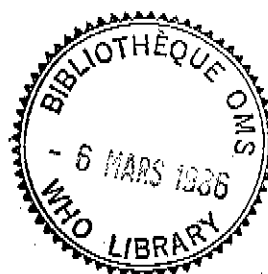




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PRIMARY PREVENTION OF CERVICAL CANCER : *report*

*on cervical dysplasia - POC
 20/85*

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Introduction

Worldwide, cervical cancer is the second most common cancer in women after breast cancer. With approximately one-half million new cases globally each year (1), cervical cancer is the most frequent cancer in women in Africa, middle America, Tropical South America, China and other Asian countries. Approximately three-quarters of the cases worldwide are in the developing countries. In North America and Europe it is the fourth most common cancer in women but a recent increase in incidence has been reported in young women. Cervical cancer represents, therefore, an important public health problem. A high potential for prevention is indicated by the large differential in incidence rates observed worldwide and by the increasing trend observed in young women in some developed countries. Recent figures from 28 developed countries indicate that cervical cancer mortality declined by approximately 30% between 1960 and 1980; early diagnosis through screening has been a major factor in this decline (2). The effectiveness of secondary prevention through the introduction of screening programmes has been clearly demonstrated in some countries. Primary prevention, directed to the elimination or reduction of exposure to established risk factors, is however a long term strategy with substantial potential for the control of cervical cancer.

The purpose of this report is to review the evidence of the main risk factors for cervical cancer, to assess the prospects of implementing primary prevention in the light of recent developments, and to recommend future research, whenever appropriate.

Possible approaches for primary prevention

1. Sexual behavior

Evidence

Epidemiological studies have pointed to the overriding importance of sexual experience with multiple partners and early onset of sexual activity in the etiology of cervical cancer (3). In addition, male sexual promiscuity may contribute to an increased risk in the female (4).

Recent studies suggest that the number of sexual partners is the most important risk factor for the disease and also that it is independent of age at first sexual intercourse. Findings fail to support the hypothesis that adolescence is a period when the cervix is most vulnerable to the effects of sexual behavior (5,6). However, most of the studies carried out so far were conducted in Western developed or developing countries; analytical epidemiological information from other parts of the world is limited, but suggests that age at first intercourse is an important factor in itself.

Other variables related to sexual behavior (such as age at marriage, number of children, history of divorce, etc) do not independently influence cervical cancer risk.

The relative risk for onset of sexual activity under the age of 15 has been shown to be as high as 12 (7) and three to four for those women starting sexual life under the age of 17; for women with six or more sexual partners the relative risk is of the order of more than 12 (5).

Prospects for primary prevention

Epidemiological evidence indicates that multiple sexual partners and early onset of sexual intercourse are the main risk factors for cervical cancer. Intervention on these two risk factors would imply advocating monogamous sexual behaviour and delaying the commencement of a sexually active life. The difficulties involved in campaigns aimed to change people's lifestyle habits are well-known. These difficulties will be considerably larger when changes in sexual behaviour are considered. It is then unlikely that intervention on these risk factors will be highly successful. However, the recent changes in sexual habits that are taking place in some areas of the developed world, due in part to concern for herpes infections and AIDS, indicate that it is possible to change sexual behaviour.

Recommendations

Information on the increased risk associated with multiple sexual partners and early onset of sexual intercourse should be given in carefully designed programmes of sexual education.

Most of the epidemiological studies on sexual behavior and cervical cancer have been carried out in western populations. There are suggestions that sexual habits might be different in other populations in which relatively few analytical studies have been performed. Therefore it is recommended that this type of study should be repeated in such populations. The main objectives of these studies would be to ascertain the extent to which the two major factors linked to sexual behaviour are also relevant in the etiology of cervical cancer in such populations.

2. Viral factors

Evidence

Although herpes simplex viruses have been suspected since 1968 to play a role in the etiology of cervical cancer, recent studies do not support this notion (8).

Evidence is accumulating for a role of specific types of human papillomaviruses (HPV 16 and 18) in cervical, penile and vulvar cancer etiology. The DNA of these viruses is found in the majority of these tumours as well as in their precursor lesions (9,10,11). Induction of dysplastic precursor lesions has been achieved in heterografted human cervical tissue (12). The state of HPV DNA malignant tumours, where it integrates at a specific site of the genome, differs from that of precursor lesions (episomal persistence). The integrated viral DNA is transcribed in a specific pattern (13).

Papillomaviruses have been found to interact with chemical and physical carcinogens (initiators) in animal as well as in human systems. It has been suggested that either enhancement of viral DNA integration by recombination events or modification (e.g., selective DNA amplifications) of host cell DNA sequences interacting with the persisting HPV DNA result in observed specific interactions (14,15).

Prospects for primary prevention

The identification of virus types associated with a high risk for malignant conversion (e.g., HPV 16 and HPV 18) permits the development of a vaccine for primary prevention as well as screening methods for early detection of these viral infections.

Since spontaneous regression of papillomas appears to be mediated by cellular immune functions, there exists a reasonable chance for immunoprevention and therapy.

Recommendations

Research on a number of fronts is necessary to provide the basis for future interventions. Since about 20% of current HPV-negative cervical cancer biopsies reveal evidence for the presence of HPV-related sequences, probably indicating the existence of new types, a screening programme is needed to identify additional HPV types infecting the human genital tract.

Studies are needed to screen for HPV DNA in populations at low and high risk for cervical cancer, to analyse the modes of transmission of genital HPV's (especially the extrasexual modes), to evaluate the role of HPV in different populations, to identify initiating co-factors and analyse their mode of interaction with HPV infection and to establish the natural history of infected individuals.

On the experimental side, development is needed of vector systems for prokaryotic and eukaryotic cells, reagents (e.g., monoclonal or polyclonal antibodies) for the detection of viral antigens in infected individuals and test systems for serological assays (e.g., ELISA). The latter developments would substantially facilitate diagnostic procedures in the routine and permit seroepidemiological approaches to study the prevalence of specific HPV infections. Further, the analysis of the presence of virus-coded early proteins (specifically those expressed from the E6-E7 open reading frames) in cellular membranes represents a precondition for the development of suitable vaccines. Attempts should be made to stimulate cell-mediated immune mechanisms by HPV-specified antigens and to determine common antigenic epitopes in various HPV types. The development of suitable vaccines and analysis of their effects in immunoprevention and immunotherapy can proceed by vaccine development using bacterial or eukaryotic expression systems and by vaccine development based on synthetic oligopeptides. The use of anti-mRNA in suitable vector systems for the prevention and treatment of HPV-induced proliferations should also be studied.

3. Genital hygiene and circumcision

Evidence

Epidemiological evidence does not support the hypothesis that the partners of circumcised men enjoy lower risk for cervical cancer when circumcision status is determined by physical examination as opposed to information solely obtained through questionnaires or interviews (16). It should be stressed though that most of the studies that addressed the issue were conducted in Western, technically more developed countries, where the standards of personal hygiene are presumably high.

Very little is known based on scientific studies in relation to genital hygiene and cervical cancer risk. The carcinogenic role of chronic infection may be enhanced in conjunction with papillomavirus infections. This is potentially of great importance in the context of developing countries, as suggested by descriptive epidemiological data from India (17).

Prospects for primary prevention

Genital hygiene provides a possible approach towards primary prevention of cervical cancer in developing countries and its role should be evaluated with properly designed case control and other studies.

Recommendations for research

In countries with high incidence of cervical cancer, effect of circumcision on the occurrence of cervical cancer should be re-evaluated.

Studies should be considered to evaluate the possible role of male genital hygiene in the etiology of cervical cancer, including the quantity of human smegma and its components and occurrence of cervical dysplastic lesions. Intervention trials on the effect of penile hygiene on the occurrence of cervical dysplasia lesions may be considered in the future.

4. Contraceptive methods

Evidence

Although cervical tissue responds to the influence of endogenous hormones, the epidemiological evidence does not indicate that they have any etiological relevance for cervical cancer risk.

Barrier methods, such as the diaphragm and condom, offer a degree of protection that cannot be explained in terms of confounding variables (such as sexual behaviour); even after adjustment for these, cervical cancer risk for diaphragm users are about one quarter of that in users of other methods (18).

Both case-control and cohort studies on use of oral contraceptives and cervical cancer risk indicate that there is a relative risk of 1.5 to 2.5 for long term users, i.e., four years or longer (19). In the analyses of such studies it is essential to control for sexual factors such as the number of sexual partners and age at first intercourse (20).

Prospects for primary prevention

On the basis of the epidemiological evidence the use of barrier methods should be encouraged. Yet, this should be done carefully and with the understanding that such methods are not as reliable as the use of oral contraceptives or intrauterine devices. Therefore, there could be a risk of increasing the number of unwanted pregnancies, particularly among younger women not within stable relationships.

Recommendations

More socio-behavioural research is required about the use of occlusive contraceptive methods, particularly among women of lower socio-economic status and among younger women. This could lead to pilot studies on the use of the diaphragm as the main contraceptive method in specific populations. The same should apply to the use of condoms, potentially an even more protective barrier to the male carcinogenic-related factor.

The long term effects of injectable progestogen contraceptives also require further investigation.

5. Cigarette smoking

Evidence

Epidemiological evidence strongly suggests that cigarette smoking is a risk factor for cervical cancer. Once again, the role of confounding factors has to be allowed for in the analysis of the results. Relative risk is of around 1.6 to 2.5 for light smokers and possible much higher for heavy smokers. Tobacco-related substances have been isolated in the cervical fluid of smokers (21). A likely mechanism of action would be to act as a co-carcinogen to an earlier viral infection. However, the absence of a dose-response relationship in some studies leaves room for doubt about the causal nature of the association.

There is a need to evaluate similar risks for other tobacco habits such as bidi smoking prevalent in several developing countries.

Prospects for primary prevention

Health education campaigns related to cigarette smoking should incorporate the message "cigarette smoking may double the risk of cervical cancer".

6. Nutritional deficiencies

Evidence

No definite conclusion is yet available about the possible increased risk for cervical cancer incurred by women with relatively low consumption or blood levels of retinol or beta carotene. Results of studies completed so far do not point in that direction.

Some evidence suggests that localized deficiency of folic acid may be associated with a higher risk for mild and moderate dysplasia.

Prospects for primary prevention

At present there are no indications that compensation for nutritional deficiencies will decrease the risk for cervical cancer.

Summary

The development of squamous cervical cancer is strongly linked with early onset of sexual activity and multiple sexual partners. Recent data provide evidence for the causation of precursor lesions of urogenital cancer by specific papillomavirus infections. This permits the design of new concepts in attempts to prevent cervical cancer.

The prospects for prevention of cervical cancer are good if agents can be developed which interfere with these infections or with co-factors essential for malignant conversion. The development of suitable vaccines for immunoprevention and immunotherapy should be pursued with high priority. Research should primarily be directed towards the analysis of the natural history of these infections and their interactions with host cells in the development of malignant tumours. The contribution of other potentially carcinogenic factors (e.g., smoking, mutagenic metabolites of bacteria and protozoa in chronic inflammation, infection by herpes viruses and exogenous hormones) and their possible interaction with papillomavirus infections requires more research.

The protective value of sexual hygiene and occlusive methods in contraception deserve further attention and study.

The presently inconclusive data on oral and injectable contraceptives, circumcision and nutritional deficiencies in modifying the risk for cervical cancer should also be substantiated by further investigations.

National programmes of sex education aimed at the young generation should include information on the increased risks of cervical cancer associated with early sexual activity and multiple sexual partners.

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