

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)

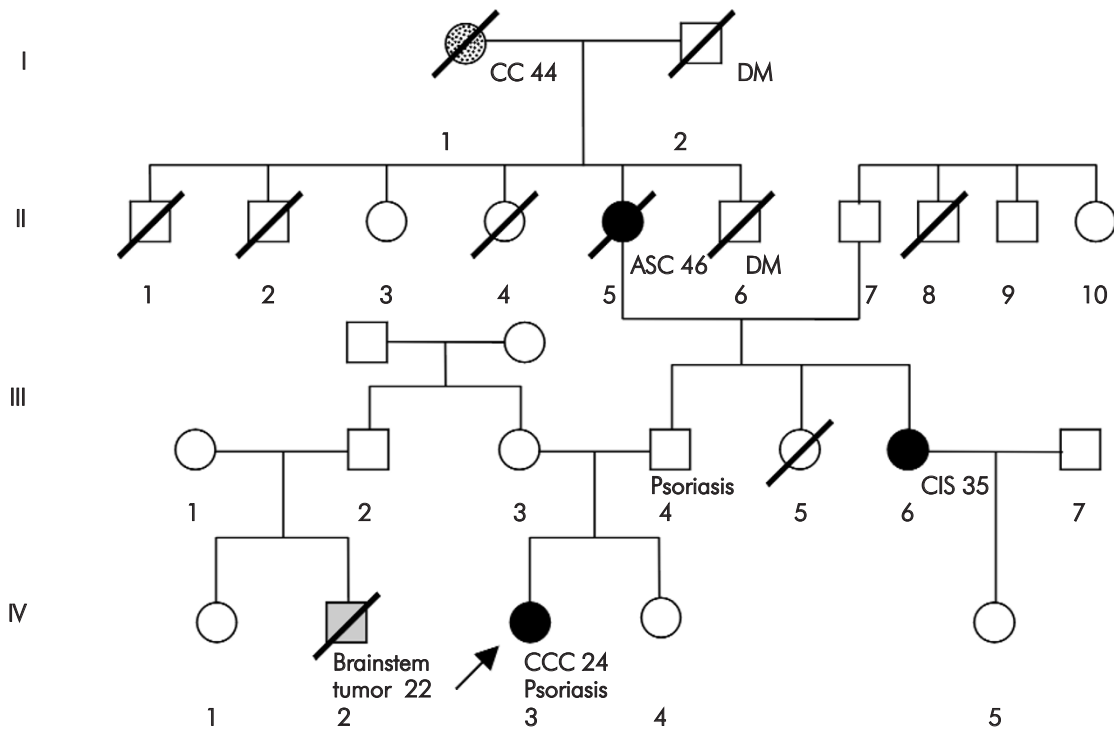


Fig. 1. Family 1

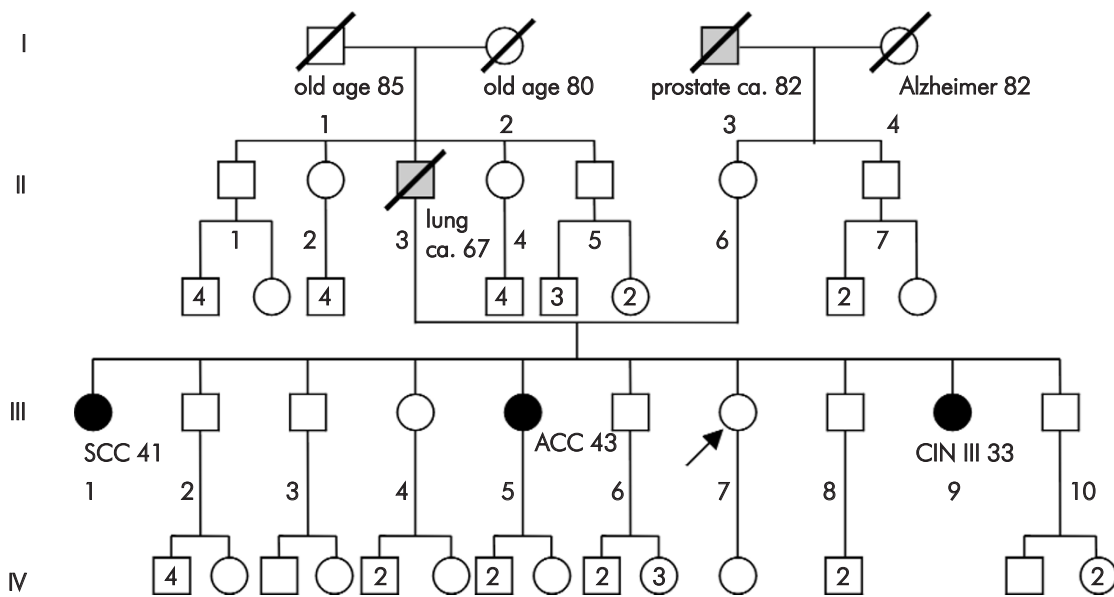


Fig. 2. Family 2

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.

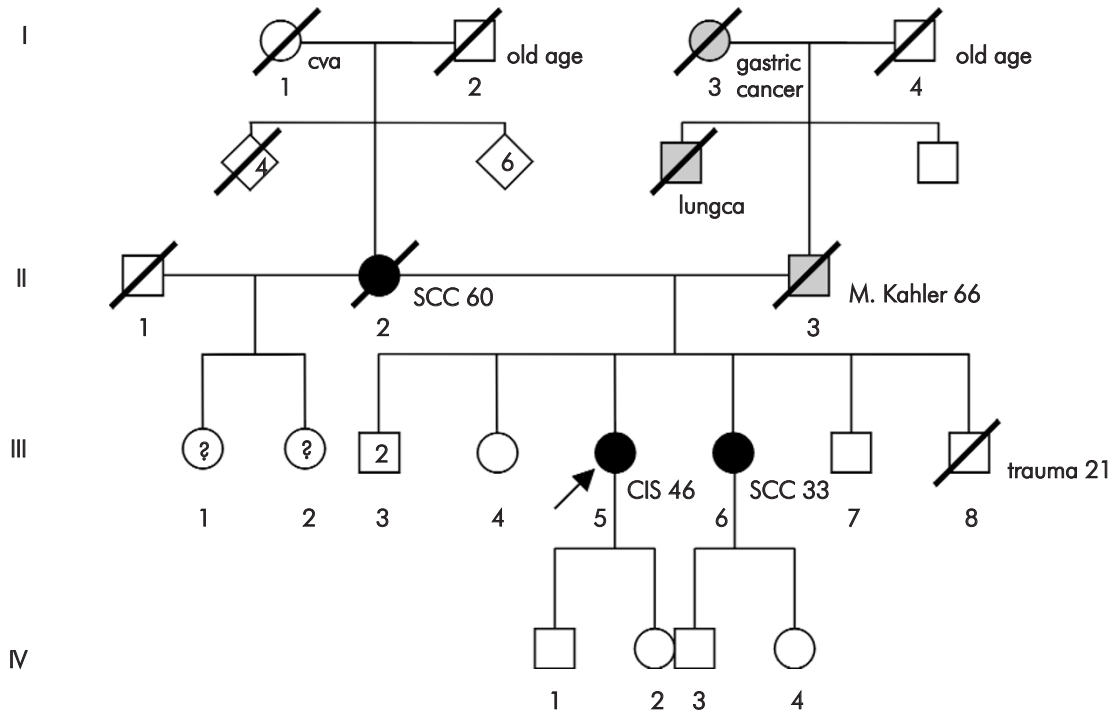


Fig. 3. Family 3

Legend to Figures 1, 2 and 3

Pedigrees of the three families with three or four women with CIN or cervical cancer. Diagnosis or cause of death and age of diagnosis or death are mentioned in the figure.

- ↗ = individual referred for genetic counselling
- black symbols = diagnosis confirmed by medical records
- grey symbols = medical records unavailable
- hatched symbols = non-cervical cancer reported by family
- numbers in the symbols = number of individuals
- CC = cervical cancer
- SCC = squamous cervical cancer
- ACC = adenocarcinoma of the cervix

- ASC = adenosquamous carcinoma of the cervix
- CCC = clear cell carcinoma of the cervix
- CIS = cervical cancer in situ
- CIN = cervical intraepithelial neoplasia
- DM = diabetes mellitus
- CVA = cerebro-vascular accident
- ? = unknown medical history

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 adenosquamous carcinoma 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 CIN, 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

Author	Type of study	Number of patients	Number of controls	Risk for first degree relative to develop CIN/CIS/CC	Comments	Heritability (%)
Furgyik et al. [20]	case-control	relatives of 180 CIS/CC patients	relatives of 105 male consorts	7.9% vs. 1.1% (p<0.01) 7.5% vs. 1.0% (p<0.01) 15.6%	% of mothers with CIS/CC % of sisters with CIS/CC % of mothers and/or sisters with CIS/CC	– –
Brinton et al. [18]	case-control	418 SCC patients 23 ASC patients 40 AC patients	801 healthy women	OR = 3.1 (p <0.05) OR = 9.9 (p <0.05) OR = 2.49 (N.S.)	family history of CC in patients vs. controls	
Ahlbom et al. [13]	longitudinal cohort study twin study	263 MZ twins 395 DZ twins MZ vs. DZ	– –	RR = 4.8 (95% CI 3.0-7.6) RR = 2.4 (95% CI 1.5-3.8) RR = 2.0 (95% CI 1.1-3.5)	risk for twin sister to develop CIS risk for twin sister to develop CIS comparing MZ and DZ twins	39-46%
Hemminki et al. [12]	longitudinal cohort study	relatives of 125,569 CIS patients relatives of 13,982 CC patients	relatives of 3,901,140 healthy women	FRR = 1.79 (95% CI 1.75-1.84) FRR = 2.30 (95% CI 1.66-2.93)	risk for daughters of patients vs. daughters of healthy women to develop CIS risk for daughters of patients vs. daughters of healthy women to develop CC	11-15% (CIS) 22-34% (CC)
Magnusson et al. [21]	nested case-control study in cohort study	relatives of 71,533 CIN/CIS/CC patients	relatives of 194,810 healthy women	FRR = 1.83 (95% CI 1.77-1.88) vs. FRR = 1.10 (95% CI 0.76-1.54) FRR = 1.93 (95% CI 1.85-2.01) vs. FRR = 1.15 (95% CI 0.82-1.57) FRR = 1.45 (95% CI 1.31-1.60)	risk for biologic vs. adoptive mothers risk for biologic vs. adoptive sisters risk for half-sisters (same mother or same father)	–
Magnusson et al. [14]	longitudinal cohort study	relatives of 65,685 CIN/CIS/CC patients	relatives of 189,635 healthy women	–	–	27%
Hemminki et al. [22]	longitudinal cohort study	relatives of 191,081 CIS patients relatives of 21,727 CC patients	relatives of 5,935,132 healthy women	RR = 1.51-1.77 (95% CI 1.33-2.10) RR = 1.73-2.12 (95% CI 1.37-3.17)	risk for relatives of patients vs. relatives of healthy women	–
Fischer et al. [19]	longitudinal cohort study	relatives of 893 CC patients	–	6.9%	% of relatives with CC	–

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

CIN = cervical intra-epithelial neoplasia

CIS = carcinoma in situ

CC = cervical cancer

SCC = squamous cell carcinoma

ASC = adenosquamous carcinoma

AC = adenocarcinoma

Table 2. Summary of the American Cancer Society guidelines on screening for cervical cancer [37]

	Start screening	Interval	Stop screening
General population	3 years after onset of vaginal intercourse, but do not start screening later than at 21 years of age	Annually; change interval to every 2 to 3 years in women older than 29 years of age who have had 3 consecutive negative cytology results	70 years of age
Women who are immunocompromised ¹	Start as in general population	Screen twice in the first year after diagnosis ² ; annually thereafter	Continue screening as long as patients are in reasonably good health
Women with a history of in utero exposure to DES	Start as in general population	Annually	Continue screening as long as patients are in reasonably good health

¹ including HIV+² diagnosis of condition associated with compromised immune system or start of immunocompromising therapy, respectively

Review and discussion

Familial clustering of cervical cancer might be coincidental, the result of shared exogenous risk factors, shared genetic risk factors or a combination of these factors. HPV is an established exogenous 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 exogenous 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 exogenous 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 lifestyle with an 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 led 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

1. Munoz N, Bosch FX, de Sanjose S, Herrero R, Castellsague X, Shah KV, Snijders PJ, Meijer CJ; International Agency for Research on Cancer Multicenter Cervical Cancer Study Group. Epidemiologic classification of human papillomavirus types associated with cervical cancer. *N Engl J Med* 2003; 348 (6): 518-527.
2. Breitburd F, Ramoz N, Salmon J and Orth G. HLA control in the progression of human papillomavirus infections. *Semin Cancer Biol* 1996; 7 (6): 359-371.
3. Odunsi KO and Ganesan TS. The roles of the human major histocompatibility complex and human papillomavirus infection in cervical intraepithelial neoplasia and cervical cancer. *Clin Oncol (R Coll Radiol)* 1997; 9 (1): 4-13.
4. Parkin DM, Pisani P and Ferlay J. Estimates of the worldwide incidence of 25 major cancers in 1990. *Int J Cancer* 1999; 80 (6): 827-841.
5. Visser O, Coebergh JWW, Schouten LJ and van Dijk JAAM. Incidence of cancer in the Netherlands 1995. Utrecht: 1997.
6. Van Ballegooijen M and Hermens R. Cervical cancer screening in the Netherlands. *Eur J Cancer* 2000; 36: 2244-2246.
7. Sijmons RH, Boonstra AE, Reefhuis J, Hordijk-Hos JM, de Walle HE, Oosterwijk JC and Cornel MC. Accuracy of family history of cancer: clinical genetic implications. *Eur J Hum Genet* 2000; 8 (3): 181-186.
8. Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, Snijders PJ, Peto J, Meijer CJ and Munoz N. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol* 1999; 189 (1): 12-19.
9. Mitchell MF, Tortolero-Luna G, Wright T, Sarkar A, Richards-Kortum R, Hong WK and Schottenfeld D. Cervical human papillomavirus infection and intraepithelial neoplasia: a review. *J Natl Cancer Inst Monogr* 1996; (21): 17-25.
10. Koutsky L. Epidemiology of genital human papillomavirus infection. *Am J Med* 1997; 102 (5A): 3-8.
11. Moreno V, Bosch FX, Munoz N, Meijer CJ, Shah KV, Walboomers JM, Herrero R, Franceschi S; International Agency for Research

- on Cancer. Multicentric Cervical Cancer Study Group. Effect of oral contraceptives on risk of cervical cancer in women with human papillomavirus infection: the IARC multicentric case-control study. *Lancet* 2002; 359 (9312): 1085-1092.
12. Hemminki K, Dong C and Vaittinen P. Familial risks in cervical cancer: is there a hereditary component? *Int J Cancer* 1999; 82 (6): 775-781.
 13. Ahlbom A, Lichtenstein P, Malmstrom H, Feychting M, Hemminki K and Pedersen NL. Cancer in twins: genetic and nongenetic familial risk factors. *J Natl Cancer Inst* 1997; 89 (4): 287-293.
 14. Magnusson PK, Lichtenstein P and Gyllensten UB. Heritability of cervical tumours. *Int J Cancer* 2000; 88 (5): 698-701.
 15. Andrews FJ, Linehan JJ and Melcher DH. Cervical carcinoma in both mother and daughter. *Acta Cytol* 1981; 25 (1): 3-4.
 16. Bender S. Carcinoma in-situ of cervix in sisters. *Br Med J* 1976; 1 (6008): 502.
 17. Bruinse HW, te Velde ER and de Gast BC. Human leukocyte antigen patterns in a family with cervical cancer. *Gynecol Oncol* 1981; 12 (2 Pt 1): 249-252.
 18. Brinton LA, Tashima KT, Lehman HF, Levine RS, Mallin K, Savitz DA, Stolley PD and Fraumeni JF Jr. Epidemiology of cervical cancer by cell type. *Cancer Res* 1987; 47 (6): 1706-1711.
 19. Fischer U, Raptis G and Horn LC. Significance of family anamnesis in cervix carcinoma. *Zentralbl Gynakol* 2001; 123 (5): 302-307.
 20. Furgyk S, Grubb R, Kullander S, Sandahl B, Wingerup L and Eydal A. Familial occurrence of cervical cancer, stages 0-IV. *Acta Obstet Gynecol Scand* 1986; 65 (3): 223-227.
 21. Magnusson PK, Sparen P and Gyllensten UB. Genetic link to cervical tumours. *Nature* 1999; 400 (6739): 29-30.
 22. Hemminki K, Li X and Mutanen P. Familial risks in invasive and in situ cervical cancer by histological type. *Eur J Cancer Prev* 2001; 10 (1): 83-89.
 23. Kiviat N. Natural history of cervical neoplasia: overview and update. *Am J Obstet Gynecol* 1996; 175 (4 Pt 2): 1099-1104.
 24. Pinto AP and Crum CP. Natural history of cervical neoplasia: defining progression and its consequence. *Clin Obstet Gynecol* 2000; 43 (2): 352-362.
 25. Storey A, Thomas M, Kalita A, Harwood C, Gardiol D, Mantovani F, Breuer J, Leigh IM, Matlashewski G and Banks L. Role of a p53 polymorphism in the development of human papillomavirus-associated cancer. *Nature* 1998; 393 (6682): 229-234.
 26. Stanczuk GA, Sibanda EN, Perrey C, Chirara M, Pravica V, Hutchinson IV and Tswana SA. Cancer of the uterine cervix may be significantly associated with a gene polymorphism coding for increased IL-10 production. *Int J Cancer* 2001; 94 (6): 792-794.
 27. Warwick A, Sarhanis P, Redman C, Pemble S, Taylor JB, Ketterer B, Jones P, Alldersea J, Gilford J, Yengi L, Fryer A and Strange RC. Theta class glutathione S-transferase GSTT1 genotypes and susceptibility to cervical neoplasia: interactions with GSTM1, CYP2D6 and smoking. *Carcinogenesis* 1994; 15 (12): 2841-2845.
 28. Warwick AP, Redman CW, Jones PW, Fryer AA, Gilford J, Alldersea J and Strange RC. Progression of cervical intraepithelial neoplasia to cervical cancer: interactions of cytochrome P450 CYP2D6 and glutathione s-transferase GSTM1 null genotypes and cigarette smoking. *Br J Cancer* 1994; 70 (4): 704-708.
 29. Chen C, Madeleine MM, Weiss NS and Daling JR. Glutathione S-transferase M1 genotypes and the risk of squamous carcinoma of the cervix: a population-based case-control study. *Am J Epidemiol* 1999; 150 (6): 568-572.
 30. Goodman MT, McDuffie K, Hernandez B, Bertram CC, Wilkens LR, Guo C, Seifried A, Killeen J and Le Marchand L. CYP1A1, GSTM1, and GSTT1 polymorphisms and the risk of cervical squamous intraepithelial lesions in a multiethnic population. *Gynecol Oncol* 2001; 81 (2): 263-269.
 31. Hogewoning CJ, Bleeker MC, Van Den Brule AJ, Voorhorst FJ, Snijders PJ, Berkhof J, Westeneid PJ and Meijer CJ. Condom use promotes regression of cervical intraepithelial neoplasia and clearance of human papillomavirus: a randomized clinical trial. *Int J Cancer* 2003; 107 (5): 811-816.
 32. Winkelstein W, Jr. Smoking and cervical cancer – current status: a review. *Am J Epidemiol* 1990; 131 (6): 945-957.
 33. Daling JR, Madeleine MM, McKnight B, Carter JJ, Wipf GC, Ashley R, Schwartz SM, Beckmann AM, Hagensee ME, Mandelson MT and Galloway DA. The relationship of human papillomavirus-related cervical tumors to cigarette smoking, oral contraceptive use, and prior herpes simplex virus type 2 infection. *Cancer Epidemiol Biomarkers Prev* 1996; 5 (7): 541-548.
 34. Kjellberg L, Hallmans G, Ahren AM, Johansson R, Bergman F, Wadell G, Angstrom T and Dillner J. Smoking, diet, pregnancy and oral contraceptive use as risk factors for cervical intra-epithelial neoplasia in relation to human papillomavirus infection. *Br J Cancer* 2000; 82 (7): 1332-1338.
 35. Ho L, Terry G, Mansell B, Butler B and Singer A. Detection of DNA and E7 transcripts of human papillomavirus types 16, 18, 31 and 33, TGF beta and GM-CSF transcripts in cervical cancers and precancers. *Arch Virol* 1994; 139 (1-2): 79-85.
 36. Szarewski A, Jarvis MJ, Sasieni P, Anderson M, Edwards R, Steele SJ, Guillebaud J and Cuzick J. Effect of smoking cessation on cervical lesion size. *Lancet* 1996; 347 (9006): 941-943.
 37. Saslow D, Runowicz CD, Solomon D, Moscicki AB, Smith RA, Eyre HJ, Cohen C; American Cancer Society. American Cancer Society guideline for the early detection of cervical neoplasia and cancer. *CA Cancer J Clin* 2002; 52 (6): 342-362.
 38. Hatch EE, Herbst AL, Hoover RN, Noller KL, Adam E, Kaufman RH, Palmer JR, Titus-Ernstoff L, Hyer M, Hartge P and Robboy SJ. Incidence of squamous neoplasia of the cervix and vagina in women exposed prenatally to diethylstilbestrol (United States). *Cancer Causes Control* 2001; 12 (9): 837-845.
 39. Koutsky LA, Ault KA, Wheeler CM, Brown DR, Barr E, Alvarez FB, Chiacchierini LM, Jansen KU; Proof of Principle Study Investigators. A controlled trial of a human papillomavirus type 16 vaccine. *N Engl J Med* 2002; 347 (21): 1645-1651.