevations in risk, and others showing no risk associated with either induced or spontaneous abortions. The scientific rationale for an association between abortion and breast cancer is based on limited experimental data in rats, and is not consistent with human data.

Studies that have attempted to evaluate the association between abortion and breast cancer have been limited by small numbers of study subjects, questions of comparability between the study groups, inability to separate induced abortions and spontaneous abortions, and incomplete knowledge of other potentially pertinent lifestyle factors. Perhaps the most serious potential weakness relates to the possible inaccuracy of reporting of abortions by study participants. Indeed, results from a study that examined the accuracy of reporting abortions indicate that women with breast cancer are more likely to accurately report having had an abortion than women without breast cancer, possibly leading to a false association between abortion and breast cancer.

Results of a 1994 U.S. study illustrate the difficulty of drawing conclusions. The study assessed the relationship between breast cancer and abortion in young women.¹ The results, based on self-reports of abortion, indicate that induced abortion was associated with 1.5 times the average risk of developing breast cancer. Some inconsistencies in the finding of the study were puzzling, however, as risk did not vary consistently with number of abortions, woman's age at abortion, or length of pregnancy, nor did the study show an increase in risk associated with spontaneous abortions.

An accompanying commentary concluded that, "While the [study] findings add to the limited evidence that induced abortion increases the risk of breast cancer, neither a coherent body of knowledge nor a convincing biologic mechanism has been established."² At the time of publication, the National Cancer Institute also released a press statement regarding the article, concluding that the inconsistencies and scarcity of available research results did not permit scientific conclusions.

A 1996 study carried out in the Netherlands found almost a twofold increased risk for breast cancer after an induced abortion.³ However, the investigators suggested that this figure may have been influenced by reporting bias attributed to the underreporting of abortions by healthy control subjects in the largely Catholic southeastern region of the Netherlands. In the western regions of the country, the association between abortion and breast cancer was statistically insignificant. The authors concluded that their "study does not support an appreciably increased risk for breast cancer after an induced abortion."³

The most recent study of this issue provides important new evidence to resolve the controversy. A large-scale Danish epidemiologic study found that the risk of developing breast cancer for women with a history of induced abortion was no different than the risk for women without such a history.⁴ The study relied on uniformly collected data on abortion in Danish registries before the diagnosis of breast cancer was made, thus avoiding the reporting bias of previous studies in which women may have been more likely to provide an inaccurate history of their abortions depending on whether or not they had breast cancer.

Even though most women will base their decision about whether to have an induced abortion on other factors, it is reassuring for women and providers alike to know that having an abortion does not appear to be associated with later adverse health effects.

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EDITOR'S NOTE: This article was adapted from the February 7, 1997, U.S. National Cancer Institute (NCI) press release series, *Cancer Facts, on Abortion and Breast Cancer*. More information on the topic can be obtained from the NCI Cancer Information Service.

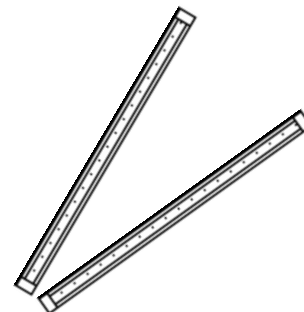
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REGULATION



U.S. Approves Implant, Availability Unclear

Women interested in using contraceptive implants, but who do not want the six-capsule Norplant® System, may have a new contraceptive option in the future. In August 1996, the U.S. Food and Drug Administration approved a two-rod levonorgestrel system (LNG Rod) as safe and effective for three years of contraceptive use. The new LNG Rod system has some significant advantages over the Norplant® System, but it currently is unavailable.

The LNG Rod system consists of two rods about the same diameter (2.5 mm) as a Norplant® capsule and 1 cm longer (4.3 cm). The rods release 30 micrograms/day of levonorgestrel over the three-year period. The LNG Rod system was developed by the Population Council. It is manufactured by Leiras Oy of Finland.

Recently published results of randomized clinical trials comparing the LNG Rod to the Norplant® System in seven countries (developed and developing countries) found the 2-rod system was as effective as the Norplant® System at three years of use.¹ No pregnancies occurred among the 1,198 women age 18-40 with either implant system during the first three years (600 women used LNG Rod and 598 used Norplant® implants). No significant differences were found between the two methods in termination rates; complaint and illness rates were similar. Overall, menstrual problems (increased number of bleeding days, irregular bleeding, and increased amount of menstrual bleeding) accounted for the highest request for removals (10 percent) among users of both implant systems. A significant advantage of the new system is easier removal. At each clinical site, the mean removal time for the LNG Rod implants was

about half that required for Norplant® implants. Mean removal times ranged from about 2 to 9 minutes for the LNG Rod system and 4 to 17 minutes for the Norplant® system.

While Norplant® implants are available in the United States and more than 50 other countries, it is not clear when the new LNG Rod implants will be available. Wyeth-Ayerst, the U.S. distributor, is not planning to market the product at this time,² but rather is continuing research and development related to an insertion device and is monitoring the U.S. contraceptive market to determine when a product launch would be feasible.² (Norplant® implant use in the United States has dropped significantly since 1994, a pattern correlated with increased litigation and negative media coverage.²) Leiras Oy, which was purchased by Schering AG in 1996, has announced that it too is taking time to develop a marketing strategy before determining when the product will be available.

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