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Cervical cancer and methods of contraception

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Abstract

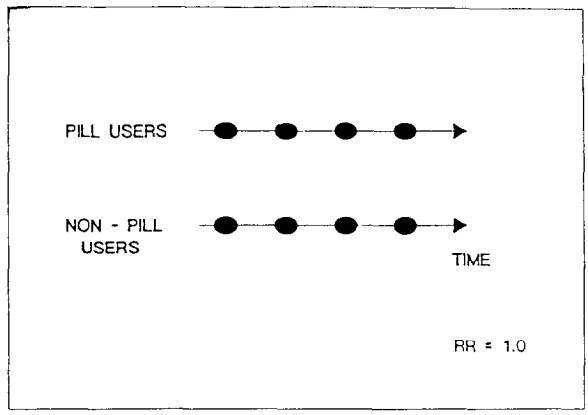
When evaluating whether the use of a particular method of contraception is associated with an increased or decreased risk of cervical cancer, it is important to be aware of the epidemiological factors which might lead to incorrect conclusions. After careful consideration of the issues, and examination of the available data, it is concluded that women who use oral contraceptives are possibly at increased risk of invasive cervical cancer; users of barrier methods probably have a decreased risk (although the protective effect may differ between the various types of barrier method); and that users of other methods of contraception do not have an altered risk.

Epidemiological considerations

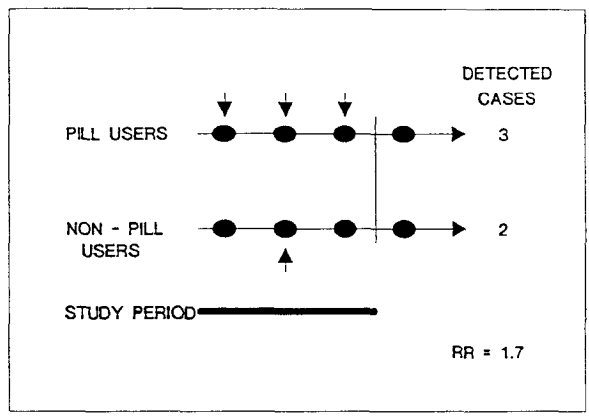
When evaluating whether the use of a particular method of contraception is associated with an increased or decreased risk of cervical cancer, it is important to be aware of the epidemiological factors which might lead to incorrect conclusions.

In developed countries most cases of cervical cancer are detected by screening with Papanicolau (Pap) smears. If the frequency of screening is related to the type of contraceptive used, and if the study fails to make appropriate adjustments for this difference, then biased results may occur. Furthermore, the effect will depend on whether incident or prevalent cases of cancer are studied.

In order to illustrate this, let us assume that two populations of women are studied: those who have used oral contraceptives and those who have not; that the populations are of equal size; that the screening is 100% efficient at detecting disease and has a zero false-positive rate; and that new cases of carcinoma occur at the same steady intervals in both groups. Since the risk of disease among both populations is identical, the study should estimate the relative risk (RR) for pill use to be 1.0 (Figure 1a).



1(a)



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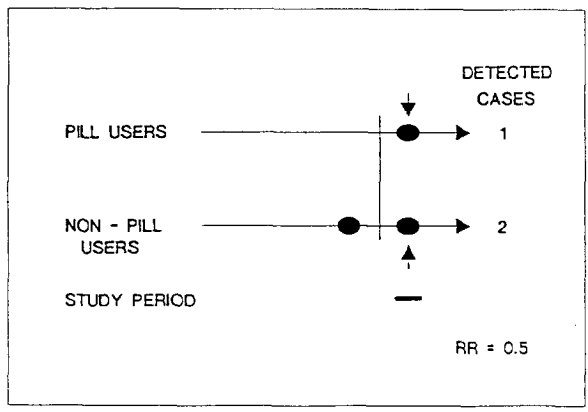

1(c)

Figure 1. Illustration of how the relative risk estimates for pill use are dependent on the frequency of screening for cervical cancer and whether incident or prevalent cases of disease are studied. 1(a) populations to be studied; 1(b) incident cases; 1(c) prevalent cases. See text for details
● New case of cervical cancer; → PAP smear

If, however, users of oral contraceptives were screened more frequently (which seems to be the situation in real life), and the study examined incident cases of cancer (i.e. new cases found during a certain period of time), then more tumors would be detected among the pill users than among the non-users (Figure 1b). Unless appropriate adjustments are made, use of the pill would, wrongly, appear to be associated with an increased risk of cervical cancer (RR = 1.7).

The opposite would occur if the study used prevalent cases (i.e. all new or pre-existing cancers detected at one point in time). The greater intensity of screening among pill users would result in the detection of more cancers in the period preceding the investigation and fewer cases during the study itself (Figure 1c). There would be more pre-existing cancers in the non-pill users and so the study might erroneously conclude that use of oral contraceptives protects against cervical cancer (RR = 0.5).

It is also important to note that different patterns of screening can influence the estimated rate of pre-invasive and invasive disease observed in each population. Women who are screened frequently are more likely to benefit from the detection of pre-invasive lesions than those who are screened less often. These abnormalities are often found at an early stage and are likely to be treated, thereby leaving fewer lesions to progress to invasive tumors. Thus, frequent screening increases the rate of pre-invasive cancers detected and reduces the rate of invasive lesions. Contraceptives which involve medical supervision, such as the pill and intrauterine devices, are particularly prone to these effects since the doctor is likely to ensure that these women are offered comprehensive screening services.

Pap smears are, in fact, associated with a high error rate, and some contraceptives may produce effects which alter these error rates. For example, women who use oral contraceptives are more likely to develop vaginal infections which, in turn, may produce changes which can be misdiagnosed as early cancer. Thus, the false-positive rate of the test might be greater in pill users. Conversely, these women may experience a lower false-negative rate, since oral contraceptives can produce cervical eversion which improves the chances of detecting the neoplasia. The pre-invasive changes of dysplasia and carcinoma-in-situ are probably more prone to these difficulties than invasive cancers. In order to minimize them, it is important to obtain histological confirmation that an abnormal smear is due to a carcinoma.

In a case–control study, the controls should be free of cervical cancer. This means that all should have been screened at least once prior to recruitment. The comparison group should also exclude women who have had a hysterectomy, since they are no longer at risk of contraceptive use or the development of cervical cancer. In addition, the contraceptives which have been used by the controls should be known. If most used barrier methods, it would be difficult to know whether any observed difference in risk were due to a protective effect of barrier methods or an adverse effect of the other contraceptive being studied.

Each investigation should include a sufficient number of cases to ensure that there is little chance of missing a real significant change in risk. In other words, the study should have reasonable statistical power. It is also important that a reasonable proportion of women in the study have been exposed to the contraceptive of interest, preferably for long periods.

Finally, the analyses must adjust for confounding factors (these are risk factors for the disease being studied which are also associated with the exposure of interest, but they are not intermediate steps in the apparent pathway between the exposure and the disease). For cervical cancer, the most important known confounding factor is sexual activity, although smoking and socioeconomic status may also be important. Thus, a woman is more likely to develop cervical cancer if she starts having sexual intercourse at an early age, and if she has had many partners (or if her partner has had multiple partners). Women who use different methods of contraception probably exhibit different patterns of sexual activity. For example, pill users are more likely to be sexually active at an earlier age, and to have more sexual partners than women who use other contraceptives. Unless these sensitive data are collected, and appropriate statistical manipulations made for any observed differences, false conclusions may be reached.

The purpose of this outline of the potential epidemiological problems has been to show how carefully the results from each study must be interpreted. The remainder of the review will concentrate on studies of invasive cervical cancer, since these should theoretically be less prone to the problems described than investigations of pre-invasive conditions. Studies which have serious methodological flaws will not be discussed.

Oral contraception

Many of the earlier studies were limited by inadequate clarification of whether incident or prevalent cases were being examined, by the investigation of a small number of cases, by the inability to adjust for confounding factors, and by a low prevalence of oral contraceptive use [1]. Furthermore, many investigated pre-invasive rather than invasive tumors.

A number of recent studies have suggested that users of the pill may be at increased risk of cervical cancer [2–9].

In 1985, the World Health Organization published interim results from a case–control study conducted in ten developing countries [2]. Some 709 incident and prevalent cases of invasive cervical cancer were compared with 3935 suitable controls. Although the increased relative risk among pill users was only of borderline significance (adjusted RR 1.2; 95% confidence interval (CI) 1.0–1.4), there was a significant increasing trend with duration of use. Statistical adjustments included age at first sexual relationship, total number of partners, and number of Pap smears.

Brinton and colleagues [3] conducted one of the best studies to examine this issue. They found that oral contraceptive users had a significantly enhanced risk of developing cervical cancer (adjusted RR 1.5; 95% CI 1.1–2.1), which increased with duration of use. The study was conducted in 5 areas of North America and was based on 647 incident cases of histologically confirmed invasive cancer. Appropriate statistical adjustments included measurements of each woman's sexual and screening history. Although these results were suggestive of a causal link, the authors were careful to note that residual confounding could still explain the observed increase in risk.

Another case–control study, conducted in Italy, initially suggested that there was no overall relationship between pill use and cervical cancer, but that there was a trend of increasing risk with duration of use [4]. When more cases were available for analysis, some 367 cases of invasive cancer, the increased risk among pill users reached borderline significance (adjusted RR 1.85; 95% CI 1.00–3.14) [5].

Three cohort studies have also reported an increased risk. In the Oxford Family Planning Association Contraceptive Study [6] the rate of cervical neoplasia (mostly pre-invasive conditions) in users of oral contraceptives was significantly greater than that among users of intrauterine devices (adjusted RR 1.7; 95% CI 1.1–2.6). The Royal College of General Practitioners' Oral Contraception Study [7] found that, compared with non-pill users, oral contraceptive users had an increased risk of invasive cervical cancer which was of borderline significance (adjusted RR 1.8; 95% CI 1.0–3.3) and a highly significant risk of carcinoma-in-situ (adjusted RR 2.9; 95% CI 2.0–4.1). Positive trends with duration of use were found in both studies. Unfortunately, neither was able to adjust for indicators of sexual activity. In the third study [8], there were only 6 cases of invasive cancer (compared with 191 pre-invasive cancers), but all, significantly, occurred in women who had used oral contraceptives.

One further piece of evidence comes from a natural history study of dysplasia of the cervix [9]. Women who developed this condition and who continued to use the pill were significantly more likely to progress to a more severe grade of dysplasia, or to a carcinoma-in-situ, than those who used other forms of contraception.

These positive studies have been contradicted by a number of other studies [10–15]. Some have been limited by the small number of cancers available for analysis [11,14]. Others have studied populations in which the prevalence of oral contraceptive use was low [15] or the use was only for relatively short periods [10]. In two studies, seemingly significant associations ceased to remain so once adjustments had been made for important confounding factors [11,12]. The study of Irwin and colleagues illustrated particularly well the biases which might be introduced by the more frequent screening of oral contraceptive users [13].

Clearly, a definite causal relationship has not yet been found. The evidence suggests, however, that there may be a possible link between oral contraceptive use and invasive cervical cancer. The results from several studies which are still in progress may help to clarify the situation.

Barrier methods

Early studies predominantly considered use of the diaphragm and investigated pre-invasive tumors [16,17]. Peters and colleagues were the first to suggest that the various barrier methods may not be equally protective [10]. They investigated 200 women who had developed invasive cervical carcinoma and found, for all barrier methods combined, a trend of reduced risk with duration of ever-use. When the individual types of method were examined by univariate analysis, a significant decreasing cancer risk was observed in women who used condoms or contraceptive foams, creams and jellies (with or without other barrier methods). Although use of

the diaphragm alone was associated with a similar inverse trend, it was not significant. Unfortunately, the study had limited statistical power because barrier methods were not commonly used by women in the study population.

Parazzini and colleagues [18] investigated ever-use of barrier methods, most of which related to condoms. A significantly decreased risk was found. They were unable to examine use of spermicidal foams and jellies. Two groups which were, found that these agents may be more important in reducing the users' risk of cancer than either the condom or diaphragm [12,14]. In another study, barrier methods were not generally protective [19], but there was, among women of high socioeconomic status, a significant protective effect of spermicidal creams, especially if used without other barrier methods. The authors postulated that these women may be more consistent users of these agents than women in the other socioeconomic groups. The one study which failed to find any relationship between barrier methods and cervical cancer [15] may have suffered from a low prevalence of use.

Thus, although the evidence is not totally consistent, much of it suggests that barrier methods protect against cervical cancer. There is a need for research to clarify whether the benefit is conferred by all barrier methods.

Injectable hormones

There have been very few studies of the cervical cancer risk associated with injectable hormones. Interim results from a World Health Organization case–control study, which looked at ever-use of depot-medroxyprogesterone acetate, were reassuring. The small increased risk was not significant and there was no relationship with duration of use [20]. Another analysis from this study examined use of monthly injectable contraceptives containing dihydroxyprogesterone acetfenide plus a short- acting estrogen. It also failed to find an elevated risk [21]. Although a similar result was found by Brinton and colleagues [15], the findings were based on a small number of women who had ever used this method of contraception.

Intrauterine devices

Isolated studies have shown a decreased risk of cervical cancer among intrauterine device users [16], while others have not [10,12,14]. These studies will be subject to the same methodological problems as for other contraceptives. It certainly seems biologically implausible that these devices should lower a user's risk. Thus, use of the intrauterine device is unlikely to be a risk factor for cervical cancer.

Withdrawal

One study has found that women whose partner withdraws during intercourse, have an increased risk of cervical cancer [15]. This was probably a chance finding, since it seems biologically implausible, and an earlier paper failed to find any risk [10].

Other methods

The rhythm method of contraception and female sterilization have not been found to be related to cervical cancer risk [15].

Conclusions

In summary, it is possible that use of oral contraceptives is associated with an increased risk of invasive cervical cancer. Barrier methods are probably associated with a decreased risk. There is little evidence of an altered risk with other methods of contraception.

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Resumé

Lorsqu'on évalue si l'utilisation d'une méthode particulière de contraception est associée à une augmentation ou à une diminution du risque de cancer du col, il importe de tenir compte du fait que les facteurs épidémiologiques peuvent amener à tirer des conclusions erronées. Après avoir convenablement examiné ces questions et les données disponibles, il est permis de conclure que les femmes qui utilisent les contraceptifs oraux sont peut-être plus exposées au risque de cancer cervical invasif; que les utilisatrices des méthodes de barrière le sont probablement moins (encore que l'effet de protection puisse varier d'un type de méthode à l'autre), et que les risques ne sont en rien modifiés dans le cas des femmes qui font appel à d'autres méthodes contraceptives.

Resumen

Al evaluarse si la utilización de un método en particular de anticoncepción está asociado a un aumento o a una disminución del riesgo de cáncer de cuello, es necesario tener en cuenta que los factores epidemiológicos pueden llevar a extraer conclusiones erróneas. Tras considerar cuidadosamente estas cuestiones y los datos disponibles, se puede llegar a la conclusión de que las mujeres que utilizan anticonceptivos orales corren posiblemente un riesgo mayor de cáncer cervical invasivo; que las usuarias de métodos de barrera probablemente corran un riesgo menor (si bien el efecto de protección puede variar de un tipo de método a otro), y que los riesgos no se modifican en absoluto entre las mujeres que utilizan otros métodos anticonceptivos.