ORAL CONTRACEPTIVES AND NEOPLASIA

Report of a
WHO Scientific Group

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WHO Scientific Group on Oral Contraceptives and Neoplasia
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1. **Introduction**

A WHO Scientific Group on Oral Contraceptives and Neoplasia met in Geneva from 3 to 5 December 1990. The meeting was opened by Dr Hu Ching-Li, Assistant Director-General, on behalf of the Director-General.

The first oral contraceptive preparation was approved for marketing in the United States of America in November 1959 (1). It contained a combination of two steroid hormones, a progestogen (noretynodrel) and an estrogen (mestranol). During the subsequent 30 years, many new oral contraceptives have been developed, most of which have contained a combination of an estrogen and a progestogen, taken over a 21-day cycle. The hormones used have been varied, and the doses of these hormones have been progressively reduced. Combined oral contraceptives include both monophasic and multiphasic (biphasic or triphasic) pills, which differ according to whether the doses of estrogen and progestogen are fixed or varied during the cycle.

A less commonly used oral contraceptive is the progestogen-only pill (or "minipill"), which contains a fixed dose of a progestogen to be taken continuously. Sequential oral contraceptives, which contain only an estrogen for approximately the first 2 weeks of the cycle followed by an estrogen-progestogen combination for the third week, are no longer used in most countries.

Oral contraception has proved to be an extremely popular method of family planning, because of its effectiveness, reversibility, and convenience. It is estimated that over 60 million women around the world, including over 38 million in developing countries, are now using oral contraceptives (2).

One recurring concern about oral contraceptives has been the possibility that they might alter the risk of neoplasia. While oral contraceptives are known to reduce the risk of certain tumours (such as cancers of the ovary and endometrium), there have been reports of positive associations with the risk of other tumours (such as cancers of the breast and cervix). The interpretation of these reports has often been controversial and difficult.

A Scientific Group was convened by WHO in 1977 to advise on steroid contraception and the risk of neoplasia (3). The Group made a number of recommendations for research and clinical practice. Attention was drawn, in particular, to the lack of relevant information from developing countries. As a consequence, WHO established a collaborative study of neoplasia and steroid contraceptives in eight developing and three developed countries. The present Scientific Group examined the results of this investigation, as well as a large amount of data from other sources.

This report is concerned solely with combined oral contraceptives. It does not deal with the progestogen-only pill or other progestogen-only methods of contraception (such as injectable preparations).
1.1 Carcinogenicity studies in animals

There is a considerable amount of information about the effects of administering estrogens and progestogens, both alone and in combination, to laboratory animals such as mice, rats, and dogs. The data have been reviewed in detail by Working Groups of the International Agency for Research on Cancer (4, 5), and will not be considered in this report; these studies indicate that the carcinogenic effects of estrogens and progestogens depend critically on the hormonal environment and the doses administered.

1.2 Epidemiological assessment of effects in humans

At least six kinds of epidemiological approaches have been used to evaluate the effects of steroid contraceptives in humans: voluntary reporting systems, monitoring of routine statistics (such as trends in cancer incidence), cross-sectional studies, case-control studies, cohort studies, and randomized controlled trials (6). For investigating possible effects on the risk of neoplasia, case-control and cohort studies are considered to be most useful.

Case-control studies are particularly useful in the investigation of uncommon or rare conditions. In these studies, cases with the disease under investigation are compared with one or more groups of controls selected from the general population or from groups of patients with other diseases admitted to the same hospital(s) as the cases. A comparison is made of the past exposure to possible etiological factors among the case and control groups. Many such factors may be considered in a single case-control study. Hence it may be possible to determine whether an apparent effect of a steroid contraceptive has been distorted by confounding variables – factors associated with use of the contraceptive and, independently, with the risk of disease – and whether there is effect modification – i.e., the effect of the contraceptive varies according to the level of some other factor. On the other hand, the case-control method may be susceptible to certain biases. For example, the procedures used to select cases and controls may mean that these two groups are not truly comparable (selection bias), or the cases and controls may differ in their accuracy of recall of past use of contraceptives (information bias).

In cohort studies, groups of women using different methods of contraception are followed over time and the incidence of neoplasia (or other events) in these groups is observed directly. The results of studies using this prospective approach generally gain reader acceptance than those of case-control studies, because they are less likely to be affected by hidden sources of bias. Nevertheless, cohort studies are not immune to bias. For example, knowledge of whether a woman is using an oral contraceptive may influence the application of procedures for detecting disease, such as cervical screening or breast examinations. Cohort studies also have other disadvantages for investigating the association between
oral contraceptives and neoplasia. They require large numbers of patients and long periods of observation, because the incidence of neoplasia of any one kind in women of reproductive age is low. As a result, only limited information can usually be obtained about variables that may be important for evaluating possible confounding or effect modification. Furthermore, many women may be lost to follow-up or may have changed their methods of contraception during the course of a study.

1.2.1 Measurement of risk

The usual measure of the strength of an association between exposure to a factor and the development of disease is termed the relative risk. This is defined as the ratio of the incidence rate of disease among women exposed to the factor (e.g., users of oral contraceptives, including previous users) to the incidence rate among women not exposed. In cohort studies the relative risk can be estimated directly, because the incidence of disease among women in the different groups can be determined. In case-control studies a different statistic (the odds ratio) is used as an estimate of the relative risk.

A relative risk of 1.0 indicates no association, whereas a relative risk significantly greater than 1.0 implies a positive association between exposure and the development of disease. Conversely, a relative risk of less than 1.0 implies that exposure may have a protective effect. It is customary to estimate a confidence interval around a relative risk estimate. If the 95% confidence interval (95% CI) does not include 1.0, the results indicate a statistically significant alteration in risk.

1.2.2 Interpretation of risk estimates

Relative risk is only an index of association, and there is a need for further evidence before a cause-and-effect relationship can be established between a factor and the development of disease.

If an increased (or decreased) relative risk is observed in an epidemiological study, four main explanations are possible: (1) chance, (2) bias, (3) confounding, and (4) a causal relationship. Accordingly, the first three possibilities must be ruled out before a cause-and-effect relationship can be established.

Several questions also need to be addressed before deciding whether an association between use of oral contraceptives and risk of disease is likely to be causal. These include the following:

- Is the relative risk large? (A causal hypothesis cannot be dismissed on the grounds that the observed association appears to be weak, but it is difficult to exclude bias or confounding as explanations for relative risks close to 1.0.)
- Have similar results been obtained by different investigators, including those using different study designs?"
• Is the risk of disease related to the dose of steroid hormones or the duration of use of oral contraceptives?
• Is the time sequence between use of oral contraceptives and the development of disease consistent with a causal explanation?
• Do the results of experiments in appropriate animals and of other laboratory research support the association, and is the association consistent with known facts about the disease?

The strongest evidence for a cause-and-effect relationship would come from an experimental (or intervention) study involving humans, but this is not a feasible way of studying the association between oral contraceptives and neoplasia. The interpretation of risk estimates from observational studies (such as case-control and cohort studies) is often very difficult, and careful judgement is required.

If a causal link can be inferred, a measure of the absolute (rather than relative) risk is required in order to assess the clinical or public health importance of the finding. This absolute risk will depend on both the relative risk and the underlying incidence of the disease concerned.

1.3 **Specific considerations**

In reviewing studies of the association between oral contraceptives and neoplasia, several specific considerations should be taken into account.

Although the development of benign and malignant neoplasia is not well understood, it is believed that cancers arise through a multi-stage process (7). Sometimes there is a long latent period between exposure to a causal factor and the appearance of a tumour. Since hormones are generally considered to act as promoters rather than initiators of tumours, it is possible that recent use of oral contraceptives may be particularly relevant. In addition, certain risk factors may produce an effect only if protracted exposure occurs.

The risk of neoplasia associated with oral contraceptives may depend not only on the duration and general timing of contraceptive use, but also on the timing of use in relation to key life events such as the menarche, the first or subsequent pregnancies, or the menopause. If these factors are not taken into consideration, studies that focus on use of oral contraceptives at any time (including in the past) may be misleading.

Accurate and detailed histories of oral contraceptive use are also essential to determine the effects of different steroid combinations and dosages. For example, some components of oral contraceptives, such as chlormadinone, are no longer used in most countries and the doses of steroid hormones in oral contraceptives have been reduced. Even in recent investigations of the association between oral contraceptives and neoplasia, much of the exposure studied may involve drugs or dosage schedules no longer in use. Studies of the effects of particular formulations of oral contraceptives are complicated by the fact that women often use a
variety of formulations during their reproductive lives. Moreover, they may have difficulty in recalling the specific types of oral contraceptives used in the past.

In many of the studies reviewed in this report, no attempt was made to distinguish between different formulations of oral contraceptives. The results of such studies are presumed to be relevant to combined oral contraceptives as a group, since most oral contraception has involved combined preparations (rather than sequential or progestogen-only pills).

Since neoplasia generally has multiple causes, etiological studies need to consider the interplay of a number of risk factors. In order to isolate any specific risks associated with the use of oral contraceptives, it is essential to study a large number of variables that might confound the results. Studies often differ in the measures adopted to detect and adjust for such confounding variables.

Finally, it is possible that oral contraceptives may affect the risk of neoplasia only in the presence of predisposing factors, or that the magnitude of any risk may be modified by such factors. The effects of steroid contraceptive use should therefore be evaluated in particular subgroups of the population, such as women with a family history of breast cancer or women who have had multiple sexual partners.

2. Neoplasia of the ovary

There are many types of ovarian tumours, both benign and malignant. The WHO classification of neoplasia of the ovary includes eight major categories (8), separated according to the most probable cell or tissue of origin. The majority of ovarian tumours arise from the surface epithelium, while most of the remainder arise from either the germ cells or the stroma of the ovary.

2.1 Benign neoplasia of the ovary

Two cohort studies (9, 10) have examined the incidence of two types of benign ovarian tumours among women who had used oral contraceptives. There was no association between use of oral contraceptives and the risk of benign teratoma of the ovary in either the Walnut Creek contraceptive study (9) in the USA or the Oxford Family Planning Association study (10) in the United Kingdom. In the Walnut Creek study the relative risk was lower in long-term users, but the difference was not statistically significant.

Similarly, no association was found between use of oral contraceptives and the risk of ovarian cystadenoma (9, 10). In the British study, however, the results suggested that the risk might be lower among women who had recently used oral contraceptives than among past users or those who had never used oral contraceptives (10).
2.2 Ovarian cancer

The great majority of ovarian cancers are epithelial tumours and, since many studies have not differentiated the histological types, most of what is known about the epidemiology of ovarian cancer applies to epithelial tumours. The non-epithelial ovarian cancers will be considered separately (section 2.2.3). Most of the available data on the relationship between oral contraceptive use and ovarian cancer are derived from studies involving exposure to oral contraceptives that were in common use before the mid-1980s.

2.2.1 Epidemiology

Ovarian cancer is an important cause of morbidity and mortality, especially in middle-aged women. It was estimated that 137,600 new cases occurred in the world in 1980 (II). The highest incidence rates are reported among white women in northern and western Europe and in North America, while ovarian cancer is less common in Chinese, Indian, and Japanese populations (12).

Epidemiological studies indicate that the risk of developing ovarian cancer is higher in women of low parity, in women who have had difficulty in becoming pregnant, and in women with a family history of the disease (13).

2.2.2 Effect of oral contraceptive use on disease risk

The association between oral contraceptive use and ovarian cancer risk has been evaluated in 15 case-control studies (Table 1). In 13 studies, the relative risk was less than 1.0 for women who had at any time used oral contraceptives. A summary relative risk based on the results of the 15 studies was 0.7 (95% CI 0.6-0.7) (29).

The protective effect of oral contraceptives has been confirmed in two British cohort studies, which reported relative risks of 0.3 (95% CI 0.1-0.7) and 0.6 (95% CI 0.3-1.4) for women who had at any time used oral contraceptives (10, 30).

Use of oral contraceptives has been associated with a lower risk of both malignant and borderline malignant tumours (23, 31) and of each of the major histological subtypes of epithelial ovarian cancer (17, 23). However, two studies did not show a protective effect against mucinous tumours (19, 28).

In several studies, the risk of ovarian cancer was evaluated in relation to the duration of use of oral contraceptives, the time since first use, and the time since last use. The relative risk was generally found to decrease with increasing duration of use. In the large Cancer and Steroid Hormone Study in the USA (23), the relative risk for women who had used oral contraceptives for 10 years or longer (compared to women who had never used the pill) was 0.2 (95% CI 0.1-0.4).

Analyses of risk in relation to the time since first use of oral contraceptives
Table 1
Case–control studies of the association between oral contraceptive use and the risk of ovarian cancer

<table>
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<th>First author and year</th>
<th>Number of cases</th>
<th>Number of controls</th>
<th>Reference number</th>
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<td>Casagrande (1979)</td>
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<td>Weiss (1981)</td>
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<td>Willett (1981)</td>
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<td>Cramer (1982)</td>
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<td>Rosenberg (1982)</td>
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<td>Tzonou (1984)</td>
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<td>La Vecchia (1986)</td>
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<td>Wu (1988)</td>
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<td>Booth (1989)</td>
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<td>Hartge (1989)</td>
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</table>

suggest that there may be a delay of several years before the protective effect of oral contraceptives against ovarian cancer becomes apparent. Two of the largest case-control studies showed a decline in risk with increasing time since first use of oral contraceptives (23, 28).

The reduced risk of ovarian cancer appears to persist for at least 10 years after oral contraception is discontinued. In the Cancer and Steroid Hormone Study (23), women who had last used oral contraceptives 15 or more years previously had a relative risk of 0.5 (95% CI 0.4-0.8).

Although the evidence is not entirely consistent, most studies suggest that the protective effect of oral contraceptives is apparent in both younger and older women (29). Oral contraceptives provide protection to both nulliparous and parous women. Two studies suggested that women of high parity might not receive any additional protection above that conferred by multiple births (23, 30), but this was not found in two other investigations (20, 28). In a WHO study conducted mainly in developing countries, women of high parity (five or more births) who had used oral contraceptives had a relative risk of 0.7 (95% CI 0.4-1.5), compared with women of the same parity who had not used the pill (28). The reduced risk observed in users of oral contraceptives does not appear to be due to confounding by infertility (a risk factor for ovarian cancer which is likely to be negatively associated with contraceptive use).

Results from the Cancer and Steroid Hormone Study (23) suggest that the protective effect is not dependent on the dose of estrogen or progestogen
in combined oral contraceptives, although further information is needed about oral contraceptives containing low doses of steroids, including triphasic preparations.

2.2.3 Nonepithelial ovarian cancer

The risk of nonepithelial ovarian cancer in users of oral contraceptives was examined in two case-control studies, conducted in China (27) and the USA (23). Nonepithelial ovarian tumours accounted for 18% and 10%, respectively, of all cancers included in these studies. The results were, however, difficult to interpret because of the small number of cases involved.

In the case-control study in Shanghai, China (27), the relative risk of nonepithelial ovarian cancer (all types combined) among women who had at any time used oral contraceptives was estimated to be 1.0 (95% CI 0.3-4.3).

In the Cancer and Steroid Hormone Study (23), the relative risk of having a germ-cell type of ovarian cancer was estimated to be 1.6 (95% CI 0.5-4.7) among women who had at any time used oral contraceptives and 1.0 (95% CI 0.2-4.0) among those who had used the pill for 5 years or longer. For the sex cord-stromal type of ovarian cancer, the relative risk was reported to vary significantly with age. Women under 45 years of age who had at any time used oral contraceptives had a relative risk of 1.4 (95% CI 0.2-11.9), whereas there were no cases reported among women aged 45 years or older who had used oral contraceptives.

2.3 Conclusions

1. Use of combined oral contraceptives protects against epithelial ovarian cancer. The reduction in risk is related to the duration of use of oral contraceptives; use for 5 or more years confers about a 50% reduction in risk. The protective effect persists for at least 10 years after use is discontinued.

2. There are insufficient data to draw any firm conclusions regarding the effects of use of combined oral contraceptives on the risk of non-epithelial ovarian cancers and benign ovarian tumours.

3. **Neoplasia of the uterine corpus**

Primary neoplasia of the body of the uterus originates either in the mucosa (endometrium) or in the smooth muscle (myometrium). There are many different types of uterine neoplasia, but the commonest are the leiomyoma (or fibroid) and endometrial carcinoma.

3.1 **Uterine fibroids**

Uterine leiomyomas (fibroids) are benign tumours that arise from the
smooth muscle of the myometrium. They are very common and account for a substantial proportion of gynaecological admissions to hospital. The risk of fibroids in relation to oral contraception has been investigated in three cohort studies, with varying results.

The 1974 report of the cohort study conducted by the Royal College of General Practitioners (32) provided an analysis of 162 women with fibroids. Current users had a significantly reduced relative risk of 0.41 ($P < 0.01$) compared with women who had never used oral contraceptives, while former users were reported to have the same risk. The reduced risk in current users was attributed partly to selection bias, because at the start of follow-up, women who had never used oral contraceptives were five times as likely as users to have a history of fibroids. Other possible sources of bias were also considered, but the possibility of a real protective effect was not ruled out.

In the Walnut Creek study (9), the relative risk of fibroids in women who had at any time used oral contraceptives was estimated to be 1.5 (95% CI 0.9-2.7). There was no clear evidence of a trend in risk with duration of use. It was suggested that the increased risk might have been due to enhanced detection of fibroids in oral contraceptive users.

In the Oxford Family Planning Association study (33), analysis of 535 women with pathologically confirmed fibroids (of whom 532 were premenopausal) revealed a significant trend of decreasing risk with increasing duration of contraceptive use. Compared to the risk in women who had never used oral contraceptives, the relative risks of fibroids associated with 1-24, 25-48, 49-96, 97-144, and 145 or more months of use were 1.04, 0.80, 0.79, 0.73, and 0.54, respectively ($P = 0.015$ for linear trend in logistic model). As in the Royal College of General Practitioners study, the reduced risk appeared to be mainly confined to current users. Other protective factors included multiparity, low body weight, cigarette smoking, and being postmenopausal. These results were interpreted as supporting the hypothesis that unopposed estrogen is the underlying cause of fibroids, and that use of combined oral contraceptives lowers the risk.

3.2 **Cancer of the uterine corpus**

Endometrial carcinoma accounts for the great majority of cancers of the uterine corpus. There are several histological types, of which the commonest is adenocarcinoma. The relationship between oral contraceptives and the rare sarcoma of the uterus will be considered separately (section 3.2.3).

3.2.1 **Epidemiology**

There were an estimated 149 000 new cases of cancer of the uterine corpus in the world in 1980 (11). The disease is rare below the age of 40, after which incidence rates begin to rise. High incidence rates have been recorded in white North American women, Hawaiians, and New Zealand
Maoris; incidence rates are much lower in Asian populations (34). Studies of migrants show that the risk increases in populations that move to areas with more “Western” life-styles (12).

Risk factors for endometrial cancer include obesity, anovulation, polycystic ovaries, nulliparity, early menarche, and late menopause (35). Cigarette smoking has been shown to confer a protective effect (36). All of these observations are consistent with the hypothesis that the development of endometrial cancer is related to endogenous estrogenic stimulation of the endometrium, with inadequate cyclical exposure to progesterone (36, 37). Exposure to exogenous estrogens has been shown to increase the risk of endometrial cancer in women who have used sequential oral contraceptives, in postmenopausal women who have received estrogen therapy without cyclical administration of progestogen, and in girls with ovarian dysgenesis who have received unopposed estrogen therapy at puberty (37).

3.2.2 Effect of oral contraceptive use on disease risk

The risk of endometrial cancer among users of oral contraceptives has been evaluated in 11 case-control studies (Table 2) and three cohort studies (9, 30, 48). Although many of the studies were small, a protective effect of oral contraception was found in all but two (38, 48), both of which had methodological limitations (49).

A combined analysis of data from the case-control and cohort studies showed a highly significant trend of decreasing risk of endometrial cancer with increasing duration of use of oral contraceptives (49). On the basis of

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<td>433</td>
<td>3191</td>
<td>45</td>
</tr>
<tr>
<td>WHO Collaborative Study of Neoplasia and Steroid Contraceptives (1988)</td>
<td>130</td>
<td>835</td>
<td>46</td>
</tr>
<tr>
<td>Koumantaki (1989)</td>
<td>83</td>
<td>164</td>
<td>47</td>
</tr>
</tbody>
</table>

* The case series in this study may have overlapped.
a regression model, the reduction in risk associated with use of combined oral contraceptives for 1, 2, 4, 8 and 12 years was estimated to be 23%, 38%, 51%, 64%, and 70%, respectively.

Two studies that reported data on histological subtypes of endometrial carcinoma showed reduced risks of similar magnitude for each subtype (45, 46).

The protective effect of oral contraceptives appears to emerge fairly soon after the start of oral contraception. In the Cancer and Steroid Hormone Study (45), the effect was apparent within 10 years after the first use of combined oral contraceptives.

Since endometrial cancer is uncommon in women of childbearing age, the protective effect needs to persist after oral contraception is stopped if it is to be of practical importance. The evidence in this respect is encouraging (49). In the Cancer and Steroid Hormone Study (45), for example, women who had used oral contraceptives for a minimum of 1 year 15 or more years previously had a relative risk of 0.3 (95% CI 0.2-0.6).

The risk of endometrial cancer is reduced as the number of full-term pregnancies increases. The results of two studies suggest that the protective effect of oral contraceptives is diminished in women of high parity (43, 45) but this was not confirmed in the WHO study (46). There have also been conflicting results as to whether the relative protection conferred by oral contraception is affected by body weight (43, 45) or subsequent use of estrogen replacement therapy (39, 40, 41).

Only limited information is available about the effects of specific formulations of combined oral contraceptives, but the results of two large case-control studies suggested that the risk of endometrial cancer was reduced to a similar degree in women who had used any of the most common formulations that were then in use (43, 45).

3.2.3 Sarcoma of the uterus

The relationship between oral contraception and the rare sarcoma of the uterus has been investigated in only one study. In the WHO Collaborative Study of Neoplasia and Steroid Contraceptives, 29 women with uterine sarcomas (which had developed from the uterine corpus in 24 cases and from the cervix in 5) were matched with 198 controls selected from other hospital patients (50). Although the statistical power of this study was limited, there was no evidence of an association between use of oral contraceptives and risk of sarcoma: the relative risk was estimated to be 0.9 (95% CI 0.3-3.2).

3.3 Conclusions

1. Use of combined oral contraceptives reduces the risk of endometrial cancer. This effect is related to duration of use; the risk of disease is reduced by about 20% after 1 year and by about 50% after 4 years' use.
The protective effect appears to be maintained for up to 15 years after discontinuation of oral contraception, but this conclusion is based on the results of a single study.

2. While there are conflicting reports of the effects of combined oral contraceptives on the risk of fibroids, the balance of evidence suggests a protective effect.

4. **Neoplasia of the uterine cervix**

Cervical neoplasms are relatively common, and the great majority are epithelial tumours. The literature concerning the effect of oral contraceptive use on the risk of cervical neoplasia is extensive and difficult to interpret.

4.1 **Cervical intraepithelial neoplasia and carcinoma**

The majority of cervical cancers are squamous cell carcinomas. It is now generally accepted that the appearance of invasive cancer is often preceded by premalignant lesions, known as cervical dysplasia and carcinoma *in situ*. Because of evidence indicating that these pre-invasive lesions are part of a continuum or spectrum of disease, they are often grouped under the term *cervical intraepithelial neoplasia*. The pre-invasive lesions are usually detected by cytological screening (using the Papanicolaou smear test).

Cervical adenocarcinoma is uncommon and has a different pathogenesis. Studies of the association between oral contraceptive use and risk of cervical adenocarcinoma will be considered separately (section 4.1.3).

4.1.1 **Epidemiology**

From a global perspective, cervical cancer is the second most common cancer among women. In 1980, there were estimated to be 465,600 new cases of cervical cancer in the world (11). Approximately 80% of these were in developing countries, where cervical cancer is the most common form of malignant neoplasia affecting women. Incidence rates are particularly high in sub-Saharan Africa, Central and South America, and south-east Asia (12).

An association between cervical cancer and sexual activity has long been recognized. Specific risk factors include multiple sexual partners (both of the woman and of her partner), commencement of intercourse at an early age, and high parity (51, 52). Attention has been focused on the likely etiological role of certain types of human papillomavirus (HPV) (53). Cigarette smoking has also been linked to the risk of cervical cancer, although there is controversy as to whether the association is causal (52, 54).

The incidence rates of cervical dysplasia and carcinoma *in situ* are more
difficult to determine, because the detection of these lesions usually depends on the intensity of cervical screening. Nevertheless, women with these conditions tend to have the same risk factors as women with invasive cancer (55).

4.1.2 Effect of oral contraceptive use on disease risk

Studies of the association between oral contraceptives and cervical cancer are difficult to interpret, primarily because use of oral contraceptives may be associated with patterns of sexual behaviour that influence the risk of cervical cancer (56). Studies have varied in the adequacy of steps taken to ascertain sexual behaviour, and most investigators have ignored the potential confounding influence of male sexual behaviour. Even if it were possible to adjust perfectly for all sexual risk factors (which is certainly not the case), these factors are probably only a crude measure of exposure to sexually transmitted infectious agents.

A second problem is that, in many societies, women who receive oral contraceptives are more likely to have regular cervical smears. This will both reduce their risk of developing invasive cancer and increase the probability that cervical abnormalities such as cervical dysplasia and carcinoma in situ will be detected. In a number of studies, adequate steps have not been taken to adjust for screening histories.

A third complexity stems from the natural history of cervical neoplasia. Since cervical squamous cell carcinoma is believed to result from a progression from normal epithelium to dysplasia to carcinoma in situ and thence on to invasive cancer, it is possible that oral contraceptives could influence any or all of these stages. Many studies have included women with a variety of these conditions.

Table 3 summarizes the main features of a number of case-control studies reported between 1977 and 1990. Although several studies found no relationship between use of oral contraceptives and the risk of cervical cancer, the majority suggested that the risk is greater among long-term users, even after adjustment for factors such as socioeconomic status, sexual behaviour, and screening history. In most of the studies that reported positive associations, the variable most strongly linked to risk was duration of use; in the well-controlled studies, the relative risk among women who had used oral contraceptives for 5 years or longer ranged from 1.3 to 1.8.

An association between oral contraceptives and cervical neoplasia has also been found in four cohort studies (30, 73–75). However, the results were difficult to interpret because only limited information was available about potential confounding factors. Thus, the strong association reported by Peritz et al. (73) has been attributed to confounding by sexual behaviour (76).

In the Oxford Family Planning Association study, the incidence of cervical
Table 3  
Case–control studies of the association between oral contraceptive use and the risk of cervical neoplasia

<table>
<thead>
<tr>
<th>First author and year</th>
<th>Type of cervical disease</th>
<th>Number of cases</th>
<th>Number of controls</th>
<th>Reference number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cry (1977)</td>
<td>Dysplasia/CIS</td>
<td>854/147</td>
<td>8553</td>
<td>57</td>
</tr>
<tr>
<td>Harris (1980)</td>
<td>CIN</td>
<td>190</td>
<td>422</td>
<td>55</td>
</tr>
<tr>
<td>Hellberg (1985)</td>
<td>CIN</td>
<td>140</td>
<td>280</td>
<td>58</td>
</tr>
<tr>
<td>Reeves (1985)</td>
<td>CIS/Invasive</td>
<td>156</td>
<td>309</td>
<td>59</td>
</tr>
<tr>
<td>WHO Collaborative Study of Contraceptives (1985)</td>
<td>Invasive</td>
<td>726</td>
<td>5246</td>
<td>60</td>
</tr>
<tr>
<td>Brinton (1986)</td>
<td>Invasive</td>
<td>479</td>
<td>789</td>
<td>61</td>
</tr>
<tr>
<td>La Vecchia (1986)</td>
<td>CIN/Invasive</td>
<td>202/225</td>
<td>202/225</td>
<td>22</td>
</tr>
<tr>
<td>Peters (1986)</td>
<td>Invasive</td>
<td>200</td>
<td>200</td>
<td>62</td>
</tr>
<tr>
<td>Celentano (1987)</td>
<td>Invasive</td>
<td>153</td>
<td>153</td>
<td>63</td>
</tr>
<tr>
<td>Ebeling (1987)</td>
<td>Invasive</td>
<td>129</td>
<td>275</td>
<td>64</td>
</tr>
<tr>
<td>Irwin (1988)</td>
<td>CIS/Invasive</td>
<td>415/149</td>
<td>764</td>
<td>65</td>
</tr>
<tr>
<td>Molina (1988)</td>
<td>CIS</td>
<td>133</td>
<td>254</td>
<td>66</td>
</tr>
<tr>
<td>Brock (1989)</td>
<td>CIS</td>
<td>117</td>
<td>196</td>
<td>67</td>
</tr>
<tr>
<td>Cuzick (1989)</td>
<td>CIN/Invasive</td>
<td>135</td>
<td>135</td>
<td>68</td>
</tr>
<tr>
<td>Slattery (1989)</td>
<td>CIS/Invasive</td>
<td>266</td>
<td>408</td>
<td>69</td>
</tr>
<tr>
<td>Brinton (1990)</td>
<td>Invasive</td>
<td>759</td>
<td>1430</td>
<td>70</td>
</tr>
<tr>
<td>Mandelson (1990)</td>
<td>Invasive</td>
<td>140</td>
<td>181</td>
<td>71</td>
</tr>
<tr>
<td>Parazzini (1990)</td>
<td>Invasive</td>
<td>367</td>
<td>323</td>
<td>72</td>
</tr>
</tbody>
</table>

Key: CIS — carcinoma in situ  
CIN — cervical intraepithelial neoplasia

neoplasia (pre-invasive and invasive) rose from 0.9 per 1000 woman-years among women with up to 2 years of oral contraceptive use, to 2.2 among those with 8 years of use (74). Similarly, Andolsek et al. (75) found evidence of an increasing rate of cervical neoplasia with duration of use, although the period of follow-up in this study was relatively short (average 4.5 years). In both these studies, all the cases of invasive cancer occurred among women who had used oral contraceptives. In the study conducted by the Royal College of General Practitioners (30), the results were adjusted for the effects of age, socioeconomic status, parity, smoking, history of sexually transmitted diseases, and the number of previous cervical smears. The risk of cervical carcinoma in situ and invasive cancer was shown to increase with duration of oral contraceptive use; the incidence among women who had used oral contraceptives for 10 years or longer was four times that among women who had never used the pill.

Detailed information about the association between oral contraceptives and cervical neoplasia has been derived mainly from case-control studies. In several investigations, recent users (including current users) were reported to be at higher risk than women who had used oral contraceptives only in the past (64, 71, 72). This finding may in some instances reflect a correlation between recent use and long-term use (61). Most studies have
not found that effects vary with the interval since first use or age at first use of oral contraceptives.

In a number of studies, attempts have been made to assess whether the effects of oral contraceptives vary according to the presence of other risk factors for cervical cancer. Parazzini et al. (72) found that the relative risk associated with oral contraception was higher among women with multiple sexual partners, while two other groups found the effects to be greatest among women with genital infections (60, 61). Enhancement of the association with oral contraceptives among women of high parity has also been reported (72, 77).

Two studies demonstrated a higher risk of cervical neoplasia among users of oral contraceptives with high estrogen potency, but the effects of dose and duration of use were difficult to distinguish (61, 67).

Although the methodological problems affecting the interpretation of the association between oral contraceptives and cervical cancer have been stressed, it should be noted that there are several plausible mechanisms by which oral contraceptives might influence cervical carcinogenesis (56). Further research is needed to resolve whether the association between long-term use of oral contraceptives and risk of cervical cancer is causal. More definitive studies may be possible when the infectious agent involved in the etiology of cervical cancer has been established.

### 4.1.3 Adenocarcinoma of the cervix

An association between oral contraceptive use and the occurrence of cervical adenocarcinoma was suggested by Dallenbach-Hellweg, on the basis of a study of 28 cases (78), the majority of whom had been long-term users of the pill. Subsequently, descriptive surveys showed a rise in the incidence of cervical adenocarcinoma among young women, and oral contraceptive use was suggested as a possible explanation (79–81). In two case-control studies, the relative risk of adenocarcinoma associated with oral contraceptive use was higher than that of squamous cell neoplasia (61, 70). In three other studies, however, no such difference was found (82–84).

### 4.2 Conclusions

1. The interpretation of a relationship between use of combined oral contraceptives and risk of cervical squamous cell carcinoma or carcinoma *in situ* is complicated by a variety of potential biases and confounding factors. Recent studies suggest that use of oral contraceptives for more than 5 years is associated with a modest increase in relative risk (ranging from 1.3 to 1.8). The extent to which this reflects a biological relationship is uncertain, particularly given the absence of reliable information on the role of possible infectious agents, such as the human papillomaviruses.
2. There are insufficient data to draw any firm conclusions regarding the effects of combined oral contraceptives on the risk of cervical adenocarcinoma.

5. **Neoplasia of the breast**

5.1 **Benign breast disease**

The breast can be affected by a variety of disorders involving nonmalignant proliferation. Such disorders are important because they often produce a lump or lumpiness in the breast, which requires investigation in order to exclude cancer. A variety of terms have been used for the pathological description of benign breast disease, and the classification of the various forms is complex. The most common disorder is usually called fibrocystic disease, although many other terms, such as mammary dysplasia, chronic mastitis, and cystic hyperplasia are also used. This is a highly variable condition characterized by proliferation and regression of the mammary tissues, with an abnormal interplay of epithelial and connective tissue elements (85). Not all forms of fibrocystic disease are neoplastic, but the Scientific Group considered it appropriate to discuss them as a group in this report.

The second most common form of benign breast disease is fibroadenoma, which is also the commonest discrete benign tumour of the breast. It involves proliferation of both connective tissue and epithelium. A variety of other benign tumours of the breast, the majority of which are rare, will not be considered further.

Benign breast disease is a frequent cause of hospital admission, and it produces much anxiety because women affected by it may naturally fear that they have cancer. It is impossible to estimate accurately the occurrence of benign breast disorders, because many women with lumps or nodules in their breasts do not consult a physician, and only a minority receive a pathological diagnosis. The risk of fibrocystic disease appears to increase with age, peaking among women aged 40 to 50 years, whereas fibroadenomas tend to occur most commonly between 20 and 39 years of age (86).

Table 4 summarizes the main features of 15 case-control studies concerning the effects of oral contraceptives on the risk of benign breast disease. Of eight studies that reported relative risks for all types of benign breast disease combined, six found relative risks of less than 1.0 and none found a significant increase in risk; the summary relative risk (based on data from all eight studies) indicated that use of oral contraceptives at any time reduced the risk of benign breast disease by about 25% (102). Results from three cohort studies are largely consistent with these findings (32, 103, 104). All three studies found a reduced risk of benign breast disease among oral contraceptive users, although in the study conducted by the Royal
Table 4
Case–control studies of the association between oral contraceptive use and the risk of benign breast disease

<table>
<thead>
<tr>
<th>First author and year</th>
<th>Type of disease analysed</th>
<th>Number of cases</th>
<th>Number of controls</th>
<th>Reference number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vessey (1972)</td>
<td>BBD/FC/FA</td>
<td>255</td>
<td>255</td>
<td>87</td>
</tr>
<tr>
<td>Boston Collaborative Drug Surveillance Program (1973)</td>
<td>BBD</td>
<td>98</td>
<td>842</td>
<td>88</td>
</tr>
<tr>
<td>Sartwell (1973)</td>
<td>FC/FA</td>
<td>79/66</td>
<td>426/67</td>
<td>89</td>
</tr>
<tr>
<td>Kelsey (1974)</td>
<td>BBD</td>
<td>364</td>
<td>364</td>
<td>90</td>
</tr>
<tr>
<td>Fasal (1975)</td>
<td>BBD</td>
<td>578</td>
<td>785</td>
<td>91</td>
</tr>
<tr>
<td>Nomura (1976)</td>
<td>BBD</td>
<td>148</td>
<td>488</td>
<td>92</td>
</tr>
<tr>
<td>Kelsey (1978)</td>
<td>FC/FA</td>
<td>211/123</td>
<td>210/123</td>
<td>93</td>
</tr>
<tr>
<td>Lees (1978)</td>
<td>BBD</td>
<td>392</td>
<td>524</td>
<td>94</td>
</tr>
<tr>
<td>Ravnhar (1979)</td>
<td>FC/FA</td>
<td>266/106</td>
<td>266/106</td>
<td>95</td>
</tr>
<tr>
<td>Brinton (1981)</td>
<td>FC/FA</td>
<td>211/74</td>
<td>211/74</td>
<td>96</td>
</tr>
<tr>
<td>Pastides (1983)</td>
<td>FC</td>
<td>125</td>
<td>129</td>
<td>97</td>
</tr>
<tr>
<td>Berkowitz (1984)</td>
<td>FC</td>
<td>775</td>
<td>789</td>
<td>98</td>
</tr>
<tr>
<td>Odenheimer (1984)</td>
<td>BBD</td>
<td>90</td>
<td>90</td>
<td>99</td>
</tr>
<tr>
<td>Parazzini (1984)</td>
<td>BBD</td>
<td>288</td>
<td>285</td>
<td>100</td>
</tr>
<tr>
<td>Canny (1988)</td>
<td>FA</td>
<td>251</td>
<td>1081</td>
<td>101</td>
</tr>
</tbody>
</table>

Key: BBD = benign breast disease
FC = fibrocystic disease
FA = fibroadenoma

College of General Practitioners (32), the protective effect was limited to current users.

Five of the case–control studies (87, 90, 91, 94, 100) and the cohort study by Hislop & Threlfall (104) examined the relative risk of benign breast disease in relation to duration of use of oral contraceptives. All showed that the risk was particularly reduced among long-term users, and most showed a trend of decreasing risk with duration of use.

Of seven case–control studies that specifically examined the risk of fibrocystic disease in relation to oral contraception, only one (98) yielded results inconsistent with a protective effect in women who had at any time used oral contraceptives. Results from cohort studies by the Royal College of General Practitioners (32) and Ory et al. (105) were consistent with a protective effect, although in the former study this was found only in current users. There is evidence from several studies to suggest that the reduction in risk of fibrocystic disease is related to the duration of use of oral contraceptives (89, 93, 95–97, 105).

Of six case–control studies that specifically examined the risk of fibroadenoma in relation to use of oral contraceptives, all except one (89) reported a protective effect. Three studies that assessed the risk associated with long-term use showed a strongly protective effect (93, 96, 101). The cohort study by Ory et al. (105) showed a reduction in risk of fibroadenoma
only after 2 years of use of oral contraceptives, but the study by the Royal College of General Practitioners (32) found no appreciable protective effect.

Although several studies have suggested that the reduction in risk of benign breast disease is related to recency of use of oral contraceptives, this has not been found consistently (102). Two studies have indicated that the protective effects of oral contraceptives against all types of benign breast disease (106) and against fibrocystic disease (96) are related to the progesterogen content, with pills containing the highest progesterogen doses providing the greatest protection.

5.2 Breast cancer

The majority of breast cancers arise in the terminal ductal lobular unit of the breast.

5.2.1 Epidemiology

Breast cancer is the most common form of malignancy affecting women in the world. There were estimated to be about 572,000 new cases in 1980 (II). Incidence rates are high in most industrialized countries, with the exception of Japan. Although breast cancer is generally less common than cervical cancer in developing countries, it is more frequent in northern Africa, temperate South America, and western Asia (II). The incidence curve for breast cancer rises with age from 30 to 70 years, but there is an inflexion at around 45-54 years, after which rates increase much more slowly (12). Studies of migrants have shown that environmental factors are important in the etiology of this disease.

Risk factors for breast cancer include high socioeconomic status, nulliparity, a late first birth, early menarche, late menopause, a history of benign breast disease, a family history of breast cancer, and exposure to radiation (106). Endogenous hormones appear to have a role in the pathogenesis of breast cancer. The epidemiological picture is complex: for example, although married women have a lower lifetime risk than single women, the risk is higher among married women under about 40 years of age (107). Certain other factors such as parity and body weight also appear to show a cross-over in effects with age (108, 109). The major causes of breast cancer remain unknown.

5.2.2 Effect of oral contraceptive use on disease risk

Table 5 summarizes the main features of 18 case-control studies that examined the association between oral contraceptives and breast cancer over a broad range of ages. All except one (120) showed no significant alteration of risk among women who had at any time used oral contraceptives, and most yielded relative risk estimates close to 1.0. Similarly, five cohort studies found no significant difference in risk
Table 5

Case-control studies of the association between oral contraceptive use and the risk of breast cancer (over a broad range of ages)

<table>
<thead>
<tr>
<th>First author and year</th>
<th>Upper age limit (years)</th>
<th>Number of cases</th>
<th>Number of controls</th>
<th>Reference number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Henderson (1974)</td>
<td>64</td>
<td>307</td>
<td>307</td>
<td>110</td>
</tr>
<tr>
<td>Paffenbarger (1977)</td>
<td>50</td>
<td>452</td>
<td>872</td>
<td>111</td>
</tr>
<tr>
<td>Sartwell (1977)</td>
<td>74</td>
<td>284</td>
<td>367</td>
<td>112</td>
</tr>
<tr>
<td>Ravnihar (1979)</td>
<td>64</td>
<td>190</td>
<td>380</td>
<td>95</td>
</tr>
<tr>
<td>Kelsey (1981)</td>
<td>74</td>
<td>330</td>
<td>1348</td>
<td>113</td>
</tr>
<tr>
<td>Harris (1982)</td>
<td>54</td>
<td>109</td>
<td>468</td>
<td>114</td>
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<tr>
<td>Vessey (1983)</td>
<td>50</td>
<td>1176</td>
<td>1176</td>
<td>115</td>
</tr>
<tr>
<td>Rosenberg (1984)</td>
<td>59</td>
<td>1191</td>
<td>5026</td>
<td>116</td>
</tr>
<tr>
<td>Talamini (1985)</td>
<td>79</td>
<td>368</td>
<td>374</td>
<td>117</td>
</tr>
<tr>
<td>Cancer and Steroid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hormone Study (1986)</td>
<td>54</td>
<td>4613</td>
<td>4576</td>
<td>118</td>
</tr>
<tr>
<td>La Vecchia (1986)</td>
<td>60</td>
<td>776</td>
<td>1282</td>
<td>22</td>
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<tr>
<td>Lee (1987)</td>
<td>58</td>
<td>155</td>
<td>748</td>
<td>119</td>
</tr>
<tr>
<td>Ravnihar (1988)</td>
<td>54</td>
<td>534</td>
<td>1989</td>
<td>120</td>
</tr>
<tr>
<td>Rohan (1988)</td>
<td>69</td>
<td>394</td>
<td>386</td>
<td>121</td>
</tr>
<tr>
<td>Yuan (1988)</td>
<td>69</td>
<td>534</td>
<td>534</td>
<td>122</td>
</tr>
<tr>
<td>Stanford (1989)</td>
<td>&gt;60</td>
<td>2022</td>
<td>2183</td>
<td>123</td>
</tr>
<tr>
<td>WHO Collaborative Study of Neoplasia and Steroid Contraceptives (1990)</td>
<td>62</td>
<td>2116</td>
<td>13072</td>
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</tr>
<tr>
<td>Paul (1990)</td>
<td>54</td>
<td>891</td>
<td>1864</td>
<td>125</td>
</tr>
</tbody>
</table>

between women who had at any time used oral contraceptives and those who had never used them (126–130). In addition, no increase in risk has been observed among women who have taken oral contraceptives for up to 15 years or after up to 20 years following initial exposure.

Although there appears to be no overall association between oral contraception and the risk of breast cancer, studies of women with breast cancer diagnosed at young ages have been less reassuring. In the cohort study conducted by the Royal College of General Practitioners, the risk of breast cancer diagnosed before the age of 35 was higher among oral contraceptive users, although this was of borderline significance (127). A joint national case-control study in Sweden and Norway, confined to women under 45 years of age in Sweden and under 40 in Norway, reported a significant association between the total duration of oral contraceptive use and breast cancer risk (131). Such an association was also found in the large United Kingdom national case-control study of women in whom breast cancer had been diagnosed before the age of 36 (132). The relative risk was estimated to be 1.4 (95% CI 0.97–2.1) for 4–8 years of use and 1.7 (95% CI 1.2–2.6) for over 8 years of use. Most other case-control studies that have examined the risk of breast cancer in women under 45 years of age have also found some increased risk among long-term users of oral contraceptives (133, 134).
Studies of the effects of early use of oral contraceptives (before the age of 25 or the first full-term pregnancy) on breast cancer risk have yielded conflicting results (133, 134). The findings of case-control studies involving women over a broad range of ages suggest, when viewed together, that women who have used oral contraceptives before their first pregnancy are at no increased risk (133). Several studies of women under 45 years of age, however, found increased risks among women who had used oral contraceptives for long periods before their first pregnancy (131, 132, 135, 136). On the other hand, a case-control study in New Zealand (where use before the first pregnancy has been common) provided no support for this hypothesis, even when the analysis was confined to women under 45 years of age (125). In the case-control study reported from the United Kingdom, the relative risk of breast cancer diagnosed before the age of 36 was no higher among women who had used oral contraceptives before rather than after the first full-term pregnancy (132).

McPherson et al. (137) suggested that the reason why some studies failed to show an association was that they did not permit the emergence of a latent adverse effect, since they included women with a relatively recent history of use of oral contraceptives before the first pregnancy. Although such a latent effect remains a theoretical possibility, it does not appear to account for the discrepant findings of recent studies (125, 130, 138, 139).

The effects of using oral contraceptives near the age of the menopause have been investigated in only a few studies. Three studies showed a higher relative risk of breast cancer among oral contraceptive users over 45 (122, 140) or 50 years of age (141), but the results of two other case-control studies were more reassuring (116, 123). In the cohort study of American nurses reported by Romieu et al. (129), recent users of oral contraceptives over 40 years of age were at increased risk. Taken together, the results showed no consistent evidence of an increased risk of breast cancer among women using oral contraceptives near the age of the menopause.

Several studies have examined the association between oral contraceptives and breast cancer in women with and without various risk factors for breast cancer, such as nulliparity, early menarche, a family history of breast cancer, or a history of benign breast disease. As reviewed elsewhere (133, 134), no consistent pattern of increased or decreased risk has emerged.

The effects of particular formulations of combined oral contraceptives have also been studied. In 1983, Pike et al. (142) reported that the relative risk of breast cancer was particularly high among women who had used oral contraceptives with a high progestogen potency before the age of 25. The validity of the classification of progestogen potency used has been challenged (143), and these findings were not confirmed by the results of the Cancer and Steroid Hormone Study (144).

McPherson et al. (136) reported an increase in risk in association with duration of use, before the first birth, of oral contraceptives containing
ethinylestradiol, but not in relation to similar use of preparations containing mestranol. Three other studies yielded negative findings (130, 139, 145), suggesting that this difference occurred by chance, especially since mestranol is converted into ethinylestradiol in the body.

Three case-control studies (118, 132, 146) examined the relative risks associated with use of specific formulations of oral contraceptives. No single formulation was consistently linked to an increased or decreased risk of breast cancer. The cohort study reported by Vessey et al. (130) also found no evidence of any alteration in risk associated with use of particular formulations.

Possible sources of bias that could affect studies of oral contraceptives and breast cancer have been reviewed in detail (134, 147). The extent to which bias and chance might explain the various study results is uncertain. At present most positive associations have been found among women who develop breast cancer at a relatively early age. These observations have not been matched by any increased risk in relation to past oral contraceptive use among women who have reached the ages at which breast cancer becomes more common.

5.3 **Conclusions**

1. Numerous studies have found no overall association between oral contraceptive use and risk of breast cancer.
2. A number of recent studies have found a weak association between long-term use of oral contraceptives and breast cancer diagnosed before the age of 36, and perhaps up to the age of 45. Such cancers represent a very small proportion of all breast cancers. It is unclear whether this observed association is attributable to bias, the development of new cases of cancer, or accelerated growth of existing cancers.
3. Evidence indicates no increased risk of breast cancer associated with prior use of oral contraceptives in women over 45 years of age.
4. Oral contraception does not appear to alter the risk of breast cancer to a greater or lesser extent in subgroups of women at high or low risk of this disease (such as those with a family history of breast cancer).
5. Varying hormonal composition of oral contraceptives does not appear to influence the risk of breast cancer.
6. Use of combined oral contraceptives appears to decrease the risk of biopsy-confirmed fibrocystic disease and fibroadenoma. The degree of protection is related to duration of use.
6. **Neoplasia of the liver**

The liver can be the site of a variety of epithelial and nonepithelial tumours (148). Benign liver tumours are rare in women of childbearing age. Primary liver cancer is also rare in young women in developed countries, but it is a significant problem in many developing countries.

6.1 **Benign liver tumours**

The benign liver tumours that occasionally affect young women are clinically significant because they may present as a mass in the liver which can be mistaken for hepatocellular carcinoma, and because they sometimes rupture, causing severe intraperitoneal haemorrhage.

An association between benign liver tumours and use of oral contraceptives was first suggested by Baum et al. (149), on the basis of seven cases in women of childbearing age who had all used oral contraceptives. There followed many case reports, mainly involving *hepatocellular adenoma* or *focal nodular hyperplasia* (150). A survey of patients with liver tumour in 749 hospitals in the USA was conducted from 1970 to 1975 (151, 152). Whereas there were similar numbers of malignant tumours in women and men, there were 212 benign tumours in women and only 15 in men. A high proportion of the women with hepatocellular adenoma or focal nodular hyperplasia whose contraceptive histories were known had used oral contraceptives.

Individual case reports do not provide strong evidence for a causal relationship between oral contraceptives and benign liver tumours, especially since there could be selective reporting of cases involving use of oral contraceptives. It should be noted, however, that there have been case reports of both hepatocellular adenoma and focal nodular hyperplasia regressing in women who stopped using oral contraceptives (150).

Although no case-control studies of focal nodular hyperplasia have been reported, there have been two case-control studies of hepatocellular adenoma. In the first (153), 34 cases drawn from a surgical registry for hepatocellular adenoma in Los Angeles, CA, USA, were compared with a control group consisting of friends of these patients. The relative risk increased with the duration of use of oral contraceptives, rising to 25 for more than 9 years' use. The second study, which was also conducted in the USA (154), involved cases reported to the United States Armed Forces Institute of Pathology, Washington, DC. Comparisons were made between 79 cases and up to three controls selected from the same neighbourhood as each patient. Again there was a striking increase in the relative risk with duration of use, with a relative risk estimate of 503 for women who had used oral contraceptives for more than 7 years. The results obtained were similar whether hepatocellular adenoma had been diagnosed before or after publication of the initial report of Baum et al., which suggested that reporting bias did not explain the association.
Whereas the first study suggested a specific association with oral contraceptives containing mestranol, this was not confirmed in the second study which found similar associations for preparations containing mestranol and ethinylestradiol (154). The risk of hepatocellular adenoma appeared to be higher in women who had used oral contraceptives with high estrogen potency and in women over 30 years of age. These observations should be interpreted with caution, however, because older women were more likely to have used the early oral contraceptive preparations (which were of high hormonal potency) and would also have had more opportunity to use oral contraceptives for long periods. The data available did not permit the relationship between age, hormonal potency, and duration of use to be worked out.

6.2 **Liver cancer**

The vast majority of primary cancers that occur in the liver are hepatocellular carcinomas. Cholangiocarcinoma (a cancer of the intra-hepatic bile ducts) is generally much less common, although it is more frequent in parts of south-east Asia.

6.2.1 **Epidemiology**

There were estimated to be about 250,000 new cases of liver cancer in the world in 1980; three-quarters of these were in developing countries (117). The incidence of liver cancer is particularly high in sub-Saharan Africa, south-east Asia, China, Japan and Melanesia. The disease is more common in males than females, with a sex ratio for incidence of about 3:1 in high-risk areas and about 1.5:1 in areas of lower risk.

The geographical distribution of liver cancer shows a relatively close correlation with the prevalence of chronic carriers of hepatitis B surface antigen. Epidemiological and laboratory investigations have established a strong and specific association between infection with hepatitis B virus (HBV) and hepatocellular carcinoma (12). It is estimated that chronic infection with HBV may account for 55–95% of hepatocellular carcinomas in high-risk populations, but only 1–10% in populations at low risk (155). Other factors that have been implicated include aflatoxin contamination of foodstuffs and alcohol (155).

6.2.2 **Effect of oral contraceptive use on disease risk**

There have been reports of hepatocellular carcinoma occurring in conjunction with hepatocellular adenoma or focal nodular hyperplasia in women who have used oral contraceptives (150). In addition there have been many other case reports of primary liver cancers in users of oral contraceptives, although these do not provide strong evidence for a causal relationship (150).

Table 6 summarizes the main features of seven case-control studies carried out to examine the association between use of oral contraceptives and the
Table 6
Case–control studies of the association between oral contraceptive use and the risk of liver cancer

<table>
<thead>
<tr>
<th>First author and year</th>
<th>Country</th>
<th>Number of cases</th>
<th>Number of controls</th>
<th>Reference number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Henderson (1983)</td>
<td>USA</td>
<td>11</td>
<td>22</td>
<td>156</td>
</tr>
<tr>
<td>Neuberger (1986)</td>
<td>UK</td>
<td>26</td>
<td>1333</td>
<td>157</td>
</tr>
<tr>
<td>Forman (1986)</td>
<td>UK</td>
<td>30(19)a</td>
<td>147</td>
<td>158</td>
</tr>
<tr>
<td>Palmer (1989)</td>
<td>USA</td>
<td>12(9)a</td>
<td>60</td>
<td>159</td>
</tr>
<tr>
<td>La Vecchia (1989)</td>
<td>Italy</td>
<td>21</td>
<td>145</td>
<td>160</td>
</tr>
<tr>
<td>WHO Collaborative Study of Neoplasia and Steroid Contraceptives (1989)</td>
<td>Multicentre b</td>
<td>122</td>
<td>802</td>
<td>161</td>
</tr>
<tr>
<td>Kew (1990)</td>
<td>South Africa</td>
<td>46</td>
<td>92</td>
<td>162</td>
</tr>
</tbody>
</table>

a Figure in parentheses refers to the number of cases of hepatocellular carcinoma.
b This study was conducted in Chile, China, Colombia, Israel, Kenya, Nigeria, the Philippines and Thailand.

risk of liver cancer. None of the five studies of hepatocellular carcinoma conducted in low-risk populations involved more than 26 cases; hence it was not possible to estimate relative risks with any precision, or to explore thoroughly the influence of potential confounding variables or factors that might have modified the effect of oral contraceptives (e.g., HBV infection or alcohol). Several of the studies also had other methodological limitations. For example, in one investigation (157), the controls were drawn from another study and different interviewers and questionnaires were used for the case and control groups.

Despite these limitations, the five studies in low-risk populations showed that the risk of hepatocellular carcinoma was increased among users of oral contraceptives. In the largest of these studies (157), the relative risk was 1.0 (95% CI 0.4-2.4) for women who had at any time used oral contraceptives. However, for 8 or more years of oral contraceptive use, the relative risk was 4.4 (95% CI 1.5-12.8). In another study (159), there was a strong association between use of oral contraceptives for at least 2 years and risk of hepatocellular carcinoma, but no evidence of an association with duration of use. The other three studies found strong associations with long-term use of oral contraceptives (156, 158, 160).

With a few exceptions, the cases included in the studies described above had non-cirrhotic livers and no evidence to suggest infection with HBV. (There was, however, no systematic investigation of this viral infection.) Clearly it is important to determine whether the relative risks observed in low-risk populations also apply in countries in which both HBV infection and hepatocellular carcinoma are common.

Two case–control studies have been carried out in high-risk populations. The larger study was conducted by WHO in seven developing countries and Israel (161). Based on data from 122 women with primary liver cancer
and 802 matched controls, the relative risk of liver cancer among women who had at any time used combined oral contraceptives was estimated to be 0.7 (95% CI 0.4-1.2). The relative risk for women with a histological diagnosis of hepatocellular carcinoma was 0.6 (95% CI 0.2-1.6), while the relative risk was 1.2 (95% CI 0.5-3.1) for women with cholangiocarcinoma and 0.5 (95% CI 0.02-1.3) for cases diagnosed on a clinical basis alone. There was no consistent trend in risk with duration of use or with time since first or last use. However, only 8 cases and 66 controls had used oral contraceptives for more than 3 years. There was also no investigation of HBV infection status.

The second case-control study was carried out in a population of black women in South Africa, and included 46 cases of histologically confirmed hepatocellular carcinoma and 92 controls (I62). Examination of serum specimens revealed serological evidence of current or past HBV infection in 44 cases. The association between oral contraceptive use and risk of hepatocellular carcinoma was not statistically significant: the relative risk estimate was 1.9 (95% CI 0.6-5.6) among women who had at any time used oral contraceptives and 1.5 (95% CI 0.3-7.2) for more than 8 years of use, based on data from 3 cases and 4 controls.

There are at least two possible explanations for the lack of association in the two case-control studies described above. First, if any increased risk of liver cancer is confined to long-term users of oral contraceptives, these studies may not have contained enough long-term users for the risk to be detected. Secondly, if the effect of oral contraceptives on liver cancer risk is independent of HBV, or even confined to women without prior HBV infection, the influence of oral contraceptives on relative risk in women from HBV-endemic areas would be small and difficult to detect. Whatever explanation applies, it appears that short-term use of oral contraceptives does not enhance the risk of hepatocellular carcinoma in countries where this disease is common.

Two of the case-control studies provided data concerning 11 and 30 women, respectively, with cholangiocarcinoma (I58, I61), but there was no evidence to suggest an association between the risk of this disease and use of oral contraceptives.

6.3 Conclusions

1. Benign hepatic adenoma is a rare consequence of oral contraceptive use.
2. In populations in which hepatocellular carcinoma is uncommon, this disease is a rare consequence of oral contraceptive use.
3. In populations in which both HBV infection and hepatocellular carcinoma are common, short-term use of oral contraceptives does not appear to be associated with an increased risk. Data on the effects of long-term use are scarce.
7. Other types of neoplasia

7.1 Malignant melanoma of the skin

Malignant melanoma has become an increasing problem in recent decades, with incidence rates in white-skinned populations doubling approximately every 10 to 15 years (I63). This increase has been occurring in males as well as females, and is probably mainly due to increased exposure to the sun (I63). One of the major risk factors for melanoma is the number of benign melanocytic naevi (or common moles) on the skin (I64, I65). These are particularly common in fair-skinned people, who tend to burn rather than tan, and people who have been heavily exposed to ultraviolet radiation from the sun (especially early in life) (I66, I67).

Hyperpigmentation of the skin is often observed during pregnancy and with use of oral contraceptives (I68). An influence of sex hormones on pigment cells is also suggested by the apparent proliferation of naevi that occurs at puberty (I69, I70).

7.1.1 Effect of oral contraceptive use on disease risk

Two studies of the association between use of oral contraceptives and number of naevi have been published (I70, I71). In a Scottish survey of 124 women aged 20-59 years, a higher mean naevus count in women using oral contraceptives was not statistically significant once the younger age of the oral contraceptive users had been taken into account (I70). An investigation of the controls selected for a hospital-based case-control study of melanoma in Glasgow and Edinburgh, Scotland (I71), revealed slightly higher naevus counts among women who had at any time used oral contraceptives than among those who had never used the pill, although again the difference was not statistically significant. The relative risk of having a high naevus count was estimated to be 1.6 (95% CI 0.5-5.6), with no trend in risk with the duration of use of oral contraceptives, the age at first use, or the time since first use. In both of these studies, no adjustment was made for the possible confounding influences of skin complexion and exposure to sunlight.

The possibility of an association between oral contraceptives and risk of malignant melanoma was examined indirectly by Stevens et al. (I72), who used data from several countries to compare temporal trends in melanoma rates among females with those among males. They reported no perturbation in incidence or mortality rates in females compared with those in males, at or up to 10 years after the introduction of oral contraceptives.

The case-control and cohort studies of the effect of oral contraceptive use on the risk of melanoma have mostly been limited by small sample sizes and by lack of accurate information on potential confounding variables, particularly phenotype with regard to sensitivity to the sun and exposure to ultraviolet radiation.
Table 7

<table>
<thead>
<tr>
<th>First author and year</th>
<th>Number of cases</th>
<th>Number of controls</th>
<th>Reference number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adam (1981)</td>
<td>110</td>
<td>340</td>
<td>173</td>
</tr>
<tr>
<td>Bain (1982)</td>
<td>141</td>
<td>2820</td>
<td>174</td>
</tr>
<tr>
<td>Holly (1983)</td>
<td>87</td>
<td>863</td>
<td>175</td>
</tr>
<tr>
<td>Beral (1984)</td>
<td>287</td>
<td>572</td>
<td>176</td>
</tr>
<tr>
<td>Helmarich (1984)</td>
<td>160</td>
<td>640</td>
<td>177</td>
</tr>
<tr>
<td>Holman (1984)</td>
<td>276</td>
<td>276</td>
<td>178</td>
</tr>
<tr>
<td>Gallagher (1985)</td>
<td>333</td>
<td>333</td>
<td>179</td>
</tr>
<tr>
<td>Green (1985)</td>
<td>91</td>
<td>91</td>
<td>180</td>
</tr>
<tr>
<td>Osterling (1988)</td>
<td>280</td>
<td>536</td>
<td>181</td>
</tr>
</tbody>
</table>

The main features of nine case-control studies are summarized in Table 7. None of these reported a significant trend in risk of cutaneous melanoma with duration of use of oral contraceptives. Long-term use, which was defined variously as use for at least 3 years to use for at least 10 years, was not associated with any significant increase in risk. The point estimates of relative risk among long-term users were above 1.0 in four studies (173, 175, 176, 178), equal to 1.0 in two studies (177, 181), and below 1.0 in three studies (174, 179, 180). Although the available data were limited, there was no consistent evidence of an increased risk of specific histological types of melanoma or of melanoma occurring at particular body sites (182). Nor was there convincing evidence of an association with use of oral contraceptives at specific ages, with use in the past, or with use of particular types of oral contraceptives (182).

Two cohort studies (173, 183) have examined the association between oral contraceptives and melanoma; both included fewer than 20 cases. In a follow-up study of 17,942 women aged 25-54 years in California, USA, there was a trend of increasing incidence with duration of use of oral contraceptives (183). The relative risk of melanoma in women who had used oral contraceptives for 4 years or more was 1.7. No adjustments were made for skin phenotype or exposure to the sun. In contrast, a report from the Oxford Family Planning Association study suggested a declining incidence with duration of use of oral contraceptives, although this conclusion was based on analysis of only 12 cases (173).

7.1.2 Conclusions

1. Available data do not suggest an association between oral contraceptive use and the risk of cutaneous melanoma.
2. While there is no evidence to suggest that oral contraceptives affect the occurrence of benign melanocytic naevi, few studies have addressed this issue.
7.2 **Colorectal cancer**

Cancers of the colon and rectum are common. There has long been interest in the possibility that sex hormones might play a role in the pathogenesis of colon cancer. This interest has stemmed from several observations, including the correlation of the incidence rate of colon cancer with the incidence rate of breast cancer in different countries, an increased risk of colon cancer among women with female endocrine cancers, and findings from several case-control studies showing that parity is associated with a reduced risk (184). McMichael & Potter (185) hypothesized that exogenous sex hormones (including oral contraceptives) might reduce the risk of colon cancer by causing changes in the production and metabolism of bile acids and cholesterol. The discovery of estrogen receptors in human colon cancers and in the surrounding tissues has further supported a possible role for hormones in the etiology of colon cancer.

7.2.1 **Effect of oral contraceptive use on disease risk**

Several studies, both case-control and cohort, have examined the effect of oral contraceptive use on the risk of colon cancer (186). Some studies showed positive associations, some found negative associations and some reported no association. Some included only cases of colon cancer, while others also included rectal cancer. The 95% confidence intervals in every study were wide, and most did not exclude unity. One study suggested an association between use of oral contraceptives and cancer in the ascending colon, but this finding was based on limited data.

7.2.2 **Conclusions**

Studies of the possible association between oral contraceptives and colon cancer show no consistent pattern. Because the number of cases in most studies has been small, the possibility has not been excluded that use of oral contraceptives is associated with a slightly increased or decreased risk of colorectal cancer or of cancer in specific parts of the colon.

7.3 **Cancer of the gallbladder and extrahepatic bile ducts**

Cancer of the gallbladder is uncommon in most countries, although in certain populations (native Americans, people living in central and eastern Europe and in Israel) it ranks among the five most common malignancies diagnosed in women (187). Cancer of the extrahepatic bile ducts tends to be less common, and unlike gallbladder cancer, occurs with similar frequency in males and females (187).

There has been interest in a possible role of oral contraceptives in the etiology of gallbladder cancer because of evidence that oral contraceptives can affect bile composition and gallbladder function (186) and epidemiological reports linking oral contraception with an increased risk of cholelithiasis and cholecystitis. The latter issue remains controversial; although the risk of surgically confirmed gallbladder disease among users
of oral contraceptives was initially reported to be twice that among non-users (88), many studies conducted subsequently have yielded inconsistent results (186). It was suggested that oral contraceptives may accelerate the development of gallbladder disease in women who are predisposed to this condition, perhaps without increasing their lifetime risk (150, 186).

7.3.1 **Effect of oral contraceptive use on disease risk**

The WHO Collaborative Study of Neoplasia and Steroid Contraceptives (188) found a nonsignificant relative risk of gallbladder cancer of 0.6 among women who had at any time used oral contraceptives. No pattern of increasing or decreasing risk was found with duration of use or with time since first or last use of oral contraceptives, nor was there any evidence to suggest an interaction between oral contraception and a history of gallbladder disease. Although this study was limited by the small number of cases, it provided some reassurance that oral contraceptives do not increase the risk of gallbladder cancer.

A hospital-based case-control study in New England, USA (189), compared 27 women with cancer of the extrahepatic bile ducts with patients with a variety of other cancers. It was reported that the risk of extrahepatic bile duct cancer was significantly increased among users of oral contraceptives, but this finding needs to be interpreted with caution, because of the small number of cases involved, the nature of the control group, and the lack of adjustment for possible confounding variables (including age and obesity).

7.3.2 **Conclusions**

There is no clear evidence to suggest that use of oral contraceptives increases the risk of cancers of either the gallbladder or the extrahepatic bile ducts.

7.4 **Pituitary tumours**

Pituitary tumours are rare, and the majority are benign adenomas. There has been interest in a possible role of oral contraception in the etiology of the prolactin-secreting tumours known as prolactinomas (190). Women with these tumours may experience menstrual disturbances and galactorrhoea. During pregnancy estrogens stimulate the growth of prolactin-secreting cells and the pituitary increases in size and weight (191, 192). Furthermore, prolactin-secreting pituitary tumours have estrogen receptors (193, 194) and their growth may be enhanced during pregnancy (192).

7.4.1 **Effect of oral contraceptive use on disease risk**

Overall, there is little evidence to suggest an increase in risk of pituitary tumours due to oral contraceptive use from either case-control or cohort studies (186).
7.4.2 **Conclusions**

Available evidence indicates that the risk of pituitary tumours is not altered by use of oral contraceptives.

8. **Relevance of existing data to developing countries**

When a WHO Scientific Group met in 1977 to consider steroid contraception and the risk of neoplasia, almost all of the available information had been derived from studies in the more developed countries (3). It was difficult to assess whether such knowledge was relevant to less developed countries, because there are marked geographical variations in the incidence of particular forms of neoplasia, the prevalence of risk factors, the patterns of use of steroid contraceptives, and the provision of relevant health services. Accordingly, the Group recommended that WHO should provide assistance with research concerning the effects of steroid contraceptive use on the risk of neoplasia in developing countries.

It was also recommended that WHO should establish a major, multicentre, hospital-based case-control study, to be conducted largely in developing countries, with the aim of determining whether various oral and injectable steroid contraceptives alter the risk of cancers of the breast, uterus (corpus and cervix), ovary, and hepatobiliary system. This WHO Collaborative Study of Neoplasia and Steroid Contraceptives was conducted in three centres in developed countries (Australia, the German Democratic Republic, and Israel) and 10 centres in eight developing countries (Chile, China, Colombia, Kenya, Mexico, Nigeria, the Philippines, and Thailand). In Thailand, two centres in Bangkok and one in Chiang Mai participated.

8.1 **Research findings in developing countries**

Published results from the WHO study pertaining to oral contraceptives have been cited in the relevant parts of this report (28, 46, 50, 60, 124, 161, 188). These results have recently been reviewed in the light of the other studies conducted in developing countries (195). The protective effects of oral contraceptives against cancers of the ovary and endometrium appear to be similar in magnitude in developing and developed countries. There is currently no evidence to suggest that oral contraception appreciably enhances the risk of liver cancer in countries where hepatitis B is endemic, and oral contraceptives do not appear to affect the risk of gallbladder cancer. In the WHO study, there was no significant difference between the results concerning oral contraceptive use and the risk of breast cancer obtained in developing and developed countries (124).

The results of the WHO study and other investigations in developing countries suggest that, as in developed countries, there is an association between prolonged use of oral contraceptives and the risk of cervical
cancer (60, 195). It is not yet clear whether this reflects a causal relationship or the confounding influence of sexual behaviour. The relative risk appears to be no greater in developing than in developed countries but, if the association were causal, the attributable risk (the difference between risk in oral contraceptive users and risk in non-users) would be highest in countries where cervical cancer is most common. Cytological screening with appropriate follow-up and treatment can be an effective means of controlling cervical cancer (196, 197), and ideally, all women who have been sexually active should be offered cervical screening. However, this may not yet be possible in some developing countries and, where resources are limited, the case for providing cervical screening programmes has to be considered in relation to other public health priorities.

On the basis of the evidence currently available, it would appear that most results from studies of oral contraceptives and cancer that have been conducted in developed countries are likely to be applicable to developing countries.

8.2 Risk–benefit considerations

The Scientific Group reviewed the evidence that oral contraceptives protect against the development of some forms of neoplasia, while they appear to increase the risk of certain others. In deciding whether to choose this method of contraception, women and family-planning providers need to consider all the benefits and risks of using oral contraceptives, not only those relating to neoplasia.

The outstanding benefit of oral contraception is that it offers a highly effective, convenient, and reversible method for preventing unplanned pregnancies. Other benefits and risks of oral contraception have been reviewed elsewhere (2, 150, 198). The benefits of using combined oral contraceptives include reductions in the incidence of menstrual problems (such as dysmenorrhea and menorrhagia), iron deficiency anaemia, pelvic inflammatory disease, ectopic pregnancy, and functional ovarian cysts. The most serious adverse effects that have been attributed to use of combined oral contraceptives are their rare cardiovascular complications, including myocardial infarction, thrombotic stroke, haemorrhagic stroke, and venous thrombosis and embolism. These risks were demonstrated mainly in studies of British and American women who were using oral contraceptives that contained higher doses of steroid hormones than those present in most modern formulations. In this regard, the World Health Organization is currently conducting a multicentre case-control study to determine whether the risks apply in developing countries and whether they are lower with modern low-dose oral contraceptives.

The benefits and risks of oral contraceptives need to be assessed in relation to the specific circumstances of particular countries or groups of countries, because they will be influenced by both the underlying incidence of diseases and the risk of maternal mortality (199). In countries where
maternal mortality is high, the effectiveness of oral contraceptives in preventing pregnancy will be of overwhelming importance. The balance of benefits and risks may also be different for certain groups of women. For example, studies in developed countries suggest that the risk of myocardial infarction associated with oral contraceptive use is mainly found in women who also smoke cigarettes.

The information reviewed in this report does not identify particular groups of women who should avoid using oral contraceptives because of a specific risk of neoplasia. Nor would the evidence currently available about neoplasia provide grounds for revising the generally favourable assessment of the benefits of oral contraception.

9. **Recommendations**

9.1 **General recommendations**

1. On the basis of the evidence currently available about neoplasia, the Scientific Group recommends no changes to family planning policies concerning the use of oral contraceptives.

2. Any assessment of benefits and risks of oral contraceptive use for individual countries should take into account the implications of unplanned pregnancies as well as effects on the frequency of various diseases.

3. Patterns of use and formulations of oral contraceptives have changed substantially over the years and continue to change. Because results from past studies may not be applicable to newer patterns of use and formulations, the Group recommends that the association between oral contraceptive use and the risk of neoplasia be reassessed periodically.

4. Because oral contraceptives were first marketed 30 years ago, the effects of oral contraceptive use on the risk of neoplasia (e.g., protection against ovarian and endometrial cancers) have been studied predominantly in women under 55 years of age. The Group recommends that studies be conducted to determine whether observed effects persist among women who have reached the ages at which many of the neoplasms occur more commonly. For example, persistent protection against ovarian cancer among older women would be of public health importance.

9.2 **Specific recommendations**

*Neoplasia of the ovary*

Studies are needed:

- to determine whether the protective effect observed after discontinuation of oral contraceptive use persists among older women who are at higher risk of ovarian cancer;
— to determine the biological mechanisms underlying the inhibitory effect of combined oral contraceptives on epithelial ovarian tumours.

**Neoplasia of the uterine corpus**

1. Studies of endometrial cancer should be conducted to determine whether past use of combined oral contraceptives continues to exert a protective effect in older women. The influence of hormone replacement therapy and body weight or body mass index should be taken into account.

2. Existing data on endometrial cancer should be re-examined to determine whether the risk of the disease varies according to relative amounts of estrogen and progestogen contained in combined oral contraceptives, and the type and amount of progestogen.

3. Epidemiological studies should be conducted to determine whether the oral contraceptives now in common use affect the risk or course of uterine fibroids.

**Neoplasia of the uterine cervix**

1. Research is needed to elucidate biological mechanisms of the effects of oral contraceptives on cervical epithelium.

2. The effect of oral contraceptives on the risk and natural history of cervical neoplasia requires further study.

3. Studies are needed to assess the possible interactive effects of oral contraceptives and infectious agents on the risk of cervical neoplasia. Both the effect of oral contraceptives on infectious agents and the response of cells to those agents should be investigated.

4. Further studies are required on the effects of combined oral contraceptives on the risk of cervical adenocarcinoma.

**Neoplasia of the breast**

1. Epidemiological studies in women over the age of 40 should be conducted to evaluate whether the relative risk of breast cancer in long-term users of oral contraceptives increases, decreases, or remains constant with age.

2. Studies are required to evaluate whether use of oral contraceptives by perimenopausal women alters their risk of breast cancer.

3. Studies are required to compare survival rates in women with breast cancer who have, or have not, used oral contraceptives.

4. Studies combining epidemiological and laboratory research methods should be encouraged to investigate any interaction between oral contraceptives and biological markers of breast cancer susceptibility. Studies on the biological behaviour of the normal and premalignant human breast, especially in relation to hormone sensitivity, are needed.
5. Research is needed on the potency of different estrogens, progestogens, and combinations of these hormones, with regard to their effects on the breast.

**Neoplasia of the liver**

Studies should be conducted on the effect of long-term use of oral contraceptives on the risk of hepatocellular carcinoma in the presence and absence of hepatitis B infection and other risk factors.

**Malignant melanoma of the skin**

Further studies should be conducted on the effects of oral contraceptive use on the development of melanocytic naevi, the major risk factor for melanoma.

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