The Good News About Hormonal Contraception and Gynecologic Cancer
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Of American women aged 15 to 44 years who are at risk of unintended pregnancy, 40% are currently using hormonal contraception, and more than 75% previously used hormonal birth control. In 1997, gynecologic cancers (e.g., breast, endometrial, ovarian, cervical) will be diagnosed in an estimated 256,000 US women and result in the deaths of 69,000. If use of hormonal contraception can reduce the risk of reproductive cancer, the public health impact and clinical implications would be significant. This review details these associations and provides reas-surance that the use of hormonal contraceptives including combination oral contraceptives (OCs), progestin-only OCs, levonorgestrel subdermal implants, and depot medroxyprogesterone acetate (DMPA) injections prevents ra- ther than promotes gynecologic cancer.

Breast Cancer
Breast cancer remains the most prevalent cancer in American women; an estimated 180,000 new cases will be diagnosed in 1997, and approximately 44,000 deaths will occur. As a cause of cancer death in women, breast cancer ranks second only to lung cancer a mortality figure that is considerably greater than the combined number of deaths from endometrial, ovarian, and cervical cancers in the United States. Because breast cancer is both common and lethal, understanding the research on potential associations between hormonal contraception and breast cancer is a high clinical priority.
A meta-analysis that reassessed 54 studies of breast cancer risk and OC use encompassed 90% of all available epidemiologic data. It included more than 53,000 breast cancer cases and 100,000 controls.

Current OC users and those who had discontinued use within the past 10 years were found to be at slightly increased risk compared with nonusers. However, breast cancers diagnosed in women with a history of OC use were more localized than those in nonusers. The most important finding of this massive reanalysis was that at 10 to 20 years after OC discontinuation, the estimated cumulative number of breast cancer cases in OC ever-users was the same as in never-users (Table).

Although follow-up data on mortality were not available from the studies assessed by this meta-analysis, the results raise the possibility that a decade or more after OC discontinuation, cumulative deaths from breast cancer may have been lower in OC ever-users than in never-users. Factors that did not impact the overall findings regarding OC use and breast cancer risk included reproductive history, family history of breast cancer, duration of OC use, age at first OC use, and steroid dosage or type. This report represents the most comprehensive study of OC use and breast cancer risk ever published and should broadly reassure both clinicians and patients.

**Endometrial Cancer**

Endometrial cancer is the most common genital cancer in the United States, with an incidence second only to that of breast cancer. In 1997, approximately 35,000 cases of endometrial cancer will be diagnosed, and an estimated 6,000 women will die from this disease.

Estrogenic proliferation of the endometrium combined with absent or inadequate progestational suppression characterizes the majority of women who develop endometrial adenocarcinoma. In women who use hormonal contraception, the endometrium is almost continuously under the influence of synthetic progestins and thus might be less susceptible to malignant transformation. Strong evidence indicates that the risk of endometrial cancer in women younger than age 60 is substantially reduced by current or prior use of OCs. Furthermore, this protection increases markedly with longer duration of OC use.

A study from the Centers for Disease Control and Prevention (CDC) assessed 433 cases of endometrial cancer in women 20 to 54 years of age and 3,191 controls. Compared with never-users, women who had used combination OCs were 50% less likely to develop endometrial cancer. Twelve other case-control studies and three cohort studies have also examined the association between endometrial cancer risk and OC use. All but two of these investigations found a protective effect.

One case-control study looked at endometrial cancer risk up to 20 years after OC discontinuation and found that the protection against endometrial cancer persisted for at least two decades. Therefore, women who use OCs in their late 30s and 40s may be able to reduce their likelihood of developing endometrial cancer for the decades when they will be at highest risk.

**Ovarian Cancer**

Ovarian cancer remains the most lethal female reproductive-tract malignancy, with regional or distant metastasis present in 75% of patients at the time of diagnosis. The incidence of ovarian cancer rises slowly during the reproductive years. It becomes more common after menopause and peaks among women in their 70s. In the United States, some 27,000 cases of ovarian cancer will be diagnosed in 1997, and an estimated 14,200 women will die from this disease. Overall, the 5-year survival rate among ovarian cancer patients is only 40%.

Epithelial tumors account for 80% to 90% of ovarian cancers. A high lifetime total of ovulatory cycles may increase ovarian cancer risk; for example, pregnancy and lactation both of which suppress ovulation reduce ovarian cancer risk. By the same token, prolonged use of ovulation-induction therapy may increase ovarian cancer risk. Since OC use suppresses ovulation, it is biologically plausible that ovarian cancer risk might be lower among women using this method of contraception. In 1987, the CDC analyzed data on 492 cases of malignant epithelial and borderline ovarian cancer and 4228 controls. It found that ovarian cancer risk in OC users was 40% lower than in nonuser controls. Furthermore, the risk of ovarian cancer declined with increasing duration of OC use, with an 80% risk reduction in women who had used OCs for 10 years or longer. Extensive worldwide literature assessing OC use and ovarian cancer risk including 20 case-control and 3 cohort studies strongly supports the CDC findings that use of combination OCs helps prevent this lethal disease.

One well-controlled study found that OC use protected against ovarian cancer for up to 20 years following discontinuation. This suggests that women in their 40s who use OCs may be able to reduce
the likelihood of developing ovarian cancer during the years when the incidence of this disease peaks. A reanalysis of the CDC data found that the protective effect of OCS applies to women at higher risk for ovarian cancer. Nulliparous women who used OCS for at least 5 years reduced their risk of ovarian cancer to a level equal to or less than that experienced by parous women. Likewise, women with a positive family history of ovarian cancer who used OCS for 10 years or more reduced their risk to a similar or lower level than that of women with a negative family history. Because lay-media publicity on ovarian cancer has focused on serum CA-125 tumor markers and vaginal ultrasonography screening, few US women are aware that OC use may reduce their ovarian cancer risk. Therefore, physicians must inform their patients that ovarian cancer risk may be decreased through use of OCS.

**Invasive Squamous Cell Cervical Cancer**

Cervical squamous cell neoplasia appears to be a sexually transmitted disease. The lifetime number of male sexual partners and incidence of human papillomavirus (HPV) infection are positively associated with cervical cancer, while use of barrier contraception (e.g., condom, diaphragm) and spermicides containing nonoxynol-9 protects against this disease. The marked decline of invasive cervical cancer incidence and mortality in the United States is presumably the result of widespread Papanicolaou cytologic screening, allowing identification and treatment of preinvasive cervical intraepithelial neoplasia.

The unique epidemiology of cervical neoplasia makes assessment of any association with OC use difficult. Women who use OCS often have more sexual partners and are less likely to use barrier contraception than other women. In addition, because of examinations associated with prescription renewals, women using OCS undergo cytologic screening more frequently than do other women. Each of these factors can confound the potential associations between OC use and cervical cancer risk. Three large, well-controlled studies failed to find a significant association between the risk of invasive cervical cancer and ever use of OCS.

**Cervical Adenocarcinoma**

Adenocarcinoma, which accounts for approximately 10% of cervical cancers, may have an epidemiology distinct from that of the more common squamous cell tumors. The incidence of adenocarcinoma appears to be increasing among US women. Although the literature is conflicting, two large, thorough case-control studies found that OC use was associated with a significantly increased risk of adenocarcinoma of the cervix.

**Cervical Intraepithelial Neoplasia**

The same inconsistent findings and methodologic challenges exist for cervical intraepithelial neoplasia (CIN) as for invasive cervical cancer. Most well-controlled studies including 3 case-controlled reports have found no association between OC use and CIN.

The declining incidence of invasive cervical cancer among US women presumably reflects widespread screening for CIN. All women at risk for cervical neoplasia, including those who use hormonal contraception, should receive regular cytologic screening. Women with a history of CIN (including those who have undergone conization, cryotherapy, laser, or loop excision) as well as those being evaluated for CIN remain appropriate candidates for hormonal birth control.

Although DMPA was first marketed in the United States in the 1960s, concern over possible links with breast and other reproductive cancers delayed Food and Drug Administration (FDA) approval of this injectable contraceptive until the early 1990s. Publication of reassuring World Health Organization (WHO) studies assessing cancer risk and DMPA played a major role in its ultimate regulatory and clinical acceptance in this country.

Overall, DMPA appears to have no impact on the risk of breast cancer. However, a pattern of increased risk in recent users but not in long-ago past users is similar to that observed with OCS and term pregnancy. Use of DMPA decreases the risk of endometrial cancer, with the WHO study observing an 80% risk reduction i.e., even greater protection than that seen with OCS.

Because DMPA suppresses ovulation, it also might be expected to reduce the risk of epithelial ovarian adenocarcinoma. However, the WHO investigators found ovarian cancer risk to be similar in DMPA users and nonusers. In the countries studied, DMPA was used only by parous women. Thus,
the investigators concluded that DMPA may not confer additional protection against ovarian cancer beyond that provided by full-term pregnancy. As with OCs, use of DMPA does not appear to alter the risk of squamous intraepithelial or invasive cervical neoplasia.

An exhaustive review found that the overall association between progestin-only OCs (minipills) and reproductive-tract cancers parallel those of combination OCs. No published data have assessed cancer risks in women using contraceptive implants.

An overwhelming body of epidemiologic data reassures clinicians that overall, hormonal contraceptive use does not increase cancer risk. Indeed, in the case of ovarian and endometrial cancers, OC use provides substantial protection. Therefore, an important public health question remains: Why are misperceptions of hormonal contraception so common, and why are so many women unaware of their associated health benefits?

A 1985 Gallup poll sponsored by the American College of Obstetricians and Gynecologists found that half the women surveyed believed the possibility of cancer and other supposed risks of OC use exceeded those of childbearing. Approximately 30% of these women thought that OCs actually caused cancer. In a survey of 247 women aged 16 to 68 years receiving care at Yale University's health clinic, 38% believed that cancer was associated with OC use. Between 80% and 95% of the women surveyed were unaware of the noncontraceptive health benefits of OC use. A 1993 Gallup poll found a national sample of US women to be similarly misinformed regarding OCs.

The responsibility to provide balanced information about hormonal contraception rests with clinicians. Time spent directly educating patients regarding the benefits and risks of these modalities is time well spent. Likewise, physicians who make themselves available to the media can help facilitate more accurate and objective reporting on this topic. While some epidemiologic issues involving gynecologic cancer remain to be resolved, clinicians can be confident that for appropriately counseled and selected candidates, the risks are far outweighed by the substantial benefits offered by hormonal contraception.

References:
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