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Prevention of Ovarian and Endometrial Cancer by Combined Oral Contraceptives: A Demographics Study

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**Prevention of Ovarian and Endometrial Cancer by Combined Oral Contraceptives:
A Demographics Study**

A Thesis Presented

by

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To the Keck Science Department
Of Claremont McKenna, Pitzer, and Scripps Colleges

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I. Abstract

Endometrial cancer is the most common gynecologic cancer with 54,870 cases occurring in the United States in 2015 and causing 10,170 deaths, an 18.5% mortality rate (Elit and Reade, 2015). Ovarian cancer, while less common, is much more fatal. In 2015 in the United States, 21,290 cases occurred and resulted in 14,180 deaths, a 66.6% mortality rate. This mortality rate makes ovarian cancer the fifth most deadly cancer for women in the United States, which is largely explained by ineffective screening strategies and limited treatment possibilities (Cramer, 2012). Thus, developing effective prevention strategies is especially important to saving the lives of women who will develop ovarian or endometrial cancer. Women taking combined oral contraceptives (COCs), a type of hormonal birth control, have shown a significant reduced risk of developing ovarian and endometrial cancer. However, the Centers for Disease Control and Prevention (CDC) does not currently recommend taking COCs for the prevention gynecologic cancer (CDC, 2014a). Since the efficacy of COCs for reducing risk of ovarian and endometrial cancer is well established, guidelines need to be determined for populations of women that should take hormonal birth control to minimize cancer risk. This paper highlights the current understanding of ovarian and endometrial cancer, populations of women at highest risk for developing either of these two cancers, and then proposes a case-control study to help determine which populations of women should take hormonal birth control to reduce their gynecologic cancer risk.

Key words: Endometrial cancer, ovarian cancer, hormonal birth control, combined oral contraceptives, risk factors, prevention

II. Introduction

Women have been using birth control pills as a primary method of contraception since they were first developed in the 1960's. In the fifty years since the pill was introduced, overwhelming scientific data has revealed many unintended health benefits to women currently taking oral contraceptives and past users. A focal point in epidemiologic study is the effect of combined oral contraceptives (COCs), which contain estrogen and progestin, on the prevention of ovarian and endometrial (uterine) cancer. While COCs are most commonly advertised for contraceptive health, it may be time to emphasize their cancer prevention benefits.

There are many different forms of combined oral contraceptives and types of hormonal birth control, however for consistency and simplicity this paper will focus on the traditional cyclical combined oral contraceptive. Cyclical COCs consist of three weeks of a daily estrogen and progestin pill and one week of placebo (Brynhildsen, 2014). Additionally, "COCs" refer to all types of cyclical COCs, which means the term does not distinguish between brands that may have slightly different hormone doses and different generations of progestins. Other methods of administration of hormonal birth control, such as the patch, the vaginal ring, the intrauterine device, or injectables, are excluded because their effects compared to COCs may be confounded by patient deviation in their prescribed use, despite that all the administration methods use the same hormones.

The Centers for Disease Control and Prevention (CDC) provides information on possible ways to reduce the risk of developing ovarian cancer. The CDC currently suggests that having used birth control pills may reduce a woman's risk of developing

ovarian cancer, but it then warns that this method (among others) should not be used as a way to prevent ovarian cancer. With so much knowledge available concerning the positive consequences of taking hormonal birth control, it is time to re-evaluate the indications for oral contraceptive use. While there are contraindications to taking COCs in some women, many studies have shown that the benefits far outweigh the risks for most women. Identifying the population of women who would most benefit from taking COCs from the women who are at risk of complications is the next step in reducing the incidence of ovarian and endometrial cancer. Further, not all forms of hormonal birth control are equivalent, so determining the COC with the highest benefit-to-risk ratio will be important to optimizing the efficacy of cancer prevention.

Opportunities for Gynecologic Cancer Prevention

Ovarian and endometrial cancer are the two main cancers that exhibit much lower incidences among women who have taken or who are currently taking COCs. Attention on prevention for these two cancers is important because few successful prevention strategies exist and treatment at onset is limited. American Cancer Screening Guidelines currently do not recommend screening for women with an average or increased risk of developing endometrial cancer (Smith et al., 2016). Only women with a very high risk, such as those with Lynch syndrome or who have another high-risk genetic mutation are recommended for screening at 35 years of age. No effective screening is available for ovarian cancer for women at average risk. Successful screening strategies are still being investigated, but have not yet proven to be effective in early diagnosis of ovarian cancer. Some promising results have come from the UK

Collaborative Trial of Ovarian Cancer Screening (UKCTOCS), which has published the results of a massive trial testing the efficacy of multimodal screening strategy (MMS) with cancer antigen 125 (CA 125) and transvaginal ultrasound (TVU) (Smith et al., 2016 as reviewed in Jacobs et al., 2016). When considering confounding factors, the researchers found a 20% reduction in deaths from ovarian cancer through use of MMS, however further follow-up is necessary before the results are used to establish new screening guidelines. The current lack of successful screening techniques emphasizes the importance of focusing on known, effective methods of preventing ovarian and endometrial cancer. The birth control pill has proved time and again to dramatically reduce the risk of developing these two types of gynecologic cancer and its role in cancer prevention is ever more important due to the lagging progress in screening options (Bahamondes et al., 2015; Beavis et al., 2016; Brynhildsen, 2014; Cibula et al., 2010; Davidson and Moorman, 2014; Maguire and Westhoff, 2011).

Additionally, while screening techniques have yet to be refined to lower the number of deaths from ovarian cancer, some prophylactic surgeries such as salpingectomy (removal of a fallopian tube) have reduced the risk of women developing ovarian cancer. A population-based study compared the risk of developing ovarian cancer among women who underwent hysterectomy (removal of the uterus), sterilization, bilateral salpingectomy, unilateral salpingectomy, and women who had no surgery (Falconer et al., 2015). All surgeries lowered the risk of developing ovarian cancer and salpingectomy was the most effective at decreasing risk (HR = 0.65, 95% CI = 0.52 to 0.81). Bilateral salpingectomy was more effective than unilateral salpingectomy with a further 50% reduction in risk. Increasing evidence suggests most

ovarian cancers originate in the fallopian tube, which explains why removing both fallopian tubes produces dramatically lower rates of ovarian cancer. Women who qualify as high-risk for ovarian cancer (known carriers of mutations such as BRCA1, BRCA2 or Lynch mutations) can reduce their risk by undergoing prophylactic bilateral salpingo-oophorectomy (removal of the two fallopian tubes and ovaries) (Walker et al., 2015). Prophylactic removal of the uterus, fallopian tubes, and ovaries or prevention by using birth control pills are currently the most effective risk-reducing strategies for ovarian and endometrial cancer. It would be beneficial to many at-risk women to establish guidelines for prevention of these cancers with one or both of these approaches.

Overview of Ovarian and Endometrial Cancer

Endometrial cancer is the most common gynecologic cancer, with 54,870 cases occurring in the United States in 2015 and causing 10,170 deaths, an 18.5% mortality rate (Elit and Reade, 2015). Ovarian cancer, while less common, is much more fatal. In 2015 in the United States, 21,290 cases of ovarian cancer occurred and there were 14,180 deaths, a 66.6% mortality rate. This mortality rate for ovarian cancer makes it the fifth most deadly cancer for women in the United States (Cramer, 2012). Endometrial and ovarian cancer are often grouped together when studying prevention strategies because the two cancers are believed to share similar etiologies and risk factors.

Characterizing Endometrial Cancer

There are two types of endometrial cancer, Type I and Type II. Type II is much less common than Type I with an incidence of 10-20% of all cases, but Type II results in 40% of deaths (Setiawan et al., 2013). Type II endometrial tumors are usually serous carcinomas or clear cell whereas Type I tumors are usually endometrial adenocarcinomas. The origin of Type I tumors is believed to be triggered by unopposed estrogen stimulation and is frequently preceded by endometrial hyperplasia. Since estrogen promotes cell proliferation through a variety of genetic signaling mechanisms, high doses of unopposed estrogen increase the likelihood of conferring oncogenic mutations and eliminating tumor-suppressive mutations in endometrial tissue (Hecht and Mutter, 2006). Examples of mutations most commonly found in Type I cancers include microsatellite instability (MSI) or alterations of PTEN, K-ras, and β -catenin. Progestins decrease the risk of endometrial cancer by inhibiting the effects of estrogen (as reviewed in Hecht and Mutter, 2006). Further, progestins modulate higher levels of expression of Bcl-2 and BAX, resulting in higher levels of cell death and thus reducing the chance of survival of cells with cancerous mutations. Conversely, Type II cancers most commonly contain mutations of p53 and have aneuploidy. Type II tumors are not caused by unopposed estrogen stimulation as are Type I tumors.

Gauging Endometrial Cancer Risk by Factors Affecting Hormone Levels

Both Type I and II endometrial cancers share similar risk factors, which include obesity, nulliparity, early menarche (first menstrual period), late-onset menopause, older age (≥ 55 years), and use of tamoxifen, all of which induce variations in hormone

levels (as reviewed in Morice et al., 2016). Abnormally high estrogen levels and/or low levels of progesterone is a leading indication for increased risk of developing endometrial cancer (Kaaks et al., 2002). The theory underlying the increased risk is known as the “unopposed estrogen theory,” which suggests that the proliferative effects of estrogen increase the likelihood of developing oncogenic mutations. Progesterone induces anti-proliferative effects, which is why progesterone is considered to “oppose” estrogen and decrease the risk of developing endometrial cancer. Consequently, identifying conditions that cause these specific changes in hormone levels will help in determining populations of women most at risk for developing endometrial cancer and who would most benefit from hormonal therapy.

Obese women are particularly likely to develop endometrial cancer, with a 2.4 to 4.5 increased risk of both types of endometrial cancer and are up to seven times as likely to develop Type I endometrial cancer as women of a healthy weight (as reviewed in Beavis et al., 2016). This large increase in risk is likely explained by the metabolic changes that occur in obese women, which affect the natural balance of hormone levels (Kaaks et al., 2002). There are three main metabolic consequences of obesity supported by the unopposed estrogen theory. First, obesity increases insulin levels, which inhibits production of sex-hormone binding globulin (SHBG) (as reviewed in Kaaks et al., 2002). SHBG is a carrier glycoprotein that binds to and inhibits the availability of hormones such as estrogens and androgens (Bulut et al., 2015). Thus, lower levels of SHBG increase the levels of active estrogen, which then increases proliferative factors that may lead to the development of endometrial cancer. The two other metabolic consequences of obesity which may contribute to endometrial cancer are increased

levels of androgens (a result of high insulin and insulin-like growth factor 1) and increased levels of estrogens (as a result of conversion from androgens) (as reviewed in Kaaks et al., 2002). These mechanisms are consistent with the finding that obese women are especially prone to developing the estrogen-dependent Type I endometrial cancer. The close association between obese women and hormonal deregulation makes them a potential beneficiary of COC therapy for cancer prevention.

Polycystic ovarian syndrome (PCOS), an endocrine disease that affects 6-10% of women, is another risk factor associated with an increased incidence of endometrial cancer. This hypothesis is more controversial than others because women with PCOS have high rates of obesity, a known cause of endometrial cancer. Additional confounding factors associated with PCOS include Type 2 Diabetes, inflammation, and metabolic syndrome. The pathology of endometrial cancer from PCOS is thought to be a result of high levels of estrogen relative to low levels of progesterone during anovulatory cycles (cycles in which no ovum is released from the ovary). Regardless of whether PCOS alone is a high risk factor, women with PCOS are more likely to develop endometrial cancer and should be considered a higher risk population.

Another high risk group for endometrial cancer is women with Lynch syndrome, which results in mutations of the mismatch repair genes MLH1, MSH2, MSH6, and PMS2 (Hall et al., 2016). Women with Lynch syndrome have a 15-60% chance of developing endometrial adenocarcinoma (Type I tumors). Hysterectomy and salpingo-oophorectomy are often recommended for women with these high-risk genetic mutations. However, it would be interesting to investigate the effectiveness of COCs alone or in combination with prophylactic surgery to better understand how

endometrial cancer incidence varies between treatment possibilities. If COCs were used among all women with high-risk genetic mutations, it is possible incidence of endometrial cancer would diminish enough so that the benefits of surgery no longer outweighed the accompanying risks. On the other hand, it is possible surgical intervention in combination with COC use is necessary for the highest reduction in incidence of endometrial cancer.

Endometriosis, an inflammatory disease which results in the growth of endometrial tissue outside the uterus and affects 6-10% of women, is a suggested precursor to endometrial cancer (Mogensen et al., 2016). A cohort study by Mogensen et al. found that women with endometriosis had a 40% increased risk for developing endometrial cancer. However, only endometrioid and clear-cell tumors resulted in higher incidence among women with endometriosis compared to the general population. The relationship between endometriosis and endometrial cancer is commonly explained by the unopposed estrogen theory and there is additional indication that the endometrium even develops resistance to the anti-proliferative effects of progesterone (Kim et al. 2013, as reviewed in Mogensen et al., 2016). This proposed etiology is consistent with the theories supporting the relationship between obesity and increased incidence of endometrial cancer. Furthermore, COCs and progestin therapy are the preferred treatments for the pain caused by endometriosis and are well-regarded for their safety and efficacy (Berlanda et al., 2016). Since these treatments are already widely used among women suffering from endometriosis, it is practical to encourage their continued use with knowledge of their added benefit to reducing the risk of developing endometrial and ovarian cancer.

Additionally, the incidence of endometrial cancer is much higher among white women (more than 77% of cases) and among postmenopausal women (more than 79% of cases). Incidence is also higher in developed countries and Northern European populations than in developing countries (Cramer, 2012). The much higher risk for endometrial cancer among these population groups suggests they may be likely candidates for a study that observes the risk-reducing effect of COCs. Advocating COC use among nulliparous, white, obese, postmenopausal, or women who had early menarche, endometriosis, PCOS, Lynch Syndrome, or other high-risk genetic mutations may yield the largest net reduction in cases of endometrial cancer.

Characterizing Ovarian Cancer

Similar to endometrial cancer, ovarian cancer has been the subject of many studies seeking to develop a comprehensive understanding of its etiology, risk factors, and prevention strategies. The two most common types of ovarian cancer are ovarian epithelial cancer (OEC) and borderline tumors of the ovary (BOT) (Schüler et al., 2013). While OEC and BOT share some histologic features, OEC is much more lethal than BOT, with a mean survival of 44% and 95%, respectively (Bonome et al., 2005 as reviewed in Schüler et al., 2013). There are numerous subcategories of OEC, including serous ovarian tumors, endometrioid tumors, clear cell ovarian tumors, and mucinous tumors (Schüler et al., 2013). OEC may also be categorized into Type I and Type II tumors (Kurman et al., 2011 as reviewed in Schüler et al., 2013). Type I is less aggressive than Type II and consists of low-grade serous, low-grade endometrioid, clear cell and mucinous carcinomas, and Brenner tumors. These tumors are usually slow growing,

relatively stable and generally present early. On the other hand, the malignant Type II OEC tumors are comprised of high-grade serous, high-grade endometrioid, carcinosarcomas, and undifferentiated carcinomas. Type II OEC tumors present in late stages of the cancer and are genetically unstable. The high lethality of OEC tumors and the difficulty in providing successful treatment stresses the importance of emphasizing prevention strategies, particularly among the highest risk populations.

Gauging Ovarian Cancer Risk by Factors Affecting Hormone Levels

Many of the increased risk factors as well as risk-reducing factors for ovarian cancer are the same as for endometrial cancer. Family history of ovarian cancer is considered one of the strongest indications for developing ovarian cancer, with first-degree relatives carrying as much as a 3.6 fold higher risk than those with no family history (as reviewed in Hunn and Rodriguez, 2012). Consistent with the indications for ovarian cancer as a hereditary disease is the higher prevalence of BRCA1 and BRCA2 mutations among women with ovarian cancer. Women carrying a BRCA1 mutation have a 30% higher lifetime risk of developing ovarian cancer than the general population and women with a BRCA2 mutation have a 27% increased risk (Ford et al., 1998, as reviewed in Hunn and Rodriguez, 2012).

Another factor which increases the risk of both endometrial and ovarian cancer is Lynch Syndrome (as reviewed in Hunn and Rodriguez, 2012). Women with Lynch syndrome have an increased lifetime risk of 12% for ovarian cancer, which is less than the risk of developing endometrial cancer, but still significant. Since women with Lynch

syndrome have both a significantly elevated risk for developing ovarian and endometrial cancer they should be considered a particularly high-risk population.

Gonadal hormones also play a significant role in the progression and prevention of ovarian cancer. Estrogen has primarily been associated with increased risk for ovarian cancer, as post-menopausal women taking estrogen supplements may have up to a two-fold risk increase (as reviewed in Hunn and Rodriguez, 2012). On the other hand, progestins have been shown to produce large protective effects against ovarian cancer. The protective effect of progestins in hormonal birth control is thought to mitigate and supersede the carcinogenic effect of estrogen. Finally, many different studies have presented evidence for and against the carcinogenic effect of androgens, but the relationship between androgens and the development of ovarian cancer remains inconclusive (Risch, 1998, Modugno, 2004, Olsen et al., 2008, and Greer et al., 2005 as reviewed in Hunn and Rodriguez, 2012).

Endometriosis is an additional condition associated with a two-fold increase in risk of ovarian cancer compared to the general population (Hunn and Rodriguez, 2012). How endometriosis causes ovarian cancer has not yet been determined, although two theories have been proposed, one suggesting that chronic inflammation associated with endometriosis induces cancerous growth and the other attributing resistance to progesterone as the reason for the increased likelihood of developing ovarian cancer (Mogensen et al., 2016). As mentioned earlier, hormonal contraceptives are one of the most common treatments for pelvic pain and suppression of endometriosis. Thus, hormonal birth control could kill three birds with one stone by reducing the discomfort caused by endometriosis and minimizing the risk of ovarian and endometrial cancer.

Other factors presumed to moderately increase the risk of ovarian cancer include obesity, pelvic inflammatory disease (PID), and the use of talcum powder (talc) (Hunn and Rodriguez, 2012). Various studies have suggested obese women have a 1.2 to 2-fold increase in risk of developing ovarian cancer compared to the general population, although obese women who had taken hormone replacement therapy were not found to have any increased risk in developing ovarian cancer (as reviewed in Hunn and Rodriguez, 2012). PID is thought to contribute to ovarian cancer through the up-regulation of the inflammatory response and as such, more cases of PID are associated with an increasing risk of ovarian cancer. One case study found a 2.46-fold increase in risk of developing ovarian cancer among women who had five or more occurrences of PID. Lastly, talc has been shown to increase the risk of ovarian cancer by as much as 33%, a risk that could easily be eliminated by discontinuing use of the carcinogen (Cramer et al., 1982, Chang et al., 1997, Harlow et al., 1992 as reviewed in Hunn and Rodriguez, 2012). Table 1 lists the increased, decreased, and indeterminate risk factors for epithelial ovarian cancer, nearly all of which are shared with endometrial cancer with the exception that PCOS increases risk for only endometrial cancer (Hunn and Rodriguez, 2012).

Table 1. Overview of the primary factors which increase or decrease risk of epithelial ovarian cancer (Hunn and Rodriguez, 2012).

<i>TABLE 1. Risk Factors for Epithelial Ovarian Cancer</i>		
Increased	Decreased	Indeterminate
Hereditary	Reproductive	Fertility drugs
Family history of ovarian cancer	Multiparity	Exercise
Personal history of breast cancer	Breastfeeding	Cigarette smoking
Alteration in BRCA1 or BRCA2	Hormonal	
Lynch syndrome	Oral contraceptives	
Reproductive	Progestins	
Advanced age	Surgery	
Nulligravida	Hysterectomy	
Infertility	Tubal ligation	
Hormonal		
Early age at menarche		
Late age at natural menopause		
Hormone replacement therapy		
Estrogen		
Androgens		
Inflammatory		
Perineal talc exposure		
Endometriosis		
Pelvic inflammatory disease		
Lifestyle		
Obesity		
Geography		
Extremes in latitude		

Gonadal Hormones

Since combined oral contraceptives provide the most promise as a prevention strategy for ovarian cancer, it is necessary to understand the hormones closely linked to promoting or inhibiting ovarian cancer development. Gonadotropin-releasing hormones (GnRH), follicle stimulating hormone (FSH), luteinizing hormone, (LH), estrogens, progestogens, and androgens are most significant to the elucidation of the pathology of ovarian and endometrial cancer (as reviewed in Schüler et al., 2013). GnRH I regulates the release of gonadotropin from the pituitary gland, but the effect of GnRH on promoting or inhibiting ovarian cancer is debated. Studies have shown both an anti-carcinogenic effect of GnRH I and II by inducing cell cycle arrest and apoptosis,

while other studies have found a carcinogenic effect of GnRH II (So et al., 2008, Emons et al., 1993, Emons et al., 1990, Emons et al., 2000, and Ling et al., 2011 as reviewed in Schüler et al., 2013).

FSH targets its receptors on granulosa cells and LH targets its receptors on theca cells, the signaling mechanism of which modulates the production of ovarian steroids (Schüler et al., 2013). The increased incidence of FSH and LH receptors has been explored for its possible contribution to OEC and BOT, but various studies show conflicting evidence of their role in causing cancer. Many studies have found correlations between overexpression of FSH-R and LH-R and higher expression of proto-oncogenes such as EGFR, c-myc and Her2/neu-receptor and treatment with FSH and LH produced a higher expression of β -Catenin, *MEIS1*, cyclin G2, insulin-like growth factor 1 (IGF-1), and β -1 integrin (as reviewed in Schüler et al., 2013). Further analysis is necessary to understand the role of FSH and LH in ovarian cancer before potential hormonal treatments may be developed to increase or decrease the levels to a non-hazardous amount.

In contrast to FSH and LH, estrogen is known to play a distinguished role in the development of OEC. Estrogen stimulates both growth and invasion of OEC cells (as reviewed in Schüler et al., 2013). The mechanisms by which estrogen stimulates growth are linked to the proteins Ezrin, Fibulin, Cathepsin D and *kallikrein* in addition to up-regulating the growth factors EGF, TGF- α , IGF, and IL-6. Interestingly, estrogen in OEC may negate the anti-proliferative effect of progesterone and GnRH. The combined regulatory effects of estrogen and progesterone have important implications for

establishing the optimal type of hormone and dosing in the birth control pill for preventing ovarian cancer.

Progesterone is an effective hormone in reducing cancer risk because of its contribution to growth suppression and apoptosis in ovarian cancer cells (as reviewed in Schüler et al., 2013). The protective effects of progesterone are thought to be involved with the cAMP-mediated activation of progesterone receptor B (PGR-B), which results in cell cycle arrest, cellular senescence and the suppression of tumorigenicity of ovarian cancer cells. A meta-analysis from 2013 found that ovarian cancer patients with higher levels of progesterone were expected to have higher survival than ovarian cancer patients with lower levels of progesterone, which supports the molecular understanding of the progesterone pathway (Zhao et al., 2013).

Theories on Etiology of Ovarian Cancer

Although specific links between ovarian cancer and particular molecular pathways have been established, the general etiology of ovarian cancer is still up for debate. Four theories currently hold the most merit, although the degree to which each supports the development of ovarian cancer is debated. The leading theories are the incessant ovulation theory, the fallopian tube theory, the gonadotropin theory, and the androgen/progesterone theory (Schüler et al., 2013). The incessant ovulation theory was first proposed in 1971 by Fathalla et al., which describes how women who undergo many ovulations in their lifetime experience higher rates of trauma to the ovarian epithelium as a consequence of releasing the ovum and necessitating cellular repair

(Fathalla, 1971). Thus, higher rates of cellular regeneration and DNA synthesis logically increase the risk of a mutation that will lead to ovarian cancer.

The fallopian tube theory is relatively new and has only gained traction in ovarian cancer research during the past few years. An increasing number of studies have shown that high-grade serous ovarian epithelial cancer originates in the fallopian tube, rather than the ovarian epithelium as previously believed (Kuhn et al., 2012). This theory suggests that a hostile environment in the fallopian tube such as reactive species in follicular fluid and microenvironmental changes from tearing the ovarian surface epithelium is the origin of ovarian epithelial cancer. The reason why cancerous cells originating from the fallopian tube migrate to the ovaries for further growth is still under investigation.

The third theory regarding gonadotropin suggests that higher levels of FSH and LH stimulate the ovarian surface epithelium, increasing the risk of ovarian epithelial cancer (Schüler et al., 2013). FSH is thought to suppress apoptosis, stimulate expression of vascular endothelial growth factor A (VEGFA), and induce angiogenesis, all of which promote the development of ovarian cancer (Bhartiya and Singh, 2015). Further support for the gonadotropin hypothesis is provided by conditions that result in abnormally high levels of FSH as well as a higher incidence of ovarian cancer, such as women of older age and elevated amounts of FSH in ovarian cyst and peritoneal fluid. As a side note, PCOS results in elevated amounts of FSH, but the condition is only correlated with a significant increase in risk for endometrial cancer and not ovarian cancer (Barry et al., 2014). Conversely, conditions that result in abnormally low levels of FSH are associated with reduced incidence of ovarian cancer, such as breast-feeding

and multi-parity, which notably are also conditions in which a female does not ovulate, supporting the original incessant ovulation theory.

Risch first introduced the androgen/progesterone theory in 1998, which suggests that ovarian cancer occurs as a result of high androgen stimulation of ovarian epithelial cells and depleted progesterone concentrations which elicit protective benefits against ovarian epithelial cancer (Risch, 1998). However, the clarity of the role of androgens in promoting ovarian epithelial cancer is disputed, as some studies have found higher risk among women with higher levels of androgen, while others found an inverse relationship (as reviewed in Schüler et al., 2013).

Arguments Against Combined Oral Contraceptives

While the risk reduction of ovarian and endometrial cancer is a tempting reason (among many other health benefits) to begin use of COCs, there are a number of contraindicating risk factors that must be carefully weighed against the benefits. The most serious risk factor incurred by taking COCs is an increase in the risk of developing venous thromboembolism (VTE) (Brynhildsen, 2014). Risk of VTE increases with higher concentrations of estrogen, which is why the estrogen component has been lowered to the concentrations most commonly used today (15-30 µg). Progestins are believed to counteract the estrogen-induced risk increase of VTE, although recent evidence shows that different types of progestins vary in their ability to minimize the risk of VTE. COCs containing third and fourth generation progestins, such as desogestrel, gestodene, etonogestrel, and drospirenone, have higher incidences of VTE than COCs containing earlier generations of progestins, such as levonorgestrel,

norethisterone, and norgestimate (Lidegaard et al., 2012, as reviewed in Brynhildsen, 2014). Table 2 highlights the relative risk of VTE for women taking these various categories of progestins. Despite these indications, the relative risk of VTE is still extremely low with 2-10 cases expected per 10,000 users of COCs, compared to never-users at 2-3 cases per 10,000. Thus, COCs should be considered safe for users who do not have a high risk of developing VTE, namely those with a history of VTE, those with first-degree relatives with VTE, and obese women. Without taking any COCs, obese women already have an elevated three-fold risk of developing VTE compared to the general population, but this risk jumps to a 10 to 24-fold increase with the use of COCs. In summary, COCs recommended to the general population should be of low estrogen dosage (15-30 µg) and contain first or second-generation progestins.

Table 2. Risk of developing venous thromboembolism in a year according to the European Medicines Agency (as reviewed in Brynhildsen, 2014).

Women not using a combined hormonal pill/patch/ring and are not pregnant	About 2 out of 10,000 women
Women using a combined hormonal contraceptive (CHC) containing levonorgestrel, norethisterone or norgestimate	About 5–7 out of 10,000 women
Women using a CHC containing etonogestrel or norelgestromin	About 6–12 out of 10,000 women
Women using a CHC containing drospirenone, gestodene or desogestrel	About 9–12 out of 10,000 women
Women using a CHC containing chlormadinone, dienogest or nomegestrol	Not yet known ¹
¹ Further studies are ongoing or planned to collect sufficient data to estimate the risk for these products.	

A second contraindication to taking COCs is the possible increase in risk of developing breast cancer (Gierisch et al., 2013). An evaluation of a combination of 29 case-control studies, 14 cohort studies, and one pooled analysis revealed a small, increased risk of developing breast cancer among women who had or currently use

COCs (OR, 10.8; 95% CI, 1.00-1.17). On the other hand, there have been numerous studies which suggest there is no significant increase in risk of breast cancer from taking COCs or if there is, the risk increase is very slight (Davidson and Moorman, 2014). For those studies that have found a very slight increase in the risk of breast cancer, the risk was shown to be highest during current use of COCs and diminish to no increase in risk by ten years after discontinuation of use. This evidence implicates that COCs may not be an ideal recommendation for women at a higher risk of developing breast cancer, such as BRCA1 and BRCA2 carriers, but this risk must be balanced with the increased likelihood of these carriers to develop ovarian cancer. While breast cancer is much more common than ovarian cancer, the risk increase of breast cancer is much smaller relative to the large risk reduction in ovarian cancer by taking COCs. Consequently, it is difficult to offer a recommendation one way or another as each patient's relative risk for certain cancers must be balanced with the risks they're willing to forgo by taking or not taking COCs.

III. Experimental Study

Experimental Rational

Aim 1

Establish the populations of women who would most benefit from taking combined oral contraceptives in order to prevent ovarian cancer

Aim 2

Establish the populations of women who would most benefit from taking combined oral contraceptives in order to prevent endometrial cancer

Prediction

“Ever use” of hormonal birth control pills containing estrogen and progestins, as defined by a year or more of continuous use, will significantly reduce the chance of women developing endometrial or ovarian cancer in all populations studied (first degree relative family history, BRCA 1 or 2 carriers, Lynch Syndrome, nulliparous, infertile, early age at menarche, late age at menopause, estrogen hormone replacements, endometriosis, and obesity).

Experimental Design

The following case-control study will be carried out to help establish recommendations for certain populations of women to take hormonal birth control in order to reduce their risk of developing endometrial or ovarian cancer. The design may be applied to each of the subsequent populations of women: first degree relative family history, BRCA 1 or 2 carriers, Lynch Syndrome, nulliparous, infertile, early age at

menarche, late age at menopause, estrogen hormone replacements, endometriosis, or obesity. This case-control study will look at the risk of developing endometrial and ovarian cancer independently.

The study will look at “ever use” of estrogen/progesterone birth control and how the treatment affects the risk of developing ovarian cancer in women with a strong family history of ovarian cancer, defined as at least one first-degree relative with ovarian cancer. Study investigators will contact gynecologic oncologists practicing in the United States and ask them to refer patients with ovarian cancer to participate in the study. Healthy women will be randomly selected throughout the United States and will be recruited to participate through phone call solicitations. The study aims to recruit 300 women with ovarian cancer and 300 healthy women. Women older than forty years of age and who have not undergone any type of prophylactic surgery are eligible to participate. All relatives will be excluded from the study. Women in the control group (healthy women) who have bleeding after menopause or three or more of the following warning signs of ovarian cancer will be excluded: pain in the pelvic or abdominal area, back pain, bloating, feeling full quickly while eating, passing urine very frequently or often, constipation, or diarrhea (CDC, 2014b). For the case-control study on endometrial cancer, women in the control group who have one or more of the following warning signs of endometrial cancer will be excluded: abnormal vaginal discharge or bleeding (particularly after menopause), or pain or pressure in the pelvis (CDC, 2014a). Finally, all women who have a history of use of any type of hormonal birth control other than combined oral contraceptives, such as the patch, vaginal ring, intrauterine device, or injectables will be excluded from the study.

Once all cases and controls are recruited, complete medical history will be collected from subjects who agree to release their medical record for the purpose of the study. History of use of a combined oral contraceptive for at least a year will be organized according to Table 3 in order to calculate the odds ratio of developing ovarian cancer for women who have taken COCs compared to women who have not taken COCs. Since ovarian cancer is a rare disease, the odds ratio (OR) will be similar to the relative risk.

Table 3. Example of how to organize data for a case-control study to determine odds of developing ovarian cancer among women who have a first-degree relative with ovarian cancer.

	Estrogen/Progesterone Birth Control Pill Use (≥ 1 Year)	
	Yes	No
Ovarian Cancer	A	B
Healthy	C	D

Odds Ratio

$p(\text{cancer} + \text{pill use})/p(\text{healthy} + \text{pill use}) = \text{odds of having cancer on pill}$

$p(\text{cancer} + \text{no pill use})/p(\text{healthy} + \text{no pill use}) = \text{odds of having cancer with no pill}$

$\text{OR} = (\text{odds of having cancer on pill})/(\text{odds of having cancer with no pill})$

$\text{OR} = (A/C)/(B/D)$

95% Confidence Interval of $\ln(\text{OR})$:

$$\left(\ln(\text{OR}) - 1.96 \sqrt{\frac{1}{A} + \frac{1}{B} + \frac{1}{C} + \frac{1}{D}} \right) \text{ to } \left(\ln(\text{OR}) + 1.96 \sqrt{\frac{1}{A} + \frac{1}{B} + \frac{1}{C} + \frac{1}{D}} \right)$$

If COCs reduce the odds of developing ovarian cancer, the odds ratio should be less than 1. If COCs have no effect on the odds of developing ovarian cancer, the odds

should be 1. If COCs increase the odds of developing ovarian cancer, the odds ratio should be greater than 1.

Null hypothesis

There is no effect of COCs on the odds of developing ovarian cancer among women with one or more first-degree relatives with ovarian cancer compared to healthy women of the same population.

OR=1 is in the 95% Confidence Interval

Alternative hypothesis

There is an effect of COCs on the odds of developing ovarian cancer among women with one or more first-degree relatives with ovarian cancer compared to healthy women of the same population.

OR=1 is *not* in 95% Confidence Interval

Table 4 and the accompanying calculations provide a hypothetical example of how the odds ratio will be calculated. Odds of developing ovarian cancer are 0.46 for women taking COCs (who have a first-degree relative with ovarian cancer) than that of women not taking COCs of the same population. The 95% confidence interval (CI) of the odds ratio (0.32, 0.67) indicates the odds of ovarian cancer are significantly lower for women taking COCs compared to women not taking COCs because the CI does not contain 1.

Table 4. Hypothetical data for a case-control study to determine odds of developing ovarian cancer for women who have taken COCs compared to women who have not taken COCs (all of whom have a first-degree relative with ovarian cancer). In this example, odds of developing ovarian cancer are 0.46 for women taking COCs compared to women not taking COCs.

	Estrogen/Progesterone Birth Control Pill Use (≥ 1 Year)	
	Yes	No
Ovarian Cancer	195	105
Healthy	240	60

$$OR = (195/240)/(105/60)$$

$$OR = 0.46$$

$$\left(\ln(0.46) - 1.96 \sqrt{\frac{1}{195} + \frac{1}{105} + \frac{1}{240} + \frac{1}{60}} \right) \text{ to } \left(\ln(0.46) + 1.96 \sqrt{\frac{1}{195} + \frac{1}{105} + \frac{1}{240} + \frac{1}{60}} \right)$$

$$-1.15 \text{ to } -0.407 \rightarrow e^{-1.15} = 0.32 \text{ to } e^{-0.407} = 0.67$$

$$CI: 0.32 \text{ to } 0.67$$

Benefits of Experimental Design

There are a number of advantages to running a case-control study, which include the need for many fewer subjects than prospective studies, a much shorter time to complete the analysis since the study is not dependent on disease progression, and a low chance of losing patients to follow-up. Additionally, the study may be applied to many different populations of women, enabling a broad survey of potential beneficiaries of combined oral contraceptives. Finally, case-control studies have a relatively low cost in comparison to prospective studies or controlled trials.

Drawbacks and Confounding Variables

There is a potential for recall bias as cases and controls may not give equally detailed or accurate information regarding their history of using COCs since women with ovarian cancer may be more interested in supporting the study. Additionally, patients only become a part of the study through physician referral and as it is difficult to detect ovarian cancer, physicians could miss referring patients who actually did have ovarian cancer. Likewise, control patients could unknowingly have ovarian cancer. Patients were also not matched for race due to the small population surveyed and the type of analysis used, so a difference in race between the control and disease populations may confound the odds ratio. Lastly, women without ovarian cancer only become part of the study if they frequently stay at home to answer the phone and this selection factor was not applied to the cases.

Assumptions

The study assumes cases and controls are randomly selected from the populations and are representative of women across the United States who have at least one first-degree relative with ovarian cancer. When selecting for controls, it is assumed subjects do not differ systematically from the cases in any way except for the absence of ovarian cancer.

Discussion: The Pill and the Population

The results of this study will provide a direction for developing a prospective study and more thorough analyses of which populations of women would most benefit from taking COCs. The study is limited in that it does not consider duration of use of COCs, daily hormone dosing, or type of progestin used, but these questions may be answered in future experiments. Once the populations are determined that would most benefit from taking COCs, specific parameters for COC recommendation should be determined (e.g. age of women when they begin COCs, age at discontinuation, method of administration, type of phasic regimen, who should be recommended COCs in combination with prophylactic surgery and at what age, COCs in combination with other therapies, and necessity of the COCs among low risk populations).

Interestingly, a retrospective study found that obese women with endometrial cancer (BMI ≥ 30) who used low-dose aspirin following a hysterectomy with subsequent chemo or radiotherapy had a significantly higher survival rate (HR 0.43, P=0.27) than women who did not use low-dose aspirin (Matsuo et al., 2016). Obese women tend to suffer from more inflammation than women with healthy BMIs, which indicates why aspirin, an anti-inflammatory drug, showed a significant effect in only obese women. Excessive inflammation is an enabling characteristic to many of the hallmarks of cancer, such as sustaining proliferative signaling, promoting angiogenesis, resisting cell death, and inducing genome instability and mutations (Hanahan and Weinberg, 2011). By reducing inflammation, aspirin may reduce inflammatory mechanisms that promote these hallmarks, thereby increasing survival among obese women who are particularly prone to inflammation. Additionally, low-dose aspirin use among younger women (≤ 60

years), women with Type I endometrial cancer, and women who had postoperative whole pelvic radiotherapy had significantly higher survival rates than their counterpart groups; older women, Type II endometrial cancer, and alternative postoperative therapies, respectively (Matsuo et al., 2016). The preventative benefit of a low-dose aspirin regimen is a potential therapy to lower the risk of developing endometrial cancer in addition to reducing the risk of recurrence. Exploring the effect of combining low-dose aspirin therapy with COCs among women experiencing excessive inflammation is a potential treatment that should be evaluated for the prevention of endometrial cancer.

Once the parameters for which populations of women should take COCs are well-established, the CDC should update its recommendations for prevention methods of ovarian and endometrial cancer. Further, as hormonal birth control will likely be recommended to many large populations of women for cancer prevention (also due to its many other health benefits), access should be increased to make it more readily available. Possibilities include making hormonal birth control over-the-counter and mandating that insurance provides free hormonal contraception coverage. Additionally, an emphasis should be placed on educating primary care physicians, obstetricians/gynecologists, patient populations, and government officials about the many benefits of hormonal birth control, which would help to maximize the number of women electing to take hormonal contraception.

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