

# DIALOGUES



## IN CONTRACEPTION®

### In This Issue

#### Benefits of Contraception to Women's Health: An Evidence-Based Perspective

#### Contraception and Cancer

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## Benefits of Contraception to Women's Health: An Evidence-Based Perspective

Ronald T. Burkman, MD, David A. Grimes, MD, Daniel R. Mishell, Jr, MD,  
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### Educational Objectives:

The health care provider should be able to:

- utilize evidence to compare the risks of contraception and pregnancy
- describe the continuing high rate of unintended pregnancy and its consequences for women and children
- describe the mechanisms of action by which contraceptive methods prevent pregnancy
- identify the noncontraceptive health benefits provided by various contraceptive methods
- explain the advantages of including education about birth control methods, as well as information about sexual abstinence, in adolescent sex education programs

Recent media reports<sup>1-5</sup> of the views of groups and individuals advocating against contraception have featured allegations, unsubstantiated by scientific evidence, that:

- use of contraception impairs women's health
- condoms are not effective for preventing sexually transmitted infections (STIs)
- sexual abstinence or nonuse of contraception is safer for women than use of contraception
- pregnancy begins at fertilization
- hormonal and intrauterine contraceptives act as abortifacients
- counseling and education about birth control lead to increased adolescent sexual activity and increased induced abortion rates among reproductive-age women

The Editorial Board of *Dialogues in Contraception*® wishes to comment on these issues to add perspective for clinicians through relevant evidence-based information.

### Unintended Pregnancy

The rate of unintended pregnancy in the United States remained virtually unchanged between 1994 and 2001.<sup>6</sup> According to the 1995 and 2002 National Surveys of Family Growth (NSFG), 49% of all pregnancies in the United States were unintended in both 1994 (3.04 million) and in 2001

(3.1 million).<sup>6,7</sup> The 2001 rate of unintended pregnancy was highest (twice the rate for women overall) among women aged 18 to 19 and 20 to 24 compared with other age groups.<sup>6</sup> Among unmarried women, the rate of unintended pregnancy in 2001 was higher than among married women (67 and 32, respectively, per 1000 women). The rate of unintended pregnancy increased by 29% between 1994 and 2001 among low-income women (ie, less than 100% of the poverty level), while this rate declined among higher-income women (ie, at or above 200% of the poverty level).

The percentage of all women aged 15 to 44 who were sexually active and not using contraception in the United States increased from 5.4% in 1994 to 7.4% in 2001, an increase of about 1.43 million women who were at risk for unintended pregnancy.<sup>8</sup> During the month when an unintended conception occurred, no contraception was used by 52% of the women in 2001, a slight increase from 49% in 1994.<sup>6</sup> Overall, the incidence of unintended birth increased from 20% of all pregnancies in 1994 to 22% in 2001, while the incidence of induced abortion declined from 24% of all pregnancies to 21% during the same period.<sup>6</sup>

The negative health and social outcomes of unintended pregnancies and births for mothers, children, and families are substantial. Not all unintended pregnancies are unwanted: some pregnancies are mistimed since they occurred when the women would rather have postponed childbearing, whether or not they were using contraception. However, all unintended pregnancies are more likely than intended pregnancies to result in low-birth-weight and small-for-gestational-age infants.<sup>9</sup> Women whose pregnancies are unintended are less likely than those whose pregnancies are intended to stop smoking during pregnancy, to attend the recommended number of prenatal care visits, to breast-feed their babies, or to continue breastfeeding for 16 weeks or more, and are more likely to engage in illicit drug use.<sup>9-13</sup> Children of unwanted pregnancies are more likely than those of wanted pregnancies to have mothers with lower levels of education, self-esteem, per capita family income, and employment before childbirth.<sup>14</sup> Compared with children of mistimed pregnancies, children of unwanted pregnancies aged 1 or older have been found to have fewer opportunities for motor and social skill development, higher levels of fearfulness, and lower levels of receptive vocabulary development, and children of mistimed pregnancies receive fewer of these educational opportunities than do wanted children.<sup>14</sup> Mothers with unwanted children have

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been found to have lower-quality emotional and social-support relationships with these children in late adolescence through early adulthood compared with mothers of wanted children, and these poor relationships also apply to other children in the family.<sup>15</sup>

## Pregnancy: Health Effects

In 2001, 6.4 million pregnancies occurred in the United States, and 51% (3.3 million) of them were intended, representing a major life choice of most people: to have children and fulfill the many emotional benefits of being parents.<sup>6</sup> Of these intended pregnancies, 80% resulted in live births. However, the risks of pregnancy and childbirth can adversely affect some women. The existence of these health risks underscores the critical importance of ensuring that all pregnancies are wanted and planned.

During the period 1991 to 1999, the United States Pregnancy Mortality Surveillance System determined that 4200 pregnancy-related (ie, during pregnancy or within 1 year of pregnancy and causally related to pregnancy) deaths occurred.<sup>16</sup> The ratio of pregnancy-related mortality was 11.8 deaths per 100,000 live births, increasing significantly from 10.3 in 1991 to 13.2 in 1999 ( $p < .001$  for trend).<sup>16</sup> Moreover, most investigators conclude that pregnancy-related mortality is often underreported or underestimated.<sup>16-18</sup> In addition, violent deaths of pregnant and postpartum women are usually excluded from reported pregnancy-related mortality data.<sup>19</sup>

The leading reported causes of pregnancy-related death in the United States (all pregnancy outcomes) were embolism (20%; ratio 2.3 per 100,000 live births), hemorrhage (17%; ratio 2.0 per 100,000 live births), and pregnancy-induced hypertension (16%; 1.8 per 100,000 live births).<sup>16</sup> Spontaneous abortion occurs in approximately 15% to 17% of pregnancies,<sup>6,20</sup> and is a leading cause of maternal morbidity during the first trimester of pregnancy.<sup>21</sup> Deaths due to spontaneous abortion are rare: 0.7 per 100,000 spontaneous abortions.<sup>20</sup>

Of the 3.1 million unintended pregnancies in the United States occurring in 2001, 42% (1.3 million) ended in induced abortion.<sup>6</sup> The mortality rate associated with induced abortion (medical or surgical) is about the same as that associated with spontaneous abortion, and lower than that of continuing pregnancy.<sup>22</sup>

A 30-year population-based cohort study conducted between 1966 and 1996 in Minnesota estimated the relative risk for venous thromboembolism (VTE; which includes both deep venous thrombosis [DVT] and pulmonary embolism [PE]) during pregnancy and 3 months postpartum.<sup>23</sup> The relative risk (RR; standardized incidence ratio) for VTE among pregnant or postpartum women was found to be 4.29 (confidence interval [CI] 3.49-5.22) compared with nonpregnant/nonpostpartum women,<sup>23</sup> and the incidence of VTE was found to be 10 cases in 10,000 pregnancies.<sup>24</sup> Analysis of data from a large multicenter registry between October 2001 and March 2002 found that approximately 66% of DVT events occurred during pregnancy and 33% postpartum (defined as first 6 weeks after pregnancy).<sup>25</sup> PE can be fatal, and the postthrombotic syndrome (progressive development of venous insufficiency), which can occur after a DVT, can cause long-term morbidity.<sup>25</sup>

## Contraceptive Use: Health Effects

Use of contraception to plan for occurrence of pregnancy, to space childbirths appropriately, and/or to avoid mistimed or unwanted pregnancies reduces or eliminates many of the risks of morbidity and mortality associated with pregnancy, thus improving women's and children's overall health.<sup>26-29</sup> Data derived primarily from population studies indicate that optimal spacing of childbirths—at least 12 months apart and not more than 60 months apart<sup>27</sup>—can provide major health benefits to mothers and their children.<sup>26,28-30</sup>

The highly effective contraceptive methods discussed in this article (ie, combination hormonal methods, progestin injectable depot medroxyprogesterone acetate [DMPA], intrauterine contraceptives [IUCs: copper T 380A IUC, and levonorgestrel-releasing intrauterine system, LNG-IUS]), used correctly and consistently, prevent almost all unintended and/or unwanted pregnancies.<sup>31</sup> By doing so, these contraceptive methods thus reduce the pregnancy-related and fetal/perinatal health risks associated with labor and delivery as well as with ectopic pregnancy, spontaneous abortion, pregnancy-induced hypertension, gestational diabetes, and trophoblastic disease. In addition, when fertility rates in a population are stable, as in the United States during the period 1997 to 2002,<sup>32</sup> rates of induced abortion have been found to decrease with increased use of contraception.<sup>33</sup>

Cardiovascular disease (CVD) is uncommon in nonsmoking women of reproductive age. Use of combination oral contraceptives (COCs) does not increase the RR of myocardial infarction (MI) or stroke in nonsmoking women without high blood pressure compared with nonusers.<sup>34</sup> Although use of COCs and other estrogen-containing hormonal methods increases risk of VTE compared with nonuse, incidence of VTE is about twice as common in pregnancy as during COC use.<sup>35</sup> There is no excess risk of CVD death among nonsmoking users of low-dose COCs of all ages and in smokers aged less than 35.<sup>36</sup> Among US nonsmokers who use COCs, the risk of death from CVD attributable to COC use is 80 times lower at ages under 35 and 4 times lower at ages 35 and older than the risk of cardiovascular death from carrying a pregnancy to term.<sup>36</sup> Although few epidemiologic data are yet available, effects of other combination hormonal contraceptive methods (transdermal contraceptive patch, vaginal ring) on cardiovascular risk are probably similar to those of COCs.

In the Royal College of General Practitioners' cohort study, the overall 25-year risk of mortality from all causes associated with ever-use of COCs did not differ from that associated with never-use: RR 1.0, CI 0.9-1.1.<sup>37</sup> The risk of death for most specific causes did not differ significantly between the 2 groups.

Use of DMPA does not increase risks of stroke, MI, or VTE, even in women with cardiovascular risk factors (including those over age 30 who smoke).<sup>34</sup>

Use of contraceptive methods is safe and causes severe health problems very rarely. At the same time, all contraceptive methods provide several noncontraceptive health benefits, further enhancing women's long-term health. A detailed discussion of cancer risk reductions associated with use of various contraceptive methods is found in "Contraception and Cancer," page 5.

In addition, current use of COCs for at least 12 months reduces risk of hospitalization for pelvic inflammatory disease by approximately 50% to 60%.<sup>38,39</sup> Use of COCs after age 40 has been found to positively affect maintenance of bone mineral density during perimenopause.<sup>40,41</sup> COC use by women in their 40s also has been found to reduce risk of postmenopausal hip fractures.<sup>42</sup> The LNG-IUS has been used effectively in the prevention and/or treatment of menorrhagia, dysmenorrhea, and endometriosis.<sup>43-53</sup> As risks of morbidity and mortality during pregnancy increase with increasing age,<sup>16,54-57</sup> as well as with preexisting medical conditions,<sup>55,57</sup> contraception to prevent unintended pregnancy is critical for health maintenance among older or ill women. For such women, as well as for women of any age who have completed childbearing, IUCs offer safe, long-term, highly effective, and rapidly reversible alternatives to sterilization.

The effectiveness of consistent condom use in preventing STIs and reducing risk of acquiring human papillomavirus has been confirmed in several studies.<sup>58-64</sup>

## Mechanisms of Action

All major medical and scientific groups, including the World Health Organization (WHO) as well as the US government, utilize the same definition of when pregnancy begins: when implantation of the embryo into the uterine wall is complete.<sup>65-68</sup> The implantation process begins with the attachment of the blastocyst to the uterine wall, 6 to 7 days postfertilization. While some contraceptive methods have multiple biologic effects on the reproductive system, providing primary and secondary contraceptive mechanisms of action, the major mechanism of action for combination hormonal methods, DMPA, and IUCs is prevention of fertilization. All hormonal methods also alter the cervical mucus, preventing or inhibiting sperm penetration.<sup>69</sup> Combination hormonal contraceptives and DMPA inhibit ovulation through action at the pituitary and hypothalamic levels.<sup>70-73</sup> Therefore, no ova are available to be fertilized. IUCs do not suppress ovulation but prevent fertilization primarily by causing a spermicidal foreign-body reaction to occur in the endometrial cavity; the LNG-IUS also prevents sperm transport through the cervical mucus by producing a thickened mucus.<sup>65,74</sup>

Emergency contraceptive (EC) regimens that utilize contraceptive hormones prevent fertilization mainly by inhibition of ovulation rather than by preventing implantation of the embryo.<sup>75-77</sup> Moreover, hormonal EC used after implantation occurs does not interrupt an established pregnancy, and there are no adverse effects on the pregnancy or the fetus.<sup>75</sup>

Further evidence of the antifertilization, rather than anti-implantation, effects of hormonal contraception, IUCs, and EC is provided by comparing the lower incidence of ectopic pregnancies associated with use of these methods than the incidence among women not using contraception when they conceived<sup>78</sup>: if prevention of implantation were the principal contraceptive mechanism of action, the rates of ectopic pregnancies among users of these contraceptive methods would be the same as among nonusers.

## Sexual Abstinence

Adolescent counseling programs that exclusively promote sexual abstinence-only-until-marriage without comprehensive sexuality and contraceptive

# Patient Education Information

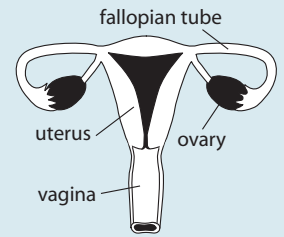
*Clinicians: The Patient Education Information sheet below may be useful as a handout in counseling women and adolescents about the mechanisms of contraceptive action of various contraceptive methods. It is provided for you to copy and use in your practice.*

## How Do Birth Control Methods Work?

If you're not ready to become pregnant or have a baby, you should know how to protect yourself against unwanted pregnancy. Of course, not having sex at all until you're really ready to become pregnant is the best way to be sure. But if you are having sex or think you might, here are some facts that will help you prevent pregnancy until you're ready.

## When Does Pregnancy Begin?

Once a woman begins to have monthly periods, her body is ready to become pregnant—even if she isn't. Having periods means that the *ovaries* (see the drawing) have started releasing eggs that are "fertile"; that means she can become pregnant. But the only way a woman can become pregnant is if the egg, first, meets the sperm that a man produces, *and* then reaches the woman's *uterus* and implants in the lining to grow. In other words, a woman is not pregnant just because her egg has met the sperm—she's not pregnant until the fertilized egg has implanted in her uterus, usually about 6 or 7 days later.



Whenever a man and a woman have sexual intercourse, there's always a possibility that the woman's egg and the man's sperm will meet in the woman's *fallopian tubes*. Without birth control, the egg may be fertilized and go on to implant in the uterus. But using an effective form of birth control can prevent this from happening nearly always. So, if you think you are going to have sexual intercourse but do not want to become pregnant, you should use birth control to stop the sperm from meeting the egg.

## How Does Birth Control Stop Pregnancy From Happening?

Most effective birth control methods work by preventing the sperm from fertilizing the egg. Some prevent the woman's monthly egg from being released at all. Others prevent the sperm from meeting the egg, either by destroying the sperm, or by creating a barrier between the sperm and the egg so the sperm can't reach the egg. Sometimes birth control methods do a little of both. Here's how some of the most popular birth control methods work.

**Birth Control Pills, Patch, Vaginal Ring, Injectable:** All these methods, which contain hormones, change the levels of a woman's natural hormones so that her eggs are not released from the ovaries in the first place. Other chemical changes in the woman's uterus also prevent sperm from reaching the fallopian tubes.

**Intrauterine Contraceptives:** These are often called IUCs or IUDs, and there are 2 kinds. One has copper in it and the other has a hormone. IUCs/IUDs don't prevent a woman's eggs from being released. Instead, they produce chemical changes to prevent the sperm from reaching or fertilizing the egg.

**Spermicides:** These agents contain an ingredient that is toxic to sperm and destroys them.

**Condoms, Diaphragms:** These methods place a physical barrier between the sperm and the egg so that the two can't meet.

For a birth control method to work properly to prevent pregnancy, a woman must use it correctly. That means using it exactly when and how it is prescribed. For example, a condom or diaphragm *must* be used *every time* a woman has sex. Birth control pills *must* be taken *every day*.

But if a woman forgets to use her birth control method, and has sex anyway, she can still protect herself against becoming pregnant by using emergency contraception:

**Emergency Contraception:** Emergency contraception is exactly what it's called—a birth control method you use only in an emergency. It works just like birth control pills (in fact, it is a form of birth control pill) by preventing release of the egg from the ovary. In order for it to work best, emergency contraception should be used as soon as possible and at least within 72 hours after unprotected sex. So it's a good idea to ask your doctor or nurse to explain how you can have emergency contraception available to use in case you need it. But remember: emergency contraception is for an emergency. If you're having sexual activity, it's much better to make sure you have a birth control method and use it regularly.

If you plan to have children and you're ready to have a baby in your life, you'll know it's time to stop using birth control. Until then, ask your doctor or nurse to help you choose a reliable birth control method to help prevent pregnancy—and make sure you use it correctly. Before you decide to become pregnant, ask your doctor or nurse about vitamins that will prevent birth defects and about other things you should do for a healthy pregnancy.

education are intended to reduce the incidence of teenage sexual activity and unintended pregnancy. However, these programs have been found to be largely ineffective in reducing incidence of sexual onset and activities before marriage.<sup>3,79-81</sup> In a systematic review of randomized controlled trials of interventions to reduce unintended pregnancies among adolescents, meta-analysis of 5 studies, 4 of which evaluated the effect of abstinence programs, reported an increase in pregnancies among partners of male participants in the programs: overall pooled estimate, odds ratio (OR) 1.54, CI 1.03-2.29.<sup>82</sup> In contrast, educational programs that include information about both abstinence and contraception have been found to be effective in delaying onset of sexual intercourse, reducing number of sexual partners, and increasing use of contraception and condoms to prevent STIs among adolescents.<sup>83-89</sup> Studies have consistently found that education programs that include discussion of contraception do not increase onset or frequency of sexual intercourse or number of sexual partners.<sup>79,81,85,87,88</sup> In other industrialized countries, such as Sweden and The Netherlands, where access to and education about contraception are more widely available than in the United States, rates of adolescent pregnancy, births, and abortions are about half the rates in the United States.<sup>90</sup>

According to an analysis of data from the National Longitudinal Study of Adolescent Health, among adolescents who reported in 1995 having taken virginity-until-marriage pledges (13%), 1 year later more than half denied having taken such a pledge.<sup>91</sup> Pledge retraction was most frequent among those who were newly sexually active (73%).<sup>91</sup> Data from the same study indicate that rates of STIs among adolescent virginity pledgers are comparable with rates among nonpledgers, and that pledgers are less aware than nonpledgers of their infected status.<sup>92</sup> Pledgers are also significantly ( $p \leq .017$ ) less likely to use condoms at first intercourse than nonpledgers. Another study reported that adolescents who take virginity pledges are one third less likely to use contraception when they do become sexually active than nonpledgers.<sup>93</sup>

## Summary and Conclusions

Some women may be concerned about recent media reports regarding the safety and pregnancy-prevention activities of contraceptive methods. Clinicians can reassure these women that evidence demonstrates that use of contraception is safe and improves the overall health of women and their families by preventing unintended pregnancy, spacing childbirths, and providing important noncontraceptive health benefits. Clinicians can also emphasize that the mechanisms of action of hormonal contraceptive methods and IUCs are to prevent fertilization, not implantation, and therefore they are not abortifacients. (See "Patient Education Information," page 3.) While total abstinence is the only absolute means of preventing pregnancy and avoiding STIs, adolescent sex education programs that only discuss abstinence have been found not to prevent sexual activity until marriage. Adolescents also need information about using effective contraception to prevent unintended pregnancy if they do become sexually active. Comprehensive sex education, including information about contraceptive methods and STI prevention as well as abstinence, has been found not to increase sexual activity but to reduce adverse outcomes.

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(continued on page 8)

# Contraception and Cancer

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## Educational Objectives:

The health care provider should be able to:

- describe evidence-based findings about the positive and negative effects of use of various contraceptive methods on cancer risks
- assess the effects of use of several contraceptives on future development of cancers after contraceptive method discontinuation
- utilize epidemiologic data to counsel women about the use of various contraceptive methods with regard to cancer risks

Concerns have been raised regarding whether or not use of current contraceptive methods increases risks of different cancers. Many epidemiologic studies have examined the relative risks of specific cancers with use of various methods compared with nonuse. The majority of the evidence provides reassurance for women about the overall safety of contraceptive methods with regard to cancer risks, underscoring the importance of cancer prevention through reducing modifiable, lifestyle-associated cancer risk factors and undergoing periodic screening. This article describes the major evidence available regarding specific cancers and the positive and negative effects associated with use of various contraceptive methods compared with nonuse. Almost all of the literature regarding cancer risks with combination hormonal methods is based on use of combination oral contraceptives (COCs) and these data are discussed below. Data are not yet available for other combination hormonal methods (transdermal contraceptive patch, vaginal ring), but the best estimate is that their effects on cancer risks will be similar to those of COCs.

## Breast Cancer

In 2006, the American Cancer Society estimates that 212,920 women in the United States will be diagnosed with breast cancer and that 40,970 will die of this condition.<sup>1,2</sup> The median age at diagnosis for cancer of the breast is 61 years, with 34% of cancers (including ductal carcinoma in situ) occurring in women aged 54 and younger. Only 1.9% of cases of breast cancer occur in women aged 20 to 34, the age group that contains most current contraceptive users.

**COCs.** A huge body of evidence has consistently found that in the general population ever-use of COCs does not increase overall risk for breast cancer diagnosis.<sup>3-9</sup> A 1996 reanalysis of 54 studies conducted in 25 countries, comprised of 53,297 women with breast cancer and 100,239 controls, reported that 10 or more years after discontinuation of COC use, there was no difference in the cumulative risk of breast cancer diagnosis between COC ever-users and never-users.<sup>3,4</sup> Only current COC use or use within 10 years was associated with a slightly increased relative risk (RR) of breast cancer diagnosis (current: RR 1.24, confidence interval [CI] 1.15-1.33; 5-9 years after stopping use, RR 1.07, CI 1.02-1.13),<sup>3</sup> with most cases occurring between ages 40 and 49,<sup>3</sup> when breast cancer incidence is higher than in younger women regardless of COC use. Breast cancers diagnosed in COC users were significantly less likely to have spread beyond the breast than those diagnosed in similarly-aged never-users (RR 0.88, CI 0.81-0.95), suggesting that much of the excess risk of breast cancer in recent users was due to an excess of localized tumors with better prognoses after diagnosis than cancers spread beyond the breast; COC use may lead (through increased surveillance associated with prescription renewal) to earlier diagnosis of existing cancers rather than having an etiologic effect.<sup>3</sup> It should be noted that much of the original data included in the reanalysis were collected from early studies in which high-dose COCs represented a substantial portion of "current use."

Further encouraging news was provided by the Women's CARE 2002 case-control study of women aged 35 to 64 (4575 with breast cancer diagnosed between 1994 and 1998, and 4682 controls), which demonstrated that current (RR 1.0, CI 0.8-1.3) or previous (RR 0.9, CI 0.8-1.0) COC use was not associated with increased risk of breast cancer.<sup>6</sup> This study found no increase in breast cancer risk associated with current or prior COC use, even later in life when the incidence of breast cancer is higher than at younger ages

(Table 1).<sup>6</sup> Risk of breast cancer was not found to be related to the duration of COC use, estrogen dose, age at first use, time since last use, or COC use by women with a family history of breast cancer.

Recent evidence indicates that COC use does not increase breast cancer risk even in high-risk subgroups.<sup>9,10</sup> One multinational case-control study found that low-dose COC use for at least 12 months was associated with a significantly decreased risk of breast cancer in *BRCA1* mutation carriers (n=31) compared with *BRCA1*-positive COC nonusers (n=16; odds ratio [OR] 0.22, CI 0.10-0.49), and no increased risk in *BRCA2* mutation carriers (n=31; OR 1.02, CI 0.34-3.09) as well as in women without mutations (n=920; OR 0.93, CI 0.69-1.24).<sup>9</sup> Similarly, a prospective Canadian cohort study of 27,318 women with a family history of breast cancer found that COC ever-use was associated with a hazard ratio of 0.88 (CI 0.73-1.07), a non-significant reduction of 12% in risk of breast cancer compared with COC never-use among such women.<sup>10</sup>

**Table 1. Risk of Breast Cancer Among Women Aged 35 to 64 With COC Use<sup>6</sup>**

Variable	Case Subjects (n=4575)	Controls (n=4882)	Odds Ratio (95% CI)
Number			
No use	1032	980	1.0
Any use	3497	3658	0.9 (0.8-1.0)
Current use*	200	172	1.0 (0.8-1.3)
Former use	3289	3481	0.9 (0.8-1.0) <sup>†</sup>
Duration of use			
<1 y	782	822	0.9 (0.8-1.1)
1 to <5 y	1200	1280	0.9 (0.8-1.0)
5 to <10 y	848	882	0.9 (0.8-1.0)
10 to <15 y	426	466	0.8 (0.7-1.0) <sup>†</sup>
>15 y	234	202	1.0 (0.8-1.3)

COCs=combination oral contraceptives.

\*Current use defined as use of COCs within 6 months preceding the reference date (for cases, date of initial, histologically confirmed diagnosis; for controls, date of screening).

<sup>†</sup>Confidence interval does not include 1.0; some confidence limits rounded to 1.0.

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The findings from these and other studies provide substantial evidence that use of currently available formulations of COCs does not increase overall risk of breast cancer. Therefore women, including those with a family history of breast cancer and/or a known genetic mutation, should not avoid use of combination hormonal contraceptives because of concern about their effect on breast cancer risk.

**Depot medroxyprogesterone acetate.** Data regarding use of depot medroxyprogesterone acetate (DMPA) are also reassuring. In a large World Health Organization (WHO) multinational case-control study, the overall RR of breast cancer with use of DMPA compared with nonuse was 1.2 (CI 0.96-1.52).<sup>11</sup> Risk did not increase with increasing duration of use but was increased in women who had initiated DMPA use within the previous 4 years (RR 2.02, CI 1.35-3.01), primarily in women aged less than 35 (RR 2.19, CI 1.23-3.89). The investigators estimated the attributable risk of breast cancer with DMPA use as 1.3 cases per 100,000 woman-years of DMPA use. In pooled data from 2 multinational case-control studies, the overall RR of breast cancer with DMPA use compared with never-use was 1.1 (CI 0.97-1.4).<sup>12</sup> However, the RR for women who had started DMPA use within the previous 5 years was found to be 2.0 (CI 1.5-2.8), but risk declined significantly with time since first use ( $p=.01$ ). There were small numbers in this study, and it is possible that there was early detection of preexisting tumors in women initiating DMPA use.

In contrast to these findings, a South African case-control study found, however, that use of DMPA did not increase risk of breast cancer compared with nonuse (RR 0.9, CI 0.7-1.2) regardless of recency of use, duration of use, or age.<sup>13</sup> In the United States, the Women's CARE case-control study found no increased risk of breast cancer with current or previous use of DMPA among women aged 35 to 64 compared with DMPA never-use (use

within 1 year, OR 0.7, CI 0.4–1.3; use within 5 years, OR 0.9, CI 0.5–1.4).<sup>14</sup> Like the data regarding COCs, the DMPA data are reassuring, indicating no overall increased risk of breast cancer with use of DMPA.

**Levonorgestrel-releasing intrauterine contraceptive.** Postmarketing data gathered from 17,360 Finnish users of the levonorgestrel-releasing intrauterine system (LNG-IUS) found no difference in breast cancer incidence between LNG-IUS users and the average Finnish female population in any of the 5-year age groups from 30 to 54.<sup>15</sup> Recognizing the need for data from larger populations, these findings are nevertheless encouraging.

## Colorectal Cancer

In 2006, the American Cancer Society estimates that 75,810 women in the United States will be diagnosed with cancer of the colon and rectum, approximately 45.3 cases per 100,000 women.<sup>16,17</sup> The median age at diagnosis is 71. Risk factors for colorectal cancer include age over 50, history of polyps, family history of colorectal cancer, smoking, and high-fat diet.<sup>18</sup>

**COCs.** During the past decade, studies of COC use and risk of colorectal cancer have produced no evidence of an adverse effect; in fact, most studies have found that ever-use of COCs reduces risk of colon and/or rectal cancer.<sup>19–25</sup> A 2000 meta-analysis of 6 cohort studies and 14 case-control studies found that, compared with COC never-use, COC ever-use was associated with a pooled RR of colorectal cancer of 0.82 (CI 0.74–0.92), a significant 18% reduction in risk.<sup>24</sup> There was an apparent increase in protection associated with recent use but no effect of duration of use. Studies published since this meta-analysis have reported similar reductions in RR of colorectal cancer with COC ever-use compared with never-use, ranging from 11% to 20%.<sup>22,23,25</sup>

Several mechanisms of action have been suggested for the colorectal cancer risk reduction afforded by use of COCs. Exogenous estrogen may decrease secretion of bile acid, which can potentially damage colonic mucosa and prompt malignant growth.<sup>21,22,24</sup> The estrogen receptors may act as tumor suppressors.<sup>21,24</sup> COC use also lowers risk of colorectal adenomatous polyps, the precursor lesions of colon cancer.<sup>20</sup>

Women with a family history of colorectal cancer, particularly those whose affected relatives have been found to have the hereditary nonpolyposis colon cancer (HNPCC) mutation, are at increased risk for colorectal cancer. The evidence of colorectal cancer risk reduction associated with COC ever-use may be of particular importance to such women in selecting contraceptive methods, as well as to women without a family history who are concerned about risk of colorectal cancer later in life.

No data are available regarding colorectal cancer risk and use of DMPA or the LNG-IUS.

## Ovarian Cancer

Ovarian cancer is the eighth most common cancer (excluding skin cancer) in women and is the fifth highest cause of cancer death in women.<sup>26</sup> About two thirds of women who develop ovarian cancer are aged 55 or older, with 63 being the median age at diagnosis.<sup>27</sup> The American Cancer Society estimates that in 2006, 20,180 women in the United States will be diagnosed with ovarian cancer and 15,310 women will die of this neoplasm.<sup>26</sup> In addition to increasing age, other risk factors for ovarian cancer include family history (particularly *BRCA* mutations), history of breast cancer, nulliparity, infertility, and early menarche.<sup>28</sup>

**COCs.** Numerous studies have found that use of any type of COC (eg, high- or low-dose) reduces subsequent risk of epithelial ovarian cancer by at least 40% compared with never-use; the risk reduction increases with increasing duration of use, and the protective effect persists for 20 years or more (Table 2).<sup>29–36</sup> Each year of COC use has been found to decrease ovarian cancer risk by approximately 10% to 12% in both parous and nulliparous women.<sup>31</sup>

COC use by women with *BRCA1* and *BRCA2* mutations and/or family history of ovarian cancer has also been investigated. Studies have found that COC use also reduces risk of ovarian cancer in these high-risk women compared with nonuse; in most studies, increasing duration of use was associated with progressively decreased risk of ovarian cancer, but study findings differ as to the degree of risk reduction.<sup>37–40</sup>

The mechanisms of action by which COCs reduce ovarian cancer risk have been postulated but not conclusively determined. Because repeated ovulation is believed to be one of the primary causes of epithelial ovarian cancer by fostering neoplastic growth, the ovulation suppression effected by COC

**Table 2. Risk of Ovarian Cancer With COC Use in a Reanalysis of Data From 6 Case-Control Studies<sup>33</sup>**

	Cases	Controls	OR (95% CI)
<b>COC use</b>			
Never	2476	5444	1*
Ever	255	830	0.66 (0.56–0.79)
<b>Duration of COC use<sup>†‡</sup> (months)</b>			
Never	2347	5251	1*
<60	202	539	0.83 (0.69–1.01)
≥60	46	242	0.42 (0.30–0.59)

COC=combination oral contraceptives; OR=odds ratio; CI=95% confidence interval.

\*Referent.

<sup>†</sup>Sum does not add to total because of some missing values.

<sup>‡</sup>Information not provided by at least 1 study included in reanalysis.

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use, similar to that provided by pregnancy, is a likely cause of the protective effect.<sup>41–43</sup> COCs also suppress gonadotropins, which—when elevated—may malignantly transform epithelial cysts.<sup>44,45</sup>

As ovarian cancer risk reduction has been established as a major noncontraceptive health benefit of COC use, COC use has been recommended to reduce the risk of ovarian cancer<sup>31,38,46</sup> in women with a high risk for developing this malignancy (eg, with family history, mutation carriers), for whom COC use presents an alternative to prophylactic oophorectomy.<sup>37,39,40</sup> As COC use by *BRCA*-positive women is not associated with an increased risk of breast cancer, this need not be a concern for women with these mutations who wish to use COCs to reduce their hereditary increased risk of ovarian cancer.<sup>47</sup> Even following oophorectomy, women carrying germ-line *BRCA* mutations are at increased risk for primary peritoneal cancer compared with noncarriers.<sup>48</sup> Some authorities speculate that COC use might reduce this risk following prophylactic removal of the ovaries.<sup>48</sup>

**DMPA.** A WHO case-control study found that risk of epithelial ovarian cancer was not altered by ever-use of DMPA compared with never-use (RR 1.07, CI 0.6–1.8).<sup>49</sup> However, most women in this study were of high parity and were at low risk of developing ovarian cancer.

**Tubal ligation.** Tubal ligation has also been found to decrease risk of ovarian cancer and ovarian cancer mortality.<sup>45,50–52</sup> One hypothesis of a mechanism of action for ovarian cancer risk reduction is that tubal ligation may prevent the ascent of environmental carcinogens.<sup>50</sup>

No data are available regarding ovarian cancer risk and use of the LNG-IUS.

## Endometrial Cancer

Endometrial cancer is the most common female gynecologic cancer in the United States. In 2006, the American Cancer Society estimates about 41,200 new cases and 7350 deaths from this cause.<sup>53</sup> About 70% of all endometrial cancer cases are diagnosed in women aged 45 to 74, with only 8% of cases occurring in younger women.

**COCs.** Substantial evidence supports the conclusion that ever-use of COCs, for as little as 1 year, reduces risk of endometrial cancer by at least 40% compared with nonuse; the protective effect persists for at least 20 years after discontinuation of COC use.<sup>54–59</sup> The longer the duration of COC use, the lower the risk of developing endometrial cancer, at least up to age 65.<sup>56,58</sup> Few studies have investigated risk of endometrial or ovarian cancer in previous COC users aged 65 or older. One mechanism of action proposed to explain the endometrial cancer risk reduction associated with use of COCs is that the progestin component of the COC may reduce endometrial DNA synthesis and thus help to prevent endometrial hyperplasia.<sup>43</sup> The long-term endometrial cancer risk reduction provided by COC use is another major noncontraceptive health benefit of this method. Use of COCs significantly reduces the risk of developing endometrial and ovarian cancers many years after discontinuation of the method, so that women in their 60s—when incidences of these cancers are highest—may benefit from COC use during their reproductive years.

**DMPA.** Ever-use of DMPA has been found in a WHO hospital-based study to reduce risk of endometrial cancer by 80% compared with nonuse (RR 0.21, CI 0.06–0.79).<sup>60</sup> The protective effect appears to last for at least 8 years after discontinuation of DMPA use.

**IUCs.** Compared with IUC nonuse, ever-use of the copper IUC has been associated with about a 40% or greater reduction in risk of endometrial cancer in several studies.<sup>61-65</sup> These studies included women using both copper and inert IUCs. It has been speculated that the protective effect is primarily due to the copper.<sup>61</sup> Although data are more limited, the LNG-IUS may also protect against endometrial cancer.<sup>66,67</sup> The LNG-IUS has been found to protect against endometrial hyperplasia in women using tamoxifen,<sup>67</sup> and has been found to be associated with regression of hyperplasia.<sup>68</sup>

## Cervical Cancer

According to American Cancer Society estimates, 9710 US women will be diagnosed with invasive cervical cancer during 2006, and 3700 women will die from this condition.<sup>69</sup> Half of women diagnosed with cervical cancer are aged between 35 and 55; slightly more than 20% of women with cervical cancer are diagnosed when they are aged over 65.<sup>70</sup> Before 1955, cervical cancer was one of the most common causes of cancer death among US women. Since then, however, the cervical cancer death rate has progressively declined, mainly because of increased use of Pap tests to detect cervical changes before cancer develops.

The most important cause of cervical cancer is sexually transmitted infection by human papillomavirus (HPV), which is present in 99.7% of cases of cervical cancer.<sup>41,71,72</sup> However, most women with HPV do not develop cervical cancer, suggesting contributory roles in cervical cancer development for other risk factors including smoking, HIV infection, chlamydia infection, and high parity.<sup>73-75</sup>

**COCs.** Before the presence of HPV was demonstrated in virtually all cervical cancers, several studies reported that COC use for 5 to 9 years was associated with a slight increase in cervical cancer risk (RR 1.37, CI 0.9-2.0).<sup>76-79</sup> However, with clarification of the necessary role of HPV in cervical cancer etiology, the perspective has changed. There is now evidence that ever-use of COCs is not associated with increased risk of HPV infection compared with nonuse,<sup>80-83</sup> and that COC use does not alter risk of developing cervical dysplasia, the precursor to cervical cancer.<sup>84,85</sup> A 2002 WHO review of data from various studies concerning a possible causal effect of COC use on increased risk of cervical cancer concluded that an increased risk of cervical cancer with long-term COC use only occurs in women with persistent HPV infection.<sup>86</sup> Because the resulting number of cervical cancers in this subgroup of COC users is likely to be very small, the WHO stated, no changes in COC prescribing practices are recommended. While some studies have reported that long-term use (more than 5 years) of COCs by HPV-positive women might increase progression of HPV infection to cervical cancer,<sup>82,87,88</sup> other studies found no such association.<sup>71,75,89</sup>

For women using combination hormonal contraceptives, cervical screening at the same intervals as for nonusers is appropriate; more or less frequent screening is not necessary. Women treated for cervical dysplasia can use combination hormonal contraception.<sup>90</sup>

**DMPA.** Several studies have found no increased risk of cervical cancer among DMPA ever-users compared with never-users.<sup>71,91,92</sup>

**IUCs.** Studies have indicated that risk of invasive cervical cancer among copper IUC users is reduced by 40% compared with nonusers.<sup>93,94</sup> LNG-IUS labeling contraindicates use in women with unresolved, abnormal Pap smears<sup>95</sup>; however, WHO guidelines classify initiation or continuation of use in women with cervical intraepithelial neoplasia (CIN) as "advantages of use generally outweigh the theoretical risk" that LNG-IUS use may enhance progression of CIN.<sup>96</sup>

## Summary and Conclusions

Although COCs contain potent steroids, the evidence regarding possible associations with various types of cancer is very reassuring. In particular, use of most hormonal contraceptive methods provides substantial protection against ovarian and endometrial cancers, and use of COCs offers significantly reduced risk of developing these malignancies. Unfortunately, most women still remain unaware of these documented noncontraceptive health benefits of COC use. The demonstrated absence of an increased risk of breast cancer with COC use, even in women with a family history of breast cancer, should allay many women's concerns. Clinicians should educate women for whom cancer risks are a concern about the substantial body of evidence supporting the safety in this regard of use of COCs and other contraceptive methods.

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