Significant Risks of Oral Contraceptives (OCPs)

Why This Drug Class Should *Not* Be Included in a Preventive Care Mandate

Rebecca Peck, M.D., C.C.D., and Charles W. Norris, M.D.*

Dr. Rebecca Peck is a board-certified family physician, certified clinical densitometer, and Marquette Method NFP teacher. Dr. Peck may be contacted at rbamer2@yahoo.com. Dr. Norris is a retired obstetrician/gynecologist and a graduate of the Georgetown University School of Medicine, class of 1957. He may be contacted at chazno@comcast.net.

Abstract

Pregnancy is not a disease. But more fundamentally, neither is human fertility. They are normal physiologic processes of the sexually mature person. By classifying pregnancy and fertility as disease states, certain entities are able to position contraception as "the cure." Currently, these same organizations want to include oral contraceptive counseling and medications in the new national health-care plan under a preventive care mandate. But it is the physician's role to counsel patients on preventive care measures. We understand that these evidenced-based screenings help to change risky behaviors and catch disease in its earliest stages, thereby reducing patients' overall morbidity and mortality. However, we believe that patients incur substantial health risks when

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choosing oral contraceptives (OCPs). This paper reviews the major risks of OCPs. The authors presume that the prevailing widespread acceptance and promotion of OCPs indicates general agreement within the medical community that OCPs are good for the patient (or at least not significantly harmful). Therefore, this paper concentrates on the studies which show increased harm and risk to the patient choosing to use OCPs. We have concentrated our efforts on three major areas: increased rates of cardiovascular disease, breast cancer, and human papillomavirus (HPV) or cervical cancer. If fertility and pregnancy are not disease states, and are, in fact, normal conditions associated with healthy individuals, OCPs fail the most important test of preventive medicine: they increase risk of disease instead of decreasing it. *Patients should not be misled or confused into believing that what they are taking is "good for them" and is of the same beneficial effect as other preventive measures.*

Introduction

Primary care physicians spend a substantial part of their clinical time counseling patients on preventive care. Some examples of these items include: providing information on diet and exercise; giving smoking cessation counseling; performing diabetes and cholesterol screenings; obtaining mammograms, Pap smears, and bone densitometry; and administering immunizations. The rationale behind such preventive screenings is to reduce morbidity and mortality by changing risky behaviors and by catching disease in its earliest stages.

Currently, there are several entities that want to include oral contraceptive counseling and medications within a preventive care platform. This proposal is ill-advised for several reasons. Firstly, oral contraceptives (OCPs) have their own significant risks, namely, an increase in cardiovascular events (such as an increase in venous thromboembolism, pulmonary embolism, myocardial infarction, and stroke) especially in older women and smokers.[1] Secondly, OCPs increase the risk of the world's most frequently occurring cancer, breast cancer.[2] Thirdly, OCP use leads to an increase in human papillomavirus (HPV) infection and an increase in cervical cancer, which is the second most common cancer worldwide.[3] Therefore, OCPs fail the most important test of preventive medicine: they *increase* the risk of disease instead of decreasing it.

Pregnancy is not a disease. But more fundamentally neither is human fertility. Rather, our fertility is a completely normal part of the physiology of the sexually mature person and is the *only* normal physiologic function medical providers treat as if it were a disease by chemical suppression, manipulation, or surgical elimination. If, for example, a physician were to suggest to a woman that he should treat her cardiovascular, respiratory, or even her neurologic functioning as he seems perfectly willing to treat her fertility—mind you, a perfectly normal physiologic process—she would not walk, but run out of his office! Further-

more, as one of the functions of oral contraceptives is to suppress ovulation and, therefore, a woman's fertility, is it advisable or even reasonable for physicians to prescribe a "medication" which, as its function, suppresses a perfectly normal physiologic process? We believe not.

This paper will focus on the medical harm caused by OCPs. Since the birth control pill is so widely prescribed, we do not focus on those research studies which support its use. Instead, we analyze the current research available, which shows increased morbidity and mortality in three key areas: 1) increased cardiovascular events, 2) increased breast cancer rates, and 3) increased HPV and cervical cancer rates. This paper will not explore the various side effects of "the Pill," such as depression, migraine headache, and weight gain, although these very real concerns may be one of the reasons why the number of women continuing use of OCPs is only 68 percent at the end of the first year of use.[4] There are also other serious risks of OCPs, such as an increase in liver tumors, especially in women with concomitant hepatitis infection, which will not be further explored in this paper.[5]

Increased Cardiovascular Morbidity and Mortality

Cardiovascular morbidity and mortality first reported in OCP users were related to the ethinylestradiol content. Since the 1960s when "the Pill" was introduced, the estrogen dose has been continually reduced. As different progesterone compounds were used, cardiovascular risks have been correlated with lipid profile changes. Progestins with androgenic properties, for example, have been partially responsible for these cardiovascular events reported in OCP users. In order to minimize the incidence of adverse drug reactions and to induce beneficial changes in lipid patterns, new progestational molecules devoid of androgenic properties have been recently synthesized. These compounds are the so-called "third-generation" progestins and were thought to have lower cardiovascular risks when they first came out.[6] Unfortunately, this has not been the case, as there are some well-known class action lawsuits against pharmaceutical companies making such OCPs known as Yaz and Yasmin.

The incidence of venous thromboembolism (VTE) among healthy women is low but increases with age.[7] Oral contraceptives are associated with a three to five times higher risk of VTE.[8] The risk appears to be proportional to the estrogen dose and the type of progestin used. According to a recent Danish study, over two thousand women were studied for six years (10.4 million woman years were recorded), with the research focused on the venous thrombotic events per type of progestin used. Compared with OCPs containing levonorgestrel and with the same dose of estrogen and length of use, the rate ratio for OCPs with norethisterone was 0.98, with norgestimate 1.19, with desogestrel 1.82, with gestodene 1.86, with drospirenone 1.64, and with cyproterone 1.88. They concluded that for the same dose of estrogen and the same length of use, the

new generation OCPs using desogestrel, gestodene, or drospirenone were associated with a significantly higher risk of venous thrombosis than the older generation OCPs using levonorgestrel. In a separate study published in *The Lancet*, researchers determined that the excess risk for nonfatal VTEs linked to this new generation of OCPs to be 16/100,000 woman years. In contrast, the older generation OCPs had rates of around 4.3/100,000 woman years. In fact, as of September of 2011, the FDA was still "concerned about the potential increased risk of blood clots with the use of drospirenone-containing birth control pills."[9] The FDA has completed a review of two 2011 studies that found a two to three times greater risk of VTEs for women who use birth control and held a meeting December 8, 2011, to discuss the risks and benefits of OCPs that contain drospirenone.[10] And a few years previously on January 18, 2008, the FDA updated the label on the Ortho Evra Patch to reflect the Boston Collaborative Drug Surveillance Program data which showed that women on the patch had higher risk for VTE.[11]

Pulmonary embolism risks are also higher in patients that use OCPs. This is, in fact, because VTE and pulmonary embolisms are similar phenomena, whereby clots can break off from the existing clot in the leg (which is defined as a VTE) and subsequently travel to and become lodged in the lungs. As stated above, pulmonary embolism is related to the estrogen dose and the type of progestin. A *Lancet* study noted that OCPs containing desogestrel or gestodene are associated with higher risks of fatal pulmonary embolisms than are those containing levonorgestrel. This is consistent with most previous studies comparing the effects of second-generation progestins on VTE.[12] As an aside, the Ortho Evra patch is another form of hormone delivered by transdermal application and has been associated with increased rates of pulmonary embolism. This patch has also made the headlines lately. The presumed mechanism is that the patch delivers a higher dose of estrogen into the circulatory system by avoiding the "first-pass" metabolism of the liver.

The risk of VTE associated with hereditary thrombophilias (such as Factor V Leiden mutation, hereditary deficiencies of antithrombin III, protein C, protein S, plasmingoen, factor XII and dysfibrinogenemia) is further increased with OCP use. The risk of VTE in women who have Factor V Leiden and use OCPs is thirty-five times higher than women who do not have the mutation and who do not use OCPs. Factor V Leiden and some of these other hereditary deficiencies are like "ticking time bombs." The women may not know that they carry the mutation until they take OCPs. Due to the extreme cost of screening for these mutations, it would not be feasible in a cost-restricted health-care environment to screen every patient for this mutation. Currently, when a VTE occurs in a patient using OCPs, the recommended blood tests for hereditary thrombophilias is carried out. Physicians should perform a detailed family history on every patient presenting for OCPs; and if there is a his-

tory of multiple family members with VTE, such hereditary conditions should be suspected. Unfortunately, in the current rushed health-care environment, complete family histories (and informed consent) are often lacking.[13]

The risk of myocardial infarction is extremely rare among reproductive-aged women. Use of low dose OCPs increases the risk of myocardial infarction by 200 percent. However the risk of myocardial infarction in OCP users who smoke (under age thirty-five) is increased tenfold over that of nonsmokers who take OCPs. For women over the age of thirty-five who smoke, the increase of risk is even higher.[14] According to the Oxford Family Planning Association study, oral contraceptive use in smokers increased the risk of fatal ischemic heart disease.[15] According to the WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception, current use of OCPs is associated with an increased risk of myocardial infarction among women with known cardiovascular risk factors and among those who have not been effectively screened, particularly for blood pressure.[16] Older women who smoke have excess risk associated with OCPs (400/100,000 woman-years). Another study showed that hypertensive OCP users were at higher risk for stroke and myocardial infarction than hypertensive non-OCP users.[17]

The risk of idiopathic cardiovascular death for women using OCPs was examined by researchers using two separate studies analyzed from the U.K. General Practice Research Database. They found that there were fifteen unexpected idiopathic cardiovascular deaths in the following proportions: 4.3/100,000 for levonorgestrel OCPs, 1.5/100,000 for desogestrel OCPs, and 4.8/100,000 for gestodene OCPs.[18]

The risk of stroke in young women is rare, but substantially increased in users of OCPs. Risk is associated with higher estrogen doses, advanced age, and smoking. The risk of stroke in women with migraines who use OCPs is also increased significantly by smoking.[19] The risk of hemorrhagic stroke in women thirty-five years and older who smoke and are taking OCPs was 2.2 times higher than non-users.[20] The estimated risk of stroke with higher-estrogen dose OCPs was associated with an eightfold increase in risk of stroke.[21]

Increased Breast Cancer Risk

According to the National Cancer Institute Surveillance Epidemiology and End Results, breast cancer is the most common female cancer in the U.S. and worldwide. According to rates obtained from 2005 to 2007, the lifetime risk that a woman will develop breast cancer is 12.15 percent (or 1 in 8 women). Another way to look at the data is to say that 122.9/100,000 women will develop breast cancer per year (across all races).[22]

Cervical cancer prevalence varies depending upon where the patient lives. For example, in Eastern Africa, cervical cancer is the leading

cause of death from cancer, while in developed countries, the rates are lower. Worldwide, the International Agency for Research on Cancer (IARC) estimates that 15.3/100,000 women will develop cervical cancer worldwide per year. In Africa, the rate increases to 25.2/100,000 women.[23] According to the SEER data, in the U.S., 8.1/100,000 women will develop cervical cancer. For blacks, this rate increases to 10.1/100,000 women and for Hispanics, 12.0/100,000 women.[24]

A recently published study analyzed global breast and cervical cancer rates from 187 countries over the period from 1980 to 2010. Results showed that the global breast cancer incidence increased from 641,000 cases in 1980 to 1.64 million cases per year during 2010, an annual rate of increase of 3.1 percent. The global incidence of cervical cancer also increased during the study period, from 378,000 to 454,000 cases per year, an annual rate of increase of 0.6 percent. The authors conclude that in developing countries in the reproductive age groups, breast and cervical cancer are significant problems of a similar importance to major global priorities such as maternal mortality.[25] One should ask why breast and cervical cancers are rising so rapidly. It is interesting to note that contraceptive use has increased worldwide overall during this period but substantially over the decade from 1995 to 2005 in the less developed regions of the world.[26]

Uterine and ovarian cancers occur at higher rates in the U.S. than they do worldwide, but they still lag way behind breast cancer, which is by far, the most frequently occurring cancer in the U.S. and worldwide. The incidence of uterine cancer is 23.5/100,000 women. The lifetime risk of developing uterine cancer is 2.58 percent (or 1 in 39 women).[27] Ovarian cancer incident rates are 12.8/100,000 women. The lifetime risk of developing ovarian cancer is 1.39 percent (or 1 in 72).[28]

Why are these rates important? Because many studies promoting the benefits of OCPs in the literature tout *lowered* risks of uterine and ovarian cancers, yet minimize the *increase* in risk of breast and cervical cancers caused by these same OCPs. Since the incident rate of breast cancer is six times higher than that of both uterine and ovarian cancers, it is important to highlight this point.[29] Even small increases in the relative risk (RR) of breast cancer caused by OCPs translate into much larger increases in absolute risk of breast cancer.

In 1972, a series of animal research studies showed that an oral contraceptive appeared to cause metastatic breast cancer in monkeys, which rarely develop breast cancer.[30] A study in 1981 found that women who took OCPs for four years prior to their first full-term pregnancy (FFTP) had a 125 percent increased risk of breast cancer before age thirty-two.[31] In 1993, the Cancer and Steroid Hormone study (CASH) showed a 40 percent increased relative risk in women taking OCPs before their first full-term pregnancy.[32] Dr. Chris Kahlenborn's meta-analysis in *Mayo Clinic Proceedings* analyzed thirty-four case-control studies of OCPs and premenopausal breast cancer and found that the

use of OCPs was associated with an increased risk of premenopausal breast cancer in general (odds ratio 1.19), but when OCPs were used before FFTP, the risk went up to 1.44.[33] The association between OCP use and breast cancer risk was greatest for women who had used OCPS for more than four years (odds ratio 1.52).[34]

In a very recent study at Harvard, 116,608 patients were enrolled in a prospective cohort study which found that current use of OCPs carries an excess risk of breast cancer with levonorgestrel accounting for much of the risk.[35] Another population-based case control study examined the relationship between use of OCPs and breast cancer; and among women in a cohort younger than forty-five years old, they found that OCP use for six months or longer was associated with a relative risk of 1.3 with the RR rising to 2.2 for users of ten or more years.[36] In another case control study (the Case Control Surveillance Study), the relative risk of breast cancer for OCP use over one year or more was 1.5. The famous "triple-negative breast cancer (TNBC)" study which came out in 2009 showed that OCP use greater than one year was associated with a 2.5-fold increased risk of triple-negative breast cancer. Among women younger than forty years of age, the RR of triple-negative breast cancer associated with OCP use greater than one year was 4.2.[37]

The largest meta-analysis, comprised of fifty-four epidemiological studies (Collaborative Group on Hormonal Factors in Breast Cancer), included 53,297 women with breast cancer and 100,239 controls. Women who were currently using OCPs had an increased RR of breast cancer (RR 1.24); and women who had used OCPs before the age of twenty had an elevated risk for breast cancer over subsequent years (RR 1.95).[38]

The Black Women's Health Study from 1995 to 2007 results indicated that OCPs increased the RR to 1.65 with a greater effect for estrogen negative than estrogen positive cancer.[39] Another retrospective case control of African American women showed that OCPs also conferred a significantly increased risk of breast cancer.[40]

Regarding the risk of breast cancer based upon the hormonal content, a U.S.-based case-control study evaluated rates of breast cancer and estrogen and progesterone formulations. They found that women who recently used OCPs containing more than 35 mcg of ethinylestradiol were at higher risk than users of lower dose preparations (RR = 1.99 and 1.27 respectively). They also found that this relationship was more marked among women younger than thirty-five years of age. They also found significant trends of increasing breast cancer risk for pills with higher progestin and estrogen potencies.[41]

There are several studies which show an increased rate of breast cancer for women who have used both OCPs as younger women and then are re-exposed as older women when they take hormone replacement

therapy (HRT). The RR increases to 2.77 for women who use both OCPs and HRT.[42]

There are now several randomized control trials that show the use of HRT increases the risk of breast cancer for postmenopausal women.[43] An important point to note is that the compounds that comprise HRT (estrogen and progesterone derivatives) are similar to compounds found in OCPs. The HRT data showed an increase in postmenopausal breast cancer after just five years of use. Young women, with susceptible breast tissue (those who have not had their first full term pregnancy yet), are exposed to stronger estrogen and progesterone derivatives for much longer periods of time. All of the case control studies cited in this paper showed an increased relative risk of breast cancer in younger women who used OCPs *before* their first full-term pregnancy, and for those that used OCPs for four or more years.

It is normal for physicians to warn their postmenopausal patients of the risks when discussing HRT. Why are we, the medical community, warning older women of the risks of HRT but *not* cautioning the younger women about these hormones? Some young women start OCPs right after menarche, while their breast tissue is highly susceptible to the effects of carcinogens.[44] The International Agency for Research on Cancer classified estrogen and progesterone as Class I carcinogens in 2005.[45] According to Angela Lanfranchi, M.D., breast surgeon, the breast goes through a series of phases whereby tissue matures and develops. It is not until the woman has reached at least 32 weeks of her first pregnancy, that those breast cells become fully matured. After the breast cells have matured to this level, they are "protected" to some extent against carcinogenic influences. Therefore, exposing young women's breasts to years of carcinogenic hormones, before they have their babies, is potentially harmful.[46]

This important issue will need to be clarified with randomized controlled trials. Why have no randomized controlled trials been performed to date? One reason may be that it would not be in the best interest of the pharmaceutical industry to perform such expensive studies, especially if we examine what happened with the HRT experience. Up until 2002, physicians mistakenly recommended HRT to postmenopausal women for cardiovascular health benefits and cancer protection. Once the results of the Women's Health Initiative were publicized in the mainstream media, prescriptions for HRT dropped by half in just a couple of months. There are currently over one hundred million prescriptions for OCPs filled worldwide. In light of the revelations from the Women's Health Initiative, the impact of the fallout of studies of OCPs and breast cancer could be just as great.

Finally, there are several problems with the existing cohort studies which show that OCPs are not harmful and are not associated with increased risks of breast cancer. Dr. Chris Kahlenborn and others have documented several problems with statistical tools like "person-years"

and the use of cohorts of women who were not exposed to OCPs as young women before their first full-term pregnancy.[47] Dr. J. Brind found, in his analysis of the RCGP oral contraception study, that the widely touted 12 percent reduction in the risk of any cancer was largely an artifact resulting from a biased exclusion criteria. When he analyzed the data, he found that there was an increase in breast cancer risk, peaking between fifteen and twenty years after cessation of use instead of disappearing ten years after cessation of use, as others have reported.[48] These findings underscore the need for reanalyzing the OCP/breast cancer research.

Increased Rates of Human Papillomavirus (HPV) and Cervical Cancer

The use of OCPs has been associated with an increased risk of cervical intra-epithelial neoplasia (CIN) and cervical cancer.[49] OCPs most likely act as a co-factor in the development of this disease. Oral contraceptives are classified by the International Agency for Research on Cancer as a cause of cervical cancer.[50] There are many possible reasons why OCPs increase the rates of cervical cancer. Although HPV appears to be the strongest factor in the causation of the disease, not all women with HPV develop cervical cancer. Oral contraceptives have been postulated to be one mechanism whereby HPV exerts its oncogenic effect on cervical tissue. The OCPs may bind to HPV DNA to either increase or suppress transcription of certain genes.[51] Other studies show that OCPs (and other factors such as smoking) may accelerate the cervical maturation process, representing increased cell proliferation and thus a possible greater vulnerability to HPV.[52] Still other studies show that long-term use of OCPs may lead to a more frequent persistence of HPV.[53]

In a 2007 meta-analysis that appeared in *The Lancet*, 16,473 women with cervical cancer and 35,509 without cervical cancer were reanalyzed centrally. The relative risk of cervical cancer is increased in current users of OCPs and declines after cessation. Ten years of using OCPs from around age twenty to thirty years is estimated to increase the cumulative incidence of invasive cervical cancer by age fifty from 7.3/1,000 to 8.3/1,000 in less developed countries and from 3.8/1,000 to 4.5/1,000 in more developed countries.[54] Another earlier meta-analysis showed that long duration use of OCPs is associated with an increased risk of cervical cancer also.[55] Still, another large prospective cohort study of 47,000 women showed that those who had used OCPs had a significantly higher rate of cervical cancer than never-users.[56]

A population-based cohort study of over 10,000 women showed positive correlation of HPV prevalence with older age and current use of OCPs. This study occurred in South Africa where cervical cancer rates are among the highest in the world.[57]

Data from a hospital-based case-control study collected between 1979 and 1988 in ten participating hospitals in eight countries were

analyzed to determine whether OCPs alter the risk of cervical cancer. Risk increased with duration of OCP use, was highest in recent and current users, and declined with time since cessation of use.[58] Other studies confirmed that the risk of HPV infection was strongly and independently associated with increasing numbers of sexual partners in a lifetime, use of OCPs, younger age, and black race.[59]

The Preventive Care Mandate

The new government contraceptive mandate requires that we, as physicians: 1) treat a normal physiologic function, fertility, as if it were a disease; 2) consider OCPs as preventive medicine; and 3) as we have demonstrated, violate our Hippocratic Oath to "do no harm."

Regarding the premise that fertility is not a disease, we have a scientific culture that has always compared the risks of contraception to the risks associated with pregnancy. Why has this convention been so successfully used? Shouldn't the risks of contraceptives be compared to the non-pregnant state? In other words, when we evaluate the risk of VTEs with OCPs, for example, why is this compared to the risk of VTE during pregnancy instead of during the non-pregnant state? Is it because the problems associated with OCPs will then appear smaller than they otherwise would? And, is it also because pregnancy and fertility have successfully been positioned as disease states rather than natural phases in the reproductive cycle of a human being? Perhaps a more appropriate comparison would be between OCPs and modern methods of delaying pregnancy (such as natural family planning).

If the goal of a government is to prevent pregnancy, as it is in China, for example, then contraceptive counseling is preventive medicine. But in the U.S., fertility seems to be defined by physicians as a "disease" if the woman does not want to become pregnant and the "cure" if she has been struggling with infertility and is finally able to achieve pregnancy. How can fertility be simultaneously disease and cure? If the physician offered contraceptive counseling to an infertile woman struggling to achieve pregnancy, this would be considered strange medicine indeed,— almost a form of harassment from the poor woman's standpoint. But shouldn't preventive medicine standards measure up equally for all patients?

And what about the physicians' oath to do no harm? In addition to all the real harms of OCPs presented in this paper, are we really going to discuss all of the other risks of premarital sex with our patients, such as the very real risk of contracting various sexually transmitted diseases (STDs) with their use of those same OCPs? Are we going to discuss the role of premature sex and acquisition of HPV leading to cervical cancer? Are we going to discuss the use of condoms along with the OCPs? How about the risk of condom rupture with condom use? Even if physicians feel ethically that they cannot "impose" their Catholic morality upon

their patients, they can rightly insist that their patients be given adequate and complete informed consent about all of the risks of oral contraceptives. More importantly, they can certainly take the opportunity to educate their patients on abstinence and NFP (natural family planning). There are no harmful risks or side effects from the use of abstinence or NFP.

Conclusion

Preventive medicine is the backbone of any medical system. Patients must have confidence that the measures physicians are recommending are going to be beneficial for their health. Oral contraceptives increase rates of cardiovascular morbidity and mortality, as well as increasing the rates of breast and cervical cancers. Patients need complete informed consent on all of the possible risks of OCPs. Complete personal and family histories need to be ascertained by health-care providers to ensure that adverse events do not occur. Patients *do* incur health risks when choosing oral contraceptives. They should not be misled or confused into believing that what they are taking is "good for them" and has similar beneficial effects to other evidence-based preventive measures.

Notes

[1] See notes 8, 12, 15, 16, 17, 18 below. And see V. Cogliano et al., "Carcinogenicity of Combined Oestrogen-Progestagen Contraceptives and Menopausal Treatment," IARC Monograph Working Group, *Lancet Oncology* 6 (2005): 552–554; A. Blanco-Molina and M. Monreal, "Venous Thromboembolism in Women Taking Hormonal Contraceptives," *Expert Review of Cardiovascular Therapy* 8 (2010): 211–215; O. Lidegaard et al., Hormonal Contraception and Risk of Venous Thromboembolism: National Follow-up Study, *British Medical Journal* 339 (2009): b2890; K.M. Curtis et al., "Contraception for Women in Selected Circumstances," *Obstetrics and Gynecology* 99 (2002): 1100–1112; H. Jick et al., "Risk of Idioipathic Cardiovascular Death and Nonfatal Venous Thromboembolism in Women Using Oral Contraceptives with Differing Progestagen Components," *Lancet* 346 (1995): 1589–1593.

[2] See notes 5, 32, 33, 34, 35, 36, 37, 38, 40, 41, 42, 48 below. And see Cogliano et al., "Carcinogenicity of Combined Oestrogen-Progestagen Contraceptives and Menopausal Treatment"; Practice Committee of the American Society for Reproductive Medicine, "Hormonal Contraception: Recent Advances and Controversies," *Fertility and Sterility* 82 (2004): 520–526; E. White et al., "Breast Cancer Among Young U.S. Women in Relation to Oral Contraceptive Use," *Journal of the National Cancer Institute* 86 (1994): 505–514; L. Rosenberg et al., "A Case-Control Study of Oral Contraceptive Use and Incident Breast Cancer," *American Journal of Epidemiology* 169 (2009): 473–479; C. Sweeney et al., "Oral, Injected and Implanted Contraceptives and Breast Cancer Risk Among U.S. Hispanic and Non-Hispanic White Women," *International Journal of Cancer* 121 (2007): 2517–2523; R. Ghiasvand et al., "Risk Factors for Breast Cancer Among Young

Women in Southern Iran," *International Journal of Cancer* 129 (2011): 1443–1449; L. Rosenberg et al., "Oral Contraceptive Use and Estrogen/Progesterone Receptor-Negative Breast Cancer Among African American Women," *Cancer Epidemiology, Biomarkers and Prevention* 19 (2010): 2073–2079; H. Lyytinen et al., "Do the Dose or Route of Administration of Norethisterone Acetate as a Part of Hormone Therapy Play a Role in Risk of Breast Cancer: National-Wide Case-Control Study from Finland," *International Journal of Cancer* 127 (2010): 185–189; J.J. Schlesselman, "Cancer of the Breast and Reproductive Tract in Relation to Use of Oral Contraceptives," *Contraception* 40 (1989): 1–38; J.H. Johnson, "Weighing the Evidence on the Pill and Breast Cancer," *Family Planning Perspectives* 21 (1989): 89–92; L. Rushton and D.R. Jones, "Oral Contraceptive Use and Breast Cancer Risk: A Meta-analysis of Variations with Age at Diagnosis, Parity and Total Duration of Oral Contraceptive Use," *British Journal of Obstetrics and Gynecology* 99 (1992): 239–246; I. Romieu, J.A. Berlin, and G. Colditz, "Oral Contraceptives and Breast Cancer. Review and Meta-analysis," *Cancer* 66 (1990): 2253–2263; E. Lund et al., "Hormone Replacement Therapy and Breast Cancer in Former Users of Oral Contraceptives: The Norwegian Women and Cancer Study," *International Journal of Cancer* 121 (2007): 645–648; M.A. Rookus and F.E. van Leeuwen, "Oral Contraceptives and Risk of Breast Cancer in Women Aged 20–54 Years," *Lancet* 344 (1994): 844–851.

[3] See notes 50, 51, 52, 53, 55, 56, 57, 58, 59 below. And see Practice Committee of the American Society for Reproductive Medicine, "Hormonal Contraception"; S. Franceschi, "The IARC Commitment to Cancer Prevention: The Example of Papillomavirus and Cervical Cancer," *Recent Results Cancer Research* 166 (2005): 277–297; R.C. Sobti et al., "Effect of NBS1 Gene Polymorphism on the Risk of Cervix Carcinoma in a Northern Indian Population," *International Journal of Biological Markers* 23 (2008): 133–139; D.J. Marais et al., "Cervical Human Papilloma Virus (HPV) Infection and HPV Type 16 Antibodies in South African Women," *Journal of Clinical Microbiology* 46 (2008): 732–739; V. Moreno et al., "Effect of Oral Contraceptives on Risk of Cervical Cancer in Women with Human Papillomavirus Infection: The IARC Multicentric Case-Control Study," *Lancet* 359 (2002): 1085–1092; S.K. Kjaer et al., "Human Papillomavirus –The Most Significant Risk Determinant of Cervical Intraepithelial Neoplasia," *International Journal of Cancer* 65 (1996): 601–606; C. La Vecchia et al., "Oral Contraceptives and Cancer: A Review of the Evidence," *Drug Safety* 14 (1996): 260–272; A. Pater, M. Bayatpour, and M.M. Pater, "Oncogenic Transformation by HPV Type 16 Deoxyribonucleic Acid in the Presence of Progesterone or Progestins from Oral Contraceptives," *American Journal of Obstetrics and Gynecology* 162 (1990): 1099–1103; R.K. Peters et al., "Increased Frequency of Adenocarcinoma of the Uterine Cervix in Young Women in Los Angeles County," *Journal of the National Cancer Institute* 76 (1986): 423–428.

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