

# Benefits and risks of oral contraceptives on cancer

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Oral contraceptives (OC) convey a protection against ovarian, endometrial and perhaps colorectal cancer. However, OC use is associated with excess risk of breast, cervical and liver cancer (IARC, 1999; La Vecchia *et al.*, 2001a; Burkman *et al.*, 2004). Benefits and risks of OC use on cancer were reviewed in 1998 by a Working Group at the International Agency for Research on Cancer, which concluded that combined OCs are carcinogenic to humans based on an increased risk for hepatocellular carcinoma (IARC, 1999). The Working Group also concluded that there is conclusive evidence that OCs have a protective effect against cancers of the ovary and endometrium. Data published after the IARC Monograph will be reviewed here, including information on ovarian, endometrial, colorectal, lung, breast and cervical cancer.

## Ovarian cancer

An indication of the favourable impact of OCs on ovarian carcinogenesis came from descriptive epidemiology. In several developed countries, young women have showed substantial declines in ovarian cancer mortality over the last few decades. Cohort analysis of trends in mortality from ovarian cancer showed that women born after 1920 (i.e. the generations who had used OCs) had reduced ovarian cancer rates, and the downward trends were greater in countries where OCs have been more widely used (IARC, 1999; La Vecchia *et al.*, 2001a). The protection was similar for modern, low-dose oestrogen-progestin pills (Ness *et al.*, 2000), as well as for various histotypes of ovarian cancer (Tung *et al.*, 2003), while it is unclear whether the protection is similar for women with hereditary ovarian cancer (Narod *et al.*, 1998; Modan *et al.*, 2001).

Quantification of the long-term effect of OC on ovarian carcinogenesis remains open to discussion. While an increasing protection with longer duration has been reported from most studies, time since first (latency) and last use (recency) have been inadequately considered. The overall estimates of protection for ever use is approximately 40%, and the favourable effect of OC on epithelial ovarian cancer persists for at least 10 years after stopping use according to the CASH study, and most likely up to 15–20 years (IARC, 1999; La Vecchia *et al.*, 2001a). The relative risk (RR) was 0.8 up to 20 years after stopping use in a pooled analysis of European studies (Bosetti *et al.*, 2002), 0.5 for 15–19 years, and 0.8 for

20 years or more since stopping OC use in a large multicentric US case-control study (Rosenberg *et al.*, 1994). In the Oxford Family Planning Association (FPA) cohort study, the RR of death from ovarian cancer was 0.4 at the 30-year follow-up (Vessey *et al.*, 2003).

## Endometrial cancer

OC use also reduces the risk of endometrial cancer by approximately 50% (IARC, 1999; La Vecchia *et al.*, 2001a). The relatively limited number of elderly women who had used OCs, however, does not allow an accurate estimation of the protection afforded after long periods, though the reduced risk of endometrial cancer seems to persist at least 15–20 years after stopped use. In the CASH study, the RR was 0.5 for 10–14 years since stopping use; in the WHO study the OR was 0.2 for high progestogen content pills 10 years or more since stopping; in a multicentric US study the OR was 0.3 for 15–19 years and 0.8 for 20 years or more after stopping OC use (IARC, 1999; La Vecchia *et al.*, 2001a). When duration and recency of use were evaluated jointly in a case-control study from Washington State (Voigt *et al.*, 1994), longer use (> 5 years) was associated with a reduced risk, irrespective of recency. In a Swiss study (Levi *et al.*, 1991), the RR was 0.4 for 10–19 years after stopping use, and 0.8 for 20 years or more. In a population-based national case-control study from Sweden (Weiderpass *et al.*, 1999), the RR was 0.2 for 10 or more years of use, and the subsequent use of hormone replacement therapy did not modify the long-term protective effect of OC. The RR of endometrial cancer death was 0.2 in the 30-year follow-up of the Oxford FPA study (Vessey *et al.*, 2003). Endometrial cancer cases were less frequently OC users also in a recent case-control study from China (Xu *et al.*, 2004).

## Colorectal cancer

A possible protective effect of OCs on colorectal cancer risk has also been suggested. A role of hormonal factors on colorectal carcinogenesis has long been suggested, starting from the observation of an excess of colorectal cancer in nuns (Fraumeni *et al.*, 1969; Fernandez *et al.*, 2000). A reduction of risk for hormone replacement therapy (HRT) in menopause has also been reported (Herbert-Croteau, 1998; IARC, 1999; La Vecchia *et al.*, 2001b), although neoplasms in combined HRT users were more advanced than those in non-users (Chlebowski *et al.*, 2004).

Several studies have provided information on OC use and the risk of colorectal cancer. The Monograph from the International Agency for Research on Cancer (IARC, 1999) reviewed four cohort studies, three of which showed RR for ever OC use below unity. Among 11 case-control studies, the RR was below unity in nine, and significant in two. 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. The RR was 0.8 for ever OC use in a recent Swiss case-control study (Levi *et al.*, 2003). Only two studies (Fernandez *et al.*, 1998; Beral *et al.*, 1999) included information on recency of use, and gave some indication that the apparent protection was stronger for women who had used OC more recently. Scanty information was available on type of OC, but no consistent pattern of trends across calendar year of use (which in several countries is a good proxy of type of preparation) was observed.

### 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% confidence interval (CI) 0.51–0.92) among ever OC users, in the absence however of any trend in risk with duration of age, 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). There is therefore inadequate evidence on the relation between OC use and lung cancer risk, but it is unlikely that any major association is present.

### Breast cancer

Most information on the relation between breast cancer and OC use derives from a collaborative reanalysis of individual data including 53 297 women with breast cancer and 100 239 controls from 54 epidemiological studies (Collaborative Group on Hormonal Factors in Breast Cancer, 1996). This provided definite evidence that current users of combined OC, and women having stopped use no more than 10 years previously, have a small increase in the RR of breast cancer (RR 1.24). However, 10 or more years after stopping use the risk levels off to approach that of never OC users. The results were similar in women with different background risks of breast cancer. Only women who had begun use before age 20 had an apparent and persistent moderate excess risk (RR 1.22) of breast cancer. Breast cancers diagnosed in ever OC users were clinically less advanced. It is not

possible to infer from these data, however, whether this could be attributable to earlier diagnosis, biological effects of OC, or a combination of reasons. Other features of OC use, such as duration, dose and type of hormone formulation, had little effect on breast cancer risk on the basis of that collaborative reanalysis.

A few additional cohort (Beral *et al.*, 1999; Grabrick *et al.*, 2000) and case-control studies of OC and breast cancer (Lipworth *et al.*, 1995; Levi *et al.*, 1996; Newcomb *et al.*, 1996; Tryggvadóttir *et al.*, 1997; Magnusson *et al.*, 1999; Ursin *et al.*, 1999; Shapiro *et al.*, 2000; Van Houten *et al.*, 2000) have been published after that collaborative reanalysis. In the Royal College of General Practitioners oral contraception study (Beral *et al.*, 1999) including 46 000 women, as well as in the Oxford FPA cohort study (Vessey *et al.*, 2003), no relevant association was found between breast cancer mortality and various measures of OC use after several decades of follow-up. Another cohort study of 426 families of breast cancer probands in Minnesota, USA (Grabrick *et al.*, 2000) suggested that ever users of earlier formulations of OC with family history of breast cancer were at high risk for the disease (RR 3.3). That study was based, however, on 38 familial case users only, and contrasted with findings of the collaborative reanalysis (Collaborative Group on Hormonal Factors in Breast Cancer, 1996) which showed no excess risk in users with a family history of breast cancer. A report from the Nurses' Health Study II cohort study (Colditz *et al.*, 2003) suggested a favourable effect of physical activity on breast cancer risk in current OC users only, but the data were too limited to adequately assess the interaction between physical activity and OC use. In the women's Contraception and Reproductive Experiences (CARE) study (Norman *et al.*, 2003), a population-based case-control study of 1847 postmenopausal women from the USA, previous OC users were not at increased breast cancer risk, and there was a negative interaction between combined hormone replacement therapy (CHRT) use and past OC use. In fact, the excess risk for CHRT use was restricted to never OC users, but it was not observed in past OC users. A few other recent studies from the USA and Norway (Marchbanks *et al.*, 2002; Althuis *et al.*, 2003; Dumeaux *et al.*, 2003) suggested that use of more recent, low-dose OC is not materially related to breast cancer risk.

### Cervical cancer

Cancer of the cervix uteri is relatively rare in developed countries, where cervical screening is widespread, but is still the third most common cancer in women worldwide, with an estimated incidence of about 470 000 cases in 2000, and the second most common in developing countries, where it accounts for about 15% of all cancers in women (Parkin *et al.*, 2001; Drain *et al.*, 2002). Also, within Europe, the difference in mortality between Western, Central and Eastern European countries was over threefold in the late 1990s, and cervical cancer rates

in Eastern Europe have been upwards since the early 1980s. Cervical cancer represents therefore a relevant indicator of the worsening of women's health conditions in Eastern Europe in the early 1990s, and an important avoidable cause of death (Levi *et al.*, 2000, 2001, 2004).

Although human papillomavirus (HPV) is virtually a necessary cause of cervical cancer (Walboomers *et al.*, 1999), other potential factors are likely to have a role in cervical carcinogenesis. Among these are tobacco smoking and exogenous female hormones, including OC (Schiffman *et al.*, 1996).

Several epidemiological studies have reported an increased risk of invasive cervical carcinoma in relation to ever OC use, and a stronger risk for a longer duration of use. The evidence of an association between OC use and adenocarcinoma of the cervix is based on more limited data (IARC, 1999).

The RR of cervical cancer was significantly elevated among long-term OC users in a study from Morocco (Chaouki *et al.*, 1998), and in three studies from the Philippines (Ngelangel *et al.*, 1998), Thailand (Chicharoon *et al.*, 1998) and the UK (Deacon *et al.*, 2000). A study from the USA (Lacey *et al.*, 1999) found no significant association between OC use and invasive or *in situ* cervical carcinoma. In that study, however, an association emerged between long-term OC use and *in situ* adenocarcinoma.

Most studies, however, could not take into account HPV infection, and biases related to sexual behaviour or screening could not be ruled out (Deligeoroglou *et al.*, 2003). Given the importance of HPV in cervical carcinogenesis, the relation between OCs and cervical cancer was assessed, restricting the analyses to carriers of HPV DNA. A pooled analysis coordinated by the IARC has been published on the role of OCs in women tested positive for HPV DNA (Moreno *et al.*, 2002). That study combined the data of eight case-control studies of invasive cervical cancer and two studies on carcinoma *in situ*, including 1676 cervical cancer cases and 255 controls. No increased risk of cervical cancer was reported for women who had used OCs for less than 5 years, but those who used OCs for 5–9 years had a RR of 2.8, as compared with never users. An even higher risk (RR 4.0) was observed for OC users for 10 or more years. OC use was not associated with HPV-positivity among controls, thus suggesting that OCs do not increase the acquisition or persistence of HPV infection, but may facilitate its progression into neoplastic cervical lesions. This confirms the time-risk relation from an Italian case-control study (Parazzini *et al.*, 1998), which indicated that OCs have a promoting effect on the process of cervical carcinogenesis, with a fall in risk after stopping use.

In a meta-analysis of 28 cohort and case-control studies of cervical cancer including information on OCs, the overall RR was 1.1 for use of less than 5 years, 1.6 for 5–9 years, and 2.2 for 10 or more years (Smith *et al.*, 2003). The data suggest that the risk decreases after OC use has stopped, but the effect of stopping use, independent of duration and other time factors, could not be adequately assessed from published studies.

## Conclusions

The inverse relation between OC use, ovarian and endometrial cancers is established and is one of the most consistent epidemiological findings, and one of the most important examples – on a public health level – of large-scale chemopreventive intervention.

The data for colorectal cancer are suggestive of a protective effect of OC, but not conclusive. A better understanding of any potential relation between OC use and colorectal cancer may therefore help informed choice of contraception (IARC, 1999; La Vecchia *et al.*, 2001a).

With reference to breast cancer, of particular relevance on a public health level is the absence of a persistent excess breast cancer risk in the medium or long term after cessation of OC use, independent of duration of use. In terms of risk assessment for OC use and indications for prescription, these data indicate that any potential increase in risk during OC use, and in the short term after stopping, is not relevant for younger women whose baseline breast cancer incidence of the disease is extremely low (Collaborative Group on Hormonal Factors in Breast Cancer, 1996; Vessey *et al.*, 2003).

As regards the public health implications of findings for cervical cancer, any risk relation is a function of the time relations including recency (i.e. of the potential – but unlikely on the basis of available data – persistence of an excess risk several years after stopping OC), since the incidence of cervical cancer rises with age. In any case, the association between OC and cervical cancer would be of major relevance in developing countries, where cervical cancer rates are higher, and cervical screening is not adequately available, as well as in selected Central and Eastern European countries, where cervical screening remains largely inadequate and cervical cancer rates are still exceedingly high (Franceschi *et al.*, 2000; Levi *et al.*, 2000, 2004; Skegg, 2002).

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