5. Summary of Data Reported and Evaluation

5.1 Exposure data

Combined estrogen–progestogen menopausal therapy involves the co-administration of an estrogen and a progestogen to peri- or postmenopausal women. These hormones may be given as individual compounds administered simultaneously or as combination preparations. Early treatment regimens included estrogen only. After a substantial increase

in the 1960s and early 1970s, the use of these regimens declined after 1975 when a strong association with endometrial cancer was found. When the addition of a progestogen was introduced as a strategy to reduce this risk, the use of hormonal menopausal therapy again increased steadily in the 1980s, particularly in developed countries. Combined estrogen–progestogen menopausal therapy is now administered to women who have not undergone a hysterectomy, whereas estrogen-only menopausal treatment tends to be prescribed to hysterectomized women. Although combined hormonal therapy was initially indicated for the control of menopausal symptoms, its application was expanded in the 1990s to include the treatment or prevention of a range of conditions related to ageing. However, since 2002, dramatic declines in use followed the report of a broad range of adverse effects in the Women's Health Initiative Estrogen Plus Progestin Trial in the USA. Reflecting this new evidence, practices are returning to a narrower set of indications directed at the short-term treatment of menopausal symptoms.

Combined estrogen–progestogen formulations are frequently used in hormonal menopausal therapy, although separate administration of each hormonal component is still prevalent. Commercial preparations are available for oral, vaginal and transdermal administration. Currently, continuous exposure to both hormones (both estrogen and progestogen at fixed daily doses) is common, particularly in the USA, whereas cyclical dosing, in which progestogen is added periodically to daily estrogen, is prevalent in other countries. Other scheduling strategies are also used occasionally. Some formulations and doses that are currently available for combined hormonal therapy are new and their possible long-term adverse effects have not been evaluated.

Combined hormonal therapy is much more commonly used in developed than in developing countries. At the peak of use in 1999, approximately 20 million women in developed countries used combined hormonal therapy, including 50% of women aged 50–65 years in the USA. Use has fallen by more than 50% since 2002, particularly for continuous combined hormonal therapy. Use in some developing countries also has declined modestly, although the data are more limited. Among peri- and postmenopausal women in developed countries, current users of combined hormonal therapy tend to be younger and more highly educated, to have a lower body mass and to use health care more regularly than non-users. The characteristics of users are known to vary between countries and to change over time.

5.2 Human carcinogenicity data

Breast cancer

Two large randomized trials, 10 cohort studies and seven case–control studies reported on the relationship between the use of combined estrogen–progestogen menopausal therapy and breast cancer in postmenopausal women. The studies consistently reported an increased risk for breast cancer in users of combined estrogen–progestogen therapy compared with non-users. The increased risk was greater than that in users of estrogen alone. The available evidence was inadequate to evaluate whether or not the risk for breast cancer

varies according to the progestogenic content of the therapy or its dose, or according to the number of days each month that the progestogens are added to the estrogen therapy. Observational studies showed that the relative risk was greater for lobular than for ductal cancers. The increase in the risk for breast cancer was largely confined to current or recent users, and the risk increased with increasing duration of use of the combined hormonal therapy.

Endometrial cancer

One randomized trial, four cohort studies and eight case–control studies reported on the relationship between use of combined estrogen–progestogen menopausal therapy and the risk for endometrial cancer in postmenopausal women. The risk for endometrial cancer was inversely associated with the number of days per month that progestogens were added to the regimen. The addition of progestogens to estrogen therapy for less than 10 days per month was associated with a significantly higher risk for endometrial cancer than never use of hormonal therapy, and the risk increased with increasing duration of use of that regimen. Estrogen therapy with daily progestogens was associated with a risk for endometrial cancer similar to, and possibly lower than, that found in women who had never used hormonal therapy. In contrast, the use of estrogens alone was associated with a considerably higher risk than that of any combined estrogen–progestogen regimen. Use of combined estrogen–progestogen menopausal therapy began relatively recently and, as yet, there is little information on its effects on the risk for endometrial cancer many years after cessation of use. The available evidence was inadequate to evaluate whether or not the risk for endometrial cancer varies according to the type or daily dose of progestogen.

Cervical cancer

The data from two randomized trials were inadequate to suggest that combined estrogen–progestogen hormonal therapy alters the risk for human papillomavirus infection or cervical cancer, and are of limited statistical power.

Ovarian cancer

Data from one randomized trial and two cohort and four case–control studies were inadequate to evaluate an association between ovarian cancer and combined estrogen–progestogen hormonal therapy.

Colorectal cancer

Two randomized trials and four cohort and three case–control studies provided information on the use of combined estrogen–progestogen hormonal therapy and the risk for colorectal cancer. None showed significantly elevated risks in women who had used these preparations for any length of time. Seven studies showed relative risks below 1.0 and the risk was significantly reduced in two, which suggests a potential protective effect. The

reduced risk tended to be observed among recent users and did not appear to be related to duration of use.

Other cancers

Large randomized trials provided the only substantial data on risk for lung cancer, which was slightly but not significantly elevated in users of combined estrogen–progestogen hormonal therapy. Observational data on lung cancer include both slightly increased and slightly reduced rates in users of such combined hormonal therapy. Data on cancer at other sites, including the liver, were too limited for evaluation.

5.3 Animal carcinogenicity data

Relatively few studies have been carried out to examine the tumorigenic effects of combined hormonal therapy in animals.

Oral administration of combined hormonal therapy in mice that are prone to develop mammary tumours resulted in similar incidences of mammary tumours in controls and in animals treated with conjugated equine estrogens alone and with conjugated equine estrogens plus medroxyprogesterone acetate. However, tumour latency was reduced in animals treated with conjugated equine estrogens plus medroxyprogesterone acetate. Conjugated equine estrogens plus medroxyprogesterone acetate suppressed the development of uterine adenomyosis.

Oral administration of conjugated equine estrogens alone or with medroxyprogesterone acetate to ovariectomized rats pretreated with the carcinogen 7,12-dimethylbenz[*a*]-anthracene increased the incidence of mammary tumours with equal frequency and to a level equal to that in non-ovariectomized controls.

5.4 Other relevant data

Absorption, distribution, metabolism and excretion

Various combinations of estrogens and progestogens are used for hormonal menopausal therapy. Since steroids penetrate normal skin easily, a variety of systems have been developed that deliver estrogens and progestogens parenterally (e.g. transdermal patches), thus by-passing the liver.

While the mechanisms of absorption and distribution of estrogens and progestogens have been known for a number of years, only recently has an understanding of the genes that encode the enzymes which control the enzymatic steps involved in steroid metabolism been acquired. This applies especially to the oxidative metabolism of estrogen. The phase I enzymes cytochrome P450 1A1 and 1B1 catalyse the production of catechol estrogen and metabolites of estrogen quinone that can induce the formation of DNA adducts. This is counteracted by the phase II enzymes, catechol-*O*-methyltransferase and glutathione

S-transferase P1, which reduce the levels of catechol and quinones by forming methoxyestrogens and glutathione conjugates. Polymorphic variants of these and other enzymes occur frequently in the population and several are associated with altered enzyme function. A large body of epidemiological data has failed to identify a consistent association between exposure to hormones and risk for cancer with any single enzyme variant. However, possible interactions between these genes need to be examined.

Progestogens are discussed in the monograph on Combined estrogen–progestogen contraceptives.

Receptor-mediated effects

The use of combined estrogen–progestogen menopausal therapy increases the rate of cell proliferation in the postmenopausal human breast, and appears to enhance significantly the modest increase in breast-cell proliferation induced by estrogen alone. Oral administration of conjugated equine estrogens alone or in combination with medroxyprogesterone acetate to ovariectomized monkeys resulted in an increase in epithelial cell proliferation and epithelial density in the mammary gland, as determined histologically, whereas the combination of conjugated equine estrogens and norethisterone acetate did not. The effects were greater with conjugated equine estrogens plus medroxyprogesterone acetate than with conjugated equine estrogens or medroxyprogesterone alone. Subcutaneous implantation of 17β-estradiol alone or in combination with progesterone for 3 days into ovariectomized monkeys resulted in a slight increase in epithelial cell proliferation in the mammary gland as did intraperitoneal administration of 17β-estradiol alone or in combination with progesterone to ovariectomized mice; the effect in mice was greater with 17β-estradiol plus progesterone than with 17β-estradiol alone. Approximately one-third of women treated with daily estrogen (by any route) plus daily oral progestogen develop increased mammographic breast density. In contrast, following treatments with estrogen daily plus progestogen less frequently than daily, a smaller proportion of women develop increased breast density. The addition of progestogens to estrogen therapy for the menopause prevents the development of endometrial hyperplasia and reduces the increased rate of endometrial cell proliferation induced by treatment with estrogen only. This effect has been found for all progestogens studied, regardless of the route of administration or dose. Inadequate data were available to the Working Group on duration of treatment or time since cessation of treatment.

Cardiovascular effects of estrogen and progestogen

Randomized trials that studied combined hormonal menopausal therapy did not show a protective effect of a fixed single dose of conjugated equine estrogens with or without medroxyprogesterone acetate on the incidence of coronary heart disease, although a large body of literature from observational studies suggests that such treatment confers benefits for this disease. These discrepancies have not been fully resolved but may arise from methodological limitations in some observational studies. Randomized trials have consis-

tently reported a small adverse effect of combined hormonal therapy on the incidence of stroke, which is generally supported by observational studies. Evidence of an increase in the incidence of venous thromboembolism from hormonal therapy, particularly with estrogen plus progestogen, has been found in both randomized trials and observational studies, and is supported by mechanistic studies. The overall evidence relies heavily on studies of conjugated equine estrogens and medroxyprogesterone acetate, the data from which suggest a small increase in risk for broadly defined cardiovascular disease as a whole. The extent to which these results apply to other estrogens and progestogens, doses or routes of administration is not known.

Other effects

The beneficial effects of combined hormonal menopausal therapy have been established unambiguously for vasomotor symptoms, osteoporosis and fractures, with moderate evidence for a reduced risk for non-insulin-dependent diabetes. The evidence for an increase in breast density and an increase in the prevalence of breast tenderness and vaginal bleeding is also unambiguous. There is strongly suggestive evidence of interference in mammographic screening associated with breast density and an increase in problems of urinary incontinence. There is consistent evidence for an increase in the risk for gallbladder disease. Results for cognitive function and dementia are less clear. In women who initiate therapy later in life (≥ 65 years of age), randomized trials have provided evidence of a small deleterious effect on cognitive function and an increased risk for dementia. The cognitive effects in women who initiate therapy at younger ages are still uncertain. Randomized trials did not show substantial effects on mortality or on the quality of life, other than the relief of symptoms related to the menopause.

Genetic and related effects

Data on the genetic effects of estrogens and their derivatives indicate that these compounds give rise to reactive metabolites and reactive oxygen species that can induce DNA damage. The evidence reported since the previous evaluation further substantiates the premise that these mechanisms could contribute to the induction of cancer by estrogens. New evidence demonstrates that DNA adducts that are expected to result from the metabolites of catechol estrogen are found in humans, experimental animals and in-vitro systems and that exposure to estrogens generates reactive oxygen species. While these new findings increase the plausibility of these pathways as mechanisms of estrogen-related carcinogenesis, they do not prove that these are the major pathways to estrogen-related cancers. The way in which progestogens might influence the genotoxicity of estrogens is not known.

Receptor-mediated responses to hormones are a plausible and probably necessary mechanism for hormonal carcinogenesis. The results of research over the past few years add considerable support for a direct genotoxic effect of hormones or their associated by-

products such as reactive oxygen species. Current knowledge does not allow a conclusion as to whether either of these mechanisms is the major determinant of hormonally induced cancer. It is entirely possible that both mechanisms contribute to and are necessary for carcinogenesis. Cessation of hormonal treatment may reduce the receptor-mediated effects while gene damage may be more persistent.

5.5 Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of combined estrogen–progestogen menopausal therapy in the breast.

There is *evidence suggesting lack of carcinogenicity* in humans for combined estrogen–progestogen menopausal therapy in the colorectum.

There is *sufficient evidence* in humans for the carcinogenicity of combined estrogen–progestogen menopausal therapy in the endometrium when progestogens are taken for fewer than 10 days per month, and there is *evidence suggesting lack of carcinogenicity* in the endometrium when progestogens are taken daily. The risk for endometrial cancer is inversely associated with the number of days per month that progestogens are added to the regimen.

There is *limited evidence* in experimental animals for the carcinogenicity of conjugated equine estrogens plus medroxyprogesterone acetate.

Overall evaluation

Combined estrogen–progestogen menopausal therapy is *carcinogenic to humans (Group 1).*