Familial Cervical Cancer: Case Reports, Review and Clinical Implications

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Abstract

We report three Dutch families with familial clustering of (pre)neoplastic cervical disease, review the literature on familial risks of cervical intraepithelial neoplasia (CIN) and cervical cancer, and discuss possible practical guidelines for women with a family history of cervical cancer. Daughters and sisters of women with cervical cancer have been reported to have a relative risk of 1.5-2.3 to develop this type of cancer. From a practical clinical point of view, we suggest that as in women with an increased non-genetic risk to develop cervical cancer (e.g. because of immunosuppressive therapy) increased surveillance to detect this tumour should be considered in women with an increased risk based on family history. Cessation of smoking should be advised. As the use of condoms at least prevents HPV re-infection its use can be recommended as a way to lower the cervical cancer risk. Future studies to determine the genetic contribution to the development of cervical cancer should include the paternal family history of cancer and, because genetic predisposition might express itself as a higher risk to develop precursors of cervical cancer, carcinoma in situ and CIN grade II-III.

Introduction

Infection with oncogenic types of human papilloma virus (HPV) is regarded as the main causal factor of cervical cancer [1]. There is evidence to suggest that genetic factors affecting an individual’s susceptibility to HPV infection may influence the risk to develop cervical cancer [2]. However, the genes involved and mutations or variants in those genes remain to be fully established [3]. As in other cancers, genetic susceptibility might manifest as familial clustering of cervical cancer. Although cervical cancer is the third most common cancer in women worldwide [4], reports on familial cases of cervical cancer, on calculated tumour risks for relatives and, even more so, on its clinical implications are relatively rare. Due to the national screening programme cervical cancer is not a common disease in the Netherlands [5, 6], and no reports have been published on familial clustering of cervical cancer in Dutch patients.

In this paper we report three Dutch families with multiple cases of cervical cancer and cervical intraepithelial neoplasia (CIN), we review the literature on familial occurrence of cervical (pre)neoplastic disease and discuss present and possible future practical clinical implications.

Case reports

Recently members of three non-related families (pedigrees shown in Figures 1, 2 and 3, respectively)
were referred to our clinic with questions regarding the possible hereditary nature of cervical cancer in their families and possible preventive options. Because family histories of cancer may be inaccurate [7], we verified the cervical cancer cases whenever possible.
In family 1, the index-patient (IV-3) was diagnosed with a clear cell carcinoma of the cervix, FIGO stage Ib1 at the age of 24. No diethylstilbestrol (DES)-use by the mother was reported. The maternal great-grandmother (I-1) was reported by the family to have been diagnosed with cervical cancer before the age of 50. The maternal grandmother (II-5) had been diagnosed with adenocarcinoma of the cervix and had died at the age of 46. The paternal aunt (III-6) had been diagnosed with squamous carcinoma in situ (CIS) of the cervix at the age of 35, which was treated with a conization. The diagnoses in IV-3, II-5 and III-6 could be confirmed by checking the medical records. The medical records of I-1 were no longer available. No cervical cancer occurred in the family of III-3. The question on referral was what advice should be given to young girls of 16 and 15 years of age (IV-4 and IV-5, respectively).

In family 2, the proband (III-7) was referred because three of her sisters (III-1, 5 and 9) had been diagnosed with cervical cancer or CIS, all confirmed by medical records. They were under the impression that their mother (II-6) had been diagnosed with cervical cancer as well. However, checking medical records revealed that she had been diagnosed with hyperplasia of the endometrium instead.

In family 3, three cases of cervical cancer or CIS, all squamous cell carcinoma, confirmed by medical records occurred in two generations (II-1, III-3 and 8). The medical history of two half-sisters (III-1 and 2) was unknown.

HPV status was unknown in families 1, 2 and 3 and the patterns of non-cervical cancer types reported in these families were not suggestive of any known hereditary cancer syndrome.
## Table 1. Reported familial risks and heritability of cervical cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of study</th>
<th>Number of patients</th>
<th>Number of controls</th>
<th>Risk for first degree relative to develop CIN/CIS/CC</th>
<th>Comments</th>
<th>Heritability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furgyik et al. [20]</td>
<td>case-control relatives of 180 CIS/CC patients male consorts</td>
<td>relatives of 105 male consorts</td>
<td>7.9% vs. 1.1% (p&lt;0.01)</td>
<td>% of mothers with CIS/CC % of sisters with CIS/CC</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Brinton et al. [18]</td>
<td>case-control relatives of 418 SCC patients 23 ASC patients 40 AC patients</td>
<td>801 healthy women</td>
<td>OR = 3.1 (p &lt;0.05)</td>
<td>family history of CC in patients vs. controls</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Ahlbom et al. [13]</td>
<td>longitudinal cohort study relatives of 263 MZ twins 395 DZ twins MZ vs. DZ</td>
<td>relatives of 13,982 CC patients</td>
<td>RR = 4.8 (95% CI 3.0-7.6)</td>
<td>risk for twin sister to develop CIS</td>
<td>39-66%</td>
<td>–</td>
</tr>
<tr>
<td>Hemminki et al. [12]</td>
<td>longitudinal cohort study relatives of 125,569 CIS patients relatives of 3,901,140 healthy women</td>
<td>relatives of 3,901,140 healthy women</td>
<td>FRR = 1.79 (95% CI 1.75-1.84)</td>
<td>–</td>
<td>11-15% (CIS)</td>
<td>–</td>
</tr>
<tr>
<td>Magnusson et al. [21]</td>
<td>nested case-control study in cohort study relatives of 71,533 CIN/CIS/CC patients</td>
<td>relatives of 194,810 healthy women</td>
<td>FRR = 1.83 (95% CI 1.77-1.88)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Magnusson et al. [14]</td>
<td>longitudinal cohort study relatives of 65,685 CIN/CIS/CC patients</td>
<td>relatives of 189,635 healthy women</td>
<td>–</td>
<td>–</td>
<td>27%</td>
<td>–</td>
</tr>
<tr>
<td>Hemminki et al. [22]</td>
<td>longitudinal cohort study relatives of 191,081 CIS patients relatives of 21,727 CC patients</td>
<td>relatives of 5,935,132 healthy women</td>
<td>RR = 1.51-1.77 (95% CI 1.33-2.10)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Fischer et al. [19]</td>
<td>longitudinal cohort study relatives of 893 CC patients</td>
<td>–</td>
<td>6.9%</td>
<td>% of relatives with CC</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

**Legend to Table 1**
- OR = odds ratio
- RR = relative risk = the risk of cases compared with the risk of controls
- FRR = familial relative risk = the risk to the relatives of cases divided by the risk to the relatives of controls
- Heritability = the proportion of total variance due to genetic variance
- MZ = monozygotic
- DZ = dizygotic
- CC = cervical cancer
- SCC = squamous cell carcinoma
- ASC = adenosquamous carcinoma
- AC = adenocarcinoma
- CIN = cervical intra-epithelial neoplasia
- CIS = carcinoma in situ
Review and discussion

Familial clustering of cervical cancer might be coincidental, the result of shared exogenic risk factors, shared genetic risk factors or a combination of these factors. HPV is an established exogenic risk factor for cervical cancer and CIN [8]. Others might be smoking and use of oral contraceptives [9-11]. All these risk factors may well be shared within families because of possible shared lifestyles. Presently there is neither indication that cervical cancer which presents in familial clusters develops at a significantly earlier age [12] than sporadic cervical cancer (considered to be a hallmark of hereditary cancer) nor that its clinical behaviour differs from that of sporadic cervical cancer. The heritability of cervical cancer has been estimated between 22% and 46% [12-14]. As publications on cases of familial clustering of cervical cancer are relatively rare, more data are needed to arrive at more precise estimations [15-17]. Reported figures on familial cervical cancer in situ (CIS) and cervical cancer are summarized in Table 1. Apart from three studies (the study by Brinton et al [18], who investigated the family history of women with cervical cancer in a North American population, the study by Fischer et al [19] in a German population and Furgyk et al [20] in a Swedish population), all other available studies used the Swedish national cancer registers. Not surprisingly the results of the Swedish studies are similar, although different methods to investigate familial risks were used and results were expressed in different types of risk units [12-14, 21, 22]. In these studies, a (familial) relative risk of about 1.5-2.3 for CIS and/or cervical cancer for first degree relatives of affected women was reported, although some histological subtypes might be associated with a higher risk. Only one study included patients with severe dysplasia (CIN III) of the cervix [21]. Because CIN III and II are considered to be the precursors of cervical cancer [23, 24], a genetic predisposition to cervical cancer might manifest itself as not only cervical cancer and CIS, but also as CIN II and III. Familial clustering of CIN II and III as well as CIS and cervical cancer might therefore be expected to occur, as shown in our family 2. Therefore, it would be logical to include CIN II and III in the analysis of familial cervical cancer risk, although CIN will not be readily observed in populations without cervical cancer screening.

So far, familial cervical cancer risk has been investigated in mother-daughter and sister-sister relationships only, but the pedigree of family 1 might suggest a paternally inherited genetic susceptibility for (pre)neoplastic cervical disease. Future studies should include the history of (cervical) cancer in the paternal branch of the family, as ignoring the possibility of paternally transmitted genetic susceptibility will underestimate the genetic contribution to cervical cancer risk.

The familial risks reported so far are in the same order of magnitude as the familial relative risks (FRRs) found in cancers with an identified hereditary component such as breast, ovarian and colon cancer [12]. In contrast to these tumour types, there is no evidence yet for the existence of a highly penetrant cervical cancer predisposition gene.

To identify candidate genes associated with genetic susceptibility to cervical cancer, genes currently under investigation are the HLA genes and other genes that are involved in cell-mediated immunity like IL-10, Tp53 and genes involved in the detoxification of carcinogens found in tobacco smoke [2, 3, 25-30]. The products of most of these genes are known to interact with the exogenic agents mentioned earlier. No definitive conclusion about genetic predisposition in familial...
clusters of cervical cancer, including those that we have reported, will be possible before genes responsible for such predisposition have been convincingly identified.

What medical advice should we give to women with a family history of cervical cancer and/or its precursor lesions? For practical purposes, and based on current literature, close female relatives of the affected women in the families we have reported and similar ones can be presumed to have a moderately increased risk to develop cervical cancer. This raises the issue of possible primary and secondary preventive options. In these women, adherence to screening programmes and reducing exposure to known exogenic risk factors might therefore be especially important. As HPV is the main causal factor for developing cervical cancer and this virus is spread mainly through sexual contact, use of condoms might be advisable, since the use of condoms at least prevents HPV re-infection and thus can be a way to lower cervical cancer risk [31]. Another well-studied risk factor for CIN and cervical cancer is smoking [32-34]. Smoking has been suggested to be a confounding effect caused by the association of smoking with a increased risk of HPV infection [35], but in other studies, adjusted for HPV, smoking appeared to be an independent risk factor [34]. Szarewski et al [36] reported that smoking cessation facilitated regression of CIN lesions. Thus, smoking cessation should be advised, particularly in women at an increased risk for cervical cancer.

Recently new guidelines for the early detection of cervical neoplasia and cancer were published by the American Cancer Society (ACS) [37]. These recommendations include more frequent cervical screening for women who have been reported to be at a higher risk for cervical cancer, because they are either immunocompromised (by organ transplantation, chemotherapy or chronic corticosteroid treatment) or have a history of in utero exposure to diethylstilbestrol (DES). Interestingly, no recommendations were included for women with a positive family history of CIN or cervical cancer although the relative risk for cervical cancer due to DES exposure [38] is comparable to that for cervical cancer due to familial clustering. Similar relative risks have lead to recommendations for increased surveillance in women with a family history of cancer of the breast, ovaries or colon. Taken together, it appears to be consistent to consider a more intensive screening policy for women with a family history of cervical cancer as well. In our opinion, this screening could follow the ACS guidelines for other groups of women with an increased cervical cancer risk, in particular those listed for women with a history of in utero exposure to DES (Table 2), until more data become available. However, whether this annual screening should continue beyond the age of 70 (ACS does not mention a fixed upper age limit for the DES-exposed group) is questionable. As in other familial cancer screening programmes, the benefits and costs (physical, psychological and economic) of increased surveillance in women with a family history of cervical cancer would need to be established and this surveillance should therefore be monitored in a research setting.

When in the future genetic predisposition to cervical cancer can be identified at a molecular level, presymptomatic genetic testing will become an option. The identification of such predisposition might stimulate compliance to screening programmes, or, in regions without population screening, it might make cervical cancer screening available to the women involved. Moreover, when genetic susceptibility indeed turns out to act through a decreased host response to HPV infection, then women with this particular susceptibility might be good candidates for prophylactic HPV vaccination [39].

References


