

# COMBINED ESTROGEN–PROGESTOGEN CONTRACEPTIVES

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Combined estrogen–progestogen contraceptives were considered by previous IARC Working Groups in 1998 and 2005 ([IARC, 1999, 2007](#)). Since that time, new data have become available, these have been incorporated into the *Monograph*, and taken into consideration in the present evaluation.

## 1. Exposure Data

Combined hormonal contraceptives consist of an estrogen and a progestogen, and act primarily by preventing ovulation through the inhibition of the follicle-stimulating hormone and luteinizing hormone. The progestogen component also renders the cervical mucus relatively impenetrable to sperm, and reduces the receptivity of the endometrium to implantation ([IARC, 2007](#)).

A variety of innovations have been developed since combined hormonal contraceptives were first available in the late 1950s, including changes in drug components, doses used, and the temporal sequencing of exposure to drugs. The dominant trends have been towards less androgenic progestogens, lower doses of estrogen and progestogen, the near abandonment of hormonal contraceptives with an estrogen-only phase, a proliferation of different product formulations, and continuing development of novel delivery systems ([IARC, 2007](#)).

### 1.1 Identification of the agents

See the *Monographs* on Estrogen-only Menopausal Therapy and Combined Estrogen–Progestogen Menopausal Therapy.

### 1.2 Use of the agents

Information for Section 1.2 is taken from [IARC \(2007\)](#), [McEvoy \(2007\)](#), and [Sweetman \(2008\)](#).

#### 1.2.1 Indications

Oral, intravaginal, injectable and transdermal estrogen–progestogen combinations are used for the prevention of conception in women.

A short-course, high-dose regimen of an oral estrogen–progestogen combination is used in women for the prevention of conception after unprotected intercourse (postcoital contraception, “morning-after” pills) as an emergency contraceptive.

Certain oral estrogen–progestogen combinations have been used for the treatment of moderate acne vulgaris in females 15 years of

age or older who are unresponsive to topical anti-acne medication.

An estrogen–progestogen combination of ethinylestradiol with drospirenone can be used for the treatment of pre-menstrual disorders.

### 1.2.2 Dosages

The large number of products that are currently available differ in several respects, including the estrogen compound used and its dose, the progestogen used, the schedule of exposure to the drugs, and the route of administration. Identical formulations may carry different brand names in different countries or even within the same country. [These products and their ingredients are presented in Annexes 1–3 of Vol.91 of the *IARC Monographs* ([IARC, 2007](#)).]

The most common estrogen in combined hormonal contraceptives is ethinylestradiol. Other estrogens have been used, including mestranol (a prodrug of ethinylestradiol) and, more recently, estradiol. In the early combined hormonal contraceptives, doses of estrogen in the range of 100–150 µg were commonly used. Contemporary combined hormonal contraceptives may be classified by estrogen dose into ‘high-dose’ (50 µg or more), ‘moderate-dose’ (30–35 µg), and ‘low-dose’ (15–20 µg).

A variety of progestogens are used in combined hormonal contraceptives. Currently, progestogens are often distinguished as ‘first-generation’ estranes (such as norethynodrel or norethisterone), ‘second-generation’ gonanes (such as levonorgestrel or norgestimate), ‘third-generation’ gonanes (gestodene and desogestrel), and ‘fourth-generation’ drospirenone. An additional class of progestogens, the pregnanes (eg. cyproterone and chlormadinone), may also be used. Estranes are highly androgenic, while pregnanes and drospirenone have anti-androgenic activity. The later gonanes are less androgenic than the earlier compounds in that series. The affinity of individual progestogens for

progesterone receptors varies considerably, and determines the daily doses required to produce endometrial differentiation. Drospirenone has the lowest affinity (typical daily dose, 3 mg), while the later gonanes have the greatest affinity (0.05–0.15 mg daily dose).

The schedule by which exposure to the drugs occurs may also vary. Most commonly, a constant combination of estrogen and progestogen is used for 3 weeks of a 4-week cycle. The doses of progestogen and (less often) estrogen may vary in two or three phases followed by a drug-free phase. Sequential exposure regimens that used prolonged exposure to estrogen-alone are no longer used ([IARC, 1999](#)), but a short, 5-day, estrogen-only sequence has been re-introduced. Cycle lengths shorter and longer than 4 weeks may be used with the aim of limiting the duration of menses or eliminating menses altogether.

Injection of an estrogen and progestogen was used early on in the development of hormonal contraception, and remains available. Innovations in drug delivery have generated transdermal patches and a vaginal device. Hormonal intrauterine contraceptive devices are also available.

#### (a) Contraception

##### (i) Oral dosage

Combined estrogen–progestogen oral contraceptives are usually classified according to their formulation: preparations containing 50 µg of estrogen; preparations containing less than 50 µg of estrogen (usually 20–35 µg); those containing less than 50 µg of estrogen with two sequences of progestogen doses; those containing less than 50 µg of estrogen with three sequences of progestogen doses; and those containing three sequences of estrogen (eg. 20, 30, 35 µg) with a fixed dose of progestogen.

Although the progestogen content of the formulations also varies, oral contraceptives are usually described in terms of their estrogen

content. The estrogenic or progestogenic dominance of an oral contraceptive may contribute to hormone-related adverse effects, and may be useful in selecting an alternative formulation when unacceptable adverse effects occur with a given formulation.

Most fixed combinations are available as 21- or 28-day dosage preparations (conventional-cycle oral contraceptives). Some 28-day preparations contain 21 hormonally active tablets and seven inert or ferrous-fumarate-containing tablets; other 28-day preparations contain 24 hormonally active tablets and four inert or ferrous-fumarate-containing tablets.

One fixed-combination extended-cycle oral contraceptive is available as a 91-day dosage preparation containing 84 hormonally active tablets and seven inert tablets. Another extended-cycle oral contraceptive is available as a 91-day preparation with 84 hormonally active tablets containing estrogen–progestogen and seven tablets containing low-dose estrogen.

#### (ii) *Intravaginal dosage*

Each vaginal contraceptive ring containing ethinylestradiol and etonogestrel is intended to be used for one cycle which consists of a 3-week period of continuous use of the ring followed by a 1-week ring-free period. After a 1-week ring-free period, a new ring is inserted on the same day of the week as in the previous cycle. Withdrawal bleeding usually occurs within 2–3 days after removal of the ring.

#### (iii) *Transdermal dosage*

When used for contraception, the transdermal system (containing ethinylestradiol 0.75 mg and norelgestromin 6 mg) is applied once weekly for 3 weeks, followed by a 1-week drug-free interval, then the regimen is repeated. Systemic exposure to estrogen is greater with the transdermal system than with oral contraceptive preparations.

#### (b) *Postcoital contraception*

When an emergency contraceptive kit is used for postcoital contraception, two tablets of an estrogen–progestogen contraceptive (each tablet containing ethinylestradiol 50 µg and levonorgestrel 0.25 mg, for a total dose of ethinylestradiol 100 µg and levonorgestrel 0.5 mg) are administered orally within 72 hours after unprotected intercourse, repeating the dose 12 hours later.

Several other regimens employing short-course, high-dose oral combinations of ethinylestradiol and norgestrel or levonorgestrel have been used for postcoital contraception. One of the most widely used regimens consists of an oral dose of 100 µg of ethinylestradiol and 1 mg of norgestrel (administered as two tablets, each containing 50 µg and 0.5 mg of the drugs, respectively) within 72 hours after unprotected intercourse, with a repeat dose 12 hours later.

Alternative combination regimens that have been used consist of a dose of 120 µg of ethinylestradiol and 1.2 mg of norgestrel or 0.5–0.6 mg of levonorgestrel within 72 hours after intercourse, repeating the dose 12 hours later.

### 1.2.3 *Trends in use*

At the time of writing, more than 100 million women worldwide, an estimated 10% of all women of reproductive age, use combined hormonal contraceptives, most as oral preparations. A higher proportion of women receive these drugs in developed countries (16%) than in developing countries (6%). Proportions of ‘ever use’ higher than 80% have been reported for some developed countries. In developing countries, 32% of women are estimated to have ever used hormonal contraception, but there is extreme variability between countries. In many countries, these preparations are mainly used by women of a younger age and a higher level of education, and who have greater access to health care (UN, 2004).

The [UN \(2004\)](#) has compiled data from multiple sources on worldwide patterns of combined hormonal contraceptive use. It was estimated that, among women in marriage or sexual unions, 7.3% currently use combined hormonal contraception orally, and 2.9% currently use hormonal injections or implants. The use of injectable preparations is greater in developing countries than in developed countries.

Data on sales of combined hormonal contraceptives indicate increasing use worldwide; a 19% increase was noted from 1994–99, and a subsequent 21% increase from 1999–2004. The largest increases occurred in eastern Europe, the Eastern Mediterranean, South-East Asia and the Western Pacific, and modest increases in Africa and South America. It should be noted that these data may not include a large amount of hormonal contraceptives that are provided by national and international family planning programmes. Several other trends are indicated from the sales data: (i) the use of higher estrogen doses ( $\geq 50 \mu\text{g}$ ) has continued to decline; (ii) growth in the use of later progestogen-containing products (gestodene, desogestrel) has slowed down, and in some countries, there has been a shift back to earlier progestogens (norethynodrel, norethisterone); and (iii) monophasic hormonal formulations have continued to predominate with some shift away from multiphasic forms ([IARC, 2007](#)).

#### 1.2.4 Sequential oral contraceptives

The sequential oral contraceptive regimen consisted of estrogen treatment in the follicular phase of the cycle when estrogens are normally present with no progesterone, and a combination of a progestational agent and the estrogen in the luteal treatment phase, a period when estrogens plus progesterone are normally present ([Dorfman, 1974](#)).

Sequential oral contraceptives were taken off the market in 1976 ([NCI, 2003](#)). No information

was available on the prevalence or duration of use of these products prior their discontinuation.

## 2. Cancer in Humans

The epidemiological evidence that combined oral contraceptives may alter risks of specific cancers in women was most recently reviewed in a previous *IARC Monograph* ([IARC, 2007](#)). The results of studies published since then, through May 2008, are summarized in this section, and a new assessment of the overall evidence is provided. All tables except Table 2.2 and Table 2.5 are from the prior *IARC Monograph*; they have been updated where appropriate to provide new information from previously cited and new studies with results published in the interim.

### 2.1 Cancer of the breast

The results of a meta-analysis of most of the epidemiological data on oral contraceptives and breast cancer were published in 1996 ([Collaborative Group on Hormonal Factors in Breast Cancer, 1996](#)). The previous evaluation ([IARC, 2007](#)) relied heavily on this effort, which included data from more than ten cohort studies and 60 case–control studies that included over 60 000 women with breast cancer. There was little, and inconsistently observed, increase in risk of breast cancer overall in women who had ever used oral contraceptives. However, the sum of the evidence suggested an increase in the relative risk of breast cancer among current and recent users. This effect was noted particularly among women under 35 years of age at diagnosis who had begun using contraceptives when young (< 20 years), whereas the increased risk declined sharply with older age at diagnosis. Ten years after cessation of use, the risk in women who had used combined hormonal contraceptives appeared to be similar to that in women who



had never used them. Confounding by important known risk factors did not appear to account for the association. The possibility that the association seen for current and recent users is due to detection bias was not ruled out, but it was considered to be unlikely in explaining the association observed in young women. Other results from individual studies that were not considered conclusive but that warranted additional investigation included: a stronger association with invasive lobular than with ductal carcinoma, absence of an association between oral contraceptives and ductal carcinoma *in situ*, an association particularly in women with a family history of breast cancer or a mutation in the *BRCA1* (but not *BRCA2*) gene, and a stronger association in women aged under 35 years using higher rather than lower dose preparations.

Updated results of two long-term cohort studies in the United Kingdom indicate that risk of breast cancer does not increase even a long time after initial exposure. The Oxford Family Planning Association Contraceptive Study (hereafter referred to as the Oxford study) included 17032 women who were 25 to 39 years old when they were recruited into the study between 1968–74 ([Vessey & Painter, 2006](#)). No associations with breast cancer risk were observed in women who ever had used oral contraceptives (relative risk [RR], 1.0; 95%CI: 0.8–1.1), with duration of use, or with time since use, including women whose last exposure was over 20 years previously (RR, 0.9; 95%CI: 0.7–1.1).

The Royal College of General Practitioners' Oral Contraceptive study (hereafter referred to as the Royal College study) recruited approximately 23000 oral contraceptive users, and an equal number of non-users in 1968–69 ([Hannaford et al., 2007](#)). No associations with risk of breast cancer were observed in women who had ever taken oral contraceptives (RR, 1.0; 95%CI: 0.9–1.1), and no significant trends were observed with duration of use or time since last use (RR in

women who last used oral contraceptives over 20 years previously, 0.54; 95%CI: 0.35–0.82).

From 1989–91, approximately 267000 women were enrolled in a randomized trial of breast self-examination in Shanghai, People's Republic of China (hereafter referred to as the Shanghai BSE trial). Information on duration of oral contraceptive use was ascertained at enrollment by in-person interviews. The women in the cohort were followed through to July 2000. The relative risk in women who ever used oral contraceptives was 0.90 (95%CI: 0.78–1.03), and there was no trend in risk with duration of use up to over 10 years of exposure (RR, 0.94; 95%CI: 0.66–1.32) ([Rosenblatt et al., 2008](#)).

Hospital based case–control studies in the Islamic Republic of Iran ([Yavari et al., 2005](#)), Kuala Lumpur, Malaysia ([Kamarudin et al., 2006](#)), Kelantan, Malaysia ([Norsa'adah et al., 2005](#)), and Turkey ([Beji & Reis, 2007](#)), reported relative risks in women who ever used oral contraceptives of 1.95 (95%CI: 1.32–2.87), 0.71 (95%CI: 0.46–1.08), 2.5 (95%CI: 1.3–4.8), and 1.98 (95%CI: 1.38–2.85), respectively. No results by duration of use, time since use, or age at use or diagnosis were given. [No attempts to validate use of oral contraceptives were made in any of these studies, and the possibility of more complete recall of oral contraceptive use by cases than controls cannot be ruled out. In addition some controls may have had conditions that precluded use of oral contraceptives. For these reasons, the Working Group did not believe that these results were sufficiently compelling to conclude that oral contraceptives, as they have been used in the countries in which these studies were conducted, had altered the overall risk of breast cancer.]

Two population-based case–control studies have yielded results that corroborate the increase in risk of breast cancer in young and recent users (see Table 2.1 available at <http://monographs.iarc.fr/ENG/Monographs/vol100A/100A-14-Table2.1.pdf>). In one study ([Jernström et al., 2005](#)), 245 cases were recruited from the South

Swedish Health Care region, and three controls were randomly selected for each case from a population-based cohort study being conducted in the same region. The odds ratio of breast cancer in women who ever used oral contraceptives was 1.65 (95%CI: 0.95–2.87). The odds ratios were significantly elevated in women who used oral contraceptives before the birth of their first child (OR, 1.63; 95%CI: 1.02–2.62), and before the age of 20 years (OR, 2.10; 95%CI: 1.32–3.33), and the risk increased with duration of use at these times in life. The risk was not significantly increased in women who used oral contraceptives after the age of 20 years. The odds ratios per year of use before the age of 20 years were 1.31 (95%CI: 1.07–1.62) in women born in 1955 or later, when most use was of low dose preparations, but only 0.95 (95%CI: 0.74–1.20) in women born in 1954 or earlier, when there was more use of higher dose products. Each year of low-dose oral contraceptives before the age of 20 years was associated with an odds ratio of 1.80 (95%CI: 1.24–2.61). No comparable estimate was given for high-dose oral contraceptives.

In a population-based case–control study conducted in four states in the United States of America, in-person interviews were conducted with 796 Hispanic cases and 919 Hispanic controls, and with 1522 non-Hispanic white cases and 1596 non-Hispanic white controls ([Sweeney et al., 2007](#)). Odds ratios were not significantly elevated in women who ever used oral contraceptives in either Hispanics (OR, 1.10; 95%CI: 0.88–1.37) or non-Hispanics (OR, 1.08; 95%CI: 0.90–1.29). When both groups were combined, the odds ratio in women who used oral contraceptives in the past 5 years was 1.27 (95%CI: 0.99–1.63), with no difference between the two ethnic groups. Risk was also increased in users of over 20 years' duration (OR, 1.50; 95%CI: 1.04–2.17), with similar estimates for both groups; however, there was no apparent trend in the magnitude of risk associated with duration of use.

The odds ratios for ever use were slightly higher for users prior 1980 compared with after 1980, suggesting that the more recently marketed low-dose products may be less strongly associated with risk of breast cancer than older, higher dose preparations, but the differences were small, and risk in relation to time since last use was not presented by decade of use.

A population-based case–control study was conducted in Los Angeles County, USA, in which 567 cases of breast carcinoma *in situ* were compared to 614 controls ([Gill et al., 2006](#)). No association was observed with any of the following features of oral contraceptive use: any use, years of use, use before first live birth, time since last use, age at first use, use of high-dose products, and use of low-dose products. [The Working Group concluded that there was insufficient evidence to determine whether newer, lower dose oral contraceptives altered the risk of breast cancer differently than older, higher dose products.]

Five studies have provided estimates of risk in relation to oral contraceptive use separately for ductal and lobular carcinomas of the breast. In a population-based case–control study of women under the age of 75 years in four states in the USA ([Newcomer et al., 2003](#)), the relative risks of ductal and lobular carcinomas were, respectively, 1.0 (95%CI: 0.7–1.3) and 1.7 (95%CI: 0.9–3.5) in women who used oral contraceptives for 15 years or more. Similarly, in a population-based case–control study in Washington State, USA ([Li et al., 2003](#)), the relative risks for lobular and ductal carcinomas in women who used oral contraceptives for 15 or more years were 2.6 (95%CI: 1.3–5.3) and 1.6 (95%CI: 1.0–2.6), respectively. In the study in four states described previously ([Sweeney et al., 2007](#)), odds ratios for ductal and lobular carcinomas were, respectively, 1.05 (95%CI: 0.90–1.22) and 1.20 (95%CI: 0.82–1.75) in ever users; 1.23 (95%CI: 0.94–1.62) and 1.21 (95%CI: 0.59–2.45) in recent users (within the past 5 years); and, 1.36 (95%CI: 0.91–2.04) and

2.08 (95%CI: 0.93–4.62) in users of over 20 years' duration.

These findings of a stronger association with lobular compared with ductal carcinoma were not confirmed in two other studies. In a case–control study in Sweden ([Rosenberg et al., 2006](#)), the use of oral contraceptives was not associated with any of three histological types of breast cancer, and the odds ratio estimates for users of over 5 years' duration were similar: 0.9 (95%CI: 0.7–1.1) for ductal, 0.9 (95%CI: 0.6–1.4) for lobular, and 1.0 (95%CI: 0.5–1.9) for tubular carcinomas. In the portion of the population-based Woman's Interview Study of Health (WISH) conducted in Atlanta, Seattle-Puget Sound, and New Jersey, USA ([Nyante et al., 2008](#)), odds ratios for ductal and lobular carcinomas were, respectively, 1.21 (95%CI: 1.01–1.45) and 1.10 (95%CI: 0.68–1.74) in ever users; 1.45 (95%CI: 1.08–1.96) and 0.33 (95%CI: 0.08–1.40) in recent users (within the past 2 years); and, 1.30 (95%CI: 1.06–1.59) and 0.92 (95%CI: 0.53–1.59) in users of over 4 years' duration. [The Working Group concluded that there is no convincing evidence that oral contraceptives use is more strongly associated with lobular carcinoma than with ductal carcinoma of the breast.]

Studies have also been conducted to assess risk in relation to oral contraceptive use separately for breast cancers with and without estrogen and progesterone receptors (ER and PR). [Cotterchio et al. \(2003\)](#) combined data from two case–control studies in Ontario, Canada. In both studies, cases were identified from the Ontario Cancer Registry, and controls were selected from roles of the Ministry of Finance. ER/PR status of the tumours was ascertained from laboratory records. Oral contraceptive use was obtained from a mailed questionnaire. The odds ratios for ER+/PR+ tumours, and for ER-/PR- tumours in women who used oral contraceptives for 10 or more years were, respectively, 0.92 (95%CI: 0.61–1.37) and 1.33 (95%CI: 0.79–2.25) in premenopausal women, and 0.95 (95%CI:

0.71–1.27) and 1.41 (95%CI: 0.96–2.08) in postmenopausal women.

In analyses of data from the study by [Sweeney et al. \(2007\)](#), based on 1214 ER+ cases, 339 ER- cases, and 2513 controls, odds ratios for ER+ and ER- breast cancers, respectively, were estimated to be 1.02 (95%CI: 0.87–1.21) and 1.38 (95%CI: 1.04–1.84) for ever users; 1.25 (95%CI: 0.93–1.70) and 1.53 (95%CI: 0.98–2.40) for users within the past 5 years; and, 1.39 (95%CI: 0.90–2.14) and 2.23 (95%CI: 1.17–4.25) in users of over 20 years' duration.

In a population-based case–control study in Los Angeles County, USA, 1794 cases from 20–49 years of age were identified from a population-based cancer registry, and compared to 444 age- and race-matched control women who were selected by a neighbourhood walk algorithm ([Ma et al., 2006](#)). ER and PR status of the tumours were ascertained from medical records. Risk of neither ER+/PR+ nor ER-/PR- tumours was significantly associated with duration of oral contraceptive use, but the odds ratios in women who used oral contraceptives for over 10 years were 0.76 (95%CI: 0.49–1.18) for ER+ PR+ tumours, and 1.27 (95%CI: 0.75–2.14) for ER- PR- tumours. [The Working Group concluded that the evidence was insufficient to determine whether oral contraceptives use is more strongly associated with ER- tumours than with ER+ tumours.]

In a population-based case–control study in North Carolina ([Conway et al., 2007](#)), with cases recruited in 1993–96, paraffin-embedded tumour blocks from 684 cases were successfully screened for mutations in the ER $\alpha$  gene (*ESR1*), which may render tissue hypersensitive to estrogen, and which has been observed in hyperplastic breast tissue. Results of in-person interviews with the 37 cases with an *ESR1* mutation, and with the 616 cases without the mutation, were compared with those from 790 control women. Although many of the odds ratio estimates for mutation-positive tumours were based on small

numbers of exposed cases, the odds ratios in relation to multiple features of oral contraceptive use were consistently greater for mutation-positive than mutation-negative tumours. Odds ratios for mutation-positive and mutation-negative tumours were, respectively, 1.72 (95%CI: 0.66–4.44) and 1.15 (95%CI: 0.87–1.52) in ever users; 3.73 (95%CI: 1.16–12.03) and 1.18 (95%CI: 0.77–1.81) in users of over 10 years duration; 3.63 (95%CI: 0.80–16.45) and 1.06 (95%CI: 0.65–1.72) in recent users (in the past 10 years); and, 6.49 (95%CI: 1.32–31.89) and 1.32 (95%CI: 0.73–2.38) in women who used oral contraceptives for over 10 years and had stopped using oral contraceptives within the past 10 years. [The Working Group noted that these results are at variance with those for ER+ and ER- tumours, and require independent confirmation before firm conclusions can be made.]

There is concern that oral contraceptives may preferentially alter the risk of breast cancer in women at high risk of this disease because of the occurrence of breast cancer in one or more family members, or because they carry a specific genetic mutation. In an investigation based on the Canadian National Breast Screening studies (Silvera *et al.*, 2005), 89835 women between the ages of 40–59 years were recruited during 1980–85, and completed a self-administered questionnaire, which included items on oral contraceptive use. The cohort was followed through 1998, 1999, or 2000, depending on the area, and cases were identified by linkage to provincial and national cancer registries. Hazard ratios of breast cancer in ever users, current users (at baseline), and users of over 7 years' duration were 0.88 (95%CI: 0.73–1.07), 1.01 (95%CI: 0.56–1.81), and 0.74 (95%CI: 0.55–0.99), respectively, in women with any family history of breast cancer. A significant decreasing trend in risk ( $P = 0.03$ ) with increasing duration of use was observed. Results were broadly similar for women with first- and second-degree relatives with breast

cancer. Comparable results for women with no family history were not given.

Four studies have assessed the risk of breast cancer in oral contraceptive users with mutations in the *BRCA1* or *BRCA2* genes. This can only be done in studies in which both cases and comparable non-cases are tested for the mutations, for instance, studies in which only cases were tested are not considered in this review. In a multicentre study conducted in 52 centres in 11 countries (Narod *et al.*, 2002), 1311 women with breast cancer and a mutation in *BRCA1* or *BRCA2* were compared to an equal number of unaffected controls with the same mutations, matched to the cases on year of birth, country, and mutation (*BRCA1* or *BRCA2*). In a study in Poland (Gronwald *et al.*, 2006), 348 cases of breast cancer were compared to 348 age-matched controls, who had not developed either breast or ovarian cancer; all were carriers of one of three Polish founder *BRCA1* mutations. A collaborative international case-control study (Haile *et al.*, 2006) included 195 cases and 302 controls with *BRCA1* mutations, and 128 cases and 179 controls with *BRCA2* mutations. In another international collaborative study (Brohet *et al.*, 2007), a cohort of 1593 women who had *BRCA1* ( $n = 1181$ ) or *BRCA2* ( $n = 412$ ) mutations was followed up and the hazard ratio of developing breast cancer in relation to several features of oral contraceptive use was estimated, based on 597 cases with a *BRCA1* mutation and 249 cases with a *BRCA2* mutation. The results of all four studies are summarized in Table 2.2 (available at <http://monographs.iarc.fr/ENG/Monographs/vol100A/100A-14-Table2.2.pdf>). The risk of breast cancer in women who ever used oral contraceptives was increased in *BRCA1* mutation carriers (Narod *et al.*, 2002; Haile *et al.*, 2006; Brohet *et al.*, 2007), and there were increasing trends in risk with total duration of use. However, the risk was not consistently increased in women who used oral contraceptives before their first full-term pregnancy, or at an early age. Among



*BRCA2* mutation carriers, the risk was increased in two of the studies in women who ever used oral contraceptives ([Haile et al., 2006](#); [Brohet et al., 2007](#)), and the risk was particularly increased in long-term users in these two studies. An increase in risk was consistently observed in relation to use before a first full-term pregnancy, and at an early age. [The Working Group noted that the preponderance of the evidence suggests that use of oral contraceptives is associated with an increased risk of breast cancer in carriers of *BRCA1* or *BRCA2* mutations. The Working Group further noted that if this association reflects a causal relationship, then it could, at least in part, explain the observation summarized in the 2005 *IARC Monograph* ([IARC, 2007](#)) that risk of breast cancer was increased in women under the age of 35 years who had begun using oral contraceptives at a young age and who were current or recent users.]

## 2.2 Cancer of the endometrium

The previous *IARC Monograph* ([IARC, 2007](#)) on oral contraceptives and endometrial cancer was based on several cohort and case–control studies (see Table 2.3 available at <http://monographs.iarc.fr/ENG/Monographs/vol100A/100A-14-Table2.3.pdf> and Table 2.4 at <http://monographs.iarc.fr/ENG/Monographs/vol100A/100A-14-Table2.4.pdf>). The results of these studies consistently showed that the risk of endometrial cancer in women who had ever taken oral contraceptives was approximately halved. The reduction in risk was generally greater with longer duration of use, and persisted for at least 15 years after cessation of use, although the extent of the protective effect could lessen over time. Few data were available on the more recent, low-dose formulations of oral contraceptives.

The cohort study in the BSE trial in Shanghai ([Rosenblatt, et al., 2008](#)) reported hazard ratios of 0.68 (95%CI: 0.45–1.04) in women who had ever used oral contraceptives, and 0.48 (95%CI:

0.27–0.85) in women who had used those for 1 or more years. The updated results from the two British cohort studies provide additional information on the effect of long-term use on the risk of endometrial cancer, and on the duration of the apparent protective effect. Estimates of the relative risks from the Royal College study ([Hannaford et al., 2007](#)) and the Oxford study ([Vessey & Painter, 2006](#)) for users of over 8 years' duration were, respectively, 0.57 (95%CI: 0.27–1.19) and 0.1 (95%CI: 0.0–0.4), and for last use more than 20 years ago were 0.63 (95%CI: 0.23–1.78) and 0.5 (95%CI: 0.3–0.9).

These results were confirmed in a population-based case–control study in Shanghai ([Tao et al., 2006](#)), in which 1204 women with endometrial cancer, who were identified through the Shanghai cancer registry, were compared to 1629 controls that were selected from the Shanghai resident registry. Women who reported ever using oral contraceptives had an odds ratio of 0.75 (95%CI: 0.60–0.93). The risk decreased with increasing duration of use ( $P$ -trend = 0.14), and the risk in women who had last used oral contraceptives 25 or more years in the past was 0.57 (95%CI: 0.42–0.78).

A case–control study was conducted in three hospitals in Japan ([Okamura et al., 2006](#); Table 2.4 online). Cases were identified from hospital admissions, and controls were selected from cervical cancer screening clinics. Based on 155 cases and 96 controls, only three and ten of which, respectively, had ever used oral contraceptives, the odds ratio in ever users was 0.16 (95%CI: 0.04–0.66). [The Working Group noted that the controls were probably not representative of the population from which the cases came.]

Data from the population-based Cancer and Steroid Hormone ([CASH, 1987a, b](#)) case–control study in the USA were re-analysed to assess the risk of endometrial cancer in relation to the potency of the estrogens and progestogens in the oral contraceptives women had taken ([Maxwell et al., 2006](#)). Based on data from in-person

interviews of 434 cases identified through the Surveillance, Epidemiology, and End Results (SEER) programme in the USA, and 2557 controls selected by random-digit dialling, the odds ratios in women who took low- and high-progestogen potency products were, respectively, 0.39 (95%CI: 0.27–0.57) and 0.20 (95%CI: 0.10–0.41). The comparable estimates for women with a body mass index (BMI) less than 22.1 kg/m<sup>2</sup> who took low- and high-progestogen potency products were, respectively, 0.30 (95%CI: 0.11–0.83) and 0.26 (95%CI: 0.13–0.52), and for heavier women were 0.16 (95%CI: 0.06–0.45) and 0.51 (95%CI: 0.33–0.80). The risk was not significantly different in users of high- and low-estrogen potency products. However, eight controls, but no cases, had used products classified as high-progestogen/low-estrogen potency, suggesting that preparations with a high ratio of progestogen to estrogen may offer particularly strong protection against endometrial cancer.

## 2.3 Cancer of the cervix

In an initial review of five cohort and 16 case-control studies of oral contraceptives and invasive cervical cancer ([IARC, 1999](#)), the Working Group could not rule out biases related to sexual behaviour, screening, and other factors as possible explanations for an observed trend in risk of cervical cancer with increasing duration of use. The previous *IARC Monograph* ([IARC, 2007](#)) considered results from three additional cohort studies and seven more case-control studies that provided information on invasive or in-situ cervical carcinoma and use of oral contraceptives. All but three of the most recent studies were summarized in a meta-analysis of published data ([Smith et al., 2003](#)) that was used in the previous *IARC Monograph*. The sum of the evidence indicated that, overall, the risk of both in-situ and invasive cervical cancer increased with increasing duration of use of oral contraceptives. The increase in risk with duration of use

was observed in studies that were restricted to women with high-risk human papilloma virus (HPV) infections, and in studies that controlled for the presence of this infection. The increase was observed for both in-situ and invasive disease, and for both squamous cell carcinoma and adenocarcinoma. The relative risk declined after cessation of use. The results were broadly similar regardless of adjustment for number of sexual partners, cervical screening, tobacco smoking, and the use of barrier contraceptives. Although the possibility that the observed associations were due to residual confounding or detection bias could not be completely ruled out, they were considered unlikely to explain fully the observed relationships.

The updated results from the two British cohort studies also show increasing risks of invasive cervical cancer with duration of use, and declining trends in risk with time since last use. Estimates of relative risks from the Royal College ([Hannaford et al., 2007](#)) and Oxford ([Vessey & Painter, 2006](#)) studies for users of over 8 years' duration were 2.73 (95%CI: 1.61–4.61) and 6.1 (95%CI: 2.5–17.9), respectively. The relative risks were not elevated between 15–20 years since last use (RR, 0.65; 95%CI: 0.23–1.83) and 20 or more years since last use (RR, 0.78; 95%CI: 0.11–5.71) in the Royal College study; and not elevated after 20 years since cessation of use (OR, 1.3; 95%CI: 0.1–7.2) in the Oxford study.

Results from a second meta-analysis have been published since the 2005 Working Group review ([Appleby et al., 2007](#)). Data on 16573 women with cervical cancer and 35509 women without this disease, from 24 epidemiological studies, were included in the analysis. The percentage of control women who had used oral contraceptives was higher in women who had had at least one Pap smear, multiple sexual partners, early age at first sexual intercourse, borne children, smoked, and who were more educated, than in women without these attributes. All analyses were controlled for these potentially confounding factors, although

the results differed little from those that were controlled only for age and study, suggesting that residual confounding was unlikely to account for the observed associations. The relative risks (floating standard error, FSE) of invasive cervical cancer in women who used oral contraceptives for less than 5 years, 5–9 years, and 10 or more years were 0.96 (FSE, 0.04), 1.20 (FSE, 0.05), and 1.56 (FSE, 0.08), respectively; and the trend was statistically significant ( $P < 0.0001$ ). There was also a significant ( $P < 0.0001$ ) decreasing trend in relative risks with time since last use: 1.65 (FSE, 0.08), 1.28 (FSE, 0.08), 1.12 (FSE, 0.06), 1.05 (FSE, 0.06), and 0.83 (FSE, 0.05) in current users and in women who last used oral contraceptives 2–4, 5–9, 10–14, and 15 or more years in the past, respectively.

As shown in Table 2.5 (available at <http://monographs.iarc.fr/ENG/Monographs/vol100A/100A-14-Table2.5.pdf>), the risk of in-situ disease was increased in users of less than 5 years' duration, but the risk of invasive disease was increased only after 5 years of use. The risk of both conditions declined with time since last use, and there was no elevation in risk of invasive disease 10 years since exposure. The relative risks of invasive cancer in women with evidence of oncogenic HPV DNA in exfoliated cervical cells was 0.80 (95%CI: 0.38–1.22) in users of less than 5 years' duration, and 1.45 (95%CI: 0.86–20.4) for 5 or more years' duration. Data from 12 studies could not be included in the meta-analysis, but evidence was presented that indicated their exclusion was unlikely to have altered the overall results. Subsequent studies of invasive cervical carcinoma (Matos *et al.*, 2005), and in-situ disease (Castle *et al.*, 2005; Massad *et al.*, 2005; Syrjänen *et al.*, 2006) did not consider risk in relation to duration of oral contraceptive use or time since last use.

## 2.4 Cancer of the ovary

The relationship between oral contraceptive use and between risk of ovarian cancer was extensively reviewed in the previous *IARC Monograph* (IARC, 2007). Based on results from six cohort studies and more than 30 case–control studies, plus six pooled analyses of data from multiple studies (see Table 2.6 available at <http://monographs.iarc.fr/ENG/Monographs/vol100A/100A-14-Table2.6.pdf> and Table 2.7 at <http://monographs.iarc.fr/ENG/Monographs/vol100A/100A-14-Table2.7.pdf>), it was clearly shown that women who had used oral contraceptives were at reduced risk of ovarian cancer. Risk declined with duration of use, and the apparent protective effect persisted for at least 20 years after last use. In most studies of specific histological types of ovarian cancer, reductions in risk of all types were observed in oral contraceptive users, although the association tended to be weaker and less consistently observed for mucinous than for other tumour types. Results for all histological types combined were confirmed in updated analyses of the two British cohort studies, although not in the Shanghai cohort, in which there were few long-term users.

Extension and clarification of all of these observations are provided by results of a meta-analysis of nearly all of the known epidemiological data on oral contraceptives and ovarian cancer available at the time of writing (Beral *et al.*, 2008). This analysis was of data from 13 prospective studies, 19 case–control studies with population controls, and 13 case–control studies with hospital controls, and included information on 23257 women with ovarian cancer and 87303 controls. Relative risks of women who used oral contraceptives for less than 1, 1–4, 5–9, 10–14, and 15 or more years were estimated to be 1.00 (95%CI: 0.91–1.10), 0.78 (95%CI: 0.73–0.83), 0.64 (95%CI: 0.59–0.69), 0.56 (95%CI: 0.50–0.62), and 0.42 (95%CI: 0.36–0.49), respectively. The apparent protective effect declined with time

since last use, but persisted for over three decades. For any time since last use, the reduction in risk was greater the longer the time oral contraceptives had been taken. The relative risk in women who had ever used oral contraceptives, and who had last used them over 30 years previously was 0.86 (95%CI: 0.76–0.97). The reduction in risk was seen for all histological types of malignant tumours, although it was weaker for mucinous when compared with other epithelial types (clear cell, endometrioid, and serous) and non-epithelial types. The reduction in risk was also less for borderline than for malignant serous tumours, and there was no reduction in risk of borderline mucinous tumours.

Independent analyses of data from a population-based study in Denmark ([Huusom et al., 2006](#)) confirmed the absence of a relationship between oral contraceptive use and borderline mucinous ovarian tumours, and the presence of a relationship with borderline serous tumours. Another population-based study in Denmark ([Soegaard et al., 2007](#)) showed decreasing trends in risk with duration of oral contraceptive use for invasive serous and endometrioid ovarian cancers, but not for invasive mucinous types. [The Working Group concluded that oral contraceptives are protective against epithelial ovarian cancers, and that the protective effect may be less for mucinous than for other histological types.]

The previous *IARC Monograph* ([IARC, 2007](#)) found no evidence that newer oral contraceptives with generally lower levels of estrogen and progestogen offered less protection than older products with generally higher levels. A recent meta-analysis also showed that the reduction in risk was similar in women who used oral contraceptives in the 1960s, 1970s, and 1980s, when most products contained relatively high, intermediate, and low doses of estrogen, respectively. In a population-based case-control study of 20–74-year-old women in North Carolina ([Moorman et al., 2008](#)), cases diagnosed in 1999–2006 were identified from a local cancer

registry, and controls were selected by random-digit dialling. The odds ratios did not significantly vary by time since first or last use after controlling for duration of use; and the odds ratios by duration of use were consistently lower for ovarian cancer in premenopausal women (who would be more likely to have used lower dose products) than in postmenopausal women (who would be more likely to have used higher dose products). The odds ratios for users of over 10 years' duration were 0.3 (95%CI: 0.2–0.6) for premenopausal women and 0.9 (95%CI: 0.6–1.5) for postmenopausal women.

In the previous *IARC Monograph* ([IARC, 2007](#)), the three studies that reported risk in relation to specific dosages all found lower odds ratios in users of relatively low- compared to high-estrogen potency products. This was also observed in an analysis of data from a population-based case-control study in Hawaii and Los Angeles ([Lurie et al., 2007](#)) that included 745 cases and 943 controls. Products with 0.035 mg or more of ethinyl estradiol were considered as having high estrogen potency, and products containing progestogens with 0.3 mg norgestrel equivalent or more were considered as having high progestogen potency. The odds ratios in women who ever used products of high- and low-estrogen potency (regardless of progestogen potency) were 0.61 (95%CI: 0.42–0.89) and 0.33 (95%CI: 0.21–0.52), respectively; and the odds ratios in relation to ever use of high- and low-progestogen potency products (regardless of estrogen potency) were 0.54 (95%CI: 0.38–0.75) and 0.41 (95%CI: 0.18–0.94), respectively. The comparable odds ratios in users of products with high doses of both hormones, high estrogen-low progestogen, low estrogen-high progestogen, and low doses of both, were 0.62 (95%CI: 0.43–0.92), 0.55 (95%CI: 0.19–1.59), 0.45 (95%CI: 0.28–0.72), and 0.19 (95%CI: 0.05–0.75), respectively. [The Working Group concluded that, although some of the differences in the odds ratio estimates for high- and low-dose products could have occurred



by chance, in the aggregate, the consistency of the results across studies suggests that the newer, lower dose products may actually offer more protection than the older preparations.]

The meta-analysis ([Beral \*et al.\*, 2008](#)) found no significant differences in odds ratio estimates in women with and without a family history of breast cancer (presumably used as a rough surrogate for the possible presence of a *BRCA* gene mutation). The previous *IARC Monograph* ([IARC, 2007](#)) included four studies in which cases and controls with mutations in the *BRCA1* or *BRCA2* genes were compared. All four showed reductions in risk of ovarian cancer in oral contraceptive users who were carriers of a mutation in one of these genes. These observations were confirmed in two subsequent investigations.

In the case–control study of breast and ovarian cancers in women with *BRCA1* mutations in Poland (described previously in the section on breast cancer), 150 cases of ovarian cancer and 150 controls with one of three Polish founder mutations in *BRCA1* were compared. Relative risks in ever users of oral contraceptives and in users of 2 or fewer years and more than 2 years' duration were 0.4 (95%CI: 0.2–1.0), 0.8 (95%CI: 0.2–2.5), and 0.2 (95%CI: 0.1–0.7), respectively ([Gronwald \*et al.\*, 2006](#)). In an expansion of one of the studies included in the previous *IARC Monograph*, 670 cases with a *BRCA1* mutation and 128 with a *BRCA2* mutation were compared to 2043 controls with a *BRCA1* mutation and 380 controls with a *BRCA2* mutation ([McLaughlin \*et al.\*, 2007](#)). Subjects came from 11 different countries and were primarily identified through high breast cancer risk genetic testing and counselling clinics. The odds ratios in women who ever used oral contraceptives were 0.56 (95%CI: 0.45–0.71) in *BRCA1* mutation carriers, and 0.39 (95%CI: 0.23–0.66) in *BRCA2* mutation carriers. The odds ratios in carriers of either gene declined with duration of use. The odds ratio estimates for users of up to 1, 1–3, 3–5, and over 5 years in *BRCA1* mutation carriers were 0.69 (95%CI:

0.50–0.95), 0.67 (95%CI: 0.47–0.96), 0.41 (95%CI: 0.27–0.63), and 0.48 (95%CI: 0.35–0.66), respectively. The corresponding estimates for *BRCA2* mutation carriers were 0.56 (95%CI: 0.28–1.10), 0.42 (95%CI: 0.20–0.88), 0.14 (95%CI: 0.05–0.46), and 0.37 (95%CI: 0.19–0.72), respectively.

## 2.5 Cancer of the liver

In the previous *IARC Monograph* ([IARC, 2007](#)), it was noted that long-term use of combined oral contraceptives was associated with an increase in the risk of hepatocellular carcinoma in populations that had low prevalence of hepatitis B virus (HBV) infection and chronic liver disease, each of which are major causes of liver cancer. This association was also seen in analyses in which women with such infections were excluded. Three cohort studies showed no significant association between the use of oral contraceptives and the incidence of, or mortality from, liver cancer, but the expected number of cases was very small, which resulted in low statistical power. Few data were available on the more recent, low-dose formulations. In the three case–control studies conducted in populations that had a high prevalence of infection with hepatitis viruses, no statistically significant increase in the risk of hepatocellular carcinoma was associated with oral contraceptive use, but little information was available on long-term use.

Results for liver cancer were not reported in the updated results from the Oxford study, and the updated results from the Royal College study ([Hannaforde \*et al.\*, 2007](#)) only included results for cancers of the liver and gallbladder combined (OR, 0.55; 95%CI: 0.26–1.17, in ever users, based on 14 cases that were users and 13 that were non-users); and there was no significant trends in risk with duration of use or time since last use. Consistent with the case–control studies in HBV-endemic areas, the cohort study in the BSE trial cohort in Shanghai ([Rosenblatt \*et al.\*, 2008](#)) did not find an increase in risk in women who

ever used oral contraceptives (RR, 0.82; 95%CI: 0.60–1.13), and no trend in risk with duration of use. The odds ratio in users of 10 or more years' duration was 0.67 (95%CI: 0.32–1.44).

A meta-analysis ([Maheshwari et al., 2007](#)) of published data from 12 case-control studies of oral contraceptive use and hepatocellular carcinoma (see Table 2.8 available at <http://monographs.iarc.fr/ENG/Monographs/vol100A/100A-14-Table2.8.pdf>) provided an estimated risk of 1.57 (95%CI: 0.96–2.45) for ever users. However, there was significant heterogeneity of results among the studies. As expected, the large study conducted in eight HBV-endemic areas ([WHO Collaborative Study of Neoplasia and Steroid Contraceptives, 1989a, b](#)) found no association with ever use of oral contraceptives (OR, 0.71; 95%CI: 0.40–1.21), and no trend in risk with duration of use. A second study in South Africa, based on seven cases and eight controls, reported an odds ratio of 1.9 (95%CI: 0.5–5.6) in ever users ( $P = 0.19$ ) ([Kew et al., 1990](#)), with no trend in risk with duration of use. All of the other reviewed studies had been conducted in areas not endemic for HBV, and all but one showed an increased risk of hepatocellular carcinoma in relation to oral contraceptive use. The exception was a collaborative study in six European countries ([Heinemann et al., 1997](#)) which reported an odds ratio of 0.75 (95%CI: 0.54–1.03) in ever users. However, in women with no serological evidence of HBV or hepatitis C virus (HCV) infection, and no history of hepatic cirrhosis, the odds ratio in users of over 6 years' duration was 2.29 (95%CI: 1.05–5.02). In the other studies in non-HBV-endemic areas, with sufficient numbers of study subjects to assess risk in relation to duration of use, risk was observed to increase with years of exposure.

## 2.6 Cancer of the skin

At the time of the previous *IARC Monograph* ([IARC, 2007](#)) four cohort and 19 case-control studies provided information on the use of combined oral contraceptives and risk of cutaneous malignant melanoma (see Table 2.9 available at <http://monographs.iarc.fr/ENG/Monographs/vol100A/100A-14-Table2.9.pdf> and Table 2.10 available at <http://monographs.iarc.fr/ENG/Monographs/vol100A/100A-14-Table2.10.pdf>). No consistent evidence for an association was found with respect to current use, duration of use, time since last use or age at first use.

The relative risks of cutaneous melanoma from the Oxford and Royal College studies did not increase with duration of use, and were, respectively, 1.0 (95%CI: 0.6–1.7) and 1.71 (95%CI: 0.96–3.06) for users of over 8 years' duration; and, they were 0.8 (95%CI: 0.4–1.5) and 0.62 (95%CI: 0.24–1.59) 20 or more years after last use. An updated analysis of data from a hospital-based case-control study in San Francisco ([Lea et al., 2007](#)) did not show an association between oral contraceptive use and risk of cutaneous melanoma (see Table 2.10 online).

## 2.7 Cancer of the colorectum

At the time of the previous *IARC Monograph* ([IARC, 2007](#)), nine cohort and 14 case-control studies provided information on oral contraceptives and risk of colorectal cancer (see Table 2.11 available at <http://monographs.iarc.fr/ENG/Monographs/vol100A/100A-14-Table2.11.pdf> and Table 2.12 at <http://monographs.iarc.fr/ENG/Monographs/vol100A/100A-14-Table2.12.pdf>). Most studies did not show an increase in risk in women who had ever used oral contraceptives, or in relation to duration of use. The results were generally similar for colon and rectal cancer when examined separately, and two case-control studies showed a significant reduction in risk of colorectal cancer in users of oral contraceptives.

The two updated British cohort studies show no significant associations between oral contraceptive use and cancers of the colon and rectum combined. Odds ratio estimates from the Oxford and Royal College studies were, respectively, 0.8 (95%CI: 0.5–1.2) and 0.95 (95%CI: 0.59–1.54) in users of over 8 years' duration, and 0.9 (95%CI: 0.6–1.4) and 1.09 (95%CI: 0.60–1.99) 20 or more years after cessation of use. In the Shanghai BSE trial cohort study (Rosenblatt *et al.*, 2008), 655 women developed cancer of the colon and 368 developed cancer of the rectum. Relative risks of colon and rectal cancer were 1.09 (95%CI: 0.86–1.37) and 1.31 (95%CI: 0.98–1.75), respectively, in women who had ever used oral contraceptives. Weak increasing trends in risk with duration of use were observed for both cancers (*P*-values for trend: 0.16 and 0.017, respectively), and the relative risks in users for 10 or more years were 1.56 (95%CI: 1.01–2.40) and 1.34 (95%CI: 0.71–2.52), respectively. However, two additional cohort studies showed inverse associations between oral contraceptive use and colorectal cancer. Of 39680 American women aged 45 years or older who were enrolled in a randomized trial of aspirin and vitamin E (Lin *et al.*, 2007), women who had ever used oral contraceptives at baseline were at significantly reduced risk of colon and rectal cancers, but among users, there was no significant trend in risk with duration of exposure up to 60 or more months of use. The hazard ratios for both colon and rectal cancers were also reduced in oral contraceptive users in a cohort of 89835 women between 40–59 years of age who were enrolled in a randomized trial of breast screening in Canada (Kabat *et al.*, 2007a). The hazard ratios were similar for cancers of the proximal and distal colon. However, there were no significant trends in risk with duration of use.

One additional population-based case–control study provided results similar to those of the cohort studies in the USA and Canada. A total of 1404 colon and rectal cancer cases that were identified from cancer registries in Ontario,

Newfoundland and Labrador were compared to 1203 population controls (Campbell *et al.*, 2007). A self-administered questionnaire was used to collect information on the use of hormonal contraceptives [presumably largely combined oral contraceptives]. The odds ratio for colorectal cancer in women who had ever used any type of hormonal contraceptive was 0.77 (95%CI: 0.65–0.91). Among users, no trend in risk with duration of use was observed.

## 2.8 Cancer of the thyroid

In the previous *IARC Monograph* (IARC, 2007), results from a pooled analysis of data from 13 studies, and reports from six additional investigations (see Table 2.13 available at <http://monographs.iarc.fr/ENG/Monographs/vol100A/100A-14-Table2.13.pdf>), revealed weak or no associations between the use of oral contraceptives and cancer of the thyroid. In the cohort study in the Shanghai BSE trial (Rosenblatt *et al.*, 2008), no increase in risk of thyroid cancer in women who ever used oral contraceptives was observed (RR, 0.75; 95%CI: 0.46–1.23, based on 161 cases, 20 of whom were users). Results of one additional population-based case–control study, in New Caledonia, France, an area with an unusually high incidence of thyroid cancer, were published (Truong *et al.*, 2005) where answers to in-person interviews of 293 cases and 354 controls selected from electoral rolls were compared. The odds ratio was 1.1 (95%CI: 0.8–1.7) for ever users of oral contraceptives, and no trend in risk with duration of use up to over 5 years was observed.

## 2.9 Lymphomas

The previous *IARC Monograph* (IARC, 2007) included two studies that did not find associations between the use of oral contraceptives and the risk of lymphomas (see Table 2.14 available at <http://monographs.iarc.fr/ENG/Monographs/vol100A/100A-14-Table2.14.pdf>). In the most

recent results from the Oxford study ([Vessey & Painter, 2006](#)), no increased risk of lymphomas and leukaemias combined in women who ever used oral contraceptives and no trend in risk with duration of use were observed.

## 2.10 Cancers of the central nervous system

One study was cited in the previous *IARC Monograph* ([IARC, 2007](#)) that showed no association between risk of tumours of the central nervous system and the use of oral contraceptives. However, the most recent results from the Royal College study ([Hannaford et al., 2007](#)) showed an increased risk of cancers of the central nervous system or pituitary gland with 8 or more years of use.

In the cohort study based on the Canadian National Breast Screening study ([Silvera et al., 2006](#)), 120 incident glioma cases occurred during an average 16.4 years follow-up. Based on answers to a self-administered questionnaire at recruitment into the cohort, the hazard ratio for gliomas was 1.01 (95%CI: 0.68–1.52) in women who ever used oral contraceptives, and there was no trend in risk with duration of use up to over 6 years of use. In a population-based case–control study of 115 women with gliomas and 323 controls in Sweden ([Wigertz et al., 2006](#)), the odds ratio in women who ever used oral contraceptives was 0.8 (95%CI: 0.5–1.4), and the risk did not vary appreciably with duration of use. In a hospital-based case–control study conducted at multiple sites in the USA ([Hatch et al., 2005](#)), 212 women with gliomas were compared to 436 controls. Based on responses to in-person interviews, the odds ratio for glioma was 0.66 (95%CI: 0.44–1.00) in women who ever used oral contraceptives, and there trend in risk with duration of use was observed.

Four case–control studies and one cohort study of meningiomas that provided information on possible associations with oral contraceptive

use were reviewed by [Claus et al. \(2007\)](#). None of the studies showed statistically significant associations with ever user of oral contraceptives, and two studies showed no increase in risk with over 10 years of use.

## 2.11 Cancer of the urinary tract

The most recent results from the Oxford study showed no association between kidney or bladder cancer combined with the use of oral contraceptives. The relative risk in women who ever used oral contraceptives was 0.8 (95%CI: 0.6–1.2), and there was no trend in risk with duration of use up to over 8 years, and no increase in risk up to over 20 years since last use ([Vessey & Painter, 2006](#)).

In the Canadian cohort study of women enrolled in a breast cancer screening trial ([Kabat et al., 2007a](#)), the hazard ratio for renal cell cancers in women who ever used oral contraceptives was 0.80 (95%CI: 0.58–1.09), and no trend in risk with duration of use was observed. In the previous *IARC Monograph* ([IARC, 2007](#)), one case–control study was cited that also showed no association between risk of renal cell cancer and ever use of oral contraceptives.

Two prospective studies in the USA have shown no increases in risk of cancers of the urinary bladder in users of oral contraceptives. During approximately 26 years of follow-up of 116598 women enrolled in the Nurse’s Health Study ([McGrath et al., 2006](#)), 336 cases of bladder cancer were detected. The use of oral contraceptives was ascertained periodically during the follow-up period by mailed questionnaire. The relative risk in women who ever used oral contraceptives was 0.84 (95%CI: 0.65–1.08), and there was no trend in risk with duration of use, up to over 6 years of use. During an average follow-up of 15.3 years, 167 cases of bladder cancer developed in a cohort of 54308 women who were enrolled in the Breast Cancer Detection Demonstration Project ([Cantwell et al., 2006](#)). Oral contraceptive use was based on answers to telephone interviews



at the time of recruitment. The relative risk of bladder cancer was 1.14 (95%CI: 0.77–1.70) in women who ever used oral contraceptives, and no trend in risk with duration of use up to over 5 years of exposure was observed.

## 2.12 Cancer of the lung

The most recent results from the Oxford ([Vessey & Painter, 2006](#)) and Royal College ([Hannaford et al., 2007](#)) studies, from the Shanghai BSE trial cohort ([Rosenblatt et al., 2008](#)), and from the Canadian National Breast Screening Study ([Kabat et al., 2007b](#)) showed no increased risk of lung cancer in oral contraceptive users, and no trends in risk with duration of use, and the two British studies also showed no increase up to 20 years or more since last use. One case–control study, summarized in the previous *IARC Monograph* ([IARC, 2007](#)) found a reduced risk in smokers who ever used oral contraceptives (OR, 0.50; 95%CI: 0.34–0.74), but not in non-smokers. Another case–control study nested in the Royal College study ([Elliott & Hannaford, 2006](#)) found no increases in the risk of lung cancer in women who ever used oral contraceptives or in relation to duration of use, or time since first or last use. Current users (at the time of diagnosis) had an odds ratio of 0.5 (95%CI: 0.1–3.3).

## 2.13 Cancer of the pancreas

In the previous *IARC Monograph* ([IARC, 2007](#)), no association was observed between ever users of oral contraceptives and risk of pancreatic cancer, and there was no trend in risk with duration of use. A cohort of 387981 postmenopausal women in the USA, the CPS-II ([Teras et al., 2005](#)), also found no significant trend ( $P = 0.19$ ) in pancreatic cancer mortality rates with years of oral contraceptive use.

## 2.14 Cancer of the gallbladder

Four of five studies reviewed in the previous *IARC Monograph* ([IARC, 2007](#)) showed no association between risk of cancer of the gallbladder and ever users of oral contraceptives. In the Shanghai BSE trial cohort ([Rosenblatt, et al., 2008](#)), no significant increase in risk in users of oral contraceptives for cancer of the gallbladder was observed.

## 2.15 Cancer of the stomach

The Oxford study found no association between risk of oesophageal and stomach cancers combined and use of oral contraceptives. The relative risks in ever users, and in users for over 8 years were 0.6 (95%CI: 0.3–1.3) and 0.5 (95%CI: 0.2–1.2), respectively ([Vessey & Painter, 2006](#)). The Shanghai BSE trial cohort ([Rosenblatt et al., 2008](#)) found a relative risk for stomach cancer of 1.02 (95%CI: 0.82–1.27), and no trend with duration of use. A hazard ratio for stomach cancer of 1.05 (95%CI: 0.70–1.58) was found in women who had ever used oral contraceptives at entry into another cohort study in Shanghai ([Freedman et al., 2007](#)), based on 154 cases of stomach cancer that occurred in 73442 women followed from 1997–2004. A population-based case–control study in ten Canadian provinces ([Frise et al., 2006](#)) compared answers to a self-administered questionnaire by 326 women with gastric adenocarcinoma to answers from an equal number of age-matched controls. The odds ratio in women who ever used oral contraceptives was 0.79 (95%CI: 0.43–1.45).

## 2.16 Other cancers

A pooled analysis of data from three hospital-based case–control studies was cited in the previous *IARC Monograph* ([IARC, 2007](#)) that estimated the odds ratio of squamous cell oesophageal cancer in women who ever used

oral contraceptives to be 0.24 (95%CI: 0.06–0.96) (Gallus *et al.*, 2001). The prior review also included two case–control studies that showed the risk of gestational trophoblastic disease to be increased in women who ever used oral contraceptives, with increasing trends with duration of use (Palmer *et al.*, 1999; Parazzini *et al.*, 2002). Also, the risk of neuroblastoma in children whose mothers took oral contraceptives during their pregnancy was observed to be increased in one study (Schüz *et al.*, 2001), but not in another (Olshan *et al.*, 1999).

## 2.17 Synthesis

There are increased risks for cancer of the breast in young women among current and recent users only, for in-situ and invasive cancer of the uterine cervix, and for cancer of the liver in populations that are at low risk for HBV infection (this risk is presumably masked by the large risk associated with HBV infection in HBV-endemic populations).

In addition, for cancer of the uterine cervix, the magnitude of the associations is similar for in-situ and invasive disease, and the risks increase with duration of use, and decline after cessation of use.

For cancer of the endometrium, the Working Group concluded that oral contraceptives are protective against endometrial cancer, that the magnitude of the protective effect increases with duration of use, and that it lasts for at least two decades after cessation of use. There is also evidence that the level of the protective effect is proportional to the progestogen potency of the preparation, and inversely proportional to its estrogen potency.

For cancer of the ovary, the Working Group concluded that oral contraceptives are protective against ovarian cancer. The reduction in risk increases with duration of use and persists for at least 30 years after cessation of use. The level of protection is at least as great for newer,

lower dose preparations or for older, higher dose oral contraceptives. The reduced risk is seen in women with and without a genetic predisposition to ovarian cancer.

For cancer of the colorectum, the Working Group concluded that it is unlikely that the use of oral contraceptives increases the risk of cancers of the colon or rectum. The aggregate information suggests that oral contraceptives may reduce the risk of colorectal cancer.

The Working Group concluded that the use of oral contraceptives is unlikely to alter the risk of cancer of the thyroid, lung, stomach, urinary tract, gallbladder, pancreas, or the risk of lymphoma, cutaneous melanoma, and tumours of the central nervous system.

## 3. Cancer in Experimental Animals

The carcinogenicity of combined estrogen–progestogen contraceptives was extensively reviewed in the previous *IARC Monograph* (IARC, 2007). Since then, no new relevant studies have been published.

The data evaluated showed a consistent carcinogenic effect of several estrogen–progestogen combinations across different animal models in several organs.

### 3.1 Estrogen–progestogen combinations

The incidence of malignant mammary tumours was increased in female and male mice by ethinylestradiol plus megestrol acetate, in female and male rats by ethinylestradiol plus ethynodiol diacetate, and in female rats by mestranol plus norethisterone and mestranol plus norethynodrel. The incidence of benign mammary tumours was increased in male rats by ethinylestradiol plus norethisterone acetate, in intact and castrated male mice by

**Table 3.1 Effects of combinations of various estrogens and progestogens on tumour incidence in mice**

Combination	Mammary tumours			Pituitary adenomas		Uterine tumours	Cervical/vaginal tumours
	Benign		Malignant	Male	Female		
	Male	Female					
Ethinylestradiol + chlormadinone acetate	+ <sup>c</sup>						
Ethinylestradiol + ethynodiol diacetate				+	+	+ <sup>b</sup>	
Ethinylestradiol + megestrol acetate	+ <sup>a</sup>	+ <sup>a</sup>					
Ethinylestradiol + norethisterone					+		
Ethinylestradiol + norethisterone acetate				+/?	+/?		
Mestranol + chlormadinone acetate				+	+		
Mestranol + ethynodiol diacetate				+	+		
Mestranol + lynestranol			+/-				
Mestranol + norethisterone				+	+		
Mestranol + norethynodrel	c		+/?	+	+		+ <sup>b</sup>

<sup>a</sup> same study

<sup>b</sup> only one study

+, increased tumour incidence; +/-, slightly increased tumour incidence; +/c, increased tumour incidence in intact and castrated animals; c, increased tumour incidence in castrated animals; +/?, increased tumour incidence, but not greater than that with the estrogen or progestogen alone

From [IARC \(1979, 1999, 2007\)](#)

ethinylestradiol plus chlormadinone acetate, and in castrated male mice by mestranol plus norethynodrel. Ethinylestradiol plus norethisterone acetate did not cause tumour formation in any tissue in one study in female monkeys ([IARC, 1999, 2007](#); [Table 3.1](#); [Table 3.2](#)).

In female and male mice, the incidence of pituitary adenoma was increased by administration of mestranol plus chlormadinone acetate, mestranol plus ethynodiol diacetate, ethinylestradiol plus ethynodiol diacetate, mestranol plus norethisterone, ethinylestradiol plus norethisterone (females only), and mestranol plus norethynodrel. The latter combination also increased the incidence of pituitary adenomas in female rats ([IARC, 1999, 2007](#)).

In female mice, the incidence of malignant non-epithelial uterine tumours was increased by ethinylestradiol plus ethynodiol diacetate, and the incidence of vaginal or cervical tumours was increased by norethynodrel plus mestranol. In

female mice treated with 3-methylcholanthrene to induce genital tumours, ethinylestradiol plus lynestrenol, ethinylestradiol plus norgestrel, and mestranol plus norethynodrel increased the incidence of uterine tumours; however, this occurred only at the highest doses of ethinylestradiol plus lynestrenol and ethinylestradiol plus norgestrel that were tested. Lower doses inhibited tumorigenesis induced by 3-methylcholanthrene alone ([IARC, 1999, 2007](#)).

Ethinylestradiol plus norethisterone acetate and mestranol plus norethisterone increased the incidence of liver adenomas in male rats. Liver foci, which are putative preneoplastic lesions, were induced in female rats by mestranol plus norethynodrel. In female rats initiated for hepatocarcinogenesis with *N*-nitrosodiethylamine, mestranol plus norethynodrel increased the formation of altered hepatic foci ([IARC, 1999, 2007](#)).

**Table 3.2 Effects of combinations of various estrogens and progestogens on tumour incidence in rats**

Combination	Mammary tumours			Liver				Pituitary adenomas	
	Benign		Malignant	Adenomas		Carcinomas		Male	Female
	Male	Female	Male	Female	Male	Female			
Ethinylestradiol + ethynodiol diacetate			+	+					
Ethinylestradiol + megestrol acetate	+/-	+/-	+/-	+/?	+/?				
Ethinylestradiol + norethisterone acetate	+			+		-	+/-		
Ethinylestradiol + norgestrel	+/-								
Mestranol + ethynodiol diacetate			?	?					
Mestranol + norethisterone				+ <sup>a</sup>	+	-			
Mestranol + norethynodrel	+/?	+/?	+	+/?	-	-	-	+/?	+

<sup>a</sup> one study only

+, increased tumour incidence; +/-, slightly increased tumour incidence; +/?, increased tumour incidence, but not greater than that with the estrogen or progestogen alone; ? conflicting result; -, no effect

From [IARC \(1979, 1999, 2007\)](#)

In one study, subcutaneous administration of levonorgestrel with ethinylestradiol or estradiol to female rabbits clearly induced deciduosarcomas in several organs (uterus, spleen, ovary, liver, and lung) ([Jänne et al., 2001](#); [IARC, 2007](#)).

### 3.2 Estrogens

The incidence of malignant mammary tumours in female and male mice and female rats was increased by ethinylestradiol and mestranol; however, mestranol did not increase the incidence of mammary tumours in female dogs in a single study.

In female mice, ethinylestradiol alone was associated with the development of uterine cancer. Ethinylestradiol also increased the incidence of cervical tumours in female mice.

The incidence of pituitary adenomas was increased by ethinylestradiol and mestranol in female and male mice, and by ethinylestradiol in female rats.

In female and male mice, ethinylestradiol increased the incidence of hepatocellular adenomas. In female rats, ethinylestradiol and mestranol increased the numbers of altered

hepatic foci. In rats, ethinylestradiol increased the incidence of adenomas in females and males, and that of hepatocellular carcinomas in females, whereas mestranol increased the incidence of hepatic nodules and carcinomas combined in females.

The incidence of microscopic malignant kidney tumours was increased in male hamsters exposed to ethinylestradiol. In male hamsters, subcutaneous implantation of estradiol was associated with the development of renal tumours of unspecified histology.

In female mice initiated for liver carcinogenesis and exposed to unleaded gasoline, ethinylestradiol increased the number of altered hepatic foci; however, when given alone after the liver carcinogen, it reduced the number of such foci.

In female rats initiated for liver carcinogenesis, ethinylestradiol and mestranol increased the number of altered hepatic foci and the incidence of adenomas and carcinomas. Ethinylestradiol also increased the incidence of kidney adenomas, renal cell carcinomas and liver carcinomas in male rats initiated with *N*-nitrosoethyl-*N*-hydroxyethylamine. In female hamsters initiated



**Table 3.3 Effects of ethinylestradiol and mestranol on tumour incidence in mice**

Estrogen	Malignant mammary tumours		Vaginal/cervical tumours	Malignant uterine tumours	Pituitary adenomas		Liver adenomas	
	Male	Female			Male	Female	Male	Female
Ethinylestradiol	+	+	+ <sup>a</sup>	+	+	+	+	+
Mestranol					+	+	–	–

<sup>a</sup> one study only

+, increased tumour incidence; –, no effect

From [IARC \(1979, 1999, 2007\)](#)

with *N*-nitrosobis(2-oxopropyl)amine, ethinylestradiol increased the incidence of renal tumours and the multiplicity of dysplasias.

In female rabbits, subcutaneous administration of ethinylestradiol alone was associated with the proliferation of hepatic bile duct cells.

Subcutaneous injection of 2-hydroxy- and 4-hydroxyestradiol induced uterine adenocarcinomas in female mice.

Oral administration of ethinylestradiol to *p53*-deficient female mice in combination with an intraperitoneal injection of the known carcinogen *N*-ethyl-*N*-nitrosourea increased the incidence of uterine atypical hyperplasias and stromal sarcomas.

In female mice initiated with *N*-ethyl-*N'*-nitro-*N*-nitrosoguanidine, subcutaneous implantation of estradiol, estrone, estriol, 16 $\beta$ -hydroxyestrone diacetate, 16 $\alpha$ -hydroxyestrone, and 17-epiestrol increased the incidence of endometrial adenocarcinomas ([IARC, 1999, 2007](#); [Table 3.3](#); [Table 3.4](#)).

### 3.3 Progestogens

The incidence of malignant mammary tumours was increased in female mice by lynestrenol, megestrol acetate, and norethynodrel. In female rats, lynestrenol and norethisterone slightly increased the incidence of malignant mammary tumours. Norethisterone also slightly increased the incidence of malignant mammary tumours in male rats, while norethynodrel increased the incidence of both benign and malignant mammary tumours in male rats. In female dogs, chlormadinone acetate, lynestrenol and megestrol acetate increased the incidence of benign and malignant mammary tumours; however, lynestrenol had a protective effect at a low dose but enhanced tumour incidence at two higher doses. Levonorgestrel did not increase the incidence of mammary tumours in one study in dogs ([IARC, 1999, 2007](#)).

Megestrol acetate increased the incidence of liver adenomas in female mice. Cyproterone

**Table 3.4 Effects of ethinylestradiol and mestranol on tumour incidence in rats**

Estrogen	Malignant mammary tumours		Liver			Pituitary adenomas
	Female	Male	Adenomas		Female	
			Female	Male		
Ethinylestradiol	+	+	+	+	+	+
Mestranol	+ <sup>a</sup>				+/-	

<sup>a</sup> one study only

+, increased tumour incidence; –, no effect; +/-, slightly increased tumour incidence

From [IARC \(1979, 1999, 2007\)](#)

**Table 3.5 Effects of various progestogens on tumour incidence in mice**

Progestogen	Mammary tumours		Liver				Pituitary adenomas	
	<i>Benign</i>	<i>Malignant</i>	<i>Adenomas</i>		<i>Carcinomas</i>		Male	Female
	Male	Female	Male	Female	Male	Female		
Chlormadinone acetate			+/-					
Cyproterone acetate			+a	+/- <sup>a</sup>	+a	+a		
Ethinodiol diacetate	c		+/-					
Lynestrenol		+	+					
Megestrol acetate		+ <sup>b</sup>			+			
Norethisterone acetate			+/-					
Norethisterone			+/-					+
Norethynodrel	c	+			+/-		+	+

<sup>a</sup> dose exceeded the maximum tolerated dose

<sup>b</sup> one study only

+, increased tumour incidence; +/-, slightly increased tumour incidence; -, no effect; c, increased incidence in castrated males

From [IARC \(1979, 1999, 2007\)](#)

acetate increased the incidence of liver adenomas and hepatocellular carcinomas in female and male mice, but at levels that exceeded the maximum tolerated dose. In rats, the incidence of liver adenomas was increased by norethisterone acetate (females and males), norethisterone (males), norethynodrel and cyproterone acetate (females and males). The numbers of altered hepatic foci in female rats were also increased by norethisterone acetate and cyproterone acetate. In male mice treated with chlormadinone acetate, ethynodiol diacetate, lynestrenol, norethisterone or norethisterone acetate, the incidence of liver adenomas was increased. In female rats treated with *N*-nitrosodiethylamine to initiate hepatocarcinogenesis, norethynodrel increased the number of altered hepatic foci. Norethynodrel alone was shown to increase the incidence of hepatocarcinomas in male rats ([IARC, 1999, 2007](#)).

The incidence of pituitary adenomas was increased by norethisterone in female mice and by norethynodrel in female and male mice, and male rats ([IARC, 1999, 2007](#)).

In female mice treated with 3-methylcholanthrene to induce uterine tumours,

norethynodrel further increased the tumour incidence. Levonorgestrel in combination with *N*-nitrosobis(2-oxopropyl)amine did not increase the incidence of renal dysplastic lesions or tumours in female hamsters ([IARC, 1999, 2007](#)).

Oral administration of dienogest induced mammary gland proliferation in female dogs but not in female rats or monkeys ([Ishikawa et al., 2000; IARC, 2007](#)).

See [Table 3.5](#), [Table 3.6](#).

### 3.4 Synthesis

Ethinylestradiol plus ethynodiol diacetate caused malignant mammary tumours in rats. Mestranol plus norethynodrel caused malignant mammary tumours in rats. Ethinylestradiol plus levonorgestrel caused deciduosarcomas of the uterus, spleen and liver in rabbits. Estradiol plus levonorgestrel caused deciduosarcomas of the uterus, spleen, ovary, liver and lung in rabbits.

Ethinylestradiol caused malignant mammary tumours in mice and rats and liver cancer in rats. Mestranol caused malignant mammary tumours in mice.

**Table 3.6 Effects of various progestogens on tumour incidence in rats**

Progestogen	Mammary tumours			Liver		Pituitary adenomas	
	Benign	Malignant		Adenomas		Carcinomas	
	Male	Male	Female	Male	Female	Male	Male
Cyproterone acetate				+ <sup>a</sup>	+ <sup>a</sup>		
Ethinodiol diacetate	+						
Lynestrenol			+/-				
Norethisterone acetate				+	+		
Norethisterone	+/-	+/-	+/-	+			
Norethynodrel	+	+ <sup>b</sup>		+	+	+ <sup>b</sup>	+

<sup>a</sup> liver adenomas detected only at high doses

<sup>b</sup> one study only

+, increased tumour incidence; +/-, slightly increased tumour incidence; -, no effect

From [IARC \(1979, 1999, 2007\)](#)

Norethynodrel caused malignant mammary tumours in mice. Lynestrenol caused malignant mammary tumours in mice.

## 4. Other Relevant Data

### 4.1 Absorption, distribution, metabolism, and excretion

The formulations of combined hormonal contraceptives continue to evolve, especially with the introduction of new progestogens ([Practice Committee of the American Society for Reproductive Medicine, 2006](#); [Sitruk-Ware, 2006](#); [Spitz, 2006](#); [Madauss et al., 2007](#)). In general, the chemical structure of a progestogen determines its relative binding affinities for the progesterone receptor and other steroid receptors, as well as sex hormone-binding globulin, which both determine its biological effects.

Estrogenic and progestogenic compounds in oral contraceptives are readily absorbed and are metabolized to varying extents by bacterial enzymes, enzymes in the intestinal mucosa, and especially enzymes in the liver. The metabolism typically involves reduction, hydroxylation, and conjugation. First-pass metabolism through the liver reduces the overall bioavailability of oral

contraceptives. Peak concentration levels in the systemic circulation are observed between 0.5–4 hours after intake. Hydroxylated metabolites are usually conjugated as glucuronides or sulfates, and are eliminated rapidly with half-lives of 8–24 hours ([IARC, 2007](#)).

Estrogens are discussed in the Monograph on Combined Estrogen–Progestogen Menopausal Therapy ([IARC, 2007](#), and this volume).

### 4.2 Genetic and related effects

#### 4.2.1 Direct genotoxicity

Since the previous *IARC Monograph* ([IARC, 2007](#)), there is additional evidence to support the hypothesis that certain estrogens are carcinogenic through genotoxic effects in addition to their presumed action via a receptor-mediated mechanism (see also Estrogen-only Menopausal Therapy in this volume). Some of the more recent data suggest that some progestogens used in combined hormonal contraceptives may also be genotoxic. In the presence but not in the absence of liver microsomes (S9), norethynodrel induced significant increases in sister chromatid exchange and chromosomal aberrations, and reduced replication index in cultured human lymphocytes, suggesting a genotoxic effect that requires a metabolic process ([Siddique & Afzal,](#)

2005). [The Working Group noted that supratherapeutic concentrations seem to have been used in this study.] In a similarly structured study using medroxyprogesterone acetate (MPA) as the progestogen, MPA treatment of cells with S9 and NADPH were found to have significant increases in sister chromatid exchange and chromosomal aberrations. Addition of superoxide dismutase increased genotoxicity, and addition of catalase reduced genotoxicity. The results suggest that reactive oxygen species generated during drug metabolism were responsible for the genotoxicity (Siddique *et al.*, 2006a). In studies that focused on agents protecting against genotoxicity in cultured human lymphocytes, the progestogen norgestrel together with cyproterone were shown to increase sister chromatid exchange and chromosomal aberrations (Siddique *et al.*, 2006b, 2008). In an assay that detects DNA double-strand breaks by the presence of phosphorylated histone H2AX as marker for genotoxicity, norethindrone was weakly positive but only at supratherapeutic concentrations (Gallmeier *et al.*, 2005). No data were available on the genetic effects of combined exposures to estrogens and progestogens.

Triplet repeat length polymorphisms in the androgen receptor were evaluated with regard to serum testosterone levels in women, oral contraceptive use, and familial breast cancer risk. Larger numbers of GGC repeats were associated with lower testosterone levels, whereas shorter repeats, particularly if bi-allelic, were more common in women with familial excess of breast cancer. No association was found with oral contraceptive use (Hietala *et al.*, 2007).

Polymorphisms in genes for enzymes that metabolize estrogen were examined in non-Hodgkin lymphoma patients. Although there were some relationships between polymorphism and haplotypes between cases and controls, the most pronounced finding was the significant reduction of risk among female patients who had taken oral contraceptives (Skibola *et al.*, 2005).

## 4.2.2 Receptor-mediated effects

### (a) Cell proliferation

Exposure to combined hormonal contraceptives increases the proliferation of human breast epithelial cells, as observed in biopsies and fine-needle aspirate samples collected during small randomized studies (IARC, 2007). Several recent studies have evaluated the effects of progestogens alone or combined with estrogens on proliferation or proliferation-related end-points in human breast cells. MPA-alone induced proliferation and the expression of pro-proliferative gene *procyclin D1* in PR+ human breast cancer cells (Saitoh *et al.*, 2005). In normal explants of premenopausal and postmenopausal human breast tissue from reduction mammoplasty, estrogen and MPA increased the expression of pro-proliferative gene products *cyclin D1* and *Ki-67*, and decreased the expression of anti-proliferative gene products *p21* and *p27* (Eigélienè *et al.*, 2008). MPA was also shown to induce expression of *caveolin-1* in a murine breast cancer cell line, and this in turn was shown to activate the *MAPK* and *PI-3K* signalling pathways that induce cell growth (Salatino *et al.*, 2006). In studies comparing normal (MCF-10A) and malignant human breast cells (MCF-7), effects of MPA or norethisterone were compared on cells treated with estrogens and growth factors. It was found that estrogen and growth factors reduced the ratio of apoptosis to proliferation; and MPA, and to a lesser extent norethisterone, reduced this effect in both cell types (Seeger *et al.*, 2005). In MCF-10A cells and breast cancer cell line HCC1500, MPA decreased the ratio of apoptosis to proliferation, norethisterone produced a lesser decrease, and progesterone had no significant effect (Krämer *et al.*, 2005). MPA and chlormadinone acetate both induced proliferation in MCF-10A cells (Krämer *et al.*, 2006). The results of these studies indicate that progestogens increase the proliferation of breast tissue cells, and the extent of the proliferative stimulus depends on the specific



progestogen ([Seeger et al., 2005](#); [Krämer et al., 2005, 2006](#)).

In organ cultures of breast tissue, estradiol, MPA or estradiol plus MPA increased proliferation and decreased apoptosis ([Eigélienè et al., 2006](#)). MPA also stimulated proliferation in xenografts of human breast cancer cell lines grown in nude mice ([Liang et al., 2007](#)). When MCF-7 and HCC1500 cells were incubated with ethinylestradiol, a common constituent of oral contraceptives, using different durations of exposure, there was a significant increase in cell proliferation with no difference observed between two treatments ([Merki-Feld et al., 2008](#)). In another study which included breast cancer cell lines and organoid cultures of normal, benign and malignant breast, estradiol and progesterone stimulated cell proliferation while tamoxifen and mifepristone (RU486), an anti-progestogen, inhibited cell proliferation ([Calaf, 2006](#)). In a study that considered the effects of MPA, megestrol acetate, norethynodrel, and norethindrone on the expression of fatty acid synthase in ER- and PR+ MCF-7 breast cancer cells, only norethynodrel and norethindrone induced the expression significantly. This is important because fatty acid synthase is required for progestogen-induced anchorage-independent growth and survival of these cells ([Menendez et al., 2005](#)). In contrast, testosterone prevented the cell proliferation increase, determined by immunohistochemistry for Ki-67/MIB-1, in breast cells collected by fine-needle aspiration from women treated with testosterone in addition to estradiol and norethisterone ([Hofling et al., 2007](#)). In a review, the issue of the binding and activation of estrogen receptor and androgen receptor by MPA was considered in relation to breast cancer risk. It was argued that the disruptive effect of MPA may affect androgen action, and thereby reduce the cancer-protective benefits of androgen action in the breast ([Birrell et al., 2007](#)). [In a commentary on the results of the WHI study, it was suggested that choosing MPA may have contributed to the

results observed due to its side-effect profile ([Lauritzen, 2005](#)).]

These hormones have also been evaluated for their effects on cell proliferation in other tissues. Combined hormonal contraceptives have atrophic and anti-proliferative effects on the endometrium that are apparently independent of the regimen or the progestogen used ([IARC, 2007](#)). In more recent studies, endometrial biopsies from women receiving depot MPA for contraception and then treated with mifepristone were examined for ER $\alpha$ , progesterone receptors A and B, Ki-67, capsase-3, and apoptosis by TUNEL assay or immunohistochemistry. The treatment with mifepristone initially produced increased cell proliferation and decreased apoptosis, but this effect was lost on prolonged (10 weeks) treatment ([Jain et al., 2006](#)). Transient transfection of progesterone receptor into endometrial carcinoma cells followed by treatment with MPA induced the expression of anti-proliferative proteins p21 and p27 ([Kawaguchi et al., 2006](#)). Proliferation of human ovarian cancer cells (OVCAR-3) was stimulated by both low and high concentrations of mifepristone and progesterone ([Fauvet et al., 2006](#)). In another study with OVCAR-3 cells, treatments with progesterone, MPA, and norethisterone were evaluated for their effects on proliferation and on growth-factor-induced cell proliferation. MPA and norethisterone but not progesterone induced cell proliferation without growth-factor induction; with growth factors, MPA but not norethisterone or progesterone inhibited proliferation ([Seeger et al., 2006](#)). Progesterone receptors A and B were evaluated in the fallopian tube and uterus of mice treated with progesterone. Progesterone reduced progesterone receptors A and B expression in both tissues and decreased p27, cyclin D2, and proliferating cell nuclear antigen only in the uterus. Treatment with anti-progestogens increased progesterone receptors A and B, and induced apoptosis ([Shao et al., 2006](#)).

The effects of progesterone and mifepristone on cell proliferation were examined in two astrocytoma cell lines. Progesterone increased cell proliferation, mifepristone reduced cell proliferation when used alone and decreased progesterone-induced proliferation. The effects of mifepristone were not the result of apoptosis ([González-Agüero \*et al.\*, 2007](#)). In rat liver, ethinylestradiol reduced the number of cycling cells together with a reduction of pro-proliferative markers and an increase in anti-proliferative gene expression consistent with a cell-cycle block before S-phase ([Koroxenidou \*et al.\*, 2005](#)). In male rats treated with estradiol, in addition to a reduction of the differentiation of sperm, there was a rise in lipid peroxidation, a fall in catalase and superoxide dismutase, and a rise in cells showing signs of apoptosis in the testicular tissue ([Chaki \*et al.\*, 2006](#)).

Estrogens or progestogens may enhance HPV gene expression in the human cervix via progesterone-receptor mechanisms, and hormone-response elements in the viral genome. In-vitro studies support this concept, and mechanisms other than those that are receptor-mediated may be involved. Experiments in transgenic mouse models that express HPV-16 genes in the cervix showed that estrogens can cause cervical cancer, probably via a receptor-mediated process. This effect was diminished after cessation of treatment with estrogens ([IARC, 2007](#)). There are a few new reports on the increase in incidence of squamous cell carcinoma of the cervix among users of oral contraceptives. In a report comparing COX-2 protein concentrations in biopsies of cervical lesions and normal tissue from a small group of patients, there was a much greater quantity of COX-2 protein in CIN1 and CIN2 lesions than in controls, but there were no significant associations with oral contraceptive use ([Saldivar \*et al.\*, 2007](#)). In an uncontrolled study of 80 cervical cancer patients, oral contraceptive use was not associated with any of the several tumour markers investigated. In contrast, strong c-myc

staining was associated with high concentrations of progesterone; low epithelial growth factor receptor staining was associated with high concentrations of estradiol in serum, and current smoking was strongly associated with an absence of p53 staining ([Lindström \*et al.\*, 2007](#)).

It was proposed that the thick and viscous cervical mucus of oral contraceptive users might prolong contact of the cervix with carcinogenic agents ([Güven \*et al.\*, 2007](#)).

Ethinylestradiol plus levonorgestrel induces ovarian epithelial cell apoptosis in intact monkeys ([Rodriguez \*et al.\*, 2002](#)).

Colon carcinogenesis in animal models is inhibited by estrogens, and there is adequate evidence to suggest that estrogens have inhibitory effects on colon cancer cells via ER $\beta$  ([IARC, 2007](#)).

#### (b) Cell differentiation

Recent reports have considered the effects of hormones in oral contraceptives on the regulation of expression of several gene products. Progesterone-induced blocking factor was shown to be induced by progesterone and this induction was counteracted by mifepristone in several cell populations ([Srivastava \*et al.\*, 2007](#)). Estradiol and progesterone inhibited the expression of gonadotropin-releasing hormone I receptor in a gonadotroph-derived cell line  $\alpha$ -T3-1 ([Weiss \*et al.\*, 2006](#)). Expression of breast cancer resistance protein was downregulated by estradiol in an ER-related manner whereas progesterone or progesterone plus estradiol upregulated breast cancer resistance protein, but these effects of progesterone appeared to be independent of progesterone receptors ([Wang \*et al.\*, 2006](#)). In mouse mammary tumour cell lines, MPA treatment strongly induced the expression of signal transducer and activator of transcription (Stat) and its binding to DNA; mifepristone inhibited induction ([Proietti, \*et al.\*, 2005](#)). In a gene expression microarray study of several synthetic progestogens used in oral contraceptives, the

altered pattern of genes expression induced by progestogen were quite comparable among the progestogens tested; drospirenone, a spironolactone analogue, had the most divergent profile ([Bray et al., 2005](#)). In ER- and PR+ MCF-7 cells, the effects of 4-hydroxytamoxifen alone or in combination with mifepristone were evaluated in relation to the expression of retinoblastoma protein. The combined treatment had cytostatic and cytotoxic effects; the apoptotic cytotoxic effect was mediated by a drug-induced decrease of retinoblastoma protein ([Schoenlein et al., 2007](#)). In human T47D breast cancer cells, treatment with progesterone or MPA, with or without estradiol, increased the expression of myoepithelial cytokeratins, which is indicative of a luminal epithelial to myoepithelial transition ([Sartorius et al., 2005](#)). Human breast cancer cells were treated with estradiol plus progestogens either continuously or in a sequential combined regimen, and the expression of estrogen-activating and -inactivating enzymes were evaluated. MPA, and to a lesser extent progesterone, induced the mRNA and protein expression of estrogen-activating genes but did not influence the expression of estrogen-inactivating enzymes. Levonorgestrel, norethindrone and dienogest had no detectable effect on either type of enzymes. This raises the question of whether MPA might be associated with a higher risk of breast cancer than other progestogens ([Xu et al., 2007](#)). Matrix metalloproteinases (MMP) 2 and 9 were evaluated in T47D breast cancer cells treated with combinations of estradiol–progesterone or estradiol–MPA, and in MCF-7 breast cancer cells treated with estradiol–progesterone, estradiol–MPA or equilin–MPA. All treatments increased MMP-2 in both cell types and MMP-9 in MCF-7 cells. Only one combined treatment was found to increase MMP-9 in T47D cells ([Abdallah et al., 2007](#)).

Endometrial specimens from women treated with progestogens for hyperplasia, with either MPA administered systemically or with a

levonorgestrel intrauterine device, were evaluated for expression of Bcl-2 (anti-apoptotic) and BAX (pro-apoptotic) by immunohistochemistry and apoptosis using the TUNEL method. The levonorgestrel intrauterine device reversed all hyperplasias whereas with MPA only 50% hyperplasias were reversed. Both treatments reduced glandular Bcl-2 expression with increased apoptosis upon prolonged therapy; in each case, the effects of the levonorgestrel intrauterine device therapy exceeded those of the systemic MPA ([Vereide et al., 2005](#)). In a similar study, progestogen therapy reduced the expression of progesterone receptor A, progesterone receptor B, ER $\alpha$  and ER $\beta$  in the endometrium with the effects of the levonorgestrel intrauterine device exceeding those of MPA ([Vereide et al., 2006](#)). In a review considering the effects of levonorgestrel intrauterine devices on the endometrium, treatment was associated with decidualization of the stromal cells, atrophy of glandular and surface epithelial cells, downregulation of sex steroid receptors with perturbation of locally acting progesterone-regulated mediators ([Guttinger & Critchley, 2007](#)). MPA enhanced expression of Forkhead Transcription Factor FOXO1 in differentiating human endometrial stromal cells with induction of cytoplasmic retention and inactivation. Upon withdrawal of MPA, FOXO1 accumulated in the nucleus, the expression of *BIM*, a pro-apoptotic target gene, was induced, and cell death occurred ([Labied et al., 2006](#)). Endometrial epithelial and stromal cells were treated with estradiol, MPA and the combination of estradiol and MPA, and the expression of interleukins (IL) 13 and 15 were evaluated. All hormone treatments induced expression of IL-13 and IL-15 but with some cell- and hormone-related variations, affecting proliferation- and inflammation-related functions ([Roberts et al., 2005](#)).

In a gene-expression microarray study of a human endometrial epithelial cell line, treatments with estradiol, MPA, estradiol plus MPA, or tibolone were compared. Tibolone-induced

gene-expression profiles resembled those found after MPA treatment ([Hanifi-Moghaddam et al., 2006](#)). Endometrial carcinoma cells made resistant to the growth-suppressive effect of progesterone by prolonged culture with progesterone were evaluated for expression of ER $\alpha$ , ER $\beta$ , and PR-B as well as transforming growth factor  $\alpha$ , and epidermal growth factor receptor. Chronic exposure to progesterone reduced the expression of ER $\alpha$  and PR-B, and increased the expression of ER $\beta$ , transforming growth factor  $\alpha$ , and epidermal growth factor receptor ([Zhao et al., 2007](#)).

### (c) Other effects

Exposure to exogenous hormones affects the proliferative activity and quantity of stromal and epithelial tissue in the breast, thereby increasing breast density assessed by mammography, a factor highly correlated with breast cancer risk ([Boyd et al., 2006](#)). In a study in Norwegian women, there was a significant dose-dependent increase in mammographic density in current users of estradiol plus norethisterone ([Bremnes et al., 2006](#)). In a related Norwegian study, in this case only considering women not currently using exogenous hormone therapy, there was an association between breast density and plasma steroid hormone-binding globulin concentration, and a weaker association with plasma estrone concentrations ([Bremnes et al., 2007](#)). In another Norwegian study, lower prevalence of mammary ductal hyperplasia in women was associated with current long-term (8 years or more) oral contraceptive use, while the onset of oral contraceptive use after the age of 35 years was associated with an increased prevalence of ductal carcinoma *in situ* ([Vamre et al., 2006](#)). The effect of hormonal contraceptives on steroid hormone receptors in biopsies of the vaginal epithelium was investigated in a Swedish study. The progesterone receptor level was significantly reduced in women receiving depot MPA as compared to controls or women receiving levonorgestrel

implants or oral contraceptives. In addition, the estrogen receptor level was significantly elevated in women treated with depot MPA, and all treatments reduced serum estradiol levels ([Ildgruben et al., 2005](#)). In review articles on human hepatic adenoma, the relationship between this lesion and oral contraceptive use has been considered. The frequency of this rare benign tumour is greater in young women and women with a history of oral contraceptive use. There is a relationship between duration of use and risk ([Giannitrapani et al., 2006](#); [Lizardi-Cervera et al., 2006](#)). Use of MPA did not have a significant effect on risk of high-grade cervical intra-epithelial neoplasia in young women ([Massad et al., 2005](#)).

## 4.3 Synthesis

Hormone-receptor-mediated responses are probably a necessary mechanism for hormonal carcinogenesis by combined estrogen-progestogen oral contraceptives. Progestogens including those used for combined estrogen-progestogen oral contraceptives appear to have the capacity to stimulate cell proliferation in human breast cells and to inhibit proliferation in human endometrial cells. The magnitude of these effects vary for different synthetic progestogens. Because estrogen mediates the expression of progesterone-receptor expression, the presence of estrogen in these combined estrogen-progestogen oral contraceptives may be essential for progestogen-mediated cell proliferation. Combined estrogen-progestogen oral contraceptives were also shown to produce increased radiological breast density, and increased proliferation of cells removed from the breast by needle biopsy. In animal models, estrogen potentiated cervical cancer, and inhibited colon cancer development.

There is also support for the involvement of genotoxic effects of the metabolic by-products of estrogenic hormones in combined estrogen-progestogen oral contraceptives or of the reactive oxygen species generated in response to them.



The estrogenic metabolites can bind to DNA, and the reactive oxygen species can also damage DNA. There are also some data consistent with some genotoxic effects of progestogens.

Current evidence suggests that the predominant effects of combined estrogen–progestogen oral contraceptives associated with hormonal carcinogenesis occur via one or more receptor-mediated process.

Cessation of hormonal treatment may reduce some receptor-mediated effects. It is plausible that hormone-induced genotoxic effects may be persistent.

## 5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of combined estrogen–progestogen oral contraceptives. Combined estrogen–progestogen oral contraceptives cause cancer of the breast, in-situ and invasive cancer of the uterine cervix, and cancer of the liver.

For cancer of the endometrium, ovary, and colorectum, there is *evidence suggesting lack of carcinogenicity*. An inverse relationship has been established between exposure to combined estrogen–progestogen oral contraceptives and cancer of the endometrium, ovary, and colorectum.

There is *sufficient evidence* in experimental animals for the carcinogenicity of several combinations of estrogen–progestogen used in oral contraceptives.

Combined estrogen–progestogen oral contraceptives are *carcinogenic to humans (Group 1)*.

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