64. Counseling to Prevent Gynecologic Cancers

RECOMMENDATION

There is insufficient evidence to recommend for or against routine counseling of women about measures for the primary prevention of gynecologic cancers. Clinicians counseling women about contraceptive practices should include information on the potential benefits of oral contraceptives, barrier contraceptives, and tubal sterilization with respect to specific gynecologic cancers (see Chapter 63). Clinicians should also promote other practices (maintaining desirable body weight, smoking cessation, and safe sex practices) that may reduce the incidence of certain gynecologic cancers and have other proven health benefits (see Chapters 21, 54, and 62).

Burden of Suffering

Gynecologic malignancies are an important cause of morbidity and mortality in women.[1] Ovarian cancer is the fourth most common cause of death from cancer among women of all ages in the U.S.[2] Estimates for 1995 anticipated that there would be 15,800 new cases and 4,800 deaths from cervical cancer, 32,500 new cases and 5,900 deaths from endometrial cancer, and 26,600 new cases and 14,500 deaths from ovarian cancer.[2] Although Papanicolaou (Pap) smear screening has helped reduce mortality from cervical cancer (see Chapter 9), there are no screening strategies that have been proved effective in reducing mortality from endometrial or ovarian cancer (see Chapter 14).

Even when cancers are detected early, the treatment of invasive cervical cancer, endometrial cancer, and ovarian cancer involves surgery and often additional radiation therapy or chemotherapy. Despite aggressive treatment, 5-year survival of women with ovarian cancer is only about 40%.[2] In addition to the costs and morbidity from treatment, the loss of reproductive function and ovarian function can have important psychological and physical consequences in premenopausal women. Compared to early detection and treatment, primary preventive strategies offer the potential to reduce both mortality and morbidity from gynecologic cancers.[3]

Efficacy of Risk Reduction

Cervical Cancer. Certain sexual behaviors are consistently associated with an increased risk for cervical cancer. Women who became sexually active at an early age and women with a high lifetime number of sex partners have a significantly increased risk of cervical cancer.[4] Use of barrier contraception (diaphragm and condoms) and spermicides (foam or contraceptive jelly) is associated with lower risk of invasive cervical cancer. Of 11 case-control studies[5–15] and one cohort study[16] examining this issue, 10 reported that at least one of these methods of contraception was associated with a significantly lower risk of cervical cancer. This protective effect persisted after controlling for the potential influence of age at first intercourse, cytology screening history, and smoking.[11,13,16] Substantial reductions in risk of invasive cervical cancer were observed among both condom users (odds ratios [OR] = 0.4–0.8, i.e., 20–60% reduction in risk)[11] and diaphragm users (OR = 0.2–0.7).[5,16] A longer duration of use was associated with greater protection.[11] In one study, barrier contraceptives reduced risk only among women with multiple sex partners.[13] Spermicides afforded protection comparable to physical barriers in three studies;[12–14] proving an independent effect of spermicides is difficult since they are often used in conjunction with other barrier methods.

The apparent protective effect of avoiding high-risk sexual activity and using barrier contraceptives or spermicides is presumably mediated through reducing the incidence of sexually transmitted diseases (STDs). Human papillomavirus (HPV) appears to be an important factor in the etiology of cervical cancers:[1,4,17] women with HPV infection have a 10-fold higher risk of developing invasive cervical cancer.[18] Direct evidence that spermicides or barrier contraception prevents HPV infection is limited, however.[19] Despite in vitro activity against many sexually transmitted viruses and bacteria, nonoxynol-9 did not inhibit papillomaviruses in one recent study.[20]

Smoking is also associated with an increased risk of invasive cervical cancer.[17,21–23] Recent case-control studies report a 2-fold increased risk among smokers versus nonsmokers; risk remained significantly elevated after controlling for other risk factors.[13,24–26] Most studies suggest a dose-response relationship between risk and cigarette use. Ex-smokers have a risk below that of current smokers, but higher than in nonsmokers.[13,25–27]

Some dietary factors, such as high levels of vitamin C, have also been associated with reduced risk of cervical cancer.[28,29] Two case-control studies have reported significantly lower risk (30–50% lower) in women with the highest versus lowest vitamin C intake.[30,31] The relationship of dietary folate, vitamin E, and dietary carotenoids to invasive cervical cancer is unclear.[4,29,32] Attributing a protective effect to any specific dietary compo-

nent is problematic, however, due to the possible influence of other dietary constituents or lifestyle factors.[29,33] The mechanisms by which dietary factors might protect against cervical neoplasia remain speculative, but include antioxidant effects or enhancement of the immune system.[30]

Long-term use (>5 years) of oral contraceptives (OCs) has been associated with an increased risk of invasive cervical cancer,[17,34,35] which remains elevated after controlling for sexual history and cytologic screening.[36–38] Two large collaborative case-control studies[36,38] and a large cohort study in the United Kingdom[39] each reported increased risks of cervical cancer among women who have ever used OCs (OR = 1.2–1.8). A meta-analysis of 18 methodologically sound epidemiologic studies[40] reported an increased risk for invasive cancer among OC users (OR = 1.21, 95% confidence interval [CI], 1.1 to 1.4), with increasing risk with longer durations of use. Although a causal association between OC use and cervical cancer is biologically plausible (OCs cause endocervical hyperplasia), it is difficult to exclude the effect of other risk factors among long-term OC users (e.g., multiple sex partners or low use of barrier contraceptives).[17,41]

Endometrial Cancer. Childbearing seems to protect against endometrial cancer,[42] and the use of combination oral contraceptives is consistently associated with a lower risk of endometrial cancer. Of 13 case-control studies,[38,43–54] and three cohort studies,[39,55,56] all but two indicated a protective effect of oral contraceptive use (OR = 0.1–0.6).[1] In the largest study, the Cancer and Steroid Hormone (CASH) study which involved 433 cases and 3191 controls, women who had used combination OCs for at least 1 year had an age-adjusted OR of endometrial cancer of 0.6 (95% CI, 0.3 to 0.9).[51] The protective effect began after 1 year of use and lasted up to 15 years after discontinuing the pills, but it was most evident in nulliparous women. Two of three cohort studies have reported similar protective effects.[39,51,56] The Royal College of General Practitioners study from the United Kingdom followed 47,000 women and found an 80% reduction in risk (RR = 0.2; 95% CI, 0.0 to 0.7) among OC users.[39]

In the CASH study, lower risk was seen with a variety of different combination OCs (OR = 0.2–0.7).[51] In one report, high-dose estrogen/low-dose progestin pills were less effective (OR = 1.1; 95% CI, 0.1 to 10.0) than low-dose estrogen/high-dose progestin pills (OR = 0.0; 95% CI, 0.0 to 1.1),[57] but the importance of formulation remains controversial.[58] Other unresolved questions include the duration of protection, since most endometrial cancer occurs after age 60, and the effects of past OC use in women taking postmenopausal hormone therapy.[58] Use of unopposed estrogen after the menopause is associated with an increased risk of endometrial cancer, but the risk is reduced or eliminated by regimens combining estrogen with progestins (see Chapter 68).[59]

Overweight women have an increased risk of endometrial cancer.[17] Nineteen reports, using varying definitions of overweight, observed relative risks ranging from 1.0–20.3 for overweight women.[42,54,60] Most RRs were above 2, and body mass was significantly correlated with cancer risk. In contrast with several other diseases, the total amount of adiposity may be more important than its distribution (i.e., waist-hip ratio) in the development of endometrial cancer.[61]

The protective effects of OCs and of normal weight may reflect the adverse effects on the endometrium of unopposed estrogen stimulation.[62] Obesity is associated with increased anovulation, increasing levels of circulating estrogens, and lower progesterone levels, due to conversion of androstenedione into estrone (an estrogen) by adipose tissue.[17] OCs containing progestins reduce the period of unopposed estrogen stimulation of the endometrium.

Ovarian Cancer. Childbearing reduces the risk of ovarian cancer,[63] and use of oral contraceptives may have a similar effect. Of 20 case-control studies[38,49,64–81] of the association between OC use and ovarian cancer, all but two found a lower risk among users of OCs.[79,80] Three cohort studies, one from the U.S.[55] and two from the U.K.,[39,82] all reported substantial protective effects of oral contraceptives (RR = 0.4, 0.6, and 0.3, respectively). In a 1992 meta-analysis of these studies, the pooled risk of ovarian cancer was 30–40% lower in OC users in case-control studies, and 60% lower in cohort studies (RR = 0.4; 95% CI, 0.3 to 0.8).[83] In the CASH study, with 546 cases and 4,228 controls,[64] a protective effect was evident after as little as 3–6 months of pill use, persisted for at least 15 years after discontinuation, increased with duration of use (80% reduction after 10 or more years), and was evident for each of 11 commonly used formulations.

Breastfeeding also appears to lower a woman's risk of ovarian cancer.[44,64,69,79,84–86] In an analysis of 12 case-control studies, women who had breast fed an infant had a 20% lower risk of ovarian cancer (OR = 0.8; 95% CI, 0.7 to 1.0) than parous women who had never breastfed;[63] each month of breastfeeding was associated with a 1% reduction in overall risk. Childbearing, OC use, and breastfeeding may reduce the risk of malignant transformation by prolonging periods of anovulation or suppressing gonadotropin levels.

Tubal sterilization is associated with a lower risk of ovarian cancer in a number of case-control studies (OR = 0.2–0.9).[63,78,80,86–89] A recent, large cohort study of nearly 78,000 premenopausal nurses demonstrated a substantial reduction in subsequent ovarian cancer among women who had tubal ligation (RR = 0.3; 95% CI, 0.2 to 0.6).[90] A meta-analysis of published studies estimated that tubal sterilization reduced risk by 40% (RR = 0.6; 95% CI, 0.4 to 0.9).[90] This protective effect may be due to isolation of the

ovaries from carcinogens imported from the external environment.[91,92] Hysterectomy, which has a simiar effect, is associated with a somewhat smaller reduction in ovarian cancer (RR = 0.6–0.7).[63,88,90]

Recent trends in the U.S. and U.K. are consistent with a protective effect of OCs on endometrial and ovarian cancer.[62,93,94] In women under 50 (those with greatest exposure to combination OCs) incidence of endometrial cancer fell 28% between 1973 and 1986 in the U.S., and incidence of ovarian cancer declined 20%, similar to changes predicted based on a protective effect of OCs.[62,95] Interpreting temporal trends is complicated by changes in other risk factors (e.g., parity, estrogen use) and in screening practices, however.

Effectiveness of Counseling

There are no data to determine whether counseling women specifically about primary prevention of gynecologic cancers influences their choice of contraception or their attention to other risk factors (sexual practices, weight control, diet, or smoking). Women and men choosing a particular method of contraception may regard other considerations—costs, effectiveness, convenience, and protection against STDs—as more important than long-term effects on gynecologic cancers, which account for less than 10% of all cancer deaths in women. Some women may place a higher value on reducing their risk of cancer, however, or have risk factors that place them at higher risk for specific cancers. These important noncontraceptive benefits of modern OCs are often not mentioned when the risks and benefits of these agents are discussed. A recent survey of female employees, students, and faculty at a large university revealed that 80% did not know that use of OCs protects against ovarian cancer.[96]

There is only limited evidence that clinical counseling can reduce the high-risk sexual behaviors in young women that put them at future risk for cervical cancer (see Chapter 62). Early sexual activity and multiple sex partners remain common among young men and women. Counseling men is more effective than counseling women in increasing regular use of condoms.[97] Although methods under female control (diaphragms, spermicides and female condom) may also be protective, they remain less popular, especially among high-risk populations.[98]

Discussion

A large body of evidence suggests that specific measures can reduce the risk of cervical, ovarian, or endometrial cancer. Although this evidence comes from epidemiologic studies rather than from controlled trials, various considerations support the conclusion that certain interventions have a protective effect against cancer:[99] the observed associations are strong,

consistent in multiple studies, biologically plausible, dose-dependent, and not explained by differences in other risk factors. Evidence of a protective effect of OCs on endometrial and ovarian cancer is compelling and stronger than that for adverse effects of OCs on cervical cancer. Furthermore, ovarian and endometrial cancers together account for four times as many deaths as cervical cancer, which can often be prevented by effective screening. Tubal sterilization, hysterectomy, and breastfeeding also appear to reduce risk of ovarian cancer, but evidence is more limited. Other measures (breastfeeding, avoiding smoking, obesity, and high-risk sexual activity) also appear to reduce the risk of specific gynecologic cancers, and there are other compelling reasons to promote these measures routinely for all patients. In contrast, the evidence is not yet sufficient to recommend specific diets to reduce the risk of cervical cancer. More information may come from ongoing chemoprevention trials of vitamin supplementation.[100]

Women selecting contraception need to consider not only the convenience and effectiveness of a given method, but other important noncontraceptive risks and benefits as well (see Chapter 63).[101,102] The favorable effects of OCs on endometrial and ovarian cancer are more consistent yet less widely appreciated than some of the possible risks of OCs, such as cardiovascular disease or breast cancer. Despite the relative safety of oral contraceptives, however, it is not clear that the potential benefits with respect to ovarian and endometrial cancer would justify the expense, inconvenience, and possible risks of OC use in women who do not otherwise need contraception. One study estimated that treating 100,000 women with OCs for 8 years might prevent 193 cases of ovarian cancer and 197 cases of endometrial cancer;[103] net benefit, however, would be negligible if OCs increase the risk of cervical or breast cancer. Nonetheless, for women with specific concerns about gynecologic cancers, information about effective measures that they can take to reduce their risk of cervical, ovarian, or endometrial cancer may be particularly useful.

CLINICAL INTERVENTION

There is insufficient evidence to recommend for or against routine counseling of female patients about measures to reduce the risk of cervical, ovarian, and endometrial cancer (“C” recommendation). Clinicians counseling women about contraceptive practices should include information about the potential benefits of specific methods with respect to gynecologic cancers (see Chapter 63). These potential benefits include reduced risks of ovarian and endometrial cancer in women using OCs, cervical cancer in women who use barrier contraception and spermicides, and ovarian cancer after tubal sterilization. All women should be counseled about effective means to prevent STDs (see Chapter 62) and about the benefits of

breastfeeding (see Chapter 56), avoiding obesity (see Chapter 21), and avoiding tobacco use (see Chapter 54).

Note: See background paper: Grimes DA, Economy KE. Primary prevention of gynecologic malignancies. Am J Obstet Gynecol 1995;172:227–235.

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