COMBINED ESTROGEN–PROGESTOGEN CONTRACEPTIVES Combined Oral Estrogen–Progestogen Contraceptives (Group 1)

4 **VOL.**: 91

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5. Summary of Data Reported and Evaluation

5.1 Exposure data

8 9 The first oral hormonal contraceptives that were were found to inhibit both ovulation 10 and implantation were developed in the 1950s and included both estrogen and progestogen. 11 Since that time, changes in component ingredients, doses used and the temporal sequencing of 12 exposure to hormones have occurred with emerging technologies and in an effort to reduce 13 adverse effects. The dominant trends in recent years have been towards the use of lower doses 14 of estrogen, use of progestogens that are less androgenic, the multiplication of product 15 formulations and the continuing development of novel delivery systems. In current 16 preparations, ethinylestradiol is the most common estrogen, although a variety of other 17 estrogens is also available. An even greater range of progestogens is used. The estrogen and 18 progestogen components are usually given together orally in a monthly cycle, e.g. 21 days of 19 constant or varying doses followed by 7 days without hormones. Combined hormonal 20 contraceptives can also be administered by injection, transdermal patch and vaginal device. In 21 addition to their regular use for contraception, other common indications for these products 22 include emergency contraception, and the treatment of acne and menstrual disorders. Some 23 commonly used formulations, doses, routes of administration and schedules of exposure are 24 new and their possible long-term adverse effects have not been evaluated. 25

26 Worldwide, more than 100 million women — an estimated 10% of all women of 27 reproductive age — currently use combined hormonal contraceptives, a large majority of 28 which are in the form of oral preparations. Current use of these drugs is greatest in developed 29 countries (16%) and is lower in developing countries (6%). Rates of 'ever use' higher than 30 80% have been reported for some developed countries. In developing countries, 32% of 31 women were estimated to have ever used hormonal contraception. Overall, the use of 32 combined hormonal contraception is increasing, but there is extreme variability between 33 countries. In many countries, these preparations are mainly used by women of younger age 34 and higher level of education, and who have greater access to health care.

36 5.2 Human carcinogenicity data

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38 Breast cancer39

40 More than 10 cohort studies and 60 case–control studies that included over 60 000 41 women with breast cancer reported on the relationship between the oral use of combined 42 hormonal contraceptives and the risk for this disease. The totality of the evidence suggested 43 an increase in the relative risk for breast cancer among current and recent users. This effect 44 was noted particularly among women under 35 years of age at diagnosis who had begun using 45 contraceptives when young (< 20 years), whereas the increased risk declined sharply with 46 older age at diagnosis. By 10 years after cessation of use, the risk in women who had used 47 combined hormonal contraceptives appeared to be similar to that in women who had never

used them. 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 that this would explain the association
observed in young women.

Endometrial cancer

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

16 *Cervical cancer*17

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

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 available suggested that the prevalence of the infection was not increased among users of 36 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.

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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.

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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.

16 Cutaneous melanoma

Four cohort and 16 case–control studies provided information on the oral use of combined hormonal contraceptives and the risk for cutaneous malignant melanoma. 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 few studies that suggested an increase in risk may reflect the possibility that women who took oral contraceptives may have had more contacts with the medical system and were thus more likely to have had pigmented lesions removed.

Colorectal cancer

Seven cohort and 13 case-control studies provided information on the oral use of
combined hormonal contraceptives and the risk for colorectal cancer. Most studies did not
show an increase in risk in women who had ever used 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.

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5.3 Carcinogenicity in experimental animals

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

3940 Estrogen-progestogen combinations

In female and male mice, the incidences of pituitary adenoma were 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, which also increased the
incidence of pituitary adenomas in female rats.

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

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norethynodrel and ethinylestradiol plus norethisterone acetate, in intact and castrated male
 mice by 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.

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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.

In female rats, the incidence of hepatocellular carcinomas was increased by ethinylestradiol plus norethisterone acetate; the latter combination and mestranol plus norethisterone also 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.

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

Estrogens

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

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

Ethinylestradiol increased the incidence of cervical tumours in female mice.

In female and male mice, ethinylestradiol increased the incidences 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 of hepatocellular carcinomas in females, whereas mestranol increased the incidence
of hepatic nodules and carcinomas combined in females.

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

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

8 In female rabbits, subcutaneous administration of ethinylestradiol alone was
9 associated with the proliferation of hepatic bile duct cells.
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In female mice, subcutaneous administration of ethinylestradiol alone was associated
 with the development of uterine adenocarcinomas. In male hamsters, subcutaneous
 implantation of ethinylestradiol in combination with menadione was associated with the
 development of renal tumours of unspecified histology.

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.

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

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

Progestogens

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The incidence of pituitary adenomas was increased by norethisterone in female mice 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

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

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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

adenomas was increased. In female rats treated with *N*-nitrosodiethylamine to initiate
hepatocarcinogenesis, norethynodrel increased the number of altered hepatic foci.

6 Norethynodrel alone was shown to increase the incidence of hepatocarcinomas in male rats.

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

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

5.4 Other relevant data

Absorption, distribution, metabolism, and excretion

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

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

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

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

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

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Genetic and related effects

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

5.5 Evaluation

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

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

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

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

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

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

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

47 There is *inadequate evidence* in experimental animals for the carcinogenicity of the48 progestogens levonorgestrel, norgestrel and dienogest.

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2 3	Overall evaluation
4 5 6 7	Combined oral estrogen-progestogen contraceptives are <i>carcinogenic to humans</i> (Group 1). There is also convincing evidence in humans that these agents confer a protective effect against cancer in the endometrium and ovary.
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