REVIEW

Oral contraception and risk of endometrial cancer

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Abstract: No placebo-controlled studies concerning hormonal contraception in general have been published, and only investigations on biological mechanisms and observational clinical studies are available. Thus, associations can be described but not their causality. Experimental studies strongly suggest protective effects of the progestagen component of hormonal contraception against development of estrogen-related (type 1) endometrial cancer. In light of this research, it seems biologically plausible that, in more than 20 published studies, a reduction in endometrial cancer risk was achieved in up to 50% of users of combined oral contraceptives (COC), compared with nonusers. Few data exist for progestin-only oral preparations. However, in view of the mechanisms involved, a reduction in cancer risk should also be expected. Whereas hormonal dose-dependency has been investigated in only a few studies, which showed a stronger risk reduction with increasing progestagenic potency, a decreased risk dependent on duration of use has been clearly demonstrated, and after stopping COC this effect has persisted for up to 20 years. Possible confounders, including family history, parity, and smoking, have been investigated in a few studies, with only a minor impact on hormonal effect of endometrial cancer risk, with the exception of obesity, which was a strong risk factor in most but not all studies. There are obvious differences in the incidence of endometrial cancer in women using COC when evaluated in absolute numbers for Western and Asian countries, being about 3–5-fold higher in the US than in Asia. Further research should include the noncontraceptive benefit of COC, especially in patients with a high risk of cancer, as in polycystic ovary disease, and should also include new contraceptive drugs using natural estradiol instead of ethinyl estradiol. Of importance is the question of the potency of hormonal intrauterine devices to protect against endometrial cancer. It can be concluded on the basis of biological plausibility and observational data that COC can strongly decrease the risk of estrogen-related endometrial cancer, with an effect persisting after withdrawal of the hormones, and a causal relationship for this protection against cancer seems reasonable.

Keywords: hormonal contraceptives, endometrial cancer

Introduction

There is an ongoing debate about whether combined oral contraceptives (COC) are able to protect against endometrial cancer even though almost all studies addressing this question over the last 30 years have demonstrated a decreased risk when comparing women who use hormonal contraception with those who do not. However, there remains the problem of the lack of placebo-controlled studies which are crucial to demonstrate a causal relationship for the risks and/or benefits of a medical treatment. We only have observational studies which primarily show associations. They may suggest causality if a clear relationship with dosage and duration can be observed, if possible confounders

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are carefully considered, and if biological plausibility of mechanisms as assessed by studies can be demonstrated, eg, the Bradford Hill criteria for epidemiology.

If studies are largely comparable in design, population, treatment, dosage, duration, and other possible confounding factors (eg, age, body mass index, family history), a meta-analysis could further elucidate the question of possible causality. However, regarding the risk of endometrial cancer, this is not the case. For this reason, we prefer to discuss the data presented here as a systematic review concentrating on the design and results of the most important studies.

Conclusions derived from observational studies need particularly careful evaluation for possible confounders, ie, calculating the risk of endometrial cancer in women taking COC. Possible confounding factors will be discussed in a later section, as far as they have been reported in the studies.

We will show that on the basis of the studies and their preconditions, protection against endometrial cancer should be the most reasonable conclusion, rather than merely a decrease of risk compared with nonusers. This should have practical implications in terms of diseases that can increase the risk of endometrial cancer. As an example, and an important one for endocrine gynecologists, we discuss if treatment with COC in patients with polycystic ovary syndrome would lead to an additional, ie, noncontraceptive, benefit due to possible protection against cancer, considering the up to five-fold increased risk of endometrial cancer associated with this disease.

This example leads finally to the question of whether future developments in hormonal contraception, eg, using natural estradiol instead of ethinyl estradiol or use of intrauterine devices in high-risk patients, may lead to an even better overall benefit/risk ratio, also considering other risks, such as cardiovascular disease.

Endometrial cancer is one of the most common gynecological malignancies, with 41,000 new cases in the US in 2006.[1] Therefore, a decrease in the risk of endometrial cancer or even protection against the disease is an important question, but the main problem is still cardiovascular risk. Even if the data described in this paper are very suggestive of protection against endometrial cancer, at this time there is no indication for prescribing COC to reduce the risk of the disease.

Mechanisms of hormonal action

A causal relationship should never be considered without biological plausibility. In this section, we summarize experimental data from various studies performed to answer the question of how sex hormones can influence the development of endometrial cancer and to determine if there are mechanisms to reduce the risk or even protect against development of this cancer.

First, we have to note that two different clinicopathological subtypes of endometrial cancer are recognized, ie, estrogen-related type 1 (endometroid), comprising 70%–80% of newly diagnosed cancer, and nonestrogen-related type 2 (nonendometroid, such as papillary serous and clear cell). The morphologic differences between these cancers are mirrored in their molecular genetic profile, with type 1 showing defects in DNA mismatch repair and mutations, particularly in phosphatase and tensin homolog, K-ras, and beta-catenin, and type 2 showing aneuploidy and p53 mutations.[2] The combination and order of additional mutations leading to invasive carcinoma differs between patients, but may include changes in K-ras and ß-catenin.[3]

Regarding the molecular mechanisms involving sex hormones, there are few data on their effects in type 1 cancer. A prerequisite for the development of this type is hyperproliferation of endometrial cancer cells. There is no proof that sex steroids can cause production of new cancer cells; perhaps they only act later in the course of tumor progression, which is driven particularly by stromal factors, eg, strong proliferation-stimulating growth factors.[4] Estrogens thereby act as positive selectors and progestagens as negative selectors of already mutated clones, ie, estrogen acts in a proliferative manner on pre-existing cancer cells and progestagens have an antiproliferative effect on endometrial tumor progression.[4] Since all hormonal contraceptives contain a progestagen as their major component, a reduction in cancer risk seems to be plausible providing the progestagen is potent enough to antagonize estradiol-induced proliferation by mechanisms leading to secretory transformation and/or endometrial atrophy.

Important critical mediators of this endometrial remodeling process are proinflammatory mechanisms which can be differentially affected by various contraception methods. For example, progesterone-regulated chemokines play an important role in the secretory phase of the cycle, in early pregnancy, and during the use of hormonal contraceptives, dependent on progestin potency.[5] Other potential biomarkers for different hormonal potency are coming to light, including those involved in the apoptosis cascade and the stroma-derived growth regulatory mechanism.[6] Again, progestagens

can modulate or inhibit endometrial growth and thereby might protect against the development of cancer.

Markers of hormonal activity also have effects at the steroid receptor level, ie, on progesterone receptor A and B, and estrogen receptors alpha and beta, which are almost completely downregulated by local uterine action using the levonorgestrel intrauterine system. This decrease is significantly less pronounced with the oral progestins in combined contraceptives or progestin-only contraceptive pills.[7,8] Based on the experimental research, the levonorgestrel intrauterine system may protect against the development of cancer.

Regarding endometrial histology, changes in histological features during hormonal contraception include different proliferative, secretory, and atrophic (like) patterns, changes in stromal factors (eg, very potent growth factors), and an increase or decrease in cytologic atypia, the latter being a most powerful marker and predictor of progestagenic potency.[9–12] Although there are important differences according to the pharmacology of progestagens (type, dosage, pharmacokinetics), the biological basis is that estrogen stimulates division of endometrial cells, whereas progestagens block this action. Progestagens induce glandular epithelial secretory activity and decidual transformation of stromal fibroblasts, such that terminal differentiated cells can no longer proliferate and are shed in withdrawal bleeding during hormonal contraception. This may explain why contraceptives can reduce the risk of hyperproliferation and with this also the risk of development of estrogen-related endometrial cancer.

In summary, all these studies of the mechanisms of hormonal action, which are still the subject of ongoing research, may explain why and how hormonal contraceptives reduce the risk of endometrial cancer. Given the strong potency of the synthetic progestagens, there is a biological plausibility for protection from endometrial cancer in users compared with nonusers of hormonal contraception.

Risk of endometrial cancer using COC

The first relevant systematic review evaluating the association between COC and endometrial cancer was published in 1995,[13] and assessed 13 case-control studies[14–28] and three cohort studies[29–30] (Figure 1).

The first report, published in 1979, was a case-control study (n = 268/268, Yale Registry) and failed to support an association between COC use and endometrial cancer (odds ratio [OR] 0.95). However, the other case-control studies found a reduction in cancer risk compared with no treatment, with an
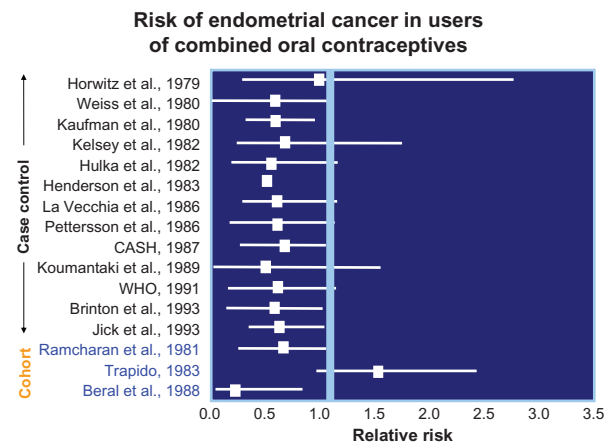

Risk of endometrial cancer in users of combined oral contraceptives

Figure 1 Risk of endometrial cancer in users of combined oral contraceptives. Adapted from Grimes DA, Economy KE. Primary prevention of gynecologic cancers. *Am J Obstet Gynecol.* 1995;172:227–235.13 Copyright © 1995, with permission from Elsevier.

OR of 0.1–0.6. This was significant in several reports,[16,22,27,28] including the largest case-control study, CASH (Cancer and Steroid Hormone) undertaken by the Centers for Disease Control and Prevention.[31,32] Only one cohort study in Eastern Massachusetts found a modest, nonsignificant increase in risk,[30] but included high-dose sequential preparations (100 µg ethinyl estradiol) combined with low-dose, short-sequential progestin, which has not been on the market for at least 20 years.

Two of the three cohort studies reported a significant risk reduction. This includes the Walnut Creek Contraceptive Drug Study from California[29] and a study from the Royal College of General Practitioners in the UK.[31,32] The UK study is the most important one,[31] evaluating 47,000 women, which found an 80% reduction in risk (relative risk [RR] 0.2; 95% confidence interval [CI] 0.0–0.7). Recently, follow-up data for 38 years was published[32] and, compared with never-users, ever-users had significantly lower rates of endometrial cancer calculated in the main data set, with a RR of 0.58 (95% CI 0.42–0.79). The standardized rate per 100,000 woman-years was 11.30 for ever-users and 19.53 for never-users (adjusted for age, parity, smoking, and social status). The risk was also assessed by duration of COC use, and although based on smaller numbers, the trend for longer use was still statistically significant. For recent use, the risk reduction decreased less than five years after stopping. Because only 566 women used a formulation with >50 µg ethinyl estradiol, this study does not clarify whether the risk reduction was dependent on the hormonal potency of the COC used.

The data evaluated in this study came from general practitioners and from linkage to the 35,000 women still in the study according to central National Health Service

registries. The recent main data set contained about 340,000 woman-years of observation for never-users and about 745,000 woman-years for ever-users. Since most of the users received combined pills, evaluations of other contraceptive use, like progesterone-only pills (3% in this cohort), in this important study can give only very limited further information on the risk of endometrial cancer.

However, according to this study and the first systematic review (Figure 1), the effect of COC in reducing endometrial cancer risk seems to be very clear. Few additional relevant studies have been published to date.[33–40] Table 1 summarizes the most important studies in chronological order of publication.

The question regarding the effect of hormone dose in reduction of risk was investigated in the World Health Organization Collaborative Study, a hospital-based case-control study classifying COC according to the dosage of ethinyl estradiol and potency/dosage of progestin.[25] High-dose ethinyl estradiol/low-dose progestin did not alter the risk (OR 1.10; 95% CI 0.13–9.96) when compared with low-dose ethinyl estradiol/high-dose progestin (not statistically significant, OR 0.0; CI 0.00–1.08) and low-dose ethinyl estradiol/low-dose progestin (OR 0.59; 0.26–1.30). However, comparing high-dose versus low-dose progestin decreased the risk significantly (OR 0.21; CI 0.05–0.84).

The multicenter, population-based, case-control study with the longest duration to date is the ongoing CASH study, with enrolment in 1980–1982 at eight US regional cancer registries participating in the Surveillance, Epidemiology

Table 1 Risk of endometrial cancer during oral contraception, with relevant studies listed in chronological sequence

Reference (years)	Country	Cases	Controls	Age (ever users)	Risk influenced by		OR/ RR
					Invest. factors	OC duration	
Horwitz[14]	USA	104	87	50		n.a.	0.94
Weiss[15]	USA	110	249	35–54	b,d	n.a.	0.5
Kaufman[16]	USA	152	516	>60	c,d	yes	0.5
Ramcharan[29] (cohort)	USA	58	16.638	>65		n.a.	0.6
Kelsey[17]	USA	37	342	45–74		yes	0.6
Hulka[18,33]	USA	79	203	n.a.	a	yes	0.3–0.6
Henderson[19]	USA	110	110	<45	b–d,f	yes	0.75
Trapido[30] (cohort)	USA	98	97300	<58		n.a.	1.4
LaVecchia[20]	Italy	170	1282	<60		n.a.	0.56
Pettersson[21]	Sweden	362	367	<60	c	n.a.	0.4
Ory (CASH) (1987)[22]	USA	433	3191	25–54	a–d,f,g	yes	0.6
Armstrong[34]	USA	130	835	25–59	a,c,e,g	no	0.55
Beral[31] (cohort)	UK	47.000	n.a.			n.a.	0.2
Koumnantaki[24]	Greece	83	164	40–79		yes	0.65
Levi[35]	Switzerland	122	309	≤75	a,c,e,f	yes	0.5
Stanford[36]	USA	405	297	n.a.	a,d,e,f	yes	0.4
WHO Collaborative (1991)[25]	USA	220	1537	>65	b,c	n.a.	1.10[1] 0.15[2] 0.59[3]
Weiderpass[37,44]	Sweden	709	3368	50–74	a–g	yes	0.5
Heinemann[38]	Germany	485	1570	32–65	a–g	yes	0.36
Maxwell (CASH) (2006)[23]	USA	434	2557	25–54	b,e,f	yes	0.21[4] 0.39[5]
Vessey (Oxford FPA)[40,41] (cohort)	UK	77	17.032 (recrution)	25–39	a–c	yes	0.1
Hannaford[31,32] (cohort)	UK	156	47.173			yes	0.58

Notes: [1]High dose estrogen/low dose progestin; [2]high dose estrogen/high dose progestin; [3]low dose estrogen/low dose progestin; [4]high potency progestin; [5]low potency progestin.
Abbreviations: na, no answer; a, duration; b, composition; c, persistence of protection; d, hormone therapy after OC; e, parity; f, weight; g, histology; ns, not significant; n.a, not applicable; CASH, Cancer and Steroid Hormone Study; OR, case/control studies; RR, cohort studies.

and End Results (SEER) centers of the National Cancer Institute. The first larger evaluation in 1987[22] included 433 cases and 3191 controls, and was limited to women aged 20–54 years. Women who had used COC for at least one year had an age-adjusted risk of 0.6 (95% CI 0.3–0.9). This risk reduction persisted for at least 15 years after cessation of COC use.

Like the World Health Organization Collaborative Study, the latest evaluation of CASH[23] focused on hormonal potencies, and included 434 endometrial cancer cases and 2557 controls. Compared with nonusers, both high-progestin and low-progestin COC decreased the risk significantly (OR 0.21, 95% CI 0.1–0.43 and OR 0.39, CI 0.25–0.60, respectively), but among women with a body mass index greater than 22, the decreased risk was significant only for high-progestin COC (OR 0.31; 95% CI 0.11–0.92).

Similarly, in a large population-based Swedish case-control study (n = 709/3368)[37] high-dose, medium-dose, and low-dose progestin COC reduced the risk, although the reduction was significant only with high and medium dosages (adjusted OR 0.7; 95% CI 0.5–0.9). The reduction in risk compared with no treatment was similar for all degrees of tumor differentiation and invasiveness. Because only postmenopausal women aged 50–74 years have been investigated, subsequent use of hormone replacement therapy could also be assessed, and the reduction of risk did not change in women using COC at a younger age. The reduction in risk was noticeable after three years of use (OR 0.5; 95% CI 0.3–0.7), and increased with duration of intake, reaching an 80% risk reduction after 10 years of use (OR 0.2; CI 0.1–0.4) and, as in the CASH study, the protective effect persisted for at least 15–20 years after cessation of COC.

Very similar results have been found in a German population-based case-control study (n = 485/1570),[38] with the reduction in risk comparable for all COC used (adjusted OR 0.36; 95% CI 0.28–0.45 for ever-users versus never-users) and comparable with low-dose COC (OR 0.30; CI 0.12–0.74). This positive effect started within five years (OR 0.63; CI 0.47–0.86), increased with duration of use, reached a 75% lower risk after 10 years (OR 0.25; CI 0.18–0.34), and persisted for more than 10 years after cessation of use.

Similar trends were observed in a recent large recent Chinese case-control study[39] (n = 1204/1212). The risk for ever-users of COC compared with never-users decreased (OR 0.75; 95% CI 0.60–0.93). This effect was stronger with duration of use (five years or more, OR 0.50; CI 0.30–0.85) and persisted 25 years after cessation of use (OR 0.57; CI 0.42–0.78).

The 2006 update on the Oxford Family Planning Association cohort study evaluating 17,032 women has recently been published (for 77 cases) with a more than 50% reduction in ever-users (RR 0.1; CI 0.0–0.4), and this effect lasted for more than 20 years after stopping COC. In this analysis,[40] data for cancers of the cervix, uterine body, and ovary have also been combined for evaluation of RR, resulting in an age-adjusted RR of 0.7 (CI 0.5–0.8). This study has also recently evaluated factors affecting mortality with special reference to oral contraceptive use.[41] Use of COC strongly reduced the risk of death from uterine cancer compared with nonuse, and the RR for ever-use was 0.3 (95% CI 0.1–0.8). This effect increased with duration of COC use and persisted for more than 20 years after cessation.

In summary, to our knowledge, only one of the studies[30] discussed here has shown an increased risk of endometrial cancer during COC. In the other studies, no effect in terms of risk reduction was observed compared with nonuse. However, a possible relationship with dosages of the hormones (decreased risk with increasing progestagen potency in relation to estrogen dose) has been investigated in some of the studies, and this is an important prerequisite for a causal relationship. In contrast, the decrease in risk related to duration of COC use seems to be very clear.

A meta-analysis[42] including 10 case-control studies[15–22,35,36] and the cohort study from the Royal College of General Practitioners[31] has calculated a significant RR of 0.44, 0.33, and 0.28 after four, eight, and 12 years of COC use, respectively. The trend of decreasing risk with increasing duration of use of COC was highly statistically significant ($P < 0.0001$). Despite the limitations of performing a meta-analysis on the basis of studies which are very heterogenous in terms of possible confounders, this analysis strongly supports a causal relationship between decrease in cancer risk and duration of COC use.

In this analysis, the cumulative incidence of endometrial cancer for the period of COC use in absolute numbers was also calculated and compared with that in women who had never used COC. The incidence rates were calculated using COC as a function of age, duration of use, and recent use, as well as cumulative incidence rates by standard life-table methods. The results are shown in Table 2 comparing data from the US and Japan for the age groups 20–54 years and 20–74 years, respectively.

Table 2 Cumulative incidence of endometrial cancer in 100,000 women using COC compared with never use comparing Western and Asian populations (US and Japan)

	Estimated number of cases			
	Age 20–54 years		Age 20–74 years	
	US	Japan	US	Japan
COC use				
Never	447	136	2396	473
4 years	283	86	1696	328
8 years	241	73	1522	292
12 years	213	65	1417	271
Lower 90% confidence limits				
4 years	203	62	1185	230
8 years	180	55	1093	211
12 years	165	50	1037	199
Upper 90% confidence limits				
4 years	394	119	2427	469
8 years	322	97	2118	405
12 years	277	84	1937	368

Note: Modifed from Schlesselman JJ. Risk of endometrial cancer in relation to use of combined oral contraceptives. A practitioner's guide to meta-analysis. *Hum Reprod.* 1997;12:1851–1863.42 Copyright © 1997, with permission from Oxford University Press.
Abbreviation: COC, combined oral contraceptives.

Risk using oral progestin-only preparations

Almost all studies of the risk of endometrial cancer have investigated the effects of COC, but only the CASH and World Health Organization Collaborative Study of Neoplasia and Steroid Contraception have tabulated users of progestin-only preparations separately, with very small numbers.[22,23] In the CASH study, only one case and six controls used progestin-only preparations exclusively, resulting in an OR of 0.6 (95% CI 0.1–5.0). The World Health Organization study comparing 220 cases from seven countries with 1537 age-matched controls found no cases and only two controls who had used progestin-only preparations exclusively.

Similarly, the more recent studies have included only small patient samples. Because in the large Royal College of General Practitioners cohort study only 3% were progestin-only users, risks were not calculated.[32] In a large Swedish case-control study,[37] including 707 cases/3368 controls, only seven of 61 cases used the minipill (OR 0.4; CI 0.2–1.4) and none of 14 cases used intramuscular depot medroxyprogesterone acetate.

Therefore, we still have very little knowledge about the endometrial effects of using progestin-only preparations. Therefore, inferences about progestin-only preparations must be made from our overall knowledge about COC, other risk factors, and biological mechanisms, as described earlier in this paper. On the basis of these experimental studies,

a reduction in risk could be expected with progestin-only preparations as well as with COC when compared with nonusers. However, because only few clinical data exist, more studies are needed to reach a conclusion about any potential carcinoprotective effect if only progestins are used for hormonal contraception.

Confounding factors regarding risk reduction

Confounding factors for risk assessment in the published studies might include factors which are known to have an impact on the associations made in the studies. Because we can only perform observational studies for contraception, possible confounders are of special importance.

It may be expected that risk factors for endometrial cancer other than use of hormonal contraceptives would include body mass index, family history, smoking, and parity. Indeed, if adjustments had been made in the studies, these factors would have been taken into account. However, the modulating effect of these factors was investigated in few studies and only in small subgroups.[36] Moreover, investigation of these risk factors has not been performed in studies using oral progestin-only preparations.

In addition, extrapolating from discussions on the risk of breast cancer, a comparison of the risk of endometrial cancer in COC users from Western versus Asian countries might allow some conclusions regarding possible confounding factors. According to the evaluation shown in Table 2, endometrial cancer incidence rates are much lower in Japan than in the US. At this time, to our knowledge, this is the only comparative evaluation to have been published, and similar assessments in China, for example, are still lacking.

The reason for the large difference in absolute risk between the US and Japan remains unclear. However, it can be speculated that known differences in obesity, nutrition, and genetic factors might be the reason for the lower risk in Asian countries.

In terms of possible confounders in the relevant studies, obesity has been shown to be the strongest risk factor in at least 20 reports, increasing the risk of endometrial cancer by 2–20-fold.[13] However, no modulating effects were observed in some studies.[34,37] Therefore, further studies are needed to investigate the effect of COC in obese women. In contrast, family history seems to have only a minor impact on risk, even with a first-degree family history of increased risk at any specific site (eg, endometrium, colon, breast).[43–45] No effect of a positive or negative family history was demonstrated

in the German study[38] (OR 0.44; CI 0.27–0.71 and OR 0.31; CI 0.23–0.41, respectively). However, this might differ for other populations, eg, Asian women.

Nulliparity, which is known to be a strong risk factor,[44,46,47] also did not influence the effect of COC on cancer risk reduction.[22,37] Surprisingly, smoking, which is known to increase the risk of endometrial cancer by up to 50% as a result of increased hepatic estrogen metabolism,[45,48] did not have any effect on risk reduction during use of COC.[37] However, in view of the mechanisms which decrease the risk of endometrial cancer, a confounding effect of COC should not be excluded.

Even advancing age, known to be a strong risk factor for most cancers, did not influence the protective effect of COC against endometrial cancer in the Swedish case-control study, and long-term exposure to endogenous estrogen had no modulating effect when women with different durations of COC use and different menopausal status were compared.[37]

All in all, it seems that, with the exception of obesity (and perhaps genetic and nutritional differences between populations), other factors may make only a minor contribution, if any, to the reduced risk of endometrial cancer in COC users compared with nonusers. Therefore, the observed decreased risk of endometrial cancer during COC use, although only identified from observational data, has to be assessed as one of the most important noncontraceptive benefits of COC, in addition to the well-known reduction in risk of ovarian cancer.

Special benefit in patients with polycystic ovary syndrome?

Additional noncontraceptive benefits of COC are important for women seeking contraception but having risk factors and/or diseases that are known to increase the risk of cancer. In the gynecological field, the most important diseases that increase the risk of endometrial (as well as ovarian) cancer are the metabolic and polycystic ovary syndromes,[49] in which a potential carcinoprotective effect of COC is possible.

For patients with polycystic ovary syndrome, there is an increased risk of ovarian cancer as well as an up to five-fold increased risk of endometrial cancer. This is due to a variety of reasons, including the increased efficacy of aromatase in producing estradiol by metabolism of androgens (increased due to hyperandrogenism), as well as obesity, hypertension, and diabetes, which are the main risk factors and sequelae, respectively, in patients with polycystic ovary syndrome, and likewise are also the main risk factors for development of endometrial cancer.[49] Thus, the carcinoprotective effect of COC

in patients with polycystic ovary syndrome wishing to avoid pregnancy might be a good argument for the use of COC.

However, so far, there are no published studies that have investigated the possible protective effect of COC against endometrial and ovarian cancer in this patient group compared with women without the disease. On the other hand, COC increases cardiovascular risk, even at lower doses, and this includes the newer COC preparations. For patients with cardiovascular risk factors, it is recommended to use progestin-only formulations. For polycystic ovary syndrome, progestagens with antiandrogenic properties are preferred, ie, cyproterone acetate, drospirenone, and (not yet available in all countries) dienogest and chlormadinone acetate. However, very limited data are available as yet on the risk of endometrial cancer for progestagen-only preparations.

Despite the increased cardiovascular risk in patients with polycystic ovary syndrome, use of COC is recommended to enhance antiandrogenic potency. Combination with ethinyl estradiol can lead to increased sex hormone binding globulin levels, which can decrease the concentration of free testosterone, which is the biologically active androgen. However, ethinyl estradiol might increase the risk of venous thromboembolism, which is already increased in patients with polycystic ovary syndrome.

Thus, the benefits in terms of a reduced risk of endometrial and ovarian cancer versus the increased cardiovascular risk with the use of COC in patients with polycystic ovary syndrome must be individually weighed regarding use and choice of hormonal contraception in these patients, and should take into account the possible benefit of reducing hyperandrogenism, which is a pathophysiologically important aspect of this disease. Until data from studies comparing the incidence of endometrial cancer in COC users with polycystic ovary syndrome and nonusers with the disease are published, the choice of contraceptive should be based on cardiovascular profile and antiandrogenic potency.

Future directions

Further research is needed, especially in patients at high risk of endometrial cancer, as identified in women with polycystic ovary syndrome, and there is still a lack of data on estrogen and progestin dose-dependent effects. With respect to the type of COC, newer contraceptive preparations are coming onto the market or are already available which contain natural estradiol as the estrogen component instead of ethinyl estradiol, together with newer progestagens. Due to the stronger efficacy of estradiol at the endometrium, the effects derived

from the progestagen component in antagonizing estrogen-induced endometrial proliferation might be decreased, and this should be investigated in further studies. Data for COC containing ethinyl estradiol should not be extrapolated to COC containing natural estradiol, although preparations containing the latter might have a better profile in terms of cardiovascular and hepatic safety.[50,51]

Safety issues have been the main problem associated with use of COC, and most side effects and risks arise from the estrogen component, ethinyl estradiol. Very recent studies show that the newer progestagens, like drospirenone, in combination with ethinyl estradiol also increase cardiovascular risk, especially the risk of venous thromboembolism, and cannot be avoided.[52,53] Progestin-only preparations are recommended for patients with increased cardiovascular risk in general. Therefore, the benefit/risk ratio of progestin-only preparations is particularly important. However, at this time, a conclusion about the effects of progestin-only preparations regarding endometrial cancer cannot be drawn on the basis of the available clinical data, and more studies are urgently needed.

An ongoing question is continued use of COC and progestin-only preparations after endometrial cancer. Also relevant in this context is whether use of progestagen-releasing intrauterine devices can be used without increasing the risk of disease recurrence. Because of the small sample sizes in the studies performed to date and their controversial results, intrauterine devices should be used only in exceptional cases after endometrial cancer, although it is well established that the levonorgestrel intrauterine devices can reduce endometrial hyperplasia effectively.[54–56] Further investigations of this issue are needed as part of determining more precisely the relationship between risk of endometrial cancer and contraception.

Conclusion

Results from experimental studies of molecular mechanisms, biological markers important for endometrial remodeling, and histological changes during use of COC, are highly suggestive of a protective effect of the progestagen component against estrogen-related (type 1) endometrial cancer. Therefore, there is biological plausibility for a carcinoprotective effect of hormonal contraceptives, given that all of them contain a progestagen as the main component. On the basis of data from observational studies, use of COC can have a large additional noncontraceptive benefit, ie, a reduction in risk of endometrial cancer of about 50%.

Only few data exist for oral progestin-only preparations. However, on the basis of the mechanisms, a decreased endometrial cancer risk should also be expected. More data are needed in patients at high risk of endometrial cancer, such as those with polycystic ovary syndrome, because a possible carcinoprotective effect might be very important in the decision to use hormonal contraceptives, despite the increased cardiovascular risk associated with this disease, which could be increased further by use of hormonal contraceptives.

Possible confounding factors like family history, parity, and smoking seem to have a minor impact on the hormonal effects, but have been investigated in only a few studies. The large differences in the incidence of endometrial cancer in COC users between Western and Asian countries warrant more research to clarify the possible contribution of confounders. However, limitations due to confounding factors in the observational studies may not be important, with the exception of obesity which, as a strong risk factor for endometrial cancer, might offset the hormonal benefit of decreased cancer risk.

Although the demonstration of causality needs placebo-controlled studies, which in general cannot be performed in the contraceptive field, we conclude that experimental research as well as a large amount of observational clinical data point to a causal relationship between COC and reduced risk of endometrial cancer, which may be one of their most important noncontraceptive benefits.

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Disclosure

The authors have no conflict of interest to disclose for this paper.

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