

COMBINED ESTROGEN–PROGESTOGEN CONTRACEPTIVES

Combined Oral Estrogen–Progestogen Contraceptives (Group 1)

VOL.: 91

5. Summary of Data Reported and Evaluation

5.1 Exposure data

The first oral hormonal contraceptives that were found to inhibit both ovulation and implantation were developed in the 1950s and included both estrogen and progestogen. Since that time, changes in component ingredients, doses used and the temporal sequencing of exposure to hormones have occurred with emerging technologies and in an effort to reduce adverse effects. The dominant trends in recent years have been towards the use of lower doses of estrogen, use of progestogens that are less androgenic, the multiplication of product formulations and the continuing development of novel delivery systems. In current preparations, ethinylestradiol is the most common estrogen, although a variety of other estrogens is also available. An even greater range of progestogens is used. The estrogen and progestogen components are usually given together orally in a monthly cycle, e.g. 21 days of constant or varying doses followed by 7 days without hormones. Combined hormonal contraceptives can also be administered by injection, transdermal patch and vaginal device. In addition to their regular use for contraception, other common indications for these products include emergency contraception, and the treatment of acne and menstrual disorders. Some commonly used formulations, doses, routes of administration and schedules of exposure are new and their possible long-term adverse effects have not been evaluated.

Worldwide, more than 100 million women — an estimated 10% of all women of reproductive age — currently use combined hormonal contraceptives, a large majority of which are in the form of oral preparations. Current use of these drugs is greatest in developed countries (16%) and is lower in developing countries (6%). Rates of ‘ever use’ higher than 80% have been reported for some developed countries. In developing countries, 32% of women were estimated to have ever used hormonal contraception. Overall, the use of combined hormonal contraception is increasing, but there is extreme variability between countries. In many countries, these preparations are mainly used by women of younger age and higher level of education, and who have greater access to health care.

5.2 Human carcinogenicity data

Breast cancer

More than 10 cohort studies and 60 case–control studies that included over 60 000 women with breast cancer reported on the relationship between the oral use of combined hormonal contraceptives and the risk for this disease. The totality of the evidence suggested an increase in the relative risk for 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. By 10 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

1 used them. Important known risk factors did not appear to account for the association. The
2 possibility that the association seen for current and recent users is due to detection bias was
3 not ruled out, but it was considered to be unlikely that this would explain the association
4 observed in young women.

5
6 *Endometrial cancer*
7

8 Four cohort studies and 21 case–control studies reported on the relationship between
9 the oral use of combined hormonal contraceptives and the risk for endometrial cancer. The
10 results of these studies consistently showed that the risk for endometrial cancer in women
11 who had taken these medications is approximately halved. The reduction in risk was generally
12 greater with longer duration of use of combined hormonal contraceptives and persisted for at
13 least 15 years after cessation of use, although the extent of the protective effect may wane
14 over time. Few data were available on the more recent, low-dose formulations.

15
16 *Cervical cancer*
17

18 Five cohort and 16 case–control studies of the oral use of combined hormonal
19 contraceptives and invasive cervical cancer were reviewed in the previous Monograph on this
20 topic. That Working Group could not rule out biases related to sexual behaviour, screening
21 and other factors as possible explanations for the observed association with increasing
22 duration of use.

23
24 Since that time, two cohort and seven case–control studies have provided new
25 information on invasive or in-situ carcinoma and oral use of combined hormonal
26 contraceptives; all but the three most recent studies were summarized in a meta-analysis of
27 published data. The totality of the evidence indicated that, overall, the risk for cervical cancer
28 increased with increasing duration of use of combined hormonal contraceptives, and was
29 somewhat greater for in-situ than for invasive cancer. The relative risk appeared to decline
30 after cessation of use. The results were broadly similar regardless of adjustment for the
31 number of sexual partners, cervical screening, smoking and the use of barrier contraceptives.
32 The association was found in studies conducted in both developed and developing countries.
33 The possibility that the observed association is due to detection bias was not ruled out, but it
34 was considered to be unlikely that this would explain the increase in risk. Studies in which
35 information on human papillomavirus infection — the main cause of cervical cancer — was
36 available suggested that the prevalence of the infection was not increased among users of
37 combined hormonal contraceptives, and the association with cervical cancer was also
38 observed in analyses that were restricted to human papillomavirus-positive cases and controls.

39
40 *Ovarian cancer*
41

42 Data from an additional three cohort and 20 case–control studies that had been
43 updated since the last Monograph or were new showed that women who had ever used
44 combined hormonal contraceptives orally had an overall reduced risk for ovarian cancer and
45 that an inverse relationship was observed with duration of use. The reduced risk appeared to
46 persist for at least 20 years after cessation of use. The effect of combined hormonal
47 contraceptives on the reduction of risk for ovarian cancer is not confined to any particular
48 type of oral formulation nor to any histological type of ovarian cancer, although it is less
49 consistent for mucinous than for other types in several studies.
50

1 *Cancer of the liver*

2
3 Long-term oral use of combined hormonal contraceptives was associated with an
4 increase in the risk for hepatocellular carcinoma in all nine case–control studies conducted in
5 populations with low prevalences of hepatitis B viral infection and chronic liver disease —
6 which are major causes of liver cancer — and in analyses in which women with such
7 infections were excluded. Three cohort studies showed no significant association between the
8 oral use of combined hormonal contraceptives and the incidence of or mortality from liver
9 cancer, but the expected number of cases was very small, resulting in low statistical power.
10 Few data were available for the more recent, low-dose formulations. In the three case–control
11 studies conducted in populations with a high prevalence of infection with hepatitis viruses,
12 there was no statistically significant increase in the risk for hepatocellular carcinoma
13 associated with the oral use of combined hormonal contraceptives, but little information was
14 available on long-term use.

15
16 *Cutaneous melanoma*

17
18 Four cohort and 16 case–control studies provided information on the oral use of
19 combined hormonal contraceptives and the risk for cutaneous malignant melanoma. No
20 consistent evidence for an association was found with respect to current use, duration of use,
21 time since last use or age at first use. The few studies that suggested an increase in risk may
22 reflect the possibility that women who took oral contraceptives may have had more contacts
23 with the medical system and were thus more likely to have had pigmented lesions removed.

24
25 *Colorectal cancer*

26
27 Seven cohort and 13 case–control studies provided information on the oral use of
28 combined hormonal contraceptives and the risk for colorectal cancer. Most studies did not
29 show an increase in risk in women who had ever used contraceptives or in relation to duration
30 of use. The results were generally similar for colon and rectal cancer when examined
31 separately, and two case–control studies showed a significant reduction in risk.

32
33 **5.3 Carcinogenicity in experimental animals**

34
35 The data evaluated in this section showed a consistent carcinogenic effect of several
36 estrogen–progestogen combinations across different animal models in several organs. There
37 was not enough evidence of carcinogenicity for one of the newer progestogens studied,
38 dienogest.

39
40 *Estrogen–progestogen combinations*

41
42 In female and male mice, the incidences of pituitary adenoma were increased by
43 administration of mestranol plus chlormadinone acetate, mestranol plus ethynodiol diacetate,
44 ethinylestradiol plus ethynodiol diacetate, mestranol plus norethisterone, ethinylestradiol plus
45 norethisterone (females only) and mestranol plus norethynodrel, which also increased the
46 incidence of pituitary adenomas in female rats.

47
48 The incidence of benign mammary tumours was increased in female and male mice by
49 ethinylestradiol plus megestrol acetate, in female and male rats by ethinylestradiol plus
50 ethynodiol diacetate, in female rats by mestranol plus norethisterone, mestranol plus

1 norethynodrel and ethinylestradiol plus norethisterone acetate, in intact and castrated male
2 mice by ethinylestradiol plus chlormadinone acetate and in castrated male mice by mestranol
3 plus norethynodrel. Ethinylestradiol plus norethisterone acetate did not cause tumour
4 formation in any tissue in one study in female monkeys.
5

6 In female mice, the incidence of malignant non-epithelial uterine tumours was
7 increased by ethinylestradiol plus ethynodiol diacetate and the incidence of vaginal or cervical
8 tumours by norethynodrel plus mestranol. In female mice treated with 3-methylcholanthrene
9 to induce genital tumours, ethinylestradiol plus lynestrenol, ethinylestradiol plus norgestrel
10 and mestranol plus norethynodrel increased the incidence of uterine tumours; however, this
11 occurred only at the highest doses of ethinylestradiol plus lynestrenol and ethinylestradiol
12 plus norgestrel that were tested. Lower doses inhibited tumorigenesis induced by 3-
13 methylcholanthrene alone.
14

15 In female rats, the incidence of hepatocellular carcinomas was increased by
16 ethinylestradiol plus norethisterone acetate; the latter combination and mestranol plus
17 norethisterone also increased the incidence of liver adenomas in male rats. Liver foci, which
18 are putative preneoplastic lesions, were induced in female rats by mestranol plus
19 norethynodrel. In female rats initiated for hepatocarcinogenesis with *N*-nitrosodiethylamine,
20 mestranol plus norethynodrel increased the formation of altered hepatic foci.
21

22 In one study, subcutaneous administration of levonorgestrel with ethinylestradiol or
23 estradiol to female rabbits induced deciduosarcomas in several organs (uterus, spleen, ovary,
24 liver and lung).
25

26 *Estrogens*

27

28 The incidence of pituitary adenomas was increased by ethinylestradiol and mestranol
29 in female and male mice and by ethinylestradiol in female rats.
30

31 The incidences of malignant mammary tumours in female and male mice and female
32 rats were increased by ethinylestradiol and mestranol; however, mestranol did not increase the
33 incidences of mammary tumours in female dogs in a single study.
34

35 Ethinylestradiol increased the incidence of cervical tumours in female mice.
36

37 In female and male mice, ethinylestradiol increased the incidences of hepatocellular
38 adenomas. In female rats, ethinylestradiol and mestranol increased the numbers of altered
39 hepatic foci. In rats, ethinylestradiol increased the incidence of adenomas in females and
40 males and of hepatocellular carcinomas in females, whereas mestranol increased the incidence
41 of hepatic nodules and carcinomas combined in females.
42

43 The incidence of microscopic malignant kidney tumours was increased in male
44 hamsters exposed to ethinylestradiol.
45

46 In female mice initiated for liver carcinogenesis and exposed to unleaded gasoline,
47 ethinylestradiol increased the number of altered hepatic foci; however, when given alone after
48 the liver carcinogen, it reduced the number of spontaneous foci.
49

1 In female rats initiated for liver carcinogenesis, ethinylestradiol and mestranol
2 increased the number of altered hepatic foci and the incidences of adenomas and carcinomas.
3 Ethinylestradiol also increased the incidences of kidney adenomas, renal-cell carcinomas and
4 liver carcinomas in male rats initiated with *N*-nitrosoethyl-*N*-hydroxyethylamine. In hamsters
5 initiated with *N*-nitrosobis(2-oxopropyl)amine, ethinylestradiol increased the incidence of
6 renal tumours and the multiplicity of dysplasias.

7
8 In female rabbits, subcutaneous administration of ethinylestradiol alone was
9 associated with the proliferation of hepatic bile duct cells.

10
11 In female mice, subcutaneous administration of ethinylestradiol alone was associated
12 with the development of uterine adenocarcinomas. In male hamsters, subcutaneous
13 implantation of ethinylestradiol in combination with menadione was associated with the
14 development of renal tumours of unspecified histology.

15
16 Oral administration of ethinylestradiol to p53-deficient female mice in combination
17 with an intraperitoneal injection of the known carcinogen, *N*-ethyl-*N*-nitrosourea, increased
18 the incidence of uterine atypical hyperplasias and stromal sarcomas.

19
20 Subcutaneous injection of estradiol induced uterine adenocarcinomas in female mice
21 and subcutaneous implantation of estradiol induced renal tumours in male hamsters.

22
23 In female mice initiated with *N*-ethyl-*N'*-nitro-*N*-nitrosoguanidine, subcutaneous
24 implantation of estradiol, estrone, estriol, 16 β -hydroxyestrone diacetate, 16 α -hydroxyestrone
25 and 17-epiestrol increased the incidence of endometrial adenocarcinomas.

26 27 *Progestogens*

28
29 The incidence of pituitary adenomas was increased by norethisterone in female mice
30 and by norethynodrel in female and male mice and male rats.

31
32 The incidence of malignant mammary tumours was increased in female mice by
33 lynestrenol, megestrol acetate and norethynodrel. In female rats, lynestrenol and
34 norethisterone slightly increased the incidence of malignant mammary tumours.
35 Norethisterone also slightly increased the incidence of malignant mammary tumours in male
36 rats, while norethynodrel increased the incidence of both benign and malignant mammary
37 tumours in male rats. In female dogs, chlormadinone acetate, lynestrenol and megestrol
38 acetate increased the incidence of benign and malignant mammary tumours; however,
39 lynestrenol had a protective effect at a low dose, but enhanced tumour incidence at two higher
40 doses. Levonorgestrel did not increase the incidence of mammary tumours in one study in
41 dogs.

42
43 In female mice treated with 3-methylcholanthrene to induce uterine tumours,
44 norethynodrel further increased the tumour incidence.

45
46 Megestrol acetate increased the incidence of liver adenomas in female mice.
47 Cyproterone acetate increased the incidences of liver adenomas and hepatocellular
48 carcinomas in female and male mice, but at doses exceeding the maximum tolerated dose. In
49 rats, the incidence of liver adenomas was increased by norethisterone acetate (females and
50 males), norethisterone (males), norethynodrel and cyproterone acetate (females and males).

1 The numbers of altered hepatic foci in female rats were also increased by norethisterone
2 acetate and cyproterone acetate. In male mice treated with chlormadinone acetate, ethynodiol
3 diacetate, lynestrenol, norethisterone or norethisterone acetate, the incidence of liver
4 adenomas was increased. In female rats treated with *N*-nitrosodiethylamine to initiate
5 hepatocarcinogenesis, norethynodrel increased the number of altered hepatic foci.
6 Norethynodrel alone was shown to increase the incidence of hepatocarcinomas in male rats.
7

8 Levonorgestrel in combination with *N*-nitrosobis(2-oxopropyl)amine did not increase
9 the incidence of renal dysplastic lesions or tumours in hamsters.

10
11 Oral administration of dienogest induced mammary gland proliferation in female dogs
12 but not in female rats or monkeys.

13 14 **5.4 Other relevant data**

15 16 *Absorption, distribution, metabolism, and excretion*

17
18 Estrogenic and progestogenic compounds in oral contraceptives are readily absorbed
19 and undergo metabolism to varying extents by bacterial enzymes, enzymes in the intestinal
20 mucosa and especially those in the liver. The metabolism typically involves reduction,
21 hydroxylation and conjugation. The so-called ‘first-pass’ through the liver reduces the overall
22 bioavailability of oral contraceptives. Peak concentration levels in the systemic circulation are
23 observed between 0.5 and 4 h after intake. Hydroxylated metabolites are usually conjugated
24 as glucuronides or sulfates and are eliminated rapidly with half-lives of 8–24 h.
25

26 The formulations of combined hormonal contraceptives continue to evolve, especially
27 with the introduction of new progestogens. In general, the chemical structure of a progestogen
28 determines its relative binding affinities for the progesterone and other steroid receptors, as
29 well as sex hormone-binding globulin, which determine its biological effects. The logic
30 involved in the development of newly synthesized progestogens, such as dienogest and
31 drospirenone, is that they are devoid of estrogenic, androgenic and antagonist effects.
32

33 Estrogens are described in the Monograph on Combined estrogen–progestogen
34 menopausal therapy.

35 36 *Receptor-mediated effects*

37
38 Exposure to combined hormonal contraceptives increases the proliferation of human
39 breast epithelial cells, as observed in biopsies and fine-needle aspirate samples collected
40 during small randomized studies. Combined hormonal contraceptives have atrophic and anti-
41 proliferative effects on the endometrium that are apparently independent of the regimen and
42 the progestogen used. Ethinylestradiol plus levonorgestrel induces ovarian epithelial apoptosis
43 in intact monkeys. Estrogen or progestogens may enhance human papillomavirus gene
44 expression in the human cervix via progesterone-receptor mechanisms and hormone-response
45 elements in the viral genome. In-vitro studies support this notion, and mechanisms other than
46 those that are receptor-mediated may be involved. Experiments in transgenic mouse models
47 that express human papillomavirus 16 genes in the cervix showed that estrogens can cause
48 cervical cancer, probably via receptor-mediated processes. This effect was diminished after
49 cessation of treatment with estrogen. Colon carcinogenesis in animal models is inhibited by
50 estrogens and there is adequate evidence to suggest that estrogens have inhibitory effects on

1 colon cancer cells via estrogen receptor- β . Various studies document the possibility of
2 complex interactions of combined hormonal contraceptives with hormonal systems. No data
3 were available to the Working Group on time since cessation of treatment or duration of
4 treatment.

5 6 *Genetic and related effects*

7
8 There is additional evidence to support the conjecture that certain estrogens function
9 as directly acting genotoxins. These findings give further credence to the hypothesis that
10 certain estrogens are carcinogenic through direct genotoxic effects in addition to their
11 presumed action via a receptor-mediated mechanism. Some of the more recent genotoxicity
12 data suggest that some progestogens used in combined hormonal contraceptives may also act
13 as direct genotoxins. Few data were available that considered the effects of combined
14 exposures to estrogens and progestogens.

15 16 **5.5 Evaluation**

17
18 There is *sufficient evidence* in humans for the carcinogenicity of combined oral
19 estrogen-progestogen contraceptives. This evaluation was made on the basis of increased risks
20 for cancer of the breast among current and recent users only, for cancer of the cervix and for
21 cancer of the liver in populations that are at low risk for hepatitis B viral infection.

22
23 There is *evidence suggesting lack of carcinogenicity* in humans for combined oral
24 estrogen-progestogen contraceptives in the endometrium, ovary and colorectum. There is
25 convincing evidence in humans for their protective effect against carcinogenicity in the
26 endometrium and ovary.

27
28 There is *sufficient evidence* in experimental animals for the carcinogenicity of the
29 combinations of ethinylestradiol plus ethynodiol diacetate, mestranol plus norethynodrel,
30 ethinylestradiol plus levonorgestrel and estradiol plus levonorgestrel.

31
32 There is *sufficient evidence* in experimental animals for the carcinogenicity of the
33 estrogens ethinylestradiol and mestranol.

34
35 There is *sufficient evidence* in experimental animals for the carcinogenicity of the
36 progestogens norethynodrel and lynestrenol.

37
38 There is *limited evidence* in experimental animals for the carcinogenicity of the
39 combinations of ethinylestradiol plus megestrol acetate, mestranol or ethinylestradiol plus
40 chlormadinone acetate, mestranol plus ethynodiol diacetate, mestranol plus lynestrenol,
41 mestranol or ethinylestradiol plus norethisterone and ethinylestradiol plus norgestrel.

42
43 There is *limited evidence* in experimental animals for the carcinogenicity of the
44 progestogens chlormadinone acetate, cyproterone acetate, ethynodiol diacetate, megestrol
45 acetate, norethisterone acetate and norethisterone.

46
47 There is *inadequate evidence* in experimental animals for the carcinogenicity of the
48 progestogens levonorgestrel, norgestrel and dienogest.

1
2 **Overall evaluation**
3

4 Combined oral estrogen-progestogen contraceptives are *carcinogenic to humans*
5 (*Group 1*). There is also convincing evidence in humans that these agents confer a protective effect
6 against cancer in the endometrium and ovary.
7

8
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10

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