HORMONAL CONTRACEPTIVES AND THE RISK OF CANCER

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Introduction

Some 55 million women throughout the world currently use hormonal contraceptives; an even greater number have used them at some time in their lives. This popularity of hormonal contraceptives is not surprising. For women who want to avoid or delay pregnancy, these methods offer a number of advantages: they are unsurpassed in effectiveness, and they are considered by many women to be convenient and discreet to use. However, one of the main concerns for women who consider whether or not to use hormonal contraceptives, is how these hormones might affect the risk of cancer. Obviously this is a question also asked by people who provide contraceptives, or who make recommendations concerning contraceptive use.

It has been known for some time that steroid hormones have an effect on the risk of cancer. Hormone-related events such as menarche, pregnancy and lactation have been shown to be related to a woman’s risk of cancer. It is well established that exogenous steroid hormones can increase cancer risk; diethylstilbesterol (DES) use has been related to the development of vaginal cancer, and conjugated estrogens used after menopause increase the risk of endometrial cancer. On the other hand, steroid hormones can also decrease cancer risk; for example, there is substantial evidence that combined oral contraceptives decrease the risk of ovarian cancer.

Since hormonal contraceptives are used by more people (women) than any other drug, with the possible exception of vaccines, and since cancer ranks high among causes of mortality among women of reproductive age, an effect of hormonal contraceptives on the risk of any of the more common cancers could have major implications for women’s health. Furthermore, unlike the cardiovascular disease risks associated with oral contraceptive use, effects on cancer risk do not generally disappear once the contraceptive is stopped.

Information available

A substantial amount of information is available on the use of oral contraceptives and the risk of some cancers, such as endometrial cancer, ovarian cancer, breast cancer and cervical cancer; however, the vast majority of the data come from a limited part of the world, namely the United States of America and Europe. Only lately have large-scale studies on this topic been initiated in developing countries, where oral contraceptive use is more recent but increasing. Most of the data come from case-control studies; only a few cohort studies have been of sufficient size and duration to allow cancer risk to be calculated.

The only other hormonal contraceptive for which data are available on the risk of cancer is depot-medroxyprogesterone acetate (DMPA), an injectable contraceptive.

Données disponibles

Il existe une somme importante de données sur la contraception orale et le risque de contracter certains cancers, endomètre, ovaire, sein et col de l'utérus notamment, mais ces données viennent pour l'essentiel d'une partie limitée du monde, à savoir les États-Unis d'Amérique et l'Europe. Il y a peu de temps seulement qu'ont été entreprises des études à grande échelle dans les pays en développement, où le recours à la contraception orale est plus récent mais en augmentation. La plupart de ces données proviennent d'études cas-témoins; quelques études de cohortes seulement ont été d'une ampleur et d'une durée suffisantes pour qu'il soit possible de calculer le risque de cancer.

Le seul autre contraceptif hormonal pour lequel existent des données sur le risque de cancer est l'acétate de médroxyprogesterone-retard (AMPR) qui est une préparation


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Other injectable contraceptives, such as norethisterone enanthate (NET-EN), have been used by too few women to allow adequate studies to be done. The implantable contraceptive, NORPLANT® has become available only recently; studies of cancer risk will need to be done once a sufficient number of women have used this contraceptive for a reasonably long period of time. Almost all of the information on DMPA use and the risk of cancer among women comes from an ongoing WHO collaborative study. Preliminary results from five centres (Kenya, Mexico and three centres in Thailand) were recently published in a report from a WHO meeting on DMPA and cancer (1). Other studies in New Zealand and Costa Rica are either under way or recently completed, but results have not yet been published. A few early studies conducted in the United States were limited by their size and design.

The information available on hormonal contraceptives and cancer is limited for several reasons. Most importantly, since cancer is relatively rare among young women, studies of cancer and hormonal contraceptives require that a very large number of women in a population have used the contraceptive of interest. Furthermore, cancer usually does not become apparent immediately following exposure to a possible carcinogen. The latency period is often as long as a decade or more; thus it is usually not meaningful to study cancer risk until long after exposure. Finally, all studies need to take into account potential confounding variables; this is discussed in more detail later.

This article reviews the data available for both oral contraceptives and DMPA, for the following cancer sites: ovary, endometrium, breast, cervix and liver.

Ovarian cancer

At least eight case-control studies of ovarian cancer and combined oral contraceptives have been published, and the consistency of the results is impressive (2-9) (Table 1). Combined oral contraceptives appear to reduce the risk of ovarian cancer by 40-50%. This protective effect also seems to persist for at least 10 years after oral contraceptives are stopped (4, 5). Some studies also show a decreasing risk with increasing duration of use (3-5).

Two studies from the United States did not suggest any change in the risk of ovarian cancer with the use of the injectable contraceptive DMPA (10, 11). However, most of the women in the study used DMPA for less than one year and the number of subjects was small, limiting the conclusions that could be drawn. WHO reported preliminary results from its ongoing study of cancer and steroid contraceptives (Table 2). The data on ovarian cancer showed a relative risk of 0.7 (95% confidence interval 0.3-1.7) with DMPA use (1). Although the data were insufficient to evaluate the effect of long-term use or use injectable. The other contraceptifs injectables, tel l’éan­nthathe de norethisterone (NET-EN), ont été utilisés par trop peu de femmes pour que des études puissant leur être consa­crées. Le contraceptif implantable NORPLANT® n’a été intro­duit que récemment. Il faudra lui consacrer des études sur le risque de cancer lorsqu’un nombre suffisant de femmes l’auront utilisé assez longtemps. La quasi-totalité des renseigne­ments disponibles sur l’AMPR et le risque de cancer chez la femme proviennent d’une étude collective de l’OMS et de cancer en cours. Les résultats préliminaires obtenus dans cinq cen­tres (Kenya, Mexique et trois centres en Thaïlande) ont récemment été publiés dans le rapport d’une réunion de l’OMS sur l’AMPR et le cancer (1). D’autres études exécutées en Nouvelle-Zélande et au Costa Rica sont en cours ou vien­nent de s’achever mais leurs résultats n’ont pas encore été publiés. Quelques études ont déjà été consacrées à ces pro­duits aux Etats-Unis mais elles étaient d’ampleur et de conception limitées.

Les renseignements existants sur les contraceptifs hormo­naux et le cancer sont limités pour plusieurs raisons. Premiè­rement, dans la mesure où le cancer est relativement rare chez les femmes jeunes, les études sur les risques éventuels d’un contraceptif hormonal exigent qu’un très grand nombre de femmes dans une population donnée ait eu recours au produit concerné. Par ailleurs, le cancer n’apparaît générale­ment pas immédiatement après l’exposition à un éventuel agent cancérigène. L’enceinte de latence dure le plus souvent une dizaine d’années ou davantage si bien qu’il ne sert générale­ment à rien d’étudier les risques de cancer peu après l’expo­sition. Enfin, il faut aussi toujours tenir compte des variables qui peuvent être sources de confusion : ce problème est exa­miné en détail plus loin.


Cancer de l’ovaire

Au moins huit études cas-témoins sur le cancer de l’ovaire et les contraceptifs oraux associés ont été publiées et la cohérence des résultats est impressionnante (2-9) (Tableau 1). Les contraceptifs oraux associés paraissent ré­duire de 40-50% le risque de cancer ovarian. Il semble en outre que cet effet protecteur persiste 10 ans au moins après l’arrêt de la prise des contraceptifs (4, 5). Enfin, d’après cer­taines études, le risque diminue en même temps que croit la durée d’utilisation (3-5).

D’après deux études réalisées aux Etats-Unis, il ne semble pas que le risque de cancer ovarian soit modifié par l’utilisa­tion du contraceptif injectable AMPR (10, 11). Toutefois, les femmes sur lesquelles a porté l’étude étaient peu nombreu­ses et la plupart avaient pris de l’AMPR pendant moins d’un an, ce qui limite les conclusions. D’après les résultats préli­minaires de l’étude de l’OMS sur le cancer et les stéroïdes contraceptifs (Tableau 2), le risque relatif de cancer ovarian pour les utilisatrices d’AMPR serait de 0,7 (intervalle de confiance à 95% : 0,3-1,7) (1). Bien que les données dispo­sibles n’aient pas permis d’évaluer les effets d’une utilisation

| TABLEAU 1. ÉTUDES CAS-TÉMOINS SUR LES CONTRACEPTIFS ORAUX ET LE CANCER DE L’OVaire |
|-----------------------------------|----------------------------------|------------------|----------------|
| **Investigateurs — Chercheurs**   | **Nombre de cas/témoins**       | **Relative risk** | **95% confidence limits** |
| Casagrande et al. (1979)          | 150/150                          | 0.7              | —                      |
| Hildreth et al. (1981)            | 62/9                            | 0.5              | (0.2, 1.7)            |
| Willet et al. (1981)              | 47/464                          | 0.8              | (0.4, 1.5)            |
| Weiss et al. (1981)               | 112/552                         | 0.6              | —                      |
| Francoeur et al. (1982)           | 161/561                         | 0.7              | (0.4, 1.1)            |
| Cramer et al. (1982)              | 144/139                         | 0.4              | (0.2, 1.0)            |
| Rosenberg et al. (1982)           | 135/539                         | 0.6              | (0.4, 0.9)            |
| CASH (1983)                       | 175/1 642                       | 0.6              | (0.4, 0.9)            |

not given — Chiffres non indiqués.
after long exposure, they did not suggest any increase in ovarian cancer risk. Nulliparous women are at a higher risk of ovarian cancer as compared to parous women. It has been suggested that the apparent protective effect of oral contraceptives may be due to nulliparous women being less likely to use oral contraceptives because they are more likely to be infertile and therefore have no need for contraception. However, in one large study, the protective effect of oral contraceptives was found in each parity group studied (4). Furthermore, among nulliparous women using contraception, and with no history of infertility, the relative risk with oral contraceptive use was 0.4.

Endometrial cancer

Substantial information is available on endometrial cancer and the use of both estrogens and progestogens. Exogenous estrogen, when taken without a progestogen, increases the risk of endometrial cancer. This has been shown to be the case for conjugated estrogens used by post-menopausal women, as well as for sequential oral contraceptives which include a number of days (usually 16 out of 21) of only estrogen.

The addition of progestogen has been shown fairly conclusively to counteract the increased risk associated with estrogens. Combined oral contraceptives, which include both an estrogen and a progestogen in each tablet, appear in fact to reduce the risk of endometrial cancer. Four case-control studies, all conducted in the United States, have shown a decrease of 50% in the risk of endometrial cancer among women who have used combined oral contraceptives (12, 15, 16). At least three studies have also shown a decreasing risk, the longer combined oral contraceptives were used (12, 15, 16).

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Localisation cancéreuse</th>
<th>Number of subjects in the analyses</th>
<th>Adjusted relative risk a</th>
<th>Risk relative ajusté b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrium</td>
<td>Endomètre</td>
<td>Cases - Cas: 57</td>
<td>0.3 (0.04-2.4)</td>
<td>—</td>
</tr>
<tr>
<td>Ovary</td>
<td>Ovaire</td>
<td>Controls - Témôns: 316</td>
<td>0.7 (0.3-1.7)</td>
<td>—</td>
</tr>
<tr>
<td>Liver</td>
<td>Foie</td>
<td></td>
<td>1.0 (0.4-2.8)</td>
<td>—</td>
</tr>
<tr>
<td>Breast</td>
<td>Sein</td>
<td></td>
<td>1.0 (0.7-1.5)</td>
<td>—</td>
</tr>
<tr>
<td>Cervix</td>
<td>Col de l’utérus</td>
<td></td>
<td>1.2 (0.9-1.5)</td>
<td>—</td>
</tr>
</tbody>
</table>

a Figures in parentheses are 95% confidence intervals.

b Controls matched with cases by age, centre and year of entry into the study.

c Adjusted for total number of live births, history of infertility, oral contraceptive use and IUD use: controls matched with cases by age, centre and year of entry into the study.

d Adjusted for oral contraceptive use and IUD use: controls matched with cases by centre, age and year of entry into the study.

e Adjusted for age, centre, age at first live birth, total number of live births, oral contraceptive use and IUD use.

f Adjusted for age, centre, total number of pregnancies, history of vaginal discharge, age at first sexual relationship, number of sexual partners, number of Pap smears, oral contraceptive use and IUD use.

Cancer of the endometrium

On possède de nombreux renseignements sur le risque de cancer de l’endomètre et l’utilisation des oestrogènes et des progestatifs. Lorsqu’ils sont administrés sans progestatifs, les oestrogènes exogènes accroissent le risque de ce type de cancer. Cet effet a été démontré pour les conjugués d’oestrogènes utilisés après la ménopause ainsi que pour les contraceptifs oraux séquentiels qui comportent la prise d’oestrogènes seuls pendant un certain nombre de jours (généralement 16 jours sur 21).

Il a été démontré de façon relativement concluante que l’addition de progestatifs annulait le risque associé aux oestrogènes. Les contraceptifs oraux associés, dont chaque comprimé contient à la fois un oestrogène et un progestatif, paraissent en fait réduire le risque de cancer de l’endomètre. Quatre études cas-témoins conduites aux États-Unis ont montré que ce risque était réduit de 50% pour les femmes ayant utilisé des contraceptifs oraux associés (12-15) (Tableau 3). Trois études au moins ont également montré que le risque diminue d’autant plus que les contraceptifs associés sont utilisés plus longtemps (12, 15, 16).

TABLE 3. CASE-CONTROL STUDIES OF ORAL CONTRACEPTIVES AND ENDOMETRIAL CANCER

<table>
<thead>
<tr>
<th>Investigators — Chercheurs</th>
<th>Number of cases/controls</th>
<th>Relative risk</th>
<th>95% confidence limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weiss &amp; Sayvetz (1980)</td>
<td>117/395</td>
<td>0.5</td>
<td>(0.2, 0.8)</td>
</tr>
<tr>
<td>Kaufman et al. (1980)</td>
<td>152/516</td>
<td>0.4</td>
<td>(0.2, 0.8)</td>
</tr>
<tr>
<td>Hulka et al. (1982)</td>
<td>79/203</td>
<td>0.4</td>
<td>—</td>
</tr>
<tr>
<td>CASH (1983)</td>
<td>187/1 320</td>
<td>0.5</td>
<td>(0.3, 0.8)</td>
</tr>
</tbody>
</table>
Data on DMPA and endometrial cancer are available from the same United States-based studies described for ovarian cancer and from the WHO collaborative study. The United States-based studies were limited in the conclusions that could be drawn, as discussed above, but did not report any increase in the risk of endometrial cancer (10, 11). The WHO study reported an adjusted relative risk of 0.3 (95% confidence interval 0.04-2.4) among women who had ever used DMPA (1). Although the confidence limits are wide, due to the small number of cases, the low relative risk point estimate of 0.3 suggests no increased risk and may be interpreted as consistent with the hypothesis that progestogens would lower the risk of endometrial cancer.

Cervical cancer

The relationship between hormonal contraceptive use and the risk of cervical cancer is notoriously difficult to study, for several reasons. First, cervical cancer has been shown to result from a progression of changes in the squamous epithelium that begins with dysplasia and ends with invasive cervical cancer. Since hormonal contraceptives could have an influence on any of the stages, studies of hormonal contraceptives and cervical cancer must examine each stage separately.

All stages of cervical cancer, including dysplasia, can be diagnosed by Pap smear, which poses additional problems for epidemiologists. It is quite possible that women who use contraceptives would be more likely to have Pap smears, as part of a routine examination in a family planning clinic. This could result in more cervical cancer being diagnosed among women using contraceptives, including hormonal contraceptives. On the other hand, if Pap smears are done sufficiently often, dysplasia may be diagnosed before it progresses to invasive cervical cancer, resulting in less invasive disease among women using contraception. Either of these results would reflect the screening activities, rather than any biological association between cervical cancer and hormonal contraceptives. Therefore, all studies on this issue must take into account practices of Pap-smear screening.

One of the most difficult methodological problems in studying cervical cancer is controlling for the important confounding factor of sexual practices. Women with multiple sexual partners, and women whose male partners have multiple sexual partners, are known to be at an increased risk of developing cervical cancer. The specific mechanism involved is not clear, but may relate to sexually-transmitted diseases, especially human papilloma virus infection. If women who have multiple sexual partners are more likely to use hormonal contraceptives, a spurious finding of higher risk of cervical cancer among hormonal contraceptive users can result. In order to study the specific effect of hormonal contraception, epidemiological studies of cervical cancer must control for this important confounding factor. However, even when information on sexual practices is obtained, it is difficult to be certain that the information is accurate.

Results from epidemiological studies of oral contraceptives and cervical cancer have been inconsistent probably largely because of the problems mentioned above. Many of the studies have not taken into account patterns of sexual behaviour. However, most of the better-designed studies have shown a small increased risk of invasive cervical cancer with oral contraceptive use. Two large prospective studies found invasive cervical cancer only in women who had used oral contraceptives (17, 18). Neither of these studies controlled for sexual practices. One recent case-control study that did attempt to take into account sexual behaviour showed an overall small but

Les études faites aux Etats-Unis sur le cancer de l'ovaire et l'étude collective de l'OMS ont également permis de réunir des données sur l'AMPR et le cancer de l'endomètre. Comme on l'a déjà dit, seules des conclusions limitées ont pu être tirées des études réalisées aux Etats-Unis, mais elles n'ont pas fait apparaître d'augmentation du risque de cancer de l'endomètre (10, 11). L'étude de l'OMS a reporté un risque relatif ajusté de 0,3 (intervalle de confiance à 95% : 0,04-2,4) chez les femmes ayant utilisé de l'AMPR (1). Bien que l'intervalle de confiance soit important, compte tenu du nombre restreint de cas, le risque relatif estimé à 0,3 ne révèle pas d'augmentation et peut donc être interprété comme conforme à l'hypothèse selon laquelle les progestatifs réduiraient le risque de cancer de l'endomètre.

Cancer du col utérin

La relation entre contraception hormonale et risque de cancer du col utérin est notablement difficile à étudier, pour plusieurs raisons. Premièrement, il est établi que ce type de cancer est l'aboutissement d'une succession de modifications de l'épithélium pavimenteux, commençant par une dysplasie et se terminant par un cancer invasif. Comme les contraceptifs hormonaux peuvent avoir une influence sur plusieurs stades qui viennent d'être évoqués, certains problèmes supplémentaires aux épidémiologistes. Il est tout à fait possible que les femmes qui utilisent des contraceptifs soient plus nombreuses à se soumettre à ce test dans le cadre des examens systématiques effectués dans les dispensaires de planification familiale. En conséquence, un nombre plus élevé de cancers du col utérin serait diagnostiqué chez les femmes qui prennent des contraceptifs, hormonaux compris. En revanche, lorsque les tests sont effectués à intervalles suffisamment rapprochés, les chances de diagnostiquer une dysplasie avant qu'elle n'ait évolué en cancer invasif sont plus grandes, de sorte que le nombre des cancers invasifs diagnostiqués chez les femmes sous contraception est moins élevé. Ces deux résultats seraient davantage le reflet des pratiques de dépistage par le test de Papanicolaou.

Dans ce domaine, l'une des principales difficultés méthodologiques réside dans la nécessité de contrôler le facteur qui risque le plus de fausser les résultats, à savoir les pratiques sexuelles. Il est connu que les femmes qui ont de multiples partenaires sexuels ou dont les partenaires masculins ont de multiples partenaires présentent un risque accru de cancer du col utérin. Le mécanisme précis en cause n'est pas très clair mais il pourrait faire intervenir des maladies sexuellement transmissibles et en particulier le papillome viral humain. Dans la mesure où les femmes qui ont de multiples partenaires ont plus de chances de recourir à la contraception hormonale, on risque d'obtenir un résultat faussé faisant état d'un risque accru de cancer du col utérin chez les utilisatrices de contraceptifs hormonaux. Il est donc essentiel que les études épidémiologiques consacrées à ce type de cancer tiennent également compte de cette variable importante pour l'évaluation des effets précis de la contraception hormonale. Quoi qu'il en soit, même lorsque l'on obtient des renseignements sur les pratiques sexuelles, il est difficile d'être certain qu'ils sont exacts.

Les résultats des études épidémiologiques sur les contraceptifs oraux et le cancer du col utérin ne sont pas cohérents, sans doute dans une très large mesure à cause des problèmes qui viennent d'être évoqués. Beaucoup de ces études n'ont pas tenu compte des schémas de comportement sexuel. Toutefois, la plupart des études les mieux conçues pourraient apparaître une légère augmentation du risque de cancer invasif chez celles qui utilisent les contraceptifs oraux. Dans deux études prospectives à grande échelle, des cancers invasifs du col utérin n'ont été décelés que chez des femmes qui avaient utilisé des contraceptifs oraux (17, 18). Les pratiques sexuelles n'avaient été prises en compte dans aucune de ces
statistically significant increase in risk (RR 1.2, 95% confidence interval 1.0-1.4) (19). This study also found an increasing risk of cervical cancer with increasing duration of use of oral contraceptives.

Even though recent studies have been better designed and have yielded more consistent results, epidemiologists have found it difficult to reach firm conclusions on the relationship between oral contraceptive use and cervical cancer. The small increase in risk that is found may indicate a true causal relationship between oral contraceptive use and cervical cancer, but may also reflect researchers' inability to take into account fully the important confounding factors discussed earlier.

Few studies have been conducted on DMPA use and cervical cancer and most are limited by a small number of subjects, short duration of DMPA use, and inadequate control for potentially confounding factors such as number of sexual partners. The most recent and largest study, and the only one to attempt to control for sexual practices, is the WHO study. Preliminary findings showed a relative risk for invasive cancer of 1.2 (95% confidence interval 0.9-1.5) among women who had ever used DMPA (1). This estimate is consistent with the findings on oral contraceptives and cervical cancer. More data are needed to determine whether long-term use of DMPA carries a greater risk of cervical cancer.

Breast cancer

The issue of hormonal contraception and the risk of breast cancer has been extensively studied and virtually all studies have shown no change in the overall risk of breast cancer among women who have used oral contraceptives (20-27). In general, no increased risk overall has been found with long-term use of oral contraceptives either, although a recent study from Sweden has shown an increased risk of breast cancer among young women who have used oral contraceptives for more than seven years (28). The subject has received much attention recently, in part because of the high prevalence of breast cancer, and in part because of conflicting reports on the risk among selected subgroups of women.

The risk of breast cancer is known to be affected by a number of hormonal factors, such as age at menarche and age at first pregnancy, and it has been hypothesized that the effect of hormonal contraceptives on cancer risk may vary, depending on which stage in a woman's life they are used. In fact, some studies have shown an increased risk of breast cancer among women who have used oral contraceptives for long periods of time at a young age or before their first full-term pregnancy (28-30). Other apparently equally well-designed studies, however, have not confirmed this (23, 31, 32). Several reasons for the discrepancy in results have been suggested, including different study design, different patterns of contraceptive use (including time since oral contraceptives were first widely used), different oral contraceptive formulations, and different approaches to data analysis.

The relationship between DMPA use and breast cancer has been a source of controversy ever since beagle dogs which were given large doses of DMPA developed breast tumours. The role that endogenous estrogens may play in the development of breast cancer has led some to suggest that progestogen-only contraceptives may in fact lower the risk of breast cancer. Others, however, have suggested that exogenous progestogens used at a young age would increase the risk of breast cancer (29). The most studies. Une étude cas-témoin récente pour laquelle on a cherché à tenir compte du comportement sexuel a fait apparaître une augmentation globalement faible mais statistiquement significative du risque (RR 1.2, intervalle de confiance à 95% : 1.0-1.4) (19). Cette étude a également montré que le risque augmentait avec la durée d'utilisation des contraceptifs oraux.

Bien que les études plus récentes aient été mieux conçues et aient donné des résultats plus cohérents, les épidémiologistes estiment difficile de produire des conclusions fermes sur la relation entre contraception orale et cancer du col utérin. En effet, le risque légèrement accru qui a été mis en évidence peut-être révélateur d'une véritable relation de cause à effet mais peut-être reflète-t-il aussi simplement l'incapacité des chercheurs à prendre pleinement en compte les importantes variables qui peuvent fausser les résultats comme on l'a vu plus haut.

L'utilisation de l'AMPRA n'a fait l'objet que de quelques études et la plupart sont limitées par le petit nombre de sujets, la brièveté d'utilisation de l'AMPRA et la difficulté qu'il y a à contrôler certains facteurs tels que le nombre des partenaires sexuels. L'étude la plus récente et la plus importante sur ce sujet est celle que les femmes ayant utilisé de l'AMPRA (1). Cette estimation reste cependant en lien avec les résultats obtenus sur les contraceptifs oraux. Il faudrait davantage de données pour déterminer si le recours à l'AMPRA pendant une période prolongée entraîne une augmentation du risque de cancer du col utérin.

Cancer du sein

Les relations entre contraception hormonale et cancer du sein ont été abondamment étudiées et presque toutes les études ne font apparaître aucune modification du risque global de cancer du sein chez les femmes ayant utilisé des contraceptifs oraux (20-27). D'une manière générale, on n'a pas observé d'accroissement du risque en cas d'utilisation à long terme, mais une étude récente réalisée en Suède a apparu comme une augmentation du risque de cancer du sein chez des jeunes femmes ayant utilisé des contraceptifs oraux pendant plus de sept ans (28). Cette question a récemment suscité beaucoup d'intérêt, en partie à cause de la prévalence élevée du cancer du sein en particulier à cause des résultats contradictoires obtenus pour des sous-groupes déterminés de femmes.

On sait que le risque de cancer du sein est influencé par plusieurs facteurs hormonaux tels l'âge aux premières règles et la première grossesse et l'on a émis l'hypothèse que les effets des contraceptifs hormonaux sur ce risque de cancer pourraient varier selon l'époque de la vie à laquelle ils sont utilisés. En effet, certaines études ont fait apparaître un risque accru chez les femmes ayant utilisé des contraceptifs oraux pendant de longues périodes alors qu'elles étaient jeunes ou avant leur première grossesse menée à terme (28-30). Toutefois, d'autres études, tout aussi bien conçues semble-t-il, n'ont pas confirmé ces résultats (23, 31, 32). Plusieurs raisons ont été avancées pour expliquer l'incohérence de ces résultats, notamment les différences dans les données utilisées dans les schémas d'utilisation des contraceptifs (y compris le temps écoulé depuis que les contraceptifs oraux ont commencé à être largement utilisés), dans les formulations des contraceptifs oraux et dans les approches adoptées pour l'analyse des données.

La relation entre l'AMPRA et le cancer du sein est un sujet très controversé depuis que des chiennes beagles auxquelles avaient été administrées des doses importantes de ce produit ont présenté des tumeurs mammaires. Le rôle que jouent peut-être les œstrogènes endogènes dans l'apparition du cancer du sein a conduit certains chercheurs à suggérer que les contraceptifs ne contenaient que des progestatifs pouvant en fait réduire le risque de cancer du sein. D'autres cependant ont suggéré que l'utilisation de progestatifs...
recent published results from the WHO study showed no change in the overall risk of breast cancer following DMPA use, and no appreciable change in risk according to duration of DMPA use or among young women specifically (1). Too few women had used DMPA before their first pregnancy to assess this issue.

Liver cancer

Liver cancer is rare in developed countries. It is somewhat more common in developing countries, where it is associated with hepatitis B infection. Two reports have recently been published in the United Kingdom showing an increased risk of liver cancer among women who have used oral contraceptives for eight or more years (33, 34). Although the data present fairly convincing evidence of an increased risk of liver cancer, the public health implications are minimal.

No data on this subject have been published from countries where the relationship between hepatitis B-associated liver cancer and oral contraceptive use could be evaluated.

The WHO study published limited data on DMPA use and liver cancer. These data showed no effect of DMPA use on liver cancer risk, although the small number of cases prevented any meaningful assessment of the effect of long-term DMPA use (1).

Conclusions

There is substantial evidence to suggest that the use of hormonal contraceptives alters the risk for some forms of cancer. The most conclusive evidence shows a marked decrease in the risk of both ovarian cancer and endometrial cancer among women who have used combined oral contraceptives. The risk for both cancers seems to be lowered by approximately 50%. There is limited data suggesting at least no increase in the risk of either of these two cancers with DMPA use.

In general, the large amount of data collected on breast cancer shows no overall change in the risk of breast cancer with oral contraceptive use. A smaller amount of data on DMPA use also suggests no change in the overall risk. Some studies have shown an increased risk of breast cancer among selected subgroups of women who have used oral contraceptives for long periods of time; other equally well-designed studies have not confirmed these findings.

Most large well-designed studies of hormonal contraceptives and cervical cancer show a small increase in the risk of cervical cancer with both oral contraceptive use and DMPA use. It is still unclear whether these findings reflect a true causal relationship or inadequate control of confounding factors such as sexual behaviour.

A small amount of data indicates reasonably conclusively that use of oral contraceptives for eight or more years increases the risk of non hepatitis B-associated liver cancer. The data available on hepatitis B-associated cancer are insufficient to draw any firm conclusions, although there is no evidence of any increase in the risk.

The public health impact of changes in cancer risk varies according to both the prevalence of hormonal contraceptive use and the background incidence of the cancer in question. In general, any influence on the risk of uncommon exogenous causes of de novo cancer is likely to be small. However, for the rare cancers such as ovarian cancer, the changes may be more substantial. The impact of these changes on public health is likely to be minimal.

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mon cancers such as liver cancer is unlikely to be of public health importance. In contrast, a change in the risk of breast cancer, one of the most common cancers in some parts of the world, would affect many more individuals.

The implications for women’s health must be considered within the context of all health effects of hormonal contraceptives—both beneficial and adverse—and options to hormonal contraceptive use. For example, the contraceptive effect of hormonal contraceptives will have a profound beneficial impact for women in areas where maternal mortality is high. In such a context, the magnitude of any overall increase in cancer risk would be overshadowed by the risk of pregnancy-related mortality. For women in areas where maternal mortality is low, and for whom other major adverse effects of hormonal contraceptives, such as cardiovascular disease, are uncommon, any increase in the risk of cancer would be of much greater importance, and might well influence the choice of contraceptive method. Another relevant issue in the case of cervical cancer is the availability of cancer-screening facilities. Women with access to cervical cancer screening can greatly reduce, if not eliminate, their risk of invasive cervical cancer. For women without ready access to screening, an increase in the risk of cervical cancer would have more serious implications.

Given the number of women who are potentially affected by side-effects of hormonal contraceptives, it is imperative that the risks and benefits associated with hormonal contraceptives be thoroughly investigated, including effects on cancer risk. Methodological problems will, however, continue to limit the conclusions that can be drawn. Emphasis needs to be placed on adequate study design and on assessing cancer risk in a variety of regions of the world.

Meanwhile, highly effective contraceptives will continue to be needed—and used—by many women throughout the world. For most of the world, any adverse risks of contraindicated adverse effects, including cancer risk, the healthier the pregnancy, it is a matter of deciding which of several contraceptive methods poses the least risks and is most acceptable. The more that is known about non-contraceptive health effects, including cancer risk, the healthier the choice that can be made.

REFERENCES — RÉFÉRENCES


