Use of oral contraceptives, depot medroxyprogesterone acetate and intrauterine contraceptive devices and the risk of cancer: a review

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Abstract

Background: The decision to use a contraceptive and the choice of method of contraception is partly informed by its effects on the health of users. The impact of a contraceptive on the incidence of cancer may be regarded as of greatest significance.
Objective: To present a review of literature on the association between cancer and use of Oral Contraceptives (OCs), Depot Medroxyprogesterone Acetate (DMPA)and Intrauterine Contraceptive Devices (IUDs).
Methods: This was a narrative review in which studies were identified through a search of the CINAHL, MEDLINE and EMBASE databases. Included are studies assessing the association between cancer and OCs, DMPA or IUDs published in English up to March, 2017. Overall, 27 studies were selected: 16 examined association with use of OCs, eight assessed association with IUDs and eight with DMPA. Data from the selected studies were extracted as reported in the studies.
Results: Oral Contraceptives (OCs) are associated with a slight or no increase in the risk of breast cancer: 49 instead of 44 per 10,000 women, confined to use within the last 10 years. However, OCs do not alter the risk of mortality from breast cancer. Use of OCs for ≥5 years in the presence of HPV infection may increase the risk of and mortality from cervical cancer. OCs are inversely associated with endometrial, colorectal and ovarian cancer (50%, 20-30%, and 30-40% lower risk for ever- compared to never-use, respectively). Overall, there was a decrease in the incidence of cancer by 10 to 45 per 100,000 women per year in OCs users. The association between DMPA and breast cancer may be similar to that of OCs use. Overall, a higher risk of cancer (7% increase in incidence) has been reported in levonorgestrel-releasing IUDs users.
Conclusion: Use of OCs is associated with a lower risk of cancer. The association between cancer and use of contraceptives other than OCs merits further assessment.

Key words: Contraceptives, Cancer, OCs, DMPA, IUDs

Introduction

Contraceptives play a big role in reducing unwanted pregnancies and lowering maternal mortality rates. Indeed, the annual global maternal mortality rate declined by 34% in the period 1990 to 2008; avoidance of 1.7 million deaths in this period was attributed to fertility decline, which may partly be due to availability of contraceptives (1). Knowledge of non-contraceptive benefits afforded by a method may improve its uptake (2).

Two of the central questions when choosing or discontinuing use of a contraceptive method are about its negative consequences and beneficial effects. Beyond the obvious question of the efficacy of any contraceptive method, it can be argued that the most important of these is possible impact on the risk of cancer, which is both a personal and a public-health issue. Although the association between Oral Contraceptives (OCs) and the risk of cancer has widely been studied, not enough attention has been given to the other methods of contraception. The aim of this review is to present an overview of current information on use of OCs, Depot Medroxyprogesterone Acetate (DMPA) and Intrauterine Contraceptive Devices (IUDs) and the risk of cancer. Knowledge of the association between contraceptives and cancer is useful for health practitioners in evidence based decision-making and practice.

Materials and Methods

For this review article, studies assessing the association between use of contraceptives and the risk of cancer were identified through a literature search using EMBASE, CINAHL and MEDLINE databases using the key words ('cancer'/'tumour'/'neoplasm) and ('injectable contraceptive agent'/ 'medroxyprogesterone acetate') and 'oral contraceptive' and ('intrauterine contraceptive device'/intrauterine contracept*') and 'cancer risk'. Included are studies published in English up to March, 2017. Reference lists were examined for additional relevant studies. Studies were not included/excluded based on quality; however, relevant comments on study limitations are made. Studies that had already been included in a pooled analysis, meta-analysis or systematic review were not again individually selected. A total of 27 articles were identified. Of these, 16 studies assessed the association of cancer and use of OCs, eight reported on the association with use of DMPA, and

eight examined the association with IUDs (some studies investigated more than one type of contraceptive). Findings were extracted as reported in the studies.

Use of combined oral contraceptives and the risk of cancer

Breast cancer

Use of hormonal contraceptives may influence the risk of breast cancer, this being a hormonally sensitive tumour. In a 1996 collaborative re-analysis of 54 studies in 24 countries, use of combined OCs was associated with higher risk of localised breast cancer in current and recent users (current users: relative risk [RR] = 1.24; 95% CI = 1.15-1.33, 1-4 years and 5-9 years after cessation of use RR = 1.16; 95% CI = 1.08-1.23, and RR = 1.07; 95% CI = 1.02-1.13, respectively). No association was observed 10 years after cessation of use, (RR = 1.01; 95% CI = 0.96-1.05). In addition, there was no difference in RR of breast cancer in relation to type of combined OCs formulation (oestrogen and progestagen type), dosage, duration of use, or family history of breast cancer. Furthermore, compared to never-users, breast cancer diagnosed in ever-users of combined OCs, including those diagnosed 10 or more years after discontinuation of use, were more likely to be localized (RR = 0.88; 95% CI = 0.81-0.95); hence, there was a better prognosis for ever-users compared to never-users of combined OCs. In this study, there were limited data regarding use beyond 20 years and participants who had stopped use ≥10 years ago were more likely to have used medium- or high-dose preparations (3). In a subsequent review article, most of the studies reported no increase in the risk of breast cancer among oral-contraceptive users. The few that reported an elevated risk, showed a progressive decline in the strength of this association following discontinuation of use. In addition, risk did not differ according to the composition of OCs used (4).

Consistent with the above findings, a case-control study in South Africa reported a higher risk of breast cancer in recent users (within 10 years) of injectable or oral contraceptives (odds ratio [OR] = 1.66; 95% CI = 1.28-2.16, P <0.001), with no difference in risk 10 or more years after last use (OR = 1.11; 95% CI = 0.91-1.36, P = 0.3) compared to never-users. There was also no relationship between risk and duration of use of hormonal contraceptives (P = 0.4). A trend towards lower risk with longer duration since last use was observed (P = 0.004). Of note is that, in this study, OCs were assumed to be combined OCs, whereas injectable contraceptives were assumed to be progestogen-only preparations. However, there was no statistically significant difference in risk among recent users of injectable contraceptives exclusively (OR = 1.83; 95% CI = 1.31-2.55), OCs exclusively (OR = 1.57; 95% CI = 1.03-2.40), and users of both (OR = 1.50, 95% CI = 1.04-2.17), P - heterogeneity = 0.6 (5).

In contrast, a cohort study found no increase in risk of breast cancer among users of OCs; on the contrary, an inverse association was observed with onset of use at less than 29 years of age (hazard ratio [HR]= 0.68; 95% CI = 0.46-1.00), compared to never-use. Participants in this study had used OCs for a short time, the median duration of use being two years. In addition, the study had low power and lacked information on specific type of OCs used (6).

The association between OCs and breast cancer could be attributed to detection bias (increased surveillance). Because women using OCs visit health facilities to renew their prescriptions, they are more likely to undergo a physical examination and therefore benefit from possible early detection of breast cancer (7). On the other hand, OCs may simply affect the rate of growth of tumours that are already present. Indeed, the observation that higher risk is confined to the first 10 years after discontinuation of use and the lack of association of risk with duration of use of combined OCs are both more in support of a promotional effect than a genotoxic effect (3). Oestrogens are thought to promote proliferation of ductal epithelial cells leading to an increase in the risk of DNA errors or replication of cells with genomic damage; progestagens may have a synergistic effect (5).

In conclusion, these studies suggest that the increase in risk of breast cancer among OC users is minimal or absent and is confined to current or recent users (4). The absolute risk of breast cancer in ever-users compared with never-users is small. For instance, for the period from onset of use until 10 years after cessation of use, there will be an extra 5 breast cancer cases (49 instead of 44) per 10,000 women if combined OCs are used for 5 years by women at the age of 25 years (3). Overall, the proportion of breast cancer cases that can be attributed to the use of OCs is less than 1%; however, for pre-menopausal women the association is stronger (about 7%) (4). Regarding mortality, Vessey *et al* (8) observed no relationship between breast cancer mortality and ever-use or duration of use of combined OCs (RR = 1.0; 95% CI = 0.8 - 1.2, for ever-use).

Cervical cancer

Long-term use of combined OCs (≥ 5years) by women with HPV infection may result in a higher risk of cervical cancer. A pooled analysis reported a statistically significant higher risk of cervical cancer in ever-users of OCs (OR = 1.47; 95% CI = 1.02-2.12) with a trend towards higher risk with longer duration of use (use for <5 years: OR = 0.77; 95% CI = 0.46-1.29, 5-9 years: OR = 2.72; 95% CI = 1.36–5.6, and ≥10 years: OR = 4.48; 95% CI = 2.24-9.36), although the p-value for trend was not reported. The risk returned to normal 5 to 10 years after discontinuation of use (9). These findings are corroborated by those of Cibula *et al* (4): use of OCs for more than 5 years was associated with a higher risk of

cervical cancer. The strength of this association declined with longer duration since cessation, and was almost absent after 10 years.

The findings of Urban *et al* (5) are consistent with this: they reported a statistically significantly higher risk of cervical cancer in recent users (within 10 years) compared to never-users of hormonal contraceptives (OR = 1.38; 95% CI = 1.08-1.77; P = 0.01). A clear decline in risk with longer time since last use was observed (P = 0.02), with a return to background risk 10 or more years after discontinuation of use (OR = 1.01; 95% CI = 0.84-1.22). However, no association was observed with duration of use (P = 0.96).

A similar relationship between OC use and mortality was observed in ever- versus never-users (OR = 7.3; CI=1.2-30.5) with a statistically significant trend toward higher risk with longer duration of use (P = 0.004) (8).

Endometrial cancer

It is well recognised that combined OCs are inversely associated with risk of endometrial cancer (4, 10, 11). Oral contraceptives have to be used for at least 4 years for this beneficial association to emerge. Duration of use is inversely related to risk with a 50% lower risk after 4 years of use and about 70% after 12 years of use (10). In one study, no inverse association was observed with use for <5 years (OR = 1.28; 95% = 0.71-2.32; P = 0.4), whereas a statistically significant lower risk (OR = 0.44; 95% CI = 0.22-0.86; P = 0.002) was seen with use for ≥5 years (P-heterogeneity = 0.007 for duration of use) (5). The trend is toward progressively higher risk after cessation of use; however, the risk of endometrial cancer is still lower for ever-users than never-users long after cessation, with up to a 50% lower risk 20 years after discontinuation (4, 10). The inverse association with endometrial cancer is most probably due to suppression of endometrial proliferation by progestogen (4, 5, 11).

In a prospective cohort study, ever-users of OCs had a statistically significantly lower risk of mortality from uterine cancer, which were mostly endometrial, (RR = 0.3; 95% CI = 0.1-0.8). A progressively lower risk was observed with longer duration of use (P-trend = 0.002): those who had used OCs for more than 8 years had a RR of 0.2 (95% CI = 0.0-1.0). This beneficial association was still present 20 years after cessation of OC use (RR = 0.4, 95% CI = 0.1-1.0) (8).

Ovarian cancer

Studies have shown that use of OCs is inversely associated with ovarian cancer with studies consistently finding a 30-40% lower risk of ovarian cancer for ever-use compared to never-use (12-14). The inverse association is more marked with longer duration of use, and is estimated at 20% for up to five years use, and nearly 60% for 15 years or more (13, 15). Similarly lower risks have been found even among women with BRCA mutations. A meta-analysis of oral contraceptive use and ovarian cancer in BRCA1/2 carriers found a 50% lower risk for ever-users, with a 20% lower risk for each five years of use (16). Worldwide, if the association is regarded as causal, OCs are estimated to have prevented over 200,000 women from developing ovarian cancer and more than 100,000 women dying from ovarian cancer (13).

Other cancers

Ever-use of combined OCs is associated with a 20% to 30% lower risk of colorectal cancer (17). OCs may be associated with a higher risk of hepatocellular adenoma; however, this condition is rare (prevalence of 3 to 4/100,000), and risk seems to be associated with duration of use and oestrogen levels in the contraceptive preparation (18). The risk of hepatocellular carcinoma, also a rare condition, is slightly higher in OC users: in a pooled analysis, the relative risk of hepatocellular carcinoma was 1.70 (95% CI = 1.12-2.59); the risk seemed to be higher with longer duration of use and returned to normal after discontinuing OC use (4).

A prospective cohort study reported a statistically significant positive association between ever-use of OCs and gallbladder cancer (HR = 2.38; 95% CI = 1.26-4.49), but there was no association with rectal, colon, or gastric cancer. These findings were based on a small number of site-specific cancers (6). Not enough evidence is available to adequately assess the impact of use of OCs on the risk of other cancers (4, 18). Overall, mortality from all cancers is lower in ever- compared to never-users of OCs (RR = 0.87; 95% CI = 0.79-0.96) (8).

Use of depot medroxyprogesterone acetate and the risk of cancer

Breast cancer

The relationship between use of DMPA, a long-acting progestogen-based contraceptive, and the risk of breast cancer is thought to be similar to that of OC use (19). In a New Zealand case-control study, overall, DMPA was found to have no association with risk of breast cancer (RR = 1.0; 95% CI = 0.8-1.3) and no relationship between risk and time since first use or duration of use. However, a higher risk was observed in DMPA users younger than 35 years of age and in recent users. A linear relationship between duration of use and risk was also noted in this group of young women. Generally, a lower risk was observed with longer duration since last use. These findings suggest that use of DMPA by young women may be associated with a higher risk of breast cancer. The observed higher risk in the first few years of use supports a promotional effect on tumours that are already initiated (20).

In a pooled analysis, which included the above study, the findings were generally comparable to those

for OC use. A higher risk of breast cancer was observed in recent users (within 5 years) of DMPA (RR = 1.17; P = 0.06, for OCs, and RR = 1.17; statistically non-significant, for injectable contraceptives). There was also no association with duration of use or age at first use. A small number of participants had used progestagen-only preparations in this study (0.8% had used OCs and 1.5% had used injectable preparations) (3).Urban *et al* (5) also observed no statistically significant difference in risk of breast cancer between users of injectable or oral contraceptives. The risk was higher in ever-users of hormonal contraceptives than never-users; no relationship with duration of use was observed; and risk trended lower with time since last use.

Cervical cancer

Overall, use of DMPA does not seem to be associated with the risk of cervical cancer (19, 21). However, there may be a higher risk in recent users (5). In a review article, no association was found between DMPA use and the risk of cervical cancer. Two case-control studies reported relative risks of 1.4 (95% CI = 0.6-3.1) and 1.1 (95% CI = 0.96-1.29). There was also no association between risk and length of use or time since cessation of use (19). A case-control study by Urban *et al* (5) reported a statistically significantly elevated risk in women who had recently used (previous 10 years) injectable contraceptives exclusively compared to those who had never used hormonal contraceptives (OR = 1.58; 95% CI = 1.16-2.15, P = 0.004). No statistically significant difference in risk was observed in recent users of injectable contraceptives only, OCs only, or both (P-heterogeneity = 0.2). These studies did not include data on HPV infection which is a necessary cause of cervical cancer.

Ovarian cancer

An association between use of DMPA and the risk of ovarian cancer has not been established. Studies have reported lower risk (OR = 0.35; 95% CI = 0.17-0.71 and OR = 0.61; 95% CI = 0.44-0.85) (5, 22) and non-statistically significant higher risk (23, 24) of ovarian cancer in users of DMPA.

Use of intrauterine contraceptive devices and the risk of cancer

Use of Intrauterine Contraceptive Devices (IUDs) has no impact on the risk of cervical cancer (4). In one study, IUD use was associated with a lower risk of breast, thyroid, lung, ovarian, and uterine body cancer, and a higher risk of rectal and stomach cancer, whereas tubal ligation was associated with a higher risk of uterine body cancer and was inversely associated with stomach cancer. The findings of this study could be attributed to chance (6). Studies assessing the association between use of IUDs and ovarian cancer have had mixed findings, with reports of higher risk (14), lower risk (25, 26), and no association (6, 24).

Different types of IUDs differ in their mechanisms of preventing pregnancy and may, therefore, have varying effects on the risk of cancer. The above studies are most probably based on older types of IUDs. The newer levonorgestrel-releasing IUDs (LNG-IUS) may have a different effect. In a Finnish cohort study involving 93, 843 women, use of LNG-IUS was associated with a lower risk of ovarian (27, 28), endometrial, lung and pancreatic cancers (27), and a higher risk of breast cancer (standardised incidence ratio [SIR] = 1.33; 95% CI = 1.20-1.46 for invasive lobular cancer, and SIR =1.20; 95% CI = 1.14-1.25 for invasive ductal cancer) (29). An increase in the risk of these two histological types of breast cancer was observed after five years of follow-up (after at least two purchases of LNG-IUS) (29). In the same study, overall, a 7% higher incidence of cancer was observed among LNG-IUS users. This increased to 20% in women who had purchased two or more LNG-IUS (27). However, in this study, there was the risk of selection bias because participants were on LNG-IUS for the treatment of menorrhagia; therefore, their risk of cancer may be different from that of the general population. In addition, the reference population included women on LNG-IUS which may have led to an underestimation of risk (27).

Net effect of use of contraceptives on the risk of cancer

It is encouraging that, so far, use of contraceptives has not been associated with a higher risk of cancer; if anything the net association is inverse. A summary of the relationship between cancer and use of OCs, IUDs, and DMPA is presented in Table 1. Studies have reported a decrease in the incidence of cancer by 10 to 45 per 100,000 women per year in OC users (18). In a cohort study, ever-use of any method of contraception was not associated with a higher overall risk of cancer (HR =1.02; 95% CI = 0.92–1.12) (6). Similarly, the Oxford-Family Planning Association (Oxford-FPA) contraceptive study observed a lower risk of mortality from cancer in ever-users of OCs (RR = 0.9, 95% CI = 0.8-1.0), the relative risk for all-cause mortality was also reduced (RR = 0.87; 95% CI = 0.79-0.96) (8). The RCGP oral contraception study reported an absolute reduction in mortality of 52 per 100,000 woman years among women who had ever used OCs. The overall death rate was also statistically significantly lower (RR = 0.88; 95% CI = 0.82-0.93) (30). Although an increase in the incidence of cancer has been reported in LNG-IUS users (27), the findings of that study may not be generalizable because participants were on LNG-IUS for the treatment of menorrhagia. In addition, LNG-IUS is a relatively recent contraceptive method; therefore, the duration of exposure may not have been long enough to be able to adequately assess

cancer risk. The benefits from preventing unwanted pregnancies, especially in developing countries, cannot be over-emphasised.

Table 1: Summary of the association between use of oral contraceptives and the risk of cancer

Type of contraceptive	Associated with:
Oral contraceptives	A higher risk of breast cancer in recent users.
	A higher risk of cervical cancer in women with HPV infection.
	A lower risk of ovarian, endometrial and colorectal cancers.
	An overall lower risk of cancer.
DMPA	A possibly increased risk of breast cancer.
	A possibly higher risk of cervical cancer among recent users. However, overall, there is no association with cervical cancer.
IUDs	An overall higher risk of cancer has been reported among users of levonorgestrel-releasing IUDs. However, these findings are not definitive.

DMPA: Depot medroxyprogesterone acetate;
IUDs: Intrauterine contraceptive devices

Conclusion

Use of OCs is associated with a lower risk of colorectal, endometrial and ovarian cancer and an overall lower risk of cancer. However, there is a slight or no increase in the risk of breast cancer (confined to recent users) and a higher risk of cervical cancer in women with HPV infection. Although studies examining the association between cancer and use of DMPA and IUDs have been done; the findings are not definitive; studies with enough power are needed to better assess these associations.

Statement on conflict of interest: There is no conflict of interest.

References

1. Zureick-Brown S, Newby H, Chou D, Mizoguchi N, Say L, Suzuki E, *et al.* Understanding global trends in maternal mortality. *Intern Perspect Sexual Reprod Health.* 2013;**39**(1):32-41.
2. Eshre Capri Workshop Group. Family planning 2011: better use of existing methods, new strategies and more informed choices for female contraception. *Hum Reprod Update.* 2012;**18**(6):670-681.
3. Calle E, Heath C, Miracle McMahill H, Coates R, Liff J, Franceschi S, *et al.* Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53, 297 women with breast cancer and 100, 239 women without breast cancer from 54 epidemiological studies. *Lancet*. 1996; **347**(9017):1713-27.
4. Cibula D, Gompel A, Mueck AO, La Vecchia C, Hannaford PC, Skouby SO, *et al.* Hormonal contraception and risk of cancer. *Hum Reprod Update.* 2010;**16**(6):631-650.
5. Urban M, Banks E, Egger S, Canfell K, O'Connell D, Beral V, *et al.* Injectable and oral contraceptive use and cancers of the breast, cervix, ovary, and endometrium in black South African women: case-control study. *PLoS Med.* 2012;**9**(3):e1001182.
6. Dorjgochoo T, Shu XO, Li HL, Qian HZ, Yang G, Cai H, *et al.* Use of oral contraceptives, intrauterine devices and tubal sterilization and cancer risk in a large prospective study, from 1996 to 2006. *Int J Cancer.* 2009;**124**(10):2442-9.
7. Nasca PC, Pastides H, editors. Fundamentals of cancer epidemiology. Second ed. Sudbury, MA: Jones and Bartlett Publishers; 2008.
8. Vessey M, Yeates D and Flynn S. Factors affecting mortality in a large cohort study with special reference to oral contraceptive use. *Contraception.* 2010;**82**(3):221-229.
9. Bosch FX and de Sanjosé S. The epidemiology of human papillomavirus infection and cervical cancer. *Dis Markers.* 2007;**23**(4):213-227.
10. Grimbizis GF and Tarlatzis BC. The use of hormonal contraception and its protective role against endometrial and ovarian cancer. *Best Practice & Res: Clin Obstet Gynaecol.* 2010; **24**(1):29-38.
11. Van der Westhuizen E and Van der Merwe E. The safety and efficacy of low-dose oral contraceptives. *SA Pharmaceut J.* 2010; **77**(1):22-28.
12. Ness RB, Grisso JA, Vergona R, Klapper J, Morgan M and Wheeler JE. Oral contraceptives, other methods of contraception, and risk reduction for ovarian cancer. *Epidemiology.* 2001;**12**(3):307-312.
13. Beral V, Doll R, Hermon C, Peto R and Reeves G. Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. *Lancet.* 2008; **371**(9609):303-314.
14. Tworoger S, Fairfield K, Colditz G, Rosner B and Hankinson S. Association of oral contraceptive use, other contraceptive methods, and infertility with ovarian cancer risk. *Am J Epidemiol.* 2007;**166**(8):894-901.
15. Webb P, Gertig D and Hunter D. Ovarian cancer. 2008. In: Textbook of cancer epidemiology [Internet]. Oxford: Oxford University Press. 2.
16. Iodice S, Barile M, Rotmensz N, Feroce I, Bonanni B and Radice P. Oral contraceptive use and breast or ovarian cancer risk in BRCA 1/2 carriers: a meta-analysis. *Eur J Cancer.* 2010;**46**(12):2275-84.
17. Potter JD and McMichael AJ. Large bowel cancer in women in relation to reproductive and hormonal factors: a case-control study. *J Natl Cancer Inst.* 1983;**71**(4):703-709.

18. Wiegratz I and Thaler CJ. Hormonal contraception: What kind, when, and for whom? [German, English] Hormonalekontrazeption - Was, wann, fur wen? *Deutsches Arzteblatt*. 2011;**108**(28-29):495-506.
19. Kaunitz AM. Depot medroxyprogesterone acetate contraception and the risk of breast and gynecologic cancer. *J Reprod Med Obstet Gynecol*. 1996;**41**(5 Suppl.):419-427.
20. Paul C, Skegg DC and Spears GF. Depot medroxyprogesterone (Depo-Provera) and risk of breast cancer. *Br Med J*. 1989;**299**:759-762.
21. Bakry S, Merhi ZO, Scalise TJ, Mahmoud MS, Fadiel A and Naftolin F. Depot-medroxyprogesterone acetate: an update. *Arch Gynecol Obstet*. 2008;**278**(1):1-12.
22. Wilailak S, Vipupinyo C, Suraseranivong V, Chotivanich K, Kietpeerakool C and Tanapat Y. Depot medroxyprogesterone acetate and epithelial ovarian cancer: a multicentre case-control study. BJOG: *Intern J Obstet Gynaecol*. 2012; **119**(6):672-677.
23. Stanford JL and Thomas DB. Depot-medroxyprogesterone acetate (DMPA) and risk of epithelial ovarian cancer. The WHO collaborative study of neoplasia and steroid contraceptives. *Int J Cancer*. 1991;**49**:191-195.
24. Shu XO, Brinton LA, Gao YT and Yuan JM. Population-based case-control study of ovarian cancer in Shanghai. *Cancer Res*. 1989;**49**(13):3670-4.
25. Ness RB, Dodge RC, Edwards RP, Baker JA and Moysich KB. Contraception methods, beyond oral contraceptives and tubal ligation, and risk of ovarian cancer. *Ann Epidemiol*. 2011;**21**(3):188-196.
26. Huang Z, Gao Y, Wen W, Li H, Zheng W, Shu XO, *et al*. Contraceptive methods and ovarian cancer risk among Chinese women: A report from the Shanghai Women's Health Study. *Int J Cancer*. 2015;**137**(3):607-614.
27. Soini T, Hurskainen R, Grénman S, Mäenpää J, Paavonen J and Pukkala E. Cancer risk in women using the levonorgestrel-releasing intrauterine system in Finland. *Obstet Gynecol*. 2014;**124**(2, Part 1): 292-299.
28. Soini T, Hurskainen R, Grénman S, Mäenpää J, Paavonen J and Pukkala E. Impact of levonorgestrel-releasing intrauterine system use on the cancer risk of the ovary and fallopian tube. *Acta Oncol*. 2016;**55**(11):1281-4.
29. Soini T, Hurskainen R, Grénman S, Mäenpää J, Paavonen J, Joensuu H, *et al*. Levonorgestrel-releasing intrauterine system and the risk of breast cancer: A nationwide cohort study. *Acta Oncol*. 2016;**55**(2):188-192.
30. Hannaford PC, Iversen L, Macfarlane TV, Elliott AM, Angus V and Lee AJ. Mortality among contraceptive pill users: cohort evidence from Royal College of General Practitioners' Oral Contraception Study. *Br Med J*. 2010;**340**:c927.