The Pill and Ovarian Cancer Prevention

By Malini Guha

Several decades ago, researchers observed a protective association between oral contraceptives (OCs) and ovarian cancer. Many observational studies across largely unselected populations using “the pill” in different patterns and formulations have replicated this finding, with many finding the risk reduced by up to half, depending on duration of use. OCs are also widely believed to reduce risk of endometrial cancer and possibly colorectal cancer.

Although U.S. women have greater access to OCs now than ever before—owing to a controversial Affordable Care Act provision requiring insurance companies to provide contraception for free—many women opt for birth control with intrauterine devices and implants, especially after a large study published last May in the New England Journal of Medicine found that they prevented pregnancy better than OCs.

And taking the pill just to prevent ovarian cancer is not something major national cancer and gynecology organizations recommend, even though most state that OC use reduces the risk of ovarian cancer. “The choice to use OCs should not be made solely for ovarian cancer prevention,” the Society of Gynecologic Oncology said in a statement. Meanwhile, specific guideline-making bodies, such as the U.S. Preventive Services Task Force, have not made the issue a priority.

“Organizations and medical societies are more comfortable issuing guidelines from evidence from randomized controlled trials (RCTs) after recent mishaps in interpreting evidence from observational studies,” said Eduardo Franco, M.P.H., Dr.P.H., of McGill University in Montreal, Canada. The most commonly cited “mishap” that has made experts particularly cautious is that of hormone replacement therapy’s (HRT) benefits in reducing risk of cardiovascular disease, which observational studies detected but RCTs later contradicted. However, said Franco, “the debate on HRT is still ongoing, and observational studies might not be too far off the truth.”

Also, some experts believe that less chance for bias or confounding exists for OCs than for HRT, with more women being excluded from taking HRT, leading to greater differences between users and nonusers.

In any case, experts generally say that conducting an RCT to definitively show that OCs reduce the risk of ovarian cancer would require tens of thousands of subjects, lasting decades and facing many logistical challenges.

“And to complicate matters, OCs are not interventions that are across the board favorable; there are some downsides too,” said Franco, including a possible slightly increased risk of breast cancer and vascular side effects.

CDC Commissions Investigative Report

Ovarian cancer is the fifth leading cause of cancer death in women and has a 5-year overall survival rate of just 44%. And with early detection methods so far showing no benefit in ovarian cancer (the U.S. Preventive Services Task Force in September reaffirmed its guidance against routine screening for average-risk women), researchers are looking at primary prevention more closely.

To investigate the overall risks and benefits of OCs, the Centers for Disease Control and Prevention (CDC) commissioned the federal Agency for Healthcare Research and Quality (AHRQ) to conduct the first comparative effective analysis to inform decisions about using OCs to prevent ovarian cancer. The draft evidence report, Oral
Contraceptive Use for the Primary Prevention of Ovarian Cancer, is being finalized.

The CDC was specifically interested in whether women who weren’t using the pill to prevent pregnancy, or had taken it for only a short time, could be advised to use it mainly to prevent ovarian cancer. Restricted to relatively common cancers or vascular events that showed consistent evidence of a positive or negative association with OC use, the analysis also excluded potential benefits related to pregnancy prevention and other outcomes.

The study, which AHRQ assigned an evidence-based practice center at Duke University to conduct, judged the evidence that OCs prevent ovarian cancer as “moderate” in a meta-analysis of 25 studies published since 1990, primarily because of the lack of RCTs included. However, said Evan Myers, M.D., M.P.H., one of the report’s authors, “From a classic epidemiology perspective, like smoking and lung cancer, it meets all the criteria.”

**Mortality Benefits Outweigh Risks in Simulation Model**

In a simulation model, the noncontraceptive benefits outweighed the harms of OCs in average-risk women when considering mortality, with the reductions in mortality from ovarian, endometrial, and colorectal cancer exceeding increases from breast cancer and vascular events. This benefit modestly increased life expectancy by 1–2 months in the general population, on the basis of current OC use patterns. A large UK cohort study published by Philip Hannaford, M.D., and colleagues in the British Medical Journal in 2010 similarly found reduced overall risk of death for OC users.

In addition to an overall mortality benefit, and in keeping with the Hannaford study, the model predicted overall reduced risk of cancer. At the ages of peak incidence, ever use of OCs was associated with an absolute reduction of 20 per 100,000 in ovarian cancer incidence, 50 per 100,000 in colorectal cancer incidence, and 55 per 100,000 in endometrial cancer incidence, whereas breast cancer increased by 20 per 100,000 and cervical cancer by 4 per 100,000.

The meta-analyses showed that ovarian and endometrial cancer had the largest relative risk reductions, whereas the relative risk increase for breast cancer was small (8%) and decreased after women stopped using the pill—largely in line with past studies. Ever use of OCs was associated with a 27% reduction in ovarian cancer risk overall and more than 50% reduction with 10 or more years of use.

Because breast cancer incidence, but not mortality, was increased in the meta-analysis and cohort studies, some speculate that the increased incidence is an artifact of increased surveillance of women on OCs, although making that determination will be difficult.

Besides breast cancer, the incidence of vascular events substantially outnumbered the prevented cases of ovarian cancer, especially in women aged 35–44 years—who are not frequent users of OCs but who might consider them for chemoprevention. In these women, the model found an increased incidence of deep venous thrombosis of 150 per 100,000, 30 per 100,000 for pulmonary embolism, 30 per 100,000 for stroke, and 12 per 100,000 for acute myocardial infarction (the increases were much less for all in women aged 20–30 years). These estimates may be too high, with the model assuming constant risk during use. Also, not all the studies on which the model was based accounted for underlying cardiovascular risk factors, and not all included today’s lower-dose estrogen pills, which have reduced risk of stroke. Experts recommended continued evaluation of today’s pills.

Ultimately, the report cited “insufficient evidence to recommend for or against the use of OCs solely to prevent ovarian cancer.” The reason is “primarily the lack of RCT data, but also missing evidence from the studies on factors such as quality-of-life or morbidity related to conditions such as stroke, which would weigh into benefit–harm calculations,” said Myers. “We are fairly comfortable that the benefit–harm ratio in terms of mortality is favorable, especially when reduction in endometrial and colorectal cancer deaths is included, but less certain about the benefit–harm ratio in terms of incidence.”

**Sidebar: In the Clinic**

Doctors emphasize that weighing the benefits and risks will be an individual decision for patients. “Doctors would need to have a discussion with patients about small increased risks of breast cancer and vascular harms while using the pill when the background risk of these is low, and greater benefits later in life when the background risk of cancer is higher,” said Hannaford. “It will be up to the individual woman to decide what she values.”

According to Society of Gynecologic Oncology president Ronald Alvarez, M.D, of the University of Alabama at Birmingham, “the guidelines should be that physicians should discuss risks and benefits of OCs, including the reduction in risk of ovarian cancer, with women.”

Ovarian cancer affects only about 1.4%, or 1 in 72, U.S. women, and unfortunately, so far no widely accepted and validated model exists to predict ovarian cancer risk for relatively low-risk women (those without BRCA mutations), although researchers are working to develop them. “We are left with what we have, trying to individualize the decision on the basis of a patient’s past medical history, family background, and epidemiologic risk factors,” said Alvarez. “I would consider OCs in women with slightly higher risk than the general population based on these variables, provided that they have no strong contraindications for
OCs, such as smoking or cardiovascular disease. A woman’s age and the duration of OC use will also be crucial to determine benefit–harm ratios. Preliminary results of the simulation model in the AHRQ-commissioned study will also be crucial to determine benefit–harm ratios. The summaries are regularly updated by six editorial boards. The following PDQ summaries were recently updated:


The PDQ (Physician Data Query) is the National Cancer Institute’s source of comprehensive cancer information. It contains peer-reviewed, evidence-based cancer information summaries on treatment, supportive care, screening, prevention, genetics, and complementary and alternative medicine. The summaries are regularly updated by six editorial boards. The following PDQ summaries were recently updated:


The PDQ Genetics of Colorectal Cancer summary and the PDQ Genetics of Breast and Ovarian Cancer summary were recently updated to include information about the risk of female breast cancer in Lynch syndrome. Retrospective studies have been inconsistent, but the largest prospective study to date of 446 unaffected mismatch repair gene mutation carriers who were followed for 10 years found an elevated risk of breast cancer, with a standardized incidence ratio (SIR) of 3.95 (95% confidence interval [CI], 1.59–8.13; P = .001). Another analysis of 764 mismatch repair gene mutation carriers who had a prior diagnosis of colorectal cancer found a 10-year risk of breast cancer following colorectal cancer of 2% (95% CI, 1%–4%), with a SIR of 1.76 (95% CI, 1.07–2.59). To review the summaries, please use the following links: http://www.cancer.gov/cancertopics/pdq/genetics/colorectal/HealthProfessional/Page4#Section_120 http://www.cancer.gov/cancertopics/pdq/genetics/breast-and-ovarian/healthprofessional/allpages#Section_2273


The PDQ Rectal Cancer Treatment summary was recently updated to include results of the German CAO/ARO/AIO-04 trial, in which 1,236 patients with clinically staged T3–T4 or clinical node-positive rectal cancer within 12 cm of the anal verge were randomly assigned to receive either concurrent chemoradiation with 5-fluorouracil (5-FU) (week 1 and week 5) or concurrent chemoradiation with 5-FU daily (250 mg/m2) and oxaliplatin (50 mg/m2). A high rate of pathologic complete response was achieved in patients who received oxaliplatin (17% vs. 13%, P = .038). There was no significant difference in the rates of overall grades 3 and 4 toxicity; however, diarrhea and nausea and vomiting were more common among those treated with oxaliplatin. The 5-FU schedules in this trial differed between the two arms, which may have contributed to the difference in outcomes noted. Longer follow-up will be necessary to determine the effect on disease-free survival, which was the primary endpoint of the study. To review the summary, please use the following link: http://www.cancer.gov/cancertopics/pdq/treatment/rectal/HealthProfessional/Page4#Section_597


The PDQ Esophageal Cancer Treatment summary was recently updated to include results of a study by the Japanese Clinical Oncology Group, in which 330 patients with clinical stage II or stage III (excluding T4 tumors) squamous cell carcinoma of the esophagus were randomly assigned to receive either two cycles of preoperative cisplatin and 5-fluorouracil followed by surgery versus surgery followed by postoperative chemotherapy with the same regimen. A planned interim analysis was conducted after patient accrual, and, although the primary endpoint of progression-free survival (PFS) was not met, there was a significant benefit in overall survival (OS) among patients treated with preoperative chemotherapy (P = .01). As a result of these findings, the Data and Safety Monitoring Committee recommended early publication. With a median follow-up of 61 months, 5-year OS was 55% among patients treated with preoperative chemotherapy compared with 43% among patients treated with postoperative chemotherapy (P = .04). However, there was no significant difference between groups with respect to PFS (5-year PFS, 39% vs. 44%; P = .22). Additionally, there were