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Efficiency of Cytological Screening for Detection of Cervical Squamous Carcinoma

A study in the county of Uppsala 1991–1994

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ABSTRACT

Squamous carcinoma of the uterine cervix accounts for a considerable mortality among gynecological malignancies, although both the incidence of and mortality from cervical cancer have decreased in the Nordic countries since 1970. The reduction is a result of the cytologic screening program, through which precursor lesions can be detected and removed. Our aim was to determine why women in the county of Uppsala get cervical cancer despite extensive gynecological screening.

A retrospective study of all women (43 cases) who developed histologically verified cervical squamous carcinoma in the county of Uppsala during the years 1991 to 1994 was undertaken. A central computer database covering all histopathological and cytological material made it possible to compare each woman's previous smears or lack of smears with her cancer diagnosis.

Twenty women (47%, mean age at diagnosis 64.4 years) had not undergone cytological screening. Twenty-three women (53%) had been screened at least once within 6 years before tumor diagnosis. Of these, 11 (mean age 47.5 years) had had normal smears for the last 6 years, 8 (mean age 44.3 years) had shown abnormal cytology for less than one year and 4 (mean age 39.0 years) had shown abnormal cytology for more than one year and up to 6 years before their cervical cancer diagnosis.

Women with cervical squamous carcinoma, who are not covered by the gynecological screening program (47%) are at increased risk of developing cervical cancer compared with other women. Consequently the average age of non-screened women developing cancer is considerably higher (64.4 years) than that of women with cancer screened previously (44.9 years). In 26% of the total group of women with cervical squamous carcinoma previous cytology displayed normal features.

INTRODUCTION

Since 1970, both the incidence of and mortality from cervical cancer have decreased in the Nordic countries (13, 21). These trends are mostly interpreted as a result of well organized nationwide screening programs (6, 8, 18). Spontaneous screening accounts for a large proportion of the cytological examinations, and no less than 75 to 80% of all smears are taken outside the organized programs in the county of Uppsala. An evaluation has shown unorganized screening as efficient to detect cancer in situ as organized screening (7).

Despite extensive screening in Sweden, 500 to 600 women in this country acquire cervical cancer every year. These women can be assigned to one of four categories, namely: 1) the woman is not covered by the organized screening (more than 49 years old), 2) the woman has not attended screening or too long an interval has elapsed between two screening tests, 3) a test is falsely interpreted as negative, or 4) a woman with positive cytology is not treated adequately.

There have been several attempts to assess the value of human papillomavirus (HPV) tests on cervical smears, as part of the screening for cervical cancer (1-4). It has been suggested that by HPV screening, infected cases could be identified and referred for further cytological test (14). Colposcopy might follow, depending on the type of HPV present and the cytological result. This assumes that in principle all high-grade lesions will be positive for oncogenic HPV. In accordance, a recent study showed that HPV tests are more effective than cytology in detecting cervical intraepithelial neoplasia (5).

Since organized and spontaneous cytological screening is at present considered to be the best documented method of reducing the incidence of cervical cancer and its mortality (6, 8, 18), the purpose of this study was to elucidate the question as to why women in the county of Uppsala get cervical cancer despite the extensive gynecological screening. For this reason we have undertaken a retrospective study of the screening activity in all women who acquired cervical cancer during the years 1991 to 1994. The investigation is intended to represent a base for further evaluation of the cytological screening program and the possible usefulness of HPV tests as an adjunct.

MATERIALS AND METHODS

Setting:

The material consisted of all women (43 cases) who developed histologically verified squamous cervical cancer in the county of Uppsala during the years 1991 to 1994. The female population of this county was 136 040 in 1990. The women were sought for in a

central computer database covering all histopathological and cytological material, where each woman could be identified through her personal national registration number.
In the county of Uppsala all women between the ages of 20 and 49 years old are invited to attend cytological screening every 3 to 4 years. All smears were classified according to the Papanicolaou (Pap) scheme (15-17) into five groups, ranging from normal squamous epithelium (Pap.I) to squamous carcinoma (Pap.V). All women with an abnormal smear, (Pap.II or more abnormal) are asked to come for a second smear, which is usually taken within 3 months. If a woman does not attend for a secondary smear, she is reminded 6 months after the first appointment. After two slightly abnormal smears or after one Pap.III smear, a biopsy specimen is taken. If this shows moderate dysplasia, severe dysplasia or carcinoma in situ, laser conization is usually performed.
Screening for cervical cancer started in Sweden in 1961, and since 1969 the results of all smears in the county of Uppsala have been collected in a computerized register. This register is synchronized with the data for all gynecological biopsy material, making it possible in this study to compare every woman's smears or lack of smears with her cancer diagnosis, including the cytological grade of atypia and the time interval between abnormal smears and diagnosis. If a woman was treated by conization, her cytological examinations before that time were excluded from the study analysis.

Categories:

The women were divided into two main groups: 1) women with no previous history of cytological examinations, including one woman with a smear taken more than 13 years ago, and 2) women who were covered by gynecological screening, both the spontaneous and the organized type. The latter group was further subdivided into a) women with normal cytology for the last 6 years preceding the cancer diagnosis, b) women with abnormal cytology less than one year before the cancer diagnosis, and c) women with abnormal cytology more than one year and less than 6 years before diagnosis.

RESULTS

Of the 43 women with cervical cancer included in this study, 23 (53%) had been cytologically screened at least once within 6 years prior to cancer diagnosis. A total of 75 smears had been taken in this period, that is a mean of 3.4 smears per patient. Nineteen women had never been examined cytologically and one woman had been examined more than 13 years previously. The mean age of these 20 women (47%) who had not been covered by cytological screening was 64.4 years. Before their cervical cancer diagnosis 11 of the 43 women (26%) had had normal smears for the last 6 years (mean age 47.5 years), 8 women (19%) had shown abnormal cytology for less than one year (mean age

44.3 years) and 4 women (9%) had shown abnormal cytology for more than one and up to 6 years before their cancer diagnosis (mean age 39.0 years) (table I).

A large number of the screened women (19 patients, 83%), had had at least one normal smear during the last 6 years and 13 patients (57%) had had a normal smear for the last 3 years. Ten smears recorded as negative from women who developed cancer within 6 years were re-examined, and it was found that only 2 of these had been correctly interpreted as negative. Of the other 8, 6 showed Pap.II and 2 of the specimens were considered to be too scanty for a correct judgement at re-examination.

Twenty-five smears (33%) displayed atypia. These were taken from 13 women altogether. The most severe grade of atypia in each of these women was slight dysplasia (Pap.II) in 3 cases (23%), moderate dysplasia (Pap.III) in 2 cases (15%), severe dysplasia (Pap.IV) in 6 cases (46%), and squamous carcinoma in 2 cases (15%).

TABLE I

The number of women with cervical cancer and average age for each category.

Categories	Number of women	Average age (years)
I (no cytology)	20 (47%)	64.4
IIa (normal cytology for the last 6 years before cancer diagnosis)	11 (25%)	47.5
IIb (abnormal cytology <1 year before cancer diagnosis)	8 (19%)	44.3
IIc (abnormal cytology >1 and <6 years before cancer diagnosis)	4 (9%)	39.0

DISCUSSION

The incidence of cervical cancer is particularly high among a number of identified risk groups. One of these consists of women with a certain sexual behavior. Since cervical cancer is associated with early sexual experience and multiple partners in both men and women, a sexually transmitted agent is suspected to be the main cause of the disease, most likely human papillomavirus of the oncogenic types. These high-risk women also attend gynecological screening to a lesser extent than the normal female population and moreover, estimations of the incidence of cervical cancer have shown a 1.7-fold increase

in the risk among non-attenders (9). Another risk group is represented by women who have not undergone cytological examinations, especially older women with a high relative risk who are not covered by the organized screening because of their age. A third risk group consists of women with cytological tests incorrectly interpreted as negative.

The results of this study are consistent with established theories concerning cervical cancer and its etiology. That is, women who are not covered by organized screening develop cancer to a greater extent than those belonging to a screened population. In this study nearly half of the cancer patients (47%) had not been examined cytologically. The average age of the non-screened population was also considerably higher (64.4 years) than that of the screened women (44.9 years).

Cytological screening apparently has various sources of error. On re-examination in this study, only two out of ten smears were found to have been correctly interpreted as negative. Inter- and intraindividual variations in the interpretation and lack of diagnostic reproducibility are two important shortcomings of cervical screening. Unsuccessful sampling and inadequacies in smear preparation may also give rise to false-negative results. Further HPV-related lesions should be associated with an increased relative risk of cancer, rather than those with other infections.

There is a strong association between various papillomaviruses and genital neoplasias. Different HPV's are classified into low-risk types 6 and 11, which predominate in condylomata acuminata and other low-grade lesions in the squamous epithelium. Medium- risk types such as types 31, 33 and 35 and the high-risk types 16 and 18, are found in both low- and high-grade squamous lesions and in invasive carcinomas. HPV 16 is detected in up to four times as many squamous cell carcinomas of the cervix as HPV 18. Furthermore, HPV 18 is not associated with precancerous lesions to the same extent as HPV 16. About 10% of the invasive carcinomas are not associated with demonstrable HPV DNA. This may be explained by still unknown, not yet detectable HPV types, or by progression of some of the cervical lesions to cancer without identified HPV infection.

Several authors claim that we are in need of a complement to cytological screening (4, 11-12, 19). Among women with atypical squamous cells of undetermined significance, a test identifying the high-risk HPV types could detect women with underlying lesions that are likely to progress and by this means select those women who would benefit from immediate referral for colposcopy (2, 4, 10). There is no convincing evidence that treatment of low-grade intraepithelial lesions will reduce the incidence of cervical cancer (20). In this situation, again a test for the oncogenic HPV types could identify women with lesions with an increased relative risk of cancer development. A large-scale study is required to fully evaluate the importance of HPV testing on smears, where all women are randomized into two subgroups, one with traditional cytological examination and another with HPV tests on smear specimens.

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