GENERAL REMARKS

This ninety-first volume of *IARC Monographs* contains evaluations of the carcinogenic hazard to humans of combined estrogen–progestogen contraceptives and combined estrogen–progestogen menopausal therapy. These hormonal drugs were evaluated previously in Supplement 7 (IARC, 1987) and Volume 72 (IARC, 1999). A recent *IARC Monographs* Advisory Group (IARC, 2003) recommended that they be re-evaluated with high priority, and cited on-going epidemiological studies at that time that might suggest possible associations with additional cancer sites.

The hormonal drugs reviewed in this volume involve co-administration of an estrogen and a progestogen. Studies that did not provide information on the use of combined estrogen–progestogen agents are not reviewed. This volume does not review studies of estrogen-only agents; because of the interactions between estrogens and progestogens, estrogen-only agents are less relevant to an evaluation of combined estrogen and progestogen agents and adequate information is available on such agents themselves. It should be noted that this volume reviews only studies that are publicly available and therefore does not include pharmaceutical test results that are not in the public domain.

Worldwide, 61% of all women of reproductive age (aged 15–49 years) who are married or in a consensual union use contraception. Nine in 10 women who use contraception rely on modern methods, including female sterilization (21%), intrauterine devices (14%) and oral pills (7%). Based on a compilation of sources, it appears that oral contraception is the most widely used method of contraception among married women in developed countries as well as in two-thirds of the developing countries. In 2000, approximately 100 million women worldwide were current users of combined hormonal contraceptives (Blackburn *et al.*, 2000; United Nations, 2004).

Hormonal menopausal therapy was developed during the first half of the twentieth century to control menopausal symptoms and mitigate ageing, and originally comprised estrogen only. Its use increased steadily in the 1960s and 1970s, almost exclusively in North America and western Europe, until 1975 when an increased risk for endometrial cancer was observed. Addition of progestogen to the treatment was found to alleviate the risk, and the use of hormonal menopausal therapy increased again, in a combined estrogen–progestogen form, to peak at about 50 million prescriptions per year in the USA in 2000. In 2002, the Women's Health Initiative identified the treatment as a risk factor for stroke and other heart disorders, and the use decreased dramatically as a consequence.

Comparison of risks and benefits

The conclusion that combined estrogen–progestogen contraceptives increase the risk for some forms of cancer and decrease the risk for others highlights the need for a rigorous quantitative assessment of risks and benefits. This would require quantitative risk estimates for each form of cancer that is increased or decreased, and calculation of absolute risks rather than the relative risks used in this volume to assess causality. A comprehensive assessment would also consider the availability and efficacy of screening for these cancers, the efficacy and side-effects of cancer treatments and the extent to which this information is known or uncertain. The efficacy of cancer screening and treatment varies between different parts of the world; accordingly, the preferred methods of contraception may be specific to a particular country and population. Cervical cancer screening and treatment, for example, vary widely between countries, and cervical cancer is more common in many countries of Africa, Asia and South America. A comprehensive assessment should also go beyond cancer to compare hormonal and non-hormonal methods of contraception, their effectiveness and cost, and adverse and beneficial health effects other than cancer. The evaluations developed in this volume identify specific forms of cancer for which the risk is increased or decreased by combined estrogen–progestogen contraceptives and provide information that will help address the health concerns and well-being of hundreds of millions of women worldwide. Such comprehensive assessments are outside the scope of the *IARC Monographs* but will have important implications for public health.

Uncertainties for women who use both contraceptives and menopausal therapy

This volume considers combined estrogen–progestogen contraceptives and combined estrogen–progestogen menopausal therapy because these two classes of pharmaceuticals have many similarities. Combined contraceptives and combined menopausal therapy both involve co-administration of an estrogen and a progestogen. There is also some concordance in the tumour sites at which the risks for cancer are increased by combined contraceptives and by combined menopausal therapy.

Consequently, there is a possibility that women who use both combined estrogen–progestogen contraceptives and menopausal therapy during their lifetime may experience effects that are greater than those experienced by women who use either contraceptives or menopausal therapy but not both. For example, the conclusion that the increased risk for breast cancer returns to background levels 10 years after cessation of use of combined contraceptives may or may not apply to women who have begun to use combined menopausal therapy. Epidemiological studies of women who have used both combined contraceptives and menopausal therapy will be important to elucidate their joint effects.

Implications for cervical cancer screening

This volume contains a conclusion that combined estrogen–progestogen contraceptives can increase the risk for cervical cancer in women who have a human papillomavirus infection. This suggests that women who use this form of hormonal contraception over a long period of time should be encouraged to participate in cervical cancer screening programmes.

Recent trends in breast cancer incidence

After the Working Group met to develop this volume of *IARC Monographs*, it has been reported that breast cancer incidence in the USA has been declining since 2003 (Jemal *et al.*, 2007; Colditz, 2007). Careful analysis is warranted to determine to what extent this decline may be attributed to the concurrent decline in the use of combined estrogen–progestogen menopausal therapy and whether similar trends are occurring in other countries.

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