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Duration of Oral Contraceptive Use, its Potency and the Risk of Ovarian Cancer

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Abstract

Ovarian cancer is the leading cause of cancer incidence and mortalityworldwide. Study shows that the use of oral contraceptive is inversely associated with the risk of ovarian cancer and is thought to be the most powerful known chemo-preventative agents. Oral contraceptive associated risk reduction was also observed among womenwith family history of ovarian cancer.Oral contraceptive reduces the risk in a duration-dependent fashion, as the beneficial effects oforal contraceptive remains for long times even after cessation of use. This long-term protection may have significant implications for individual risk assessment andfor public health, since the incidence of ovarian cancer rises withage.

Keywords: Ovarian cancer; Oral contraceptive; Women; Estrogen; Progestin.

Introduction

Ovarian cancer is a silent killer and accounts for an estimated 239,000 new cases and 152,000 deaths worldwide annually (Ferlay et al., 2013). A woman's lifetime risk of developing ovarian cancer is 1 in 75, and her chance of dying of the disease is 1 in 100 (Reid et al., 2017). To date, no efficient early recognition techniques have been identified, and thus primary prevention isvery important for reducing ovarian cancer morbidity and mortality rate (Goodman, 2004), as most women with ovarian cancer diagnosed with advanced disease condition at the time of diagnosis (Fathalla, 2013).It is predicted that,by the year 2040, the mortality rate of ovarian cancer will rise significantly (Bray et al., 2018). Despite the public health significance, the etiology of thislethal disease is poorlyunderstood(Huang et al., 2015).

However, oral contraceptives are thought to be the most powerful known chemo-preventative agents for ovarian cancer (Ness et al., 2000). Oral contraceptives, as an exogenous female hormone, are used regularly by a substantial fraction of women at some time in their lives (Siskind et al., 2000). Thus, understanding the effect of oral contraceptives on the ovarian cancer risk reduction is very important, because of the limited scope for early detection and subsequent poor prognosis of ovarian cancer (Siskind et al., 2000).

Methodology

Literatures were researched from 1971 to 2018 on the association between oral contraceptive and ovarian cancer using electronic search engines like PubMed and Google Scholar. Cross references of all selected papers were also used to identify further

relevant papers. The keywords used were 'ovarian cancer', 'oral contraceptive and ovarian cancer', 'duration of oral contraceptive use and the risk of ovarian cancer', 'oral contraceptive potency and the risk of ovarian cancer', 'contraceptive use and the risk of ovarian cancer' and 'oral contraceptive and the risk of ovarian cancer'. Published papers for the present review were selected from available published papers in English language. At first, the title of the papers and abstracts were reviewed for relevance, and then potential relevant full text papers or abstracts, where full texts were not available were extracted. Papers without full text where abstracts were also unavailable were excluded from the review.

Results and Discussion

Oral contraceptive and ovarian cancer

Epidemiological studieshave consistently reported that the use of oral contraceptive is inversely associated with the risk of ovarian cancer (Whittemore et al., 1992; Tworoger et al., 2007; Reid et al., 2017).Oral contraceptives reduces the risk in a duration-dependent fashion, as the beneficial effects oforal contraceptives may last for at least 20 years after cessation of use (Beral et al., 2008; Ness et al., 2011). Moreover, the result of case-control studyshowed that oral contraceptive also decreasesthe risk of fatal and advanced ovarian cancer (Poole et al., 2013).

Study demonstrated that ever use of oral contraceptives reduces the risk of ovarian cancer by 40–50% for ever users compared to non-users (Royar et al., 2001). Moreover, women who havetaken oral contraceptives are about one-third less likely todevelop ovarian cancer than are women who have neverused oral contraceptives (Stanford, 1991; Whittemore et al., 1992).Beral et al.(2008) in a study reported a relative risk of 0.73 forever verses never users of oral contraceptives for ovarian cancer.In another study in Denmark among women of reproductive ages Iversen et al., (2018) found that ever use of any contemporary hormonalcontraception was associated with a reduced risk ofovarian cancer.However the protective role of oralcontraception has not been observed in some studies also (Riman et al., 2001). Like, a recent study demonstrated lack of significant association between ever use of oralcontraceptive and ovarian cancer risk in Chinese women (Huang et al., 2015).

It was observed that, women with endometriosis are at an increased risk of epithelial ovarian cancer (Goodman, 2004) and study showed that an estrogen-rich, progesterone-poor hormonal environment may encourage thegrowth of endometriosis and promote its malignanttransformation to ovarian cancer (Ness, 2003). However, case-control studies have shown that oralcontraceptives also protect against cancer of the endometriumand epithelial ovarian cancer (Vessey and Painter, 1995) (Table 1).

Interestingly, oral contraceptive is also associated with a significant reduction in most ovarian cancer subtypes (Jacobs and Menon, 2004; Tworoger et al., 2007), and thus indicating a common underlying etiologic pathway for the effect of oral contraceptives on ovarian carcinogenesis (Tworoger et al., 2007). Study also demonstrated that carriers ofBRCA1mutations had similarovarian cancer risk reductions associated with oral contraceptive use (McGuire et al., 2004). A case-control study also similarly noted oral contraceptive associated risk reductions among womenwith a family history of ovarian cancer (Walker et al., 2002). The beneficial effect oforal contraceptives to reduce the risk of ovarian cancer among women carrying BRCA mutations might be the reason for prescribing oral contraceptives as a chemo-preventive agent among high-risk women (Ness et al., 2001).However, in a population based case–control study among women in Israel, Modan et al. (2001) found no differences in beneficial effect of oral contraceptive use when compared with patients carrying one of the three common BRCA1 or BRCA2 founder mutations with control women from the general Israeli population.

However, mechanisms underlying this protective role of oral contraceptive are not clear. It is believed that ovulation, with its associated disruption and subsequent repair of theovarian epithelium, can lead to the acquisition of genetic damagein ovarian epithelial cells and, in turn, to ovarian cancer insusceptible individuals (Fathalla, 1971; Schildkraut et al., 2002). However, it has long been hypothesized that oral contraceptive may protect from ovarian cancer by suppressing ovulation(Siskind et al., 2000; Ness et al., 2001; Schildkraut et al., 2002)and altering the tumor-promoting milieu (Siskind et al., 2000).Moreover, the decreased risk of ovarian cancer associated with oralcontraceptive use not only due to anovulation alone. Oral contraceptives also suppress the secretion of gonadotropic hormones from the pituitarygland, including folliclestimulating hormone and luteinizinghormone, which are suggested to increase ovarian cancer risk by

Table 1: Oral contraceptive and ovarian cancer.

Authors	Year	Area of study	Study design	Major findings
Vessey and Painter	1995	England and Scotland	Cohort study	There was a strong negative relationship between duration of oral contraceptive use and ovarian cancer risk. In comparison with never users of oral contraceptives, the relative risk for users of up to 48 months' duration was 1.0, while the relative risk for users of 97 months' duration or more was only 0.3.
Ness et al.	2000	Delaware Valley, including contiguous counties in eastern Pennsylvania, southern New Jersey, and Delaware.	Population-based case– control study	Use of low-estrogen/low-progestin pills afforded an estimated risk reduction that was identical to that for high-estrogen/high-progestin pills.
Schildkraut et al.	2002	Multicenter includind New Mexico, Iowa and Utah.	Population-based case-controlled	The combination oral contraceptives formulations with high-progestin potency appear to be associated with a greater reduction in ovarian cancer risk than those with low-progestin potency.
Modugno et al.	2004	United States	Case-controlled	Women with endometriosis were at an increased risk of ovarian cancer. The use of oral contraceptives for >10 years was associated with substantial reduction in risk among women with endometriosis.
Tworoger et al.	2007	United States	Prospective study	Duration of oral contraceptive use was inversely associated with risk, but no clear trend was observed for years since last use.
Lurie et al.	2008	Hawaii and Los Angeles	Population-based case-control study	Epithelial ovarian cancer risk was reduced 5 or more years after initiation of oral contraceptives use. Each year of use provided a 5% reduction in risk. Women who used oral contraceptives for a year or more were protected for at least 3 decades after they stopped use.
Tsilidis et al.	2011	European countries	Prospective Study	Women who used oral contraceptives for 10 or more years had a significant 45% lower risk compared with users of 1 year or less.
Faber et al.	2013	Denmark	Population-based case– control study	The use of combined oral contraceptives only and the mixed use of combined and progestin-only pills decreased the risk of ovarian cancer, while no association was found with exclusive use of progestin-only pills.
McGuire et al.	2016	California, Florida, Louisiana, New Jersey, North Carolina, Pennsylvania, and the metropolitan areas of Atlanta and Detroit.	Cohort study	Prior oral contraceptive use is important for ovarian cancer risk assessment among women of all ages. Moreover, the protective effects of oral contraceptive use persist for decades after the menopause.
Iversen et al.	2018	Denmark	Cohort study	Use of contemporary combined hormonal contraceptives is associated with a reduction in ovarian cancer risk in women of reproductive age—an effect related to duration of use, which diminishes after stopping use. The study also suggests no protective effect from progestogen-only products

increased cell growth and inhibition of apoptosis (Konishi, 2006; Huang et al., 2015). Furthermore, oral contraceptives also reduceovarian cancer risk by increasing progestin stimulation (Risch, 1998;Faber et al., 2013).

Duration of oral contraceptive use and the risk of ovarian cancer

A number of studies demonstrated an association between duration of oral contraceptive use and the risk of ovarian cancer (Goodman, 2004; Tsilidis et al., 2011). Tworoger et al. (2007) in a study demonstrated38% reduction in the incident of ovarian cancer with 10 years of oral contraceptive use. It was observed that the risk reduction increases with duration of oral contraceptive use (Franceschi et al., 1991; Rosenberg et al., 1994). Lurie et al. (2008) in a population based case-control study in Hawaii and Los Angeles also demonstrated an inverse association of epithelial ovarian cancer risk with years of oral contraceptive use. A study by Whittemore et al. (1992) in US revealed that the risk reduction associated with ever use of oral contraceptive was 34%, and that associated with 6 or more years of use of oral contraceptive was 70%. Royar et al. (2001) in a study found that the risk of ovarian cancer reduced by over 70% for those who are using oral contraceptive for more than 15 years. Hankinson et al. (1992) demonstrated 50% decrease in risk of ovarian cancer after 5 years of use of oral contraceptive andalso found that this reduced risk appeared to persist at least 10 years after cessation of use.Study also demonstrated that women who used oral contraceptives for a year or more were protected from ovarian cancer for at least 3 decades after they stopped use (Lurie et al., 2008). However, study in U.S. women revealed that the relative decrease in incidence rates due to the protective effect of oral contraceptive use declines with age (Gnagy et al., 2000).

It was also observed that women who had started using oral contraceptive at younger ages and continued for longer time since first use also had a stronger protection form ovarian cancer (Bosetti et al., 2002). Royar et al. (2001) demonstrated an increasing protective effect of oral contraceptive with longer duration use, with an estimated 7% annual decrease in risk. Similarly, Siskind et al. (1971) in anearlier study in Australia demonstrated an estimated 9% annual decrease in ovarian cancer risk with longer duration of oral contraceptive use. In another study Faber et al. (2013) found that each extra year of oral contraceptive use decreased the risk of ovarian cancer by 6%. Study also suggested that the protective effects of oral contraceptive use persist for decades even after the menopause (McGuire et al., 2016). Some studies witnessed an added protective influence of oral contraceptive, if its use was started before the age of 25 years (Royar et al., 2001). Even, short term use of oral contraceptive was also associated with reduced risk of ovarian cancer. It was observed that 3 or more years of oral contraceptive use reduces the risk of developing epithelial ovarian cancer by 30%–50% (Whittemore et al., 1992; Schildkraut et al., 2002). However, the protective role of oral contraceptive increases with duration of use. As study revealed that women who used oral contraceptives for 10 or more years had a 45% lower risk compared with users of 1 year or less, which corresponded to a 13% lower risk per 5 years of use (Tsilidis et al., 2011).Interestingly,the protective benefit of long-term oral contraceptive use to decrease the risk of ovarian cancer was also observed among women carryingmutant BRCA1 or BRCA2 allele. Study suggested that oral contraceptives may play an important protective role for women with elevated genetic risk for ovarian cancer (Narod et al., 1998). Moreover, the reduction in risk was 14% among ever users and 38% among long-term users carrying mutations of BRCA1 or BRCA2, which was, however, somewhat weaker than reductions observed in the general population (Whittemore et al., 2004). McGuire et al. (2004) also demonstrated a greater risk reduction with increasing duration of oral contraceptive use amongBRCA1 mutation carriers. However, Huang et al. (2015) demonstratedno significant association between long durationof oral contraceptive use and ovarian cancer risk in Chinese women.

Estrogen and progestin potency of oral contraceptive and the risk of ovarian cancer

There were some studies, which examined the effect of high and lowpotencycontraceptives on ovarian cancer risk, however, thefindings were inconclusive.A case–controlstudy in Germanyby Royar et al. (2001) showed comparatively greater protection of low dose estrogen pills (<50 µg ethinyl estradiol) than highdose estrogen pills(≥50 µgethinyl estradiol) on ovarian cancer risk. Contrary to that, another case–control study by Rosenblatt et al. (1992) demonstrated less protection againstovarian cancer with lowestrogen formulations than withhighestrogen formulations. However, Cibula et al. (2010) revealed that the protectiveeffect of oral contraceptives against ovarian cancer riskdid not differ between users of high and low estrogenformulations.Study also demonstrated that the protection afforded

by oral contraceptives against ovarian cancer appeared to be independent of the dose of estrogen or progestin and bothhigh and low dose oral contraceptivesformulationsshowed a strong and equal protective effectagainst ovarian cancer (Ness et al., 2000).Though, lowdose oral contraceptive formulations have gained an increasing popularity with a substantialproportion of the market share (Royar et al., 2001), study demonstrated that oral contraceptive containing <50 µg estrogen are equally effective in suppressing ovulation when compared with oral contraceptive containing ≥50 µg estrogen(Scott et al., 1978; Ness et al., 2000). However, lowdose oral contraceptive formulations have lower ability to suppress gonadotropin levels as compared to higher dose formulations (Scott et al., 1978; Ness et al., 2000), and it was observed that high gonadotropin levels may elevate the risk for ovarian cancer (Cramer and Welch, 1983). Thus,lowerdose pills may not be as protective as higher dose oral contraceptives (Ness et al., 2000).

Comparative study to understand the effect of oral contraceptives on the basis of estrogen and progestin potency revealed that oral contraceptive formulations with higher progestin potencyconferred a greater reduction in risk of ovarian cancer than those with lower progestin potency, irrespective of the estrogen content and duration of use (Schildkraut et al., 2002). However, due to the lower prevalence of use, comparatively fewer studies have been done on the effect of progestin only contraceptives, but the available study suggestedthat progestinonly contraceptives also loweredthe risk of ovarian cancer (Reid et al., 2017). A previous case–control study found that the use of low progestin formulations reducedthe risk of ovarian cancer more significantlycompared to the highprogestinformulations (Lurie et al., 2007). Contrary to that Faber et al. (2013) found no significant differences in the protective effect ofthose with high and lowpotency progestin. It was also observed that combined oralcontraceptives do not differ from progestogen only pills in their risk of ovarian cancer (Kumle et al., 2004). Moreover, presentor recent use of progestogen only products implied a smaller effect on ovarian cancer riskestimates, compared with users of combined products (Iversen et al., 2018).

Conclusion

In conclusion, the present review demonstrated a protective effect of oral contraceptives on ovarian carcinogenesis and also found that this protection persists for a long time even after cessation of oral contraceptive use. The persistence of long term protection from oral contraceptives against ovarian cancer may have significant implications for individual risk assessment and for public health since the incidence of ovarian cancer rises withage.

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