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Hormonal contraception and risk of cancer

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BACKGROUND: Fear from increased cancer risk is one of the most significant reasons for low acceptance of reliable contraceptive methods and low compliance.

METHODS: In this review, we included all cohort and case–control studies published in English up to December 2008. They were identified through a search of the literature using Pubmed and EMBASE.

RESULTS: Data about breast cancer risk indicate a slightly increased risk among current users of oral contraceptives (OC), an effect which disappears 5–10 years after stopping. Combined OC have a significant protective effect on the risk of ovarian cancer, and the protection increases with duration of use (relative risk decreased by 20% for each 5 years of use). The significant risk reduction has been confirmed for BRCA 1 and 2 mutation carriers. The risk of endometrial cancer is reduced by about 50% in ever users, a benefit which is greater with increasing duration of use. An association has been found between increased risk of cervical cancer and long-term OC use. Current OC use has been associated with an excess risk of benign liver tumours and a modest increased risk of liver cancer. None of large prospective cohort studies with prolonged follow-up has observed an increased overall risk of cancer incidence or mortality among ever users of OC, indeed several have suggested important long-term benefits. Specifically, protective effect of OC can be used as chemoprevention in young women who are BRCA mutation carriers.

CONCLUSIONS: Women wishing to use combined OC can be reassured that their decision is unlikely to place them at higher risk of developing cancer.

Key words: hormonal contraception / ovarian cancer / cervical cancer / endometrial cancer / colorectal cancer

Introduction

It is well documented that reproductive factors significantly modulate risk of certain cancers. Data from prospective controlled studies documented that hormonal replacement therapy in post-menopausal women may increase the risk of breast and ovarian cancer, whereas decreasing the risks of endometrial cancer (Anderson *et al*., 2003). Benefits and risks of oral contraceptives (OC) use on cancer were reviewed in 1998 by Working Groups of the International Agency for Research on Cancer (IARC/WHO), which concluded that combined OC are carcinogenic to humans, based on an increased risk for hepatocellular carcinoma (IARC, 1999), breast and cervical cancer (IARC, 2007). Colorectal cancer was considered possibly inversely related to OC use. The evidence for other cancers in relation to OC use was considered inadequate (IARC, 2007).

The research concerning the relationship between cancer risk and OC use is complicated by a number of other factors: peak incidence of the majority of cancers at an older age with a long interval from last or first OC use, the use of multiple hormonal formulations during the women's life, the existence of many confounding factors, some of which may be directly related to contraceptive use (number of pregnancies, breast-feeding, age of first pregnancy, the number of sexual partners, the use of barrier contraceptives, etc.), different composition of OC formulations. Moreover, it should be emphasized that it will never be possible to conduct a prospective controlled study on the use of OC, with the number of subjects and length of follow-up sufficient to assess the risk of malignancy. Nevertheless, much consideration has been given to the relationship between OC use and the risk of cancer, and good quality data are being regularly published. The aim of our review is to summarize the data available and to provide an update for current clinical practice, especially the counselling of women before and during contraception use.

Methods

Included were all cohort and case–control studies published in English up to December 2008. They were identified through a search of the literature using Pubmed and EMBASE with the keywords ('oral contraceptives' or 'combined oral contraceptives') AND ('cancer' or 'neoplasm' or 'ovarian cancer' or 'breast cancer' or 'endometrial cancer' or 'cervical cancer' or 'liver cancer' or 'colorectal cancer') AND ('case–control study' or ' cohort study'). We retrieved and assessed potentially relevant articles, and checked the reference lists of all papers of interest to identify additional relevant publications. Studies were considered only if they considered information on OC separately from hormone replacement therapy or other hormonal therapies. We did not consider abstracts and case reports.

Breast cancer

Introduction

Breast cancer is the leading cause of cancer in women worldwide. It is a multifactorial disease. Moreover, there are multiple biological profiles of breast cancer. Major risk factors (increasing the relative risk more than 4-fold) are family history, increased breast density, previous diagnosis of atypical hyperplasia and thoracic radiotherapy. Other factors act with a relative lower increase risk (less than a 2-fold increase; Cummings *et al*., 2009), including endogenous and exogenous hormones.

The age of the first full term pregnancy (FFTP) has dramatically changed in Western world since the end of the 70s and oral contraceptives (OC) are used thus much longer prior FFTP than in past. There is a serious concern that OC could be responsible in part for the burden of breast cancer, which was reinforced by the recent classification of OC as carcinogenetic agents by IARC (2007). However, analysis of the current knowledge challenges this assertion.

Underlying mechanisms

Experimental data strongly suggest that estrogens have a role in the development and growth of breast cancer. Estrogens promote the development of mammary cancer in rodents and exert both direct and indirect proliferative effects on cultured breast cancer cells. The role of progestin is more controversial. They have been reported to be either anti-proliferative or proliferative, very likely depending on the phenotype of the cell, the micro-environment and the species (Medina *et al*., 2007). Progestins are able to bind different steroid receptors and progesterone is converted to metabolites with different properties (Pasqualini, 2007). These pharmacological properties may also explain their different actions on breast tissues. More recently, some *in vitro* data suggest that they could exert a proliferative activity on myoepithelial/basal breast cells/progenitor cells (Graham *et al*., 2009). The FFTP promotes differentiation of breast tissue, which can be protective against potentially carcinogenic substances, especially if it occurs early in life (Russo *et al*., 2005). OC may exert different effect according to the age when they are used and the state of breast tissue.

Invasive cancer risk

Two meta-analyses and several observational studies have reported on breast cancer risk and mostly failed to show any robust association with the use of OC. The Collaborative Group on Hormonal Factors in Breast Cancer meta-analysis pooled 54 studies from 25 countries (Table I; CGHFBC, 1996). This study reported that current and recent use of OC, rather than a long duration of use, carries a small increase in the relative risk (RR) in current users (Table I) which disappeared within 10 years of stopping. This could suggest a promoter effect of hormone therapy on pre-existing lesions or bias of screening in OC users. The RR increased with a young age (<20 years) at start. Because of the low incidence of breast cancer in this age group, the absolute numbers remain very low: the attributable numbers of breast cancer cases in the USA and in Europe per 10 000 women within 10 years after stopping the OC were 0.5 [95% confidence interval (CI): 0.3–0.7], 1.5 (95% CI: 0.7–2.3) and 4.7 (95% CI: 2.7–6.7) for age groups between 16–19, 20–24 and 25–29 years, respectively. In addition, breast cancers diagnosed in OC users were of better prognosis with a better differentiation (CGHFBC, 1996).

Since the above publication, some other important studies have been published and confirmed very low or absent increase in the risk. The Nurses' Health study reported on 3383 cases of breast cancer among 1.6 million person-years of follow-up (Hankinson *et al*., 1997). Women at entry were 30–55 years old and 6% of them reported current OC use, 40% past use and 54% never use of OC. Authors observed no increased risk among the whole population,

Table I Effect of OC use on breast cancer risk.

Study	Number		RR	95% CI
	Cases	Controls		
Oxford meta-analysis (CGHFBC, 1996)	53 297	100 239	Current/recent users: 1.24	1.15–1.33
Nurses' (cohort) (Hankinson *et al.*, 1997)	3383		1.11 >5 years use 0.96	0.94–1.32 0.65–1.43
RCGP (cohort) (Hannaford *et al.*, 2007)	46 000 (744 000 women-years)		0.98	0.87–1.10
Oxford Family Planning (cohort) (Vessey and Painter, 2006)	17 032		1.0	0.8–1.1
Women's CARE (Marchbanks *et al.*, 2002)	4575	4682	1.0	0.8–1.1
Women's Lifestyle and Health study (cohort) (Kumle *et al.*, 2002)	103 027		Former users: 1.2	1.1–1.4
			Current/recent users: 1.6	1.2–2.0
Mayo Clinic (meta-analysis) (Kahlenborn *et al.*, 2006)	Premenopausal breast cancer		Ever users: 1.19	1.09–1.29

in women who used OC for over 10 years, in a subgroup of women <45 years old or after >5 years of use (Table I).

The British large cohort of women recruited for the Royal College of General Practitioners' (RCGP) Oral Contraception Study, which included 46 000 women followed up since 1968–1969, did not find an increased risk of breast cancer among ever users (Hannaford *et al.*, 2007; Table I). In this study, 75% of the ever users had used an OC containing 50 μg ethinylestradiol (EE) and 63.6% of the women were below 30 years when they started using OC (Hannaford *et al.*, 2007). Similarly, The Oxford Family Planning Association (FPA) study included 17 032 women 25–39 years between 1968 and 1974 and has not observed any increase in the RR (Vessey and Painter, 2006).

The Women's Contraceptive and Reproductive Experiences (Women's CARE) study did not observed any increase in the RR in the whole cohort (Table I; Marchbanks *et al.*, 2002). Interestingly, more than 2500 women had begun using OC before the age of 20 and no increase in the RR was observed in users. In this study, most of the women used newer OC formulations than in the studies analysed in the Oxford meta-analysis, which could explain the difference in the results. They also found that women 45–64 years old who had ever used OC, had a small but significant reduction in the RR of breast cancer. A complementary study has looked at the effect of a short duration use (≤6 months) and the possible interaction with other risk factors on 1025 cases and 2032 controls. No overall increase in the risk was reported. There was a small increase in women with premenopausal breast cancer (OR = 1.3; 95% CI: 1.0–1.7). An earlier age of menarche, infertility, later age at FFTP and first degree of family history was associated with a higher risk of breast cancer in OC users. Moreover, a mammogram performed in the last 2 years was associated with an increased risk (RR = 1.6; 95% CI: 1.1–2.5). These observations strongly suggest that OC use allowed for more frequent or earlier breast cancer diagnosis in women at higher risk. Alternatively, women in whom breast cancer has been recently diagnosed are more likely to recall previous OC use. Similarly, increase risk in women who have used OC for other indications than contraception (menstrual cycle disturbances, endometriosis) could be explained by the fact that they carry other risk factors for breast cancer (Folger *et al.*, 2007).

The Women's Lifestyle and Health study observed an increase risk in users of OC after >5 years. This study enrolled 103 027 women between 1991 and 1999, followed up on registries in Norway and Sweden (Kumle *et al.*, 2002). There was a small increase for current, recent and former users (Table I). The increase in RR before FFTP and below age of 20 was not influenced by OC use.

In the Norwac cohort study, the increase in the RR was associated with the estrogen cumulative dose (RR = 1.3 for 50–99 mg; RR = 1.5 for ≥100 mg; Dumeaux *et al.*, 2003), but not with the progestin dose, whereas a relation with the progestin dose was observed in another study but with very few cases in the category of high-progestin dose and before 35 years, which precludes any conclusion (Althuis *et al.*, 2003).

Finally, a meta-analysis published in 2006 estimated the premenopausal breast cancer risk from 34 previous studies (Kahlenborn *et al.*, 2006; Table I). Multiparous women who have used OC before the FFTP had an OR = 1.44 (95% CI: 1.28–1.62), higher than those who started after the FFTP (OR = 1.15; 95% CI: 1.06–1.26). Duration of use >4 years before FFTP was associated with an OR = 1.52 (95% CI: 1.26–1.82). Nulliparous women had no increase of the risk irrespective of the duration of use. Results of this study suggest that pregnancy could reveal breast cancer risk promoted by OC. This meta-analysis used only case–control studies and crude odd ratio (not adjusted), which could have increased the RR values.

In most studies, mortality rates from breast cancer diagnosed in OC users were lower or equivalent to non-users (dos Santos Silva and Swerdlow, 1995; Trivers *et al.*, 2007; Wingo *et al.*, 2007; Barnett *et al.*, 2008).

Histological types of breast cancer

Only a few studies have addressed potential impact of OC use on different histological types of breast cancer. No strong difference has been observed between lobular or ductal subtypes (Newcomer

et al., 2003; Nyante et al., 2008). Two case–control studies did not find any increase related to OC use for ER+ or ER− breast cancer (Cotterchio et al., 2003; Ma et al., 2006). A recent study showed that OC use significantly increases (2.5-fold) the RR of triple negative cancer diagnosed before the age of 40 (Dolle et al., 2009); however, these data were not confirmed in the CARE study (except for a subset of breast cancers among women of 45–64 years who started OC use before age 18 years; Ma et al., 2010). BRCA status was not known in any of the above studies.

Three studies have addressed the risk of *in situ* cancer in OC users. A case–control study in the USA recruited 567 cases newly diagnosed with breast carcinoma *in situ* (BCIS) and 614 controls between 1995 and 1998. OC use was not associated with risk of BCIS (OR = 1.04; 95% CI: 0.76–1.42). Risk did not increase with longer use, use before FFTP, age at first use or time since last use (Gill et al., 2006).

In another large case–control study from the USA on 1878 BCIS and 8041 controls ever use was associated with a non-significant OR = 1.11 (95% CI: 0.99–1.25) for BCIS and for ductal carcinoma *in situ* (DCIS; OR = 1.15; 95% CI: 1.01–1.31; Nichols et al., 2007). A marginal but already significant increase in risk was observed only in former users, but not in current users and there was no effect with increasing duration of use. These studies also suggest bias of earlier detection in OC users.

Another case–control study compared 446 cases with DCIS to 1808 with invasive cancer. Ten or more years of OC use showed no association with comedo-type DCIS (OR = 1.31; 95% CI: 0.70–2.47), a positive association for invasive cancer (OR = 2.33; 95% CI: 1.06–5.09), but a possible inverse association for non-comedo DCIS (OR = 0.51; 95% CI: 0.25–1.04). This could suggest that OC could promote the more transformed phenotypes of DCIS, however, the evidence is weak (Phillips et al., 2009).

Confounding factors

None of the previous studies has highlighted any predictive factor for an increase risk of breast cancer in OC users, except possibly a long use before FFTP or at young age. However, it is important for a clinician to know if, in women with specific conditions which have been linked to an increase in breast cancer risk, OC can further alter the risk.

Benign breast disease

Fibroadenoma does not increase the RR of breast cancer. Fibrocystic disease especially with proliferative lesions is associated with an increased risk. Hyperplasia with atypia is considered as precancerous lesions with an important increase in the risk of breast cancer. It was reported by several studies that OC use significantly decreases the incidence of benign breast disease (BBD; fibroadenoma and fibrocystic diseases) with increase duration of use, and this was recently confirmed with the new OC formulations (Ory et al., 1976; Vessey and Yeates, 2007). However, some studies shown that the OC protective effect concerned only BBD without atypia and that risk of BBD with atypia were not decreased and possibly even increased by OC (LiVolsi et al., 1979; Rohan and Miller, 1999). This observation is consistent with the fact that progestin may act as mitogenic agent on transformed cells but as anti-proliferative agent in normal or non-transformed cells.

Family history

The effect of OC in women with family history is an important issue, related to the question whether OC should be recommended to women with first or second degree relatives with breast cancer. Analysis of the literature shows that the data remains controversial, likely due to lack of statistical power, different populations or different definitions of family history (Gaffield et al., 2009). To date, in addition to the Oxford pooled analysis, there have been three cohort studies on OC use and breast cancer risk among women with a family history of breast cancer, and without data on the BRCA status.

In 2001, an analysis on the risk of breast cancer was published by the Collaborative Group on Hormonal Factors in Breast Cancer (CGHFBC, 2001). Data were collected from 52 published and two unpublished studies concerning first degree relatives with breast cancer in 58 209 women with breast cancer and 101 986 without cancer. Together 7496 (12.9%) women with breast cancer and 7438 (7.3%) controls reported that one or more first degree relatives had a history of breast cancer. The RR of breast cancer was increased by the family history, but use of OC did not alter the risk. Even in women younger than 50 years with an affected relative, the RR of breast cancer was similar for OC users in the previous 10 years (RR = 3.85; 95% CI: 2.41–6.13) and those who had never used OC (RR = 2.91; 95% CI: 2.15–3.93).

In the Nurses' Health Study (71 incident cases), no association was observed between OC use and a family history of breast cancer (Lipnick et al., 1986). These data were reanalysed in 1996 including 310 incident cases (but only four current OC users) and found statistically non-significant 2.5-fold increased risk (95% CI: 0.88–6.94) among current OC users with a family history of breast cancer (Colditz et al., 1996).

An original study, which included 426 families with a breast cancer diagnosed between 1944 and 1955, analysed 394 sisters and daughters, 3002 grand-children or nieces and 2754 spouses. A RR of 3.3 (95% CI: 1.6–6.7) was observed in women with a first but not a second degree relative and in women who used OC before 1975 (Grabrick et al., 2000).

A Canadian study has analysed data from 27 975 women with any family history of breast cancer and 1707 incident cases and found conflicting results. They showed significant effect in the whole cohort and a protective effect of marginal significance ($P = 0.03$ for trend) in women with long use (>7 years) and a first degree relative with breast cancer (Silvera et al., 2005). In all these reports, the BRCA status was not known.

BRCA mutation carriers

Several recent studies have reported conflicting data on the RR in OC users who are carriers of BRCA1/2 mutations (Jernstrom et al., 1999; Heimdal et al., 2002; Narod et al., 2002; Milne et al., 2005; Haile et al., 2006; Brohet et al., 2007; Lee et al., 2008; Dolle et al., 2009). These studies are retrospective, information recall is not similar, in some studies cases were matched to controls without mutation (Milne et al., 2005; Haile et al., 2006) and some studies are under-powered due to low number of cases. In addition certain proportion of the mutation carriers have underwent prophylactic mastectomy during the follow-up.

Table II Effect of OC use on breast cancer risk in BRCA mutation carriers.

Study	Mutation	Number	RR	CI 95%
Sweden (Jernstrom *et al.*, 1999)	BRCA1/2	245	1.65	0.95–2.87
			Use <20 years 2.10	1.02–2.62
			Before FFTP 1.63	1.32–3.33
Norway (Heimdal *et al.*, 2002)	Familial	1423	0.90	0.68–1.18
	BRCA1	96	2.00	0.36–10.9
USA, Canada, Australia (Haile *et al.*, 2006)	BRCA1	497/195cases	0.77	0.53–1.12
	BRCA2	307/128cases	Use >5 years 2.06	1.08–3.94
			Before FFTP 3.46	2.10–5.70
USA, Canada, Australia	BRCA1	47 cases	0.22	0.10-
(Milne *et al.*, 2005)	BRCA2	36 cases	0.93	0.34–3.09
USA, Canada, Europe (Narod *et al.*, 2002)	BRCA1	981 pairs	1.18	1.01–1.38
			Use <5 years NS	
			Use >5 years 1.33	1.11–1.60
	BRCA2	330 pairs	0.93	0.72–1.21
Europe (Brohet *et al.*, 2007)	BRCA1	1181/597 cases	1.4	1.13–1.91
			Before FFTP + greater than 4 years: 1.49	1.05–2.11
	BRCA2	412/249 cases	1.49	0.8–2.70
			Before FFTP + greater than 4 years: 2.58	1.21–5.49
USA (Lee *et al.*, 2008)	BRCA1/2	94 cases	NS	
USA (Figueiredo *et al.*, 2010)	BRCA1	109 cases	2.38	0.72–7.83
	BRCA2	72 cases	0.82	0.21–3.13

In the majority of published studies, there was a mild or moderate increase in the RR for OC users (Table II), but with a low power. In a large study (Narod *et al.*, 2002), the increased RR was observed only for BRCA1 women and for breast cancer at young age. The multivariate OR for ever use of OC was 1.38 (95% CI: 1.11–1.72) for BRCA1 carriers who were diagnosed with breast cancer before the age of 40 and 0.96 (95% CI: 0.75–1.24) for BRCA1 carriers who were diagnosed at the age of 40 or older. In the second large study (Brohet *et al.*, 2007), there was an increase in the risk if OC was used before FFTP for at least 4 years (Table II). However, the RR was not dramatically different from that in women without any family risk.

The RR of breast cancer in these selected patients may be weakly increased, but uncertainty remains; in addition the balance of benefit/risk in women with BRCA mutations is positively driven by a significant protective effect of OC on substantially increased risk of ovarian cancer (see later).

Composition of OC formulations

So far, there is no robust indication of variable effect on breast cancer risk in relation to different OC formulations. Most data, due to the need of long-term follow-up to see any effect on breast cancer risk, have predominantly concerned formulations containing $\geq$50 μg of EE. There is no evidence for a different risk of breast cancer in users of newer formulations but strong evidence is lacking. A Norwegian cohort study reported a positive correlation between the estrogen content and breast cancer risk but remains the only study with such finding (Dumeaux *et al.*, 2003).

Conclusions

In a majority of studies there is no increase in the risk of breast cancer reported in OC users. When the RR was shown to be increased, this effect disappeared progressively after stopping OC use. Long duration of OC use at a young age before the FFTP seems to be the most important risk factor, as hormones act on a less differentiated tissue. The number of events attributable to OC use remains below 1% of the total breast cancers and 7% for premenopausal breast cancer if the RR of the Oxford meta-analysis is applied to calculate the attributable fraction of breast cancer in France (CGHFBC, 1996).

The level of the increase in the RR is so low that it is not fully convincing and may have concerned the first generation of OC formulations. Although the modest and inconsistent associations may be attributable to variation in study design, it is also possible that they result from disease heterogeneity. Furthermore, significant involvement of screening or recall bias cannot be excluded (Marchbanks *et al.*, 2002; Rosenberg *et al.*, 2009; Shapiro, 2009). None of these studies has shown a role for the composition of OC on breast cancer risk. The possible, whereas currently unconfirmed, small increase in the risk of breast cancer in OC users with BRCA1/2 mutations is strongly counterbalanced by the benefits in terms of ovarian cancer protection.

Ovarian cancer

Introduction

Each year the Journal of Clinical Oncology publishes an analysis of major achievements in oncology. In 2008, the whole field of onco-

gynaecology was represented by a single issue, the confirmation of a significant risk reduction of ovarian cancer in OC users (Winer et al., 2009). Although this positive and important effect of OC has been discussed since 1970s, a good quality meta-analysis was published in 2008, not only summarizing most relevant articles, but also using source data from all 45 studies (Beral et al., 2008). We refer to the results of the meta-analysis here, but focus more extensively on areas which so far have received little or marginal attention.

Underlying mechanisms

Several possible mechanisms have been suggested for ovarian cancerogenesis and each are potentially influenced by hormonal contraceptives.

The incessant ovulation hypothesis (Fathalla, 1971) assumes that the development of ovarian cancer is a consequence of repeated microtrauma to the ovarian surface epithelium (OSE) during ovulation. It is hypothesized that repeated DNA damage during ovulation and dysfunction of its recognition and repair are crucial for ovarian cancerogenesis. The inhibition of ovulation could thus explain the protective influence of hormonal contraception, pregnancy and breast-feeding. This does not, however, fully explain other epidemiological findings. The protective effect of even short-term OC use, as well as that of pregnancy go beyond what a simple reduction in the number of ovulations would suggest (Gwinn et al., 1990; Siskind et al., 2000; Greer et al., 2005). Moreover, some diseases causing chronic anovulation, in particular polycystic ovary syndrome, do not have the protective effect (Schildkraut et al., 1996).

The gonadotrophin hypothesis states that malignant transformation can be caused by the exposure of OSE to excessive gonadotrophin levels (Cramer and Welch, 1983). This theory would explain both the protective effect of OC that significantly inhibit gonadotrophin levels (Spona et al., 1996), as well as the sharp increase of ovarian cancer incidence after the menopause. On the other hand, it runs counter to the protective role of breast-feeding, as lactating women have raised FSH levels, and it fails to explain why hormonal treatment in post-menopause, which also reduces gonadotrophin levels, increases the risk of ovarian cancer (Anderson et al., 2003; Beral et al., 2007).

The hormonal hypothesis presumes a decisive role for ovarian hormones, progesterone in particular. In experimental studies progesterone up-regulated p53 tumour suppressor gene expression and inhibited proliferation of cultured sheep ovarian epithelial cells (Murdoch and Van Kirk, 2002), or induced apoptosis in normal and malignant human ovarian epithelial cell lines (Bu et al., 1997; Syed and Ho, 2003). Progesterone had an inhibitory effect on proliferation in ovarian epithelium cell cultures obtained from premenopausal and post-menopausal women (Ivarsson et al., 2001). Moreover, in a 3-year randomized controlled trial in monkeys it was demonstrated that synthetic progestin levonorgestrel can induce apoptosis in OSE (Rodriguez et al., 1998). These experimental data allow us to speculate that exposure to high progesterone levels in pregnancy or progestins contained in OC may lead to a 'clearing' of cells in OSE containing sub-lethal DNA damage by the induction of apoptosis.

A new theory is emerging from recent data concerning the possibility of developing epithelial cancers from one precursor cell derived from the Müllerian duct (Shih Ie and Kurman, 2004). The Müllerian duct forms the fallopian tube, uterus, cervix and upper vagina, and HOX genes play a significant role in such differentiation (Cheng et al., 2005). OC might interfere with the mechanisms of cancerogenesis through several mechanisms: the inhibition of ovulation prevents the invagination of cells from the Müllerian duct, sex steroids may directly regulate the expression of HOX genes, one can also speculate on the possible interference with endometrium and tubal epithelium transformation, decreasing risk of shedding cells derived from the Müllerian duct.

None of these theories explain the epidemiology data in full. Moreover, there is an overlap in mechanisms involved in individual hypotheses. It is therefore very likely that several mechanisms contribute to the protective effect of OC.

Risk in OC users

A possible positive influence of OC on the risk of ovarian cancer has been discussed since 1970s (Casagrande et al., 1979). A number of epidemiological retrospective analyses assessing the risk and protective factors of ovarian cancer, and large-scale prospective trials have been conducted. The broadest meta-analysis to date was published in 2008 (Beral et al., 2008) endorsing the findings of previous meta-analyses (Hankinson et al., 1992; Whittemore, 1992; Bosetti et al., 2002). It included all studies published up to January 2006 which recruited at least 100 women with ovarian cancer. They analysed data from 23 257 cases and 87 303 controls. An important strength of the study was the fact that source data from all the 45 studies were available. The meta-analysis confirmed a significantly reduced RR of ovarian cancer for ever OC users, which was comparably reduced regardless of the study design in 13 major prospective (RR = 0.74; SE: 0.03), 19 population-based case–control (RR = 0.69; SE: 0.03) and 13 hospital-based case control studies (RR = 0.81; SE:0.05; Beral et al., 2008). Another important supporting argument is a confirmed trend between the RR of ovarian cancer and the duration of OC use. After adjustment for various potential confounding factors, the RR decreased by 20% for each 5 years of use.

Since the meta-analysis was published, its results have been endorsed by several other studies. The Oxford FPA prospective cohort study recruited more than 17 000 women between 1968 and 1974 and followed them until 2004. It found a significantly reduced RR of ovarian cancer in ever OC users (RR = 0.5; 95% CI: 0.3–0.7), although it was incapable of confirming the trend regarding the duration of use (Vessey and Painter, 2006). A significantly reduced risk was observed as early as after 1 year of use (OR = 0.47;95% CI: 0.33–0.67), and an average odds ratio reduction of 5% per each year of OC use was observed in population-based case–control study carried out in USA, which included 813 cases of ovarian cancer and 992 controls (Lurie et al., 2008). Significant risk reductions of ovarian cancer, together with decreasing trend with duration of OC use, were also confirmed in large RCGP Oral Contraception Study (Hannaford et al., 2007). RR of 0.54 (95% CI: 0.40–0.71) was shown in the whole cohort and 0.38 (95% CI: 0.16–0.88) for users of OC ≥ 97 months. On the contrary, a large prospective Chinese trial with median follow-up of 7.5 years, which followed a cohort of more than 66 000 women, failed to confirm a reduced risk in OC users although a positive trend was seen with ≥2 years of OC use

(Dorjgochoo *et al.*, 2009). However, only 19% of women had ever used OC in the Chinese study and only 94 cases of ovarian cancer were diagnosed during the follow-up.

Confounding factors

Evidence from a number of epidemiological studies indicates that there are numerous other reproductive factors significantly affecting the risk of ovarian cancer, in particular parity and breast-feeding (Gwinn *et al.*, 1990; Jordan *et al.*, 2008). It is therefore important to ascertain whether these factors influence the protective effect of OC. In a meta-analysis of 12 case–control studies conducted between 1956 and 1986, protection was more pronounced in women who breastfed for a long period, but this finding was only seen in population studies (Whittemore, 1992). The majority of other studies found no difference in the protective effect of OC depending on other reproductive factors. In one meta-analysis, a number of parameters were assessed including ethnicity, BMI or tobacco use, but none of the15 parameters assessed, with the exception of age at diagnosis and menopausal status, significantly changed the declining trend in RR (Beral *et al.*, 2008). Similar protection was also confirmed among women with and without endometriosis (Modugno *et al.*, 2004). Thus, the protective effect of OC is probably not significantly influenced by other parameters, including those which constitute significant risk or protective factors for the development of ovarian cancer.

Time dependency of risk modulation

The incidence of ovarian cancer increases with age, peaking at about 70 years of age, whereas the use of OC is limited to the fertile period of life. Consequently the duration of protection after the cessation of OC is significant for reduction of absolute risk. The protective effect of OC diminishes slowly 10 years after cessation, although a protective effect has been confirmed after >20 years (Moorman *et al.*, 2008) or >30 years (Beral *et al.*, 2008; Lurie *et al.*, 2008). The Beral meta-analysis showed a reduction of the RR for ovarian cancer by 48, 38 and 31%, respectively, in women who used OC for 5–9 years and ceased <10 years, 10–19 years or 20–29 years previously. The most important factor determining the duration of protection was the duration of OC use, whereas the age of first or last use seems to be less important (Tworoger *et al.*, 2007; Beral *et al.*, 2008; Lurie *et al.*, 2008; Moorman *et al.*, 2008).

Considering the absolute lifetime risk of ovarian cancer, regardless of the duration of protection, it is crucial whether the same level of protection is maintained in post-menopausal women. Menopause was one of the few factors that diminished the decline in RR of ovarian cancer in the meta-analysis by Beral *et al.* (2008). Reduction of RR per 5 years of OC use reached 27% (SE 3.2) versus 16.6% (SE 2.5) in pre- versus post-menopausal women. It should be stressed, however, that the average age of women included in the meta-analysis was 56 years and fewer than one-third of ovarian cancer cases were diagnosed in patients over 65 years old. Furthermore, a number of other studies have shown smaller or even non-existent protection in post-menopausal women (Lurie *et al.*, 2008; Moorman *et al.*, 2008). This might significantly affect the estimated reduction of absolute ovarian cancer risk post-menopause.

Histological types of ovarian cancer

A number of studies found different risk factors for mucinous ovarian cancers compared with two other frequent histological types, serous and endometrioid cancers. In accordance with this different epidemiological nature, a lower degree of risk reduction by OC use was observed for mucinous invasive cancers (Risch *et al.*, 1996; Tung *et al.*, 2003; Soegaard *et al.*, 2007). These findings are confirmed by the results of the meta-analysis by Beral which showed a risk reduction of ≥20% per 5 years of use for endometrioid and serous cancers, although the risk was reduced by just 12% for mucinous cancers.

Of much greater importance is whether the protective effect of OC is maintained for borderline ovarian tumours (BTO) occurring at a much younger age than invasive cancers. Epidemiological studies confirmed similar reproductive risk factors in BTO as in invasive ovarian cancers (Risch *et al.*, 1996; Riman *et al.*, 2001; Huusom *et al.*, 2006). The data concerning the protective effect of OC on BTO risk are more heterogeneous. A number of studies did not find significantly decreased RR (Riman *et al.*, 2001; Kumle *et al.*, 2004; Huusom *et al.*, 2006); however, others present a positive trend and the absence of significance is probably related to the smaller number of cases (Kumle *et al.*, 2004; Huusom *et al.*, 2006). Moreover, a comparable level of protection by OC for serous BTO and serous invasive ovarian cancer was confirmed in the Beral meta-analysis, although not significant due to wide CIs.

Composition of OC formulations

The majority of published prospective and retrospective trials investigating ovarian cancer risk and OC use included women between 50 and 70 years old (Beral *et al.*, 2008). In the meta-analysis of 2008 only 20% of ovarian cancer patients used OC within the preceding 10 years. Thus, the majority of women included in those studies used older OC formulations with higher hormonal doses.

The differences in the estrogen component have been easier to study. The majority of studies compare the effect of older formulations containing >50 μg EE (or equivalent dose of mestranol) to a lower dose (Rosenblatt *et al.*, 1992; Rosenberg *et al.*, 1994; Ness *et al.*, 2000; Sanderson *et al.*, 2000). Rosenblatt did not find significant differences in protection, even though the OR was lower for doses >50 μg, another study reported a comparable modest risk reduction for both doses (Rosenberg *et al.*, 1994), and the Sanderson study observed an even lower OR in users of ≤50 μg EE (OR 0.6; 95% CI: 0.3–1.1 versus OR 0.8; 95% CI: 0.5–1.2). In a population-based case–control study, identical protection was reported for formulations containing ≥50 μg EE in combination with high-potency progestin (OR = 0.5; 95% CI: 0.3–0.6) and <50 μg EE in combination with low-potency progestin (OR = 0.5; 95% CI: 0.3, 0.7; Ness *et al.*, 2000). All these studies are limited by small number of cases. The Beral meta-analysis utilized an interesting methodology to compare the protective effect of OC by decade of use from 1960s till 1980s, and found a comparable RR of ovarian cancer of 0.52–0.55 (Beral *et al.*, 2008). The dramatic reduction of estrogen dose over the 30 years did not weaken the protective effect. These data, however, do not reflect the formulations containing ≤35 μg of EE, which only gained dominance in the market in 1980s.

Only four studies enabled differentiation of users of formulations with <35 μg EE, and there was no significant difference found in

risk reduction in any of those studies compared with formulations with >35 μg EE (Royar et al., 2001; Pike et al., 2004; Lurie et al., 2007).

An evaluation of the role of the progestin component is complicated by a large variety of different compounds used, and the absence of unified classification or methodology for assessing progestin potency. Older literature quoted risk for individual formulations (CASH, 1987; Rosenberg et al., 1994), but lately efforts have been made at clustering according to progestin potency measured by the delay of menstruation test, or induction of secretory transformation in endometrium (Dickey and Stone, 1976). The available findings are divergent, claiming both comparable risk reduction (Ness et al., 2000), as well as stronger protection in formulations with higher progestin potency (Schildkraut et al., 2002; Pike et al., 2004). A major recent publication using photographs of OC packages to improve women's recall, made a separate assessment of women who reported exclusive use of the same formulation during all OC use episodes, and found a lower OR for users of low-potency progestin in combination with low-dose of estrogen (OR = 0.19; 95% CI: 0.05–0.75) as opposed to high-potency progestin and high estrogen dose (OR = 0.62; 95% CI: 0.43–0.92; Lurie et al., 2007). It must be emphasized, however, that those studies are limited by a low number of subjects.

In conclusion, the data available, albeit limited due to the small numbers of subjects, suggest that the protective effect of OC is maintained in formulations with <50 μg EE, just as in low-dose formulations with <35 μg.

BRCA mutation carriers

Women with higher risk of ovarian cancer, particularly carriers of BRCA 1/2 mutation, constitute an important target group for any protective effect from the use of OC.

Since 1998, six studies have investigated OC use in BRCA carriers, of which only one failed to confirm a protective effect (Modan et al., 2001). A population-based case–control study in Jewish women confirmed the protective effect of OC use in general population (≥5 years of use OR 0.53; 95% CI: 0.34–0.84), but did not find this protection in mutation carriers (0.2% risk reduction for each year of use). The specific ethnic background, as well as the small number of OC users, may provide an explanation for this discrepancy, but the study provides no further details. All five other case–control studies showed conclusively decreased ovarian cancer risk in OC users who were carriers of BRCA mutations (Narod et al., 2002; McGuire et al., 2004; Whittemore et al., 2004; McLaughlin et al., 2007; Antoniou et al., 2009). The largest study included both BRCA mutation carriers (670 with BRCA 1 and 128 with BRCA 2) and population controls (2043 with BRCA 1 and 380 with BRCA 2; McLaughlin et al., 2007). The use of OC was associated with highly significant risk reduction of ovarian cancer for mutation carriers (OR = 0.53; 95% CI: 0.43–0.66). Numbers of subjects were sufficient for separate analysis and confirmed similar protective effect for both BRCA 1 and BRCA 2.

For young women with a hereditary increased risk of ovarian cancer who plan further pregnancy, or do not accept prophylactic salpingo-oophorectomy, the recent data confirms a protective effect in BRCA 1 mutation carriers.

Conclusion

The use of OC has a significant protective effect on the risk of ovarian cancer and the risk reduction is dependent on the duration of use. The exact mechanism of action has not been elucidated, ovulation inhibition seems to be the most important factor, but suppression of gonadotrophin levels and direct effect of progestin compounds may also play a role. The reduction in RR is maintained for several decades, but diminishes in post-menopausal women. The risk reduction applies to all main histotypes, including BTO, with the exception of mucinous tumours. The data available provide evidence of maintained protective effect even in modern formulations containing ≤35 μg EE. Recent studies confirm a significant risk reduction in BRCA 1 and 2 mutation carriers.

Endometrial cancer

Underlying mechanisms

A total of 41 000 new cases of endometrial cancer were diagnosed in the USA in 2006 (ACS, 2006). Two different clinicopathological subtypes are recognized: the estrogen-related type 1 (endometroid), comprising 70–80% of newly diagnosed cancer and the non-estrogen-related type 2 (non-endometroid such as papillary serous and clear cell).

Regarding histology, the biological basis is that estrogen stimulates endometrial cell division, whereas progestins block that effect. During progestin action, cell proliferation ceases despite continuous exposure to estrogen levels (like in the luteal phase). Progestins protect from estrogen-induced hyperplasia and changes in proliferative status. They induce glandular epithelial secretory activity and decidual transformation of stromal fibroblasts; these terminally differentiated cells can no longer proliferate and are shed in withdrawal bleedings (if implantation not occur), with strong differences dependent on the pharmacology of progestins used (type, dosage, pharmacokinetics etc.; Pike and Spicer, 2000). Interestingly comparing OC containing EE/norethindrone in different dosages with hormone replacement therapy containing conjugated equine estrogen/MPA, the subjects using OC had significantly less endometrial proliferation and in consequence also less progestin-induced pro-secretory effects (Portman et al., 2003).

However, changes in histological features during OC include different proliferatory, secretory and atrophic (like) patterns, changes in gland-to-stroma ratio, stromal factors (e.g. very potent growth factors), architectural structures (e.g. cribiform and/or papillary patterns), glandular cellularity, cytoplasmic changes, mitotic activity, (tumour-)angiogenesis and increases or decreases in cytologic atypia. The latter of these are powerful markers and predictors for progestin potency (Portman et al., 2003; Amant et al., 2005; Wheeler et al., 2007). All these effects may explain, why and how OC use can reduce the risk of endometrial cancer.

Risk in OC users

The first relevant systematic review using the criteria of the U.S. Preventive Services Task Force and evaluating the association between OC and endometrial cancer was published in 1995 (Grimes and Economy, 1995), assessing 13 case–control studies (Fig. 1).

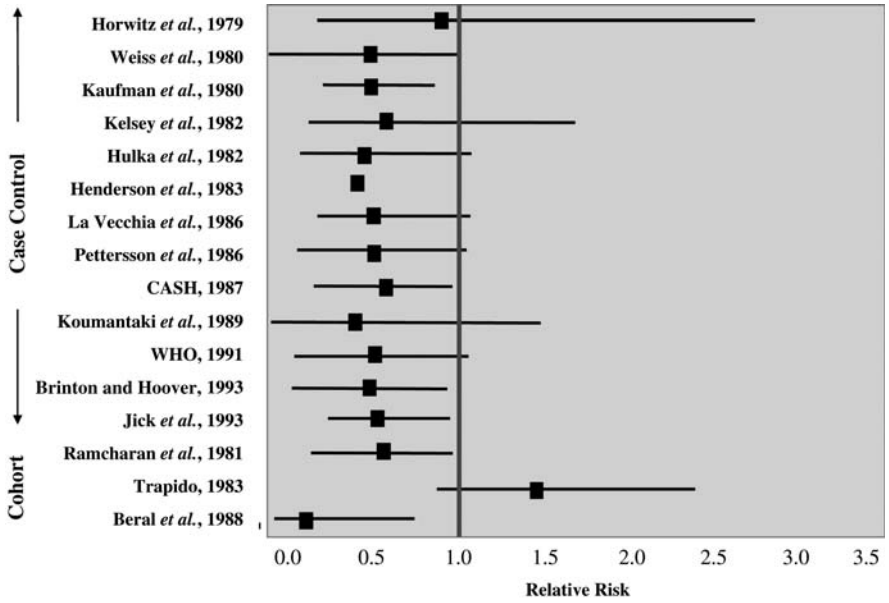

Figure 1 Effect of OC use on risk of endometrial cancer (adapted from Grimes and Economy, 1995).

Only one cohort study found a modest, non-significant increase in risk (Trapido, 1983), but included high-dose sequential preparations (100 μg EE) combined with low-dose, short sequential progestin, a formulation which has been unavailable for >20 years. Two of the three cohort studies reported a significant protective effect. This includes the Walnut Creek Contraceptive Drug Study from California (Ramcharan *et al.*, 1981) and the RCGP Oral Contraception Study (Beral *et al.*, 1988). The UK study is the most important cohort study, which in a report published in 1988 found an 80% reduction in risk among ever users of OC compared with non-users (RR 0.2; 95% CI: 0.0–0.7).

According to this first systematic review (Fig. 1) the protective effect in preventing endometrial cancer using OC seems to be very clear, despite placebo-controlled studies being impossible. Few further relevant studies have been published since, especially investigating follow-up of earlier large studies or investigating risk factors which could modulate the effect of OC use. Table III summarizes the most important studies of OC use and risk of endometrial cancer.

The most important study using incident cohort data in large patient samples is the RCGP Oral Contraception Study (Beral *et al.*, 1988), and the recently published new data for the 46 000 women in the cohort, followed for up to 38 years (Hannaford *et al.*, 2007). The data came from six monthly reports from the women's general practitioners until 1996, and from linkage of the 35 050 women still in the study in the mid-1970s to National Health Service central registries. The main dataset contained ~339 000 woman years of observation for never users and 744 000 woman years for ever users. Most of the users received a combined formulation, whereas 3% used the progesterone-only pill.

Compared with never users, ever users had statistically significant lower rates of cancers of the uterine body, calculated in the main data set with RR 0.58 (95% CI: 0.42–0.79), standardized rate per 100 000 woman years, 11.30 for ever and 19.53 for never users (adjusted for age, parity, smoking and social status). The risk was also assessed by duration of OC use, and although based on smaller numbers the trend for longer use was statistically significant. Regarding recent use, <5 years after stopping reached significance. Since only 566 women exclusively used a formulation with >50 μg EE, this study does not elucidate whether the risk reduction is dependent on the hormonal potencies of the OC used.

The WHO Collaborative Study (WHO, 1991) classified OC use according to the dosage of EE and potency/dosage of progestin. Neither high-dose EE/low-progestin nor low-EE/low-progestin (OR 0.59; 95% CI: 0.26–1.30) altered the risk. When high- and low-progestin combinations were assessed independently of EE dosage, significant risk reduction was shown (OR 0.21; 95% CI: 0.05–0.84).

The Cancer and Steroid Hormone Study (CASH; Maxwell *et al.*, 2006) also focused on hormonal potencies, and evaluated 434 endometrial cancer cases and 2557 controls. Compared with non-users, both high-progestin and low-progestin OC users had a significantly reduced risk (OR 0.21; 95% CI: 0.10–0.43 and OR 0.39; 0.25–0.60), but among women with BMI > 22 only high-progestin OC were protective (OR 0.31; 95% CI: 0.11–0.92).

Likewise, in a large population-based Swedish case–control study ($n = 709/3368$; Weiderpass *et al.*, 1999) high-, medium- and low-progestin OC use reduced the risk, although significantly so only with high and medium dosages (adjusted OR 0.7; 95% CI: 0.5–0.9). This protective effect was similar for all degrees of tumour differentiation and invasiveness. Since only post-menopausal women aged 50–74 years have been investigated, subsequent use of hormone replacement therapy was assessed, and did not modify the protective effect of the OC used in younger age. The reduction of risk was measurable after 3 years of use (OR 0.5; 95% CI: 0.3–0.7), and increased with duration of intake, reaching 80% lower risk after 10 years of use

Table III Effect of OC use on risk of endometrial cancer (relevant studies listed in chronological sequence).

First author	Country	Cases	Controls	Age (years)	Risk influenced by		RR (ever users)
					Invest. factors	OC-duration	
Horwitz and Feinstein (1979)	USA	104	87	50		n.a.	0.94
Weiss and Sayvetz (1980)	USA	110	249	35–54	b,d	n.a.	0.5
Kaufman *et al.* (1980)	USA	152	516	>60	c,d	yes	0.5
Ramcharan *et al.* (1981)	USA	58	16 638 (cohort)	>65		n.a	0.6
Kelsey *et al.* (1982)	USA	37	342	45–74		yes	0.6
Hulka *et al.* (1982)	USA	79	203	n.ans.	a	yes	0.3–0.6
Henderson *et al.* (1983)	USA	110	110	<45	b,c,d,f	yes	0.75
Ory (CASH), (1983)	USA	187	1320	20–54	b,c,d	yes	0.5
Trapido (1983)	USA	98	97 300 (cohort)	<58		n.a.	1.4
La Vecchia *et al.* (1986)	Italy	170	1282	<60		n.a.	0.56
Pettersson *et al.* (1986)	Sweden	362	367	<60	c	n.a.	0.4
CASH (1987)	USA	433	3191	25–54	a,b,c,d,f,g	yes	0.6
Beral *et al.* (1988)	UK		47 000 (cohort)	n.ans.		n.a.	0.2
Koumantaki *et al.* (1989)	Greece	83	164	40–79		yes	0.65
Levi *et al.* (1991)	Switzerland	122	309	≤75	a,c,e,f	yes	0.5
WHO (1991)	USA	220	1537	>65	b,c	n.a.	1.10[1]; 0.15[2]; 0.59[3]
Stanford *et al.* (1993)	USA	405	297	n.ans.	a,d,e,f	yes	0.4
Weiderpass *et al.* (1999)	Sweden	709	3368	50–74	a–g	yes	0.5
Heinemann *et al.* (2003)	Germany	485	1570	32–65	a–g	yes	0.36
Maxwell (CASH) (2006)	USA	434	2557	25–54	b,e,f	yes	0.21[4]; 0.39[5]
Vessey and Painter (2006)	UK	77	17 032 (cohort)	25–39 (recrution)	a,b,c	yes	0.1
Hannaford *et al.* (2007)	UK	156	47 173 (cohort)			yes	0.58

n.ans., no answer; a, duration; b, composition; c, persistence of protection; d, hormone therapy after OC; e, parity; f, weight; g, histology; n.s., not significant; n.a., not applicable; CASH, Cancer and Steroid Hormone Study. [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.

(OR 0.2; 0.1–0.4), and as in the CASH study, the protective effect persisted for at least 15–20 years after cessation of OC use.

Similar results have been found in a German population-based case–control study ($n = 485/1570$; Heinemann *et al.*, 2003). The reduction of risk was comparable for all OC formulation used (adjusted OR 0.36; 95% CI: 0.28–0.45, ever versus never), including low-dose OC (OR 0.30; 95% CI: 0.12–0.74). The protective effect started within 5 years usage (OR 0.63; 0.47–0.86), increased with duration of use, reaching 75% reduced risk after 10 years (OR 0.25; 0.18–0.34) and persisted for >10 years after cessation of OC.

Similar trends also were observed in large recent Chinese case–control study (Tao *et al.*, 2006; $n = 1204/1212$). The risk for ever users of OC was decreased (OR = 0.75; 95% CI: 0.60–0.93), the protective effect increased with duration of use (5 years or more: OR = 0.50; 95% CI: 0.30–0.85) and persisted for 25 years after cessation of use (OR = 0.57; 95% CI: 0.42–0.78).

The 2006 update of the Oxford FPA cohort study, evaluating 17 032 women and 77 cases, showed a >50% risk reduction in ever users (RR = 0.1 for 97+ months; 95% CI: 0.0–0.4) and a protective effect lasting >20 years after OC cessation (Vessey and Painter, 2006). In this analysis the data for the cancers of the cervix, uterine body and ovary were combined, resulting in age-adjusted RR of 0.7 (95% CI: 0.5–0.8).

Time dependency of risk modulation

The increasing protective effect with duration of OC use has been found in most studies investigating this issue. A systematic meta-analysis (Schlesselman, 1997) including 10 case–control studies and the RCGP cohort study (Beral *et al.*, 1988), calculated a significant reduction of risk with RR of 0.44, 0.33, 0.28 after 4, 8 and 12 years of OC use, respectively, on the basis of 33 time-dependent estimates of RR, adjusted for age, adiposity, parity and use of estrogen replacement therapy. The trend of decreasing risk with increasing duration of OC use was highly significant ($P < 0.0001$, one-sided).

In this meta-analysis, the adjusted RR was also calculated by recency of use, based on 19 RR estimates. After OC cessation, the risk decrease persisted for 20 years after discontinuation, and the trend for decrease of risk reduction was significant ($P = 0.011$, one-sided), but still remained about 50% (RR 0.33, 0.41, 0.51 after 5, 10, 20 years after discontinuation). Of interest is the fact that the residual protective effect from prior OC use continues through menopause, a time when the risk of endometrial cancer is greatest.

Confounding factors

As previously described, the hormonal dosage has only a minor impact on the protective effect of OC, although use of higher progestin

potency components in women of higher risk, especially in obese women has been suggested (Tao *et al*., 2006). Although a number of studies have adjusted for factors such as age, family history, BMI, parity and smoking, these studies are limited by small subgroup numbers (Stanford *et al*., 1993). On the basis of the available data, it appears that these factors have only minor influence, if at all, on the protective effect of OC.

Age, a strong risk factor for endometrial cancer, did not influence the protective effect in the Swedish case–control study, and long-term exposure to endogenous estrogen had no modulating effect, comparing women with different intervals of OC use and menopause (Weiderpass *et al*., 1999). Positive or negative family history was also without effect, as demonstrated in the German study (Heinemann *et al*., 2003; OR 0.44; 95% CI: 0.27–0.71 and OR 0.31; 95% CI: 0.23–0.41), whereas genetics may have only minor impact on endometrial cancer risk, even with first degree family history of any specific site (e.g. endometrium, colon, breast; Olson *et al*., 1999; Terry *et al*., 1999).

Obesity is a well-known strong risk factor for endometrial cancer; 2–20-fold increase of risk was observed in more than 20 reports (Grimes and Economy, 1995). For women on OC, the protective effect against endometrial cancer was found to be decreased in obese compared with non-obese women (Henderson *et al*., 1983; Maxwell *et al*., 2006), however, no modulating effect of obesity has also been reported (WHO, 1988; Weiderpass *et al*., 1999). Nulliparity, strong risk factor for endometrial cancer (Parazzini *et al*., 1998; Salvesen *et al*., 1998; Terry *et al*., 1999), did not influence the protective effect of OC (Weiderpass *et al*., 1999; Maxwell *et al*., 2006). Likewise smoking did not have any effect on the cancer protection caused by the use of OC (Weiderpass *et al*., 1999) although the risk of endometrial cancer in smokers is reduced up to 50% due to increased hepatic estrogen metabolism (Mueck and Seeger, 2003).

Conclusions

More than 15 case–control studies and at least four large cohort studies demonstrated a decrease of the risk of endometrial cancer of about 50% with ever use of OC. In most of these studies this protective effect persisted for up to 20 years after stopping of OC use. Longer duration of use is associated with an increased protective effect. The beneficial effect is independent of the OC formulation and not dependent on modulating or known risk factors of endometrial cancer, although in high-risk patients OC formulations with higher progestin potency seem to be more beneficial. OC use effectively reduces endometrial hyperplasia, but should only be used in exceptional cases in patients with or after endometrial cancer.

Cervical cancer

Introduction

The causal role of human papillomavirus (HPV) infections in cervical cancer has been documented beyond reasonable doubt (Cogliano *et al*., 2005a, b; Leppaluoto, 2006). Co-factors that modify the risk among HPV DNA-positive women include contraceptive method, smoking, high parity and previous exposure to other sexually transmitted diseases such as chlamydia trachomatis and herpes simplex virus type 2. The identification of such co-factors, however, requires an adequate control for the strong effect of HPV and a large study population.

Risk in OC users

IARC conducted a study between 1985 and 1993 in 10 countries which covers the demands for adequate control and study population to detect of the reproductive co-factors. This study included nearly 2000 women with cervical cancer and a similar number of healthy control women recruited from high-risk areas for cervical cancer in Colombia, Brazil, Peru, Paraguay and Morocco, from intermediate-risk areas in Thailand and the Philippines, and from Spain, a low-risk country. To take into account the strong causative effect of HPV, the main analyses were restricted to women who were infected by the virus. Two reports from the IARC study have been published. One analyses the effects of parity (Munoz *et al*., 2002) whereas the other concerns combined OC (Moreno *et al*., 2002). The data demonstrated that women who had five children or more had a 3-fold increase in risk compared with women with no children. Women who had an HPV infection and who have used OC for over 5 years have a 3-fold increase in the risk of cervical cancer compared with never users. The impact of parity has been verified in a later meta-analysis (ICESCC, 2006) and may partly explain the differences in cervical cancer between developed and developing countries.

A systematic review (Smith *et al*., 2003) confirmed the association between long-term OC use and increased risk of cervical cancer and in 2005, a Working Group for the IARC classified OC as carcinogenic to the human uterine cervix (Cogliano *et al*., 2005a, b). The IARC statement was based upon the results of clinical, *in vitro* and animal studies, suggesting in concordance that estrogens and progestins may enhance expression of certain HPV genes and stimulate cell proliferation in the human cervix through hormone-response elements in the viral genome and through receptor-mediated mechanisms. However, there is reason for caution. Although cervical cancer is caused by HPV infection, exposure to genital HPV is not independent of OC use (Hogewoning *et al*., 2003). Women using OC are more likely to be exposed to HPV than are those using barrier contraceptive methods or not having sexual intercourse. OC formulations used in the late 1960s and 1970s contained higher dosages of EE and different types and doses of progestins than the currently used formulations. Thus, long-term OC users would have started with higher dose OCs, with a progressive switch to the lower dose formulations used today. The incidence of cervical cancer increases with age and so the contribution of OC to the lifetime incidence of cervical cancer will depend largely on the effects at ages, when most women are past users. The public health concern and the key question is to what extent any adverse effect of OC use persists after women stop taking them. In the 2006 update on the Oxford FPA study significantly increased RR are apparent in the 49–144 months group (RR = 3.9; 95% CI: 1.4–12.3) and the 145–240 months group (RR = 4.6; 95% CI: 1.5–15.6) suggesting that some adverse effect of OC on cervical cancer may persist for many years after cessation of use (Vessey and Painter, 2006). Less convincing is the update on the cohort data from the RCGP Oral Contraceptive Study. It demonstrates no increased risk of invasive cervical cancer, although a significant increasing trend in RR was found in the subgroup of women after OC use for more than 8 years (2.73; 1.61–4.61; Hannaford *et al*., 2007). The

recent meta-analysis from the International Collaboration of Epidemiological Studies of Cervical Cancer has provided the most important information on the effect of duration on OC use. Information from 24 studies worldwide including individual data for 16 573 women with cervical cancer and 35 509 without cervical cancer were reanalysed centrally. RR of cervical cancer was estimated by conditional logistic regression, stratifying by study, age, number of sexual partners, age at first intercourse, parity, smoking and screening. Among current users of OC the RR of invasive cervical cancer increased with increasing duration of use (5 or more years use RR = 1.90; 95% CI: 1.69–2.13). The risk declined after use ceased, and by 10 or more years had returned to that of never users. A similar pattern of risk was seen both for invasive and *in situ* cancer, and in women who tested positive for high-risk HPV. The interpretation from the authors is that the RR of cervical cancer is increased in current users of OC and declines after use ceases. Ten years' use of OC from around age 20–30 years is estimated to increase the cumulative incidence of invasive cervical cancer by age 50 from 7.3 to 8.3 per 1000 in less developed countries and from 3.8 to 4.5 per 1000 in more developed countries.

Conclusion

Cervical cancer is caused by HPV infection. It is of obvious importance to elucidate what factors affect the development of cervical cancer in women exposed to HPV. Exposure to genital HPV is significantly related to contraceptive method with condom use preventing infection and ameliorating cure and IUD/LNG-IUS without significant impact on subsequent cancer development. Despite the risk of residual confounding from non-hormonal co-variables, early and more recent studies demonstrate an association, whether causal or promoting, with long-term (>5 years) use of OC. The association is diminished after cessation of OC use and is very weak 10 years after last use. Consequently long-term users of OC deserve specific targeting for cervical cancer screening programmes. Improved screening programmes and initiation of vaccination against HPV infection in the adolescence period establish a new paradigm in cervical cancer control and fear of the disease should not be a reason to avoid OC use.

Other cancers

Benign and malignant liver tumours

Benign liver tumours, including hepatocellular adenoma (HA), focal nodular hyperplasia (FNH) and hepatic haemangiomas (HH) are more common in women than in men and have been associated with female hormones and hormone-related factors, including pregnancy and OC use (La Vecchia and Tavani, 2006). However, these diseases are exceedingly rare in young women (Hannaford *et al.*, 1997).

With reference to HA, in a case–control study from the USA, 82% of 34 cases had ever used OC versus 56% of 34 controls. The RR were 1.3 for 1–3 years of OC use, 5.0 for 5–7 years, 7.5 for 8–11 years and 25 for >11 years (Edmondson *et al.*, 1976). In another USA study, 91% of 74 cases of HA and 45% of 220 controls had used OC for >12 months. The RR was 9 for 13–36 months, 116 for 37–60 months, 123 for 61–84 months and 503 for ≥85 months (Rooks *et al.*, 1979). In a more recent multicentric case–control study of 51 HA cases and 240 population controls from Germany, the RR for ever OC use was 1.25 (95% CI: 0.37–4.22; Heinemann *et al.*, 1998). There was no relation between duration and age at first or last OC use and the prevalence of HA. The data mainly reflected recent low-dose OC. There is therefore evidence that HA is strongly related to current and recent (first generation, high-dose) OC use. Low-dose OC appears less strongly associated with HA, if at all. Moreover, HA remains exceedingly rare in young women, even among long-term OC users.

A role for female hormones has also been suggested in FNH, given the female predominance of the disease. Of women diagnosed with FNH, 51–75% of cases are OC users, particularly those with symptoms and large nodules. In a study of 216 women, OC use did not influence the size of FNH, and pregnancy was unrelated to FNH changes or complications (Mathieu *et al.*, 1998). However, in a multicentric case–control study of 143 cases of FNH and 240 population controls, the RR for ever OC use was 1.96 (95% CI: 0.85–4.57). The RR increased with longer duration and more recent usage (Heinemann *et al.*, 1998). In another case–control study of 25 FNH cases and 94 controls, the multivariate RR was 2.8 (95% CI: 0.8–9.4) for ever OC use and increased to 4.5 (95% CI: 1.2–16.9) for OC use lasting ≥3 years. The trend in risk with duration was significant (Scalori *et al.*, 2002).

Liver cancer (hepatocellular carcinoma) is also exceedingly rare in young women. The evidence of OC and liver cancer is based on at least 12 case–control studies, including 739 cases and 5223 controls, which were reviewed in a meta-analysis (Maheshwari *et al.*, 2007). The overall RR was 1.57 (95% CI: 0.96–2.54), with some evidence of duration-risk association in six studies. Exclusion of a recent multinational European study increased the pooled RR to 1.70 (95% to 1.12–2.59) and decreased heterogeneity. The association is less strong in studies from developing countries, where hepatitis B and C infections are more common (IARC, 2007). It is also possible that the RR is smaller for recent, low hormone OC formulations.

There was no evidence of persistent liver cancer excess risk after stopping OC use. Thus, there was no excess liver cancer incidence in the long-term follow-up of the RCGP Oral Contraceptive Study, based on 27 cases of liver and gallbladder cancer (Hannaford *et al.*, 2007). Consequently, the long-term public health implications of any modest excess liver cancer risk among current OC users are also minimal.

Colorectal cancer

In a meta-analysis of epidemiological studies on colorectal cancer published up to June 2000, and including quantitative information on OC use, the pooled RR of colorectal cancer for ever OC use was 0.81 from eight case–control studies, 0.84 from four cohort studies and 0.82 from all studies combined (Fernandez *et al.*, 2001). However, no relation with duration of use was observed. The pattern of risk was similar for colon and rectal cancer. Among studies published after that meta-analysis, the RR was 0.8 (95% CI: 0.4–1.7) for ever OC use in a Swiss case–control study on 131 women with colorectal cancer (Levi *et al.*, 2003). The Oxford FPA cohort study, including 46 cases of colorectal cancer, reported no association with OC use (Vessey *et al.*, 2003). In a cohort study of female textile workers in China, including 655 women with colorectal cancer, the RR was

1.56 (95% CI: 1.01–2.40) for women who had used OC for over 3 years, in the absence, however, of any trend in risk with duration of OC use (Rosenblatt *et al.*, 2004). In a nested case–control study within the RCGP Oral Contraception Study, there were 146 cases of colorectal cancer (Hannaford and Elliott, 2005). The RR was 0.84 for ever users, with greater reduction in risk for current (RR = 0.38) than for former (RR = 0.89) users. In a later paper (of up to 38 years of follow-up) there were 323 cases of colorectal cancer and a RR of 0.72 for ever OC users (Hannaford *et al.*, 2007). In a case–control study from USA, including 1722 cases of colon cancer, 366 of rectal cancer and 4297 population controls, the overall RR for ever OC use was 0.89 (95% CI: 0.75–1.06) with no difference between colon (RR = 0.88) and rectal (RR = 0.87) cancer. For rectal, but not for colon cancer, there was some indication of a stronger inverse relation for recent use (Nichols *et al.*, 2005). In the 11 years follow-up of the Women's Health Study, including 267 cases of colorectal cancer, the RR for ever OC use was 0.67 (95% CI: 0.50–0.89), with little evidence, however, of duration-risk relation (Lin *et al.*, 2007). In a cohort study of Canadian women within a breast cancers screening program, followed for an average of 16.4 years, there were 1142 incident colorectal cancers. The overall RR for ever OC use was 0.83 (95% CI: 0.73–0.94). There was no relation with duration of OC use (Kabat *et al.*, 2008).

Table IV gives the main results from 11 case–control studies giving information on OC and colorectal cancer risk, and Table V corresponding data from nine cohort studies. The overall RR was 0.82 for both case–control and cohort studies, and the summary RR, including both case–control and cohort studies, was also 0.82 (95% CI: 0.72–0.93). Corresponding values were 0.85 (95% CI: 0.79–0.83) for colon and 0.80 (95% CI: 0.70–0.92) for rectal cancer (Bosetti *et al.*, 2009).

Only a few studies (Fernandez *et al.*, 1998; Beral *et al.*, 1999; Levi *et al.*, 2003; Nichols *et al.*, 2005; Hannaford *et al.*, 2007) included information on recency of use, and gave some indication that the apparent protection was stronger for women who had used OC more recently. Scant information was available on type of OC, however, no consistent pattern of trends was observed across calendar year of use (which in most countries is a good proxy of type of OC formulation).

Lung cancer

A population-based case–control study of 811 women with lung cancer and 922 controls from Germany (Kreuzer *et al.*, 2003) showed a reduced lung cancer risk (RR 0.69, 95% CI: 0.51–0.92) among ever OC users, in the absence, however, of any trend in risk with duration of use, age at first use, or calendar year at first use. The RR was non-significantly above unity in the 30-year follow-up of the Oxford FPA cohort study (Vessey *et al.*, 2003), and 1.05 (95% CI: 0.82–1.35) in the 35-year follow-up of the RCGP cohort study, based on 297 cases (Hannaford *et al.*, 2007). There is therefore

Table IV Case–control studies on effect of OC use and colorectal cancer risk.

Reference	Country, study acronym	Site	No. of cases	No. of controls	Relative risk[a] (95% CI)
Weiss *et al.* (1981)	Washington State, USA	Colorectum	143	707	1.58 (0.80–3.10)
Potter and McMichael (1983)	Adelaide, Australia	Colorectum	155	311	0.61 (0.52–0.72)
		Colon	199		0.50 (0.25–1.00)
		Rectum	56		0.70 (0.29–1.71)
Furner *et al.* (1989)	Chicago, USA	Colorectum	90	208	0.62 (0.28–1.36)
Kune *et al.* (1990)	Melbourne, Australia	Colorectum	190	200	1.36 (0.21–1.53)
		Colon	108		1.17 (0.59–2.31)
		Rectum	82		2.04 (1.00–4.15)
Peters *et al.* (1990)	Los Angeles, USA	Colon	327	327	1.03 (0.64–1.66)
Wu-Williams *et al.* (1991)	North America	Colorectum	189	494	0.84 (0.75–0.94)
		Colon	114		1.20 (0.52–2.78)
		Rectum	75		0.40 (0.17–0.96)
Wu-Williams *et al.* (1991)	China	Colorectum	206	618	0.70 (0.61–0.82)
		Colon	78		0.55 (0.19–1.59)
		Rectum	128		0.70 (0.34–1.46)
Kampman *et al.* (1997)	USA, KPMC	Colon	894	1120	0.86 (0.67–1.10)
Fernandez *et al.* (1996)	Italy	Colorectum	1232	2793	0.64 (0.49–0.85)
Talamini *et al.* (1998)		Colon	803		0.63 (0.45–0.88)
Fernandez *et al.* (1998)[b]		Rectum	429		0.66 (0.43–1.01)
Levi *et al.* (2003)	Switzerland	Colorectum	131	373	0.83 (0.40–1.71)
Nichols *et al.* (2005)	WI, USA	Colorectum	1488	4297	0.89 (0.75–1.06)
		Colon	1112		0.87 (0.72–1.06)
		Rectum	366		0.87 (0.65–1.17)

KPMC, Kaiser Permanente Medical Care.
[a]Ever versus never use.
[b]Pooled analysis of data from Fernandez *et al.* (1996) and Talamini *et al.* (1998).

Table V Cohort studies on effect of OC use and colorectal cancer risk.

Reference	Country, study acronym	Site	No. of cases	Cohort size	Follow-up	Relative risk[a] (95% CI)
Martinez et al. (1997)	USA, NHS	Colorectum	501	89 448	12 years	0.84 (0.69–1.02)
		Colon	396	89 448		0.64 (0.40–1.02)
		Rectum	105	89 448		0.76 (0.49–1.18)
Bostick et al. (1994)	IA, USA, WHS	Colon	212	35 215	4 years	0.96 (0.67–1.38)
Troisi et al. (1997)	USA, BCDDP	Colorectum	330	57 529	10 years	1.00 (0.73–1.37)
Van Wayenburg et al. (2000)	Netherlands	Colorectum	95[b]	10 671	18 years	0.68 (0.21–2.21)
Vessey et al. (2003)	UK, OPFA	Colorectum	46[b]	17 032	30 years	0.92 (0.57–1.51)
Rosenblatt et al. (2004)	China	Colon	655	267 400	10 years	1.09 (0.86–1.38)
Hannaford et al. (2007)	UK, RCGP OC	Colorectum	323	46 000	35 years	0.72 (0.58–0.90)
Lin et al. (2007)	USA, WHI	Colorectum	267	39 680	11 years	0.67 (0.50–0.89)
		Colon	205			0.73 (0.52–1.02)
		Rectum	55			0.52 (0.28–0.96)
Kabat et al. (2008)	Canada, CNBSS	Colorectum	1142	89 835	16 years	0.83 (0.73–0.94)
		Colon	790			0.81 (0.70–0.94)
		Rectum	366			0.85 (0.66–1.05)

BCDDP, Breast Cancer Detection Demostration Project; CNBSS, Canadian National Breast Screening Study; NHS, Nurses' Health Study; OFPA, Oxford Family Planning Association; OC, oral contraceptives; RCGP, Royal College of General Practitioners; WHI, Women's Health Initiative; WHS, Women Health Study.
[a]Ever versus never use.
[b]Deaths.

inadequate evidence on the relation between OC use and lung cancer risk, but it is unlikely that any major association is present.

Other cancers

Information on OC use and cutaneous malignant melanoma was available from at least 4 cohorts at 18 case–control studies (IARC, 2007). There was no consistent association and a pooled analysis of case–control studies gave an overall RR of 1.0 (95% CI: 0.9–1.0).

The results of 13 case–control studies of thyroid cancer were also reviewed in a collaborative re-analysis of original data (La Vecchia et al., 1999). The overall RR for current OC users was 1.5 (95% CI: 1.0–2.1), which declined to 1.1 10 years after cessation of OC use. Six subsequent studies were revised (IARC, 2007), of which, one gave a RR below unity, one above unity, and the remaining four close to unity.

OC use was considered in a small number of studies for various additional neoplasms, including oesophageal, gastric, pancreatic, gallbladder, renal cell, neuroblastoma and Hodgkin's and non-Hodgkin's lymphomas (IARC, 2007). For none of them, there was adequate evidence of association. Only gestational trophoblastic disease was directly associated with OC use in two studies with RR of 1.8 (Palmer et al., 1999) and 1.5 (Parazzini et al., 2002), both of borderline significance.

Conclusion

Current, but not past OC use, is associated with excess risk of benign liver tumours, and a modest excess risk of liver cancer. There was no evidence of association between OC use and lung, other digestive tract neoplasms, cutaneous malignant melanoma, thyroid cancer and any of the other neoplasms investigated (IARC, 2007). The data for colorectal cancer are suggestive of a favourable effect of OC, in the absence, however, of any consistent duration or recency risk relation. A better understanding of any potential relation between OC use and colorectal cancer may therefore help informed choice of contraception (La Vecchia et al., 2001; IARC, 2007).

Net cancer effect

Several researchers have constructed statistical models to estimate the net effect of oral contraception on combined risk of all reproductive cancers (Petitti and Porterfield, 1992), or breast, uterine cervix, endometrial, ovarian and liver cancer (Schlesselman, 1995). Such modelling makes several important assumptions, which cohort studies do not need to make since they measure directly the risks and benefits associated with an exposure, although any combining of events implies equivalence of importance.

Twelve-year mortality data from the Nurses Health Study of 167 000 women recruited in North America in 1976, revealed no difference in the risk of death from any cancer among ever and never users of OC (adjusted RR (ARR) 0.92, 95% CI 0.81–1.03; Colditz, 1994). Similarly, there was no difference in the rate of any cancer death in the same groups among 46 000 British women recruited to the RCGP Oral Contraception Study in the late 1960s and followed up for 25 years (ARR 1.0, 95% CI: 0.8–1.1; Beral et al., 1999).

Several cohort studies have examined the risk of various combinations of incident cancer among OC users. In 1988, the RCGP study reported on all invasive genital cancer, using data available at the end of the late 1980s (Beral et al., 1988). The balance of events among ever users of OC was neutral, when compared with never users (ARR 1.0, 95% CI: 0.5–1.7). A Norwegian study of 96 000 women recruited between 1991 and 1997, and followed up to 1999, found no significant association between OC use and the combined risk of breast, endometrial and ovarian cancer (Kumle et al.,

2003). Follow-up to December 2004 of 17 000 women recruited in Britain between 1968 and 1974 for the Oxford Family FPA Oral Contraceptive Study, to December 2004, revealed a significantly reduced risk of any gynaecological cancer among OC ever users compared with never users (ARR 0.7, 95% CI: 0.5–0.8; Vessey and Painter, 2006). An almost identical reduction in risk of all main gynaecological cancers was also found by the RCGP study in 2007 when it examined incident cancers accumulated during 36 years of follow-up (ARR 0.71, 95% CI: 0.60–0.85; Hannaford *et al*., 2007). The changing risk estimate from the RCGP study over time, suggests that as OC users age persisting protection against ovarian and endometrial cancer has a progressively greater impact on the balance of cancers experienced.

The latest RCGP analysis also examined the overall risk of any type of incident cancer among ever and never users of OC (Hannaford *et al*., 2007). Ever users had a statistically significant 12% relative reduction in cancer risk (ARR 0.88, 95% CI: 0.83–0.94), which translated into an absolute risk reduction of about 45 fewer cases of cancer for every 100 000 woman years of OC use. The effect, however, was not uniform among all OC users. Subgroup analyses indicated that, compared with never users, women who used OC for short to medium-term lengths of time had a reduced risk of any cancer (up to 4 years: ARR 0.93, 95% CI: 0.82–1.06, 4–8 years use: ARR 0.85, 95% CI: 0.74–0.98), whereas long-term users had a significantly increased risk (more than 8 years: ARR 1.22, 95% CI: 1.07–1.39). The increased risk in long-term users was mostly because of a higher risk of invasive uterine cervical cancer. Importantly, most OC users in the study used the method for relatively short periods (median duration 44 months), so were not exposed to the higher risks of long-term use.

The experience of women living in Britain may not reflect that of women residing elsewhere, where levels of OC usage, duration of use, age at stopping and incidence of cancer may be different. A study of 259 000 Chinese textile workers recruited between 1989 and 1991, and followed up to 2000, found no association between OC use and overall risk of 12 site-specific (breast, colon, gallbladder, liver, lung, ovary, pancreas, rectum, stomach, thyroid, uterine cervix and uterine corpus) cancers (ARR 0.94, 95% CI: 0.88–1.01; Rosenblatt *et al*., 2009). This result is reassuring, although an important limitation of the study was the low prevalence of OC use, for relatively short durations.

There have been few studies examining the balance of cancer risks and benefits among users of other contraceptives. The Chinese cohort study of textile workers also examined the site-specific and combined risk of 12 cancers associated with use of monthly combined injectable contraceptives (Rosenblatt *et al*., 2007). There was no evidence of an altered risk of all cancers combined among users of the monthly injection (ARR 0.91, 95% CI: 0.81–1.03), although the prevalence and duration of use was low, thereby limiting the statistical power of the study. A smaller population-based Chinese cohort of 67 000 urban dwellers in Shanghai, recruited between 1997 and 2000 and follow-up for a median of 7.5 years, observed no increased overall risk of 11 major cancers (all of those reported in the textile worker study except uterine cervical cancer) among ever users of any contraceptive method, including OC, contraceptive injections, intrauterine devices and tubal sterilization (adjusted hazards ratio 1.02, 95% CI: 0.92–1.12; Dorjgochoo *et al*., 2009). Combined results for particular contraception methods were not reported separately, although site-specific findings were. An analysis of data from the RCGP study found that women who had a tubal sterilization had a similar risk of any cancer as that of those who did not have this operation (adjusted hazards ratio 0.92, 95% CI: 0.78–1.08; Iversen *et al*., 2007).

In conclusion, although the number of studies is small, several large cohort investigations have assessed, with prolonged follow-up, the risk of different combinations of cancer among contraceptive users. It is reassuring, therefore, that none of the studies have indicated an overall increased cancer risk among ever users of different contraceptives. Indeed, several have suggested, from a population perspective, important long-term benefits among ever users of OC.

Authors' roles

D.C.: author of chapter 'Ovarian cancer' and editor of the whole article. A.G.: author of chapter 'Breast cancer'. A.O.M.: author of chapter 'Endometrial cancer'. P.C.H.: author of chapter 'Net effect'. C.L.V.: author of chapter 'Other cancers'. S.O.S.: author of chapter 'Cervical cancer'. M.Z.: co-editor of the article. L.D.: statistician.

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