Vaginal and (Uncommon) Cervical Cancers in the Netherlands, 1989–2003

Maaike A. van der Aa, PhD, Th. J. M. Helmerhorst, PhD, MD,† Sabine Siesling, PhD,* Sietske Riemersma, PhD, MD,‡ and Jan Willem Coebergh, PhD, MD§||*

Background: The clinical and prognostic evaluation of cervical and vaginal tumors other than squamous cell and adenocarcinomas is hampered by the low incidence, and clinical and epidemiological studies on these uncommon tumors are scarce. Having close affinity with the pathology laboratories, the Netherlands Cancer Registry offers a great opportunity to study frequency, stage, treatment, and survival of uncommon tumors in the cervix and vagina and separately, the clear cell adenocarcinoma of the vagina and cervix.

Methods: All invasive cervical tumors (n = 10,570) and all in situ and invasive vaginal tumors (n = 778) diagnosed in the Netherlands during 1989–2003 were selected from the Netherlands Cancer Registry. Age, stage at diagnosis, and treatment were described for each histological subgroup to find differences between common and uncommon tumors, including 5-year relative survival rates.

Results: Twenty-five patients (3%) with cervical cancer subsequently developed a vaginal tumor (during 1989–2003), and 19 of these patients underwent hysterectomy for their cervical cancer. A significantly worse prognosis was found for patients with small cell neuroendocrine cervical tumors and for patients with vaginal melanomas. Patients with clear cell adenocarcinoma of the vagina and cervix were found across all age categories.

Conclusions: The less common histological types of cervical and vaginal cancers were clearly different from squamous cell carcinomas, especially with respect to age at diagnosis and survival rates. Spreading population-based knowledge of effects of treatment of these uncommon tumors should help clinical decision making and therefore improve prognosis.

Key Words: Vaginal cancer, Cervical cancer, Histology, Clear cell adenocarcinoma, Survival

(*Int J Gynecol Cancer* 2010;20: 638–645)

Regions where 1 type of epithelium replaces another (metaplasia) seem to be predilections for cancer formation, and environmental factors are closely related to this metaplastic carcinogenesis. In particular, cancers of the cervix uteri and vagina are both hosts for the human papillomavirus (HPV) primarily at the transformation zone.[1,2] The transformation zone is a region, mostly situated at the (ecto)cervix but sometimes also partially at the vagina, where original columnar epithelium is replaced by squamous epithelium by the physiological process of metaplastic transformation. Squamous cell carcinomas and adenocarcinomas of the cervix uteri and vagina both develop in the transformation zone, and these 2 tumor sites therefore presumably share some etiologic features.[3] Moreover, on both localizations, clear cell adenocarcinoma (CCAC) can develop.

Cervical cancer and its precursors follow basically 2 histological lineages depending on whether they originate in squamous or in glandular cervical epithelium. Most cases are squamous cell carcinomas, but adenocarcinomas also represent a major group.[4] The latter are in general associated with lower relative survival rates as compared with squamous cell carcinomas.[5] Other tumors in the cervix are for example melanomas, lymphomas, and sarcomas.

*Comprehensive Cancer Centre North East; †Laboratory of Pathology Eastern Netherlands, Enschede; Departments of ‡Obstetrics and Gynecology and §Public Health, Erasmus Medical Centre, Rotterdam; and ||Eindhoven Cancer Registry, Comprehensive Cancer Centre South, Eindhoven, the Netherlands.

Address correspondence and reprint requests to Maaike A. van der Aa, PhD, Comprehensive Cancer Centre North East, Hoedemakerplein 2, 7511 JP Enschede, the Netherlands. E-mail: m.vd.aa@ikst.nl.

ISSN: 1048-891X
DOI: 10.1111/IGC.0b013e3181a44f4

TABLE 1. Number, age, stage, and treatment of (uncommon) cervical tumors, diagnosed in the Netherlands in the period 1989–2003

			%	Age, yr			FIGO Stage						Treatment				
Histology	**Cases**	**%**	**Within Group**	**<25**	**25–49**	**50–74**	**75+**	**IA**	**IB-IIA**	**IIB-IVA**	**IVB**	**X**	**Local**	**Surg**	**RT**	**Other**	**None**
Squamous cell carcinoma	7752	73	99	0.6	51	35	14	27	38	29	4.2	2.3	8.1	49	37	1.3	5.1
Verrucous carcinoma	15	0.1	0.2	6.7	33	60	0.0	40	27	27	6.7	0.0	6.7	40	40	6.7	6.7
Papillary squamous cell carcinoma	26	0.2	0.3	0.0	27	46	27	7.7	42	50	0.0	0.0	3.8	23	73	0.0	0.0
Lymphoepitheliomalike carcinoma	8	0.1	0.1	0.0	50	38	13	13	88	0.0	0.0	0.0	0.0	100	0.0	0.0	0.0
Adenocarcinoma	1516	14	87	0.4	57	30	12	29	44	19	5.1	3.4	5.9	64	21	2.3	6.1
Mucinous adenocarcinoma	55	0.5	3.2	1.8	71	20	7.3	20	62	15	3.6	0.0	7.3	75	16	1.8	0.0
Endometrioid adenocarcinoma	34	0.3	1.9	0.0	35	50	15	15	47	24	15	0.0	2.9	62	32	0.0	2.9
CCAC	121	1.1	6.9	5.8	33	40	22	11	51	28	9.1	0.8	2.5	61	30	0.8	5.8
Serous adenocarcinoma	4	0.0	0.2	0.0	25	50	25	25	25	25	0.0	25	0.0	50	50	0.0	0.0
Mesonephric carcinoma	4	0.0	0.2	0.0	50	0.0	50	0.0	0.0	0.0	0.0	100	0.0	100	0.0	0.0	0.0
Well-differentiated villoglandular carcinoma	11	0.1	0.6	0.0	100	0.0	0.0	18	73	9.1	0.0	0.0	36	64	0.0	0.0	0.0
Other epithelial tumors	485	4.6	55	1.2	65	24	9.9	61	12	13	7.6	6.4	16	56	15	2.7	12
Adenosquamous carcinoma	313	3.0	36	1.3	56	36	7.7	17	52	23	5.4	1.6	3.2	68	25	0.6	3.5
Glassy cell carcinoma	3	0.0	0.3	0.0	67	33	0.0	0.0	67	33	0.0	0.0	0.0	67	0.0	33	0.0
Mucoepidermoid carcinoma	5	0.0	0.6	0.0	60	40	0.0	0.0	60	0.0	40	0.0	0.0	60	20	20	0.0
Adenoid cystic carcinoma	2	0.0	0.2	0.0	0.0	100	0.0	50	0.0	50	0.0	0.0	0.0	50	50	0.0	0.0
Adenoid basal carcinoma	2	0.0	0.2	0.0	0.0	50	50	50	50	0.0	0.0	0.0	0.0	50	0.0	0.0	50
Small cell neuroendocrine carcinoma	67	0.6	7.6	0.0	43	37	19	6.0	30	28	30	6.0	1.5	30	36	24	9.0
Large cell neuroendocrine carcinoma	1	0.0	0.1	0.0	100	0.0	0.0	0.0	100	0.0	0.0	0.0	0.0	100	0.0	0.0	0.0
Typical carcinoid tumor	3	0.0	0.3	0.0	100	0.0	0.0	33	33	0.0	0.0	33	0.0	100	0.0	0.0	0.0
Small (oat) cell carcinoma	1	0.0	0.1	0.0	0.0	100	0.0	0.0	100	0.0	0.0	0.0	0.0	100	0.0	0.0	0.0
Mesenchymal tumors	8	0.0	24	13	50	25	13	0.0	0.0	0.0	0.0	100	0.0	75	13	13	0.0
Leiomyosarcoma	25	0.2	76	8.0	32	56	4.0	0.0	0.0	0.0	0.0	100	0.0	84	4.0	8.0	4.0
Mixed epithelial and mesenchymal tumors	33	0.3	100	3.0	21	42	33	0.0	0.0	0.0	0.0	100	0.0	64	18	6.1	12
Miscellaneous tumors	—	0.5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Melanoma	3	0.0	9.4	0.0	33	33	33	0.0	0.0	0.0	0.0	100	0.0	100	0.0	0.0	0.0
Lymphoma	29	0.3	91	3.4	17	52	28	0.0	0.0	0.0	0.0	100	0.0	21	41	35	3.4
Other	44	0.4	100	4.5	14	43	39	0.0	4.5	0.0	0.0	96	0.0	11	18	11	59

Surg, surgery; RT, radiotherapy.

TABLE 2. Five-year relative survival related to histological classification of patients with cervical cancer in the Netherlands, diagnosed from 1989–2003

	5-Year Relative Survival				5-Year Relative Survival per Group			
Histology	**Cases**	**5-Year %**	**95% CI**	***P***	**Cases**	**5-Year %**	**95% CI**	***P***
Squamous cell carcinoma	4608	77	76–79	Ref	4643	77	76–79	Ref
Adenocarcinoma	870	76	72–79	0.4	1007	76	72–79	0.3
Mucinous adenocarcinoma	35	81	60–93	0.4	—	—	—	—
Endometrioid adenocarcinoma	20	73	44–91	0.9	—	—	—	—
CCAC	68	71	56–82	0.1	—	—	—	—
Other epithelial tumors	256	83	77–88	0.04	519	78	73–82	0.9
Adenosquamous carcinoma	206	77	70–83	0.8	—	—	—	—
Small cell neuroendocrine carcinoma	49	52	35–68	<0.001	—	—	—	—
Mixed epithelial and mesenchymal tumors	41	73	52–87	0.3	41	73	52–87	0.3

Ref, reference category.

Cancer of the vagina is frequently found as either a synchronous or a metachronous neoplasm with cervical cancer[6] and accounts for approximately 1% to 2% of all gynecological malignancies.[7] Little is known about the risk factors for vaginal cancer, most of which occurs at older ages.

In 1971, diethylstilbestrol (DES), formerly used to prevent adverse outcomes of pregnancy, was first linked to CCAC of the vagina in young women exposed in utero.[8] Later, this strong association between intrauterine DES exposure and risk of CCAC of the vagina and also of the cervix was confirmed by others.[9,10] Nonetheless, the absolute risk remains small: 1 per 1000 DES daughters will eventually develop a CCAC.[11,12]

The clinical and prognostic evaluation of cervical and vaginal tumors other than squamous cell and adenocarcinomas is hampered by the low incidence, and clinical and epidemiological studies on these uncommon tumors are scarce. The Netherlands Cancer Registry (NCR) offers a great opportunity to study the frequency, stage, treatment, and survival of uncommon cervical and vaginal tumors and separately, the CCAC of the vagina and cervix.

METHODS

The NCR consists of 9 regional cancer registries, and it includes all invasive and in situ malignancies diagnosed from 1989 onwards in the Netherlands. Notification is obtained from the National Automated Pathology Archive and hematology departments in the region. Other sources are the radiotherapy departments of the hospitals and the National Registry of Hospital Discharge Diagnosis, which accounts for up to 8% of new cases.[13] From the medical records, data

TABLE 3. Number, age, stage, and treatment of (uncommon) vaginal tumors, diagnosed in the period 1989–2003 in the Netherlands

			Age, yr				FIGO Stage							Treatment		
Histology	**Cases**	**%**	**<25**	**25–49**	**50–74**	**75+**	**In Situ**	**I**	**II**	**III**	**IVA**	**IVB**	**X**	**Surg**	**RT**	**Other/None**
Squamous cell carcinoma	518	67	0.2	17	43	39	12	29	21	12	12	6.0	8.5	28	57	15
Adenocarcinoma	109	14	3.7	28	37	32	0.9	40	18	4.6	11	10	15	39	39	22
Other epithelial tumors	62	8.0	0.0	23	48	29	34	9.7	11	6.5	8.1	8.1	23	34	40	26
Mesenchymal	17	2.2	12	29	35	24	0.0	0.0	0.0	0.0	0.0	0.0	100	77	0.0	24
Mixed epithelial and mesenchymal tumors	5	0.6	0.0	0.0	20	80	0.0	0.0	0.0	0.0	0.0	0.0	100	20	40	40
Melanomas	59	7.6	0.0	8.5	41	51	0.0	0.0	0.0	1.7	5.1	0.0	93	76	12	12
Other	8	1.0	13	0.0	38	50	0.0	0.0	0.0	0.0	0.0	0.0	100	13	0.0	8

TABLE 4. Five-year relative survival of patients with vaginal cancer in the Netherlands, 1989–2003

	5-Year Relative Survival, N = 385				Multivariate Survival Analysis, N = 385		
Factor	**Cases**	**5-Year %**	**95% CI**	***P***	**RER**	**95% CI**	***P***
Age group							
<25	16	72	9–96	0.9	1.5	0.2–11.9	0.7
25–49	76	76	62–86	Ref	1	Ref	Ref
50–74	139	45	36–54	0.001	2.6	1.3–5.2	0.006
75+	99	27	17–39	<0.001	3.8	1.9–7.5	<0.001
FIGO stage							
In situ	52	95	75–102	Ref	1	Ref	Ref
I-II	89	58	47–68	0.03	56	—	0.4
III-IVA	45	16	7–29	0.002	146	—	0.3
IVB	21	15	3–42	<0.001	405	—	0.2
X	65	26	14–40	0.002	100	—	0.3
Histology							
Squamous	171	52	44–60	Ref	1	Ref	Ref
Adeno	80	38	23–53	0.2	1.4	0.9–2.4	0.2
Epithelial	50	47	25–69	0.5	2.6	0.9–3.6	0.09
NOS melanoma	29	9	2–24	<0.001	1.8	1.4–4.9	0.004
Treatment							
RT	152	39	30–48	Ref	1	Ref	Ref
Surg	123	61	49–71	0.002	0.6	0.4–0.9	0.04
Other/none	55	31	17–48	<0.001	2.4	1.5–3.8	<0.001

were collected concerning identifying information (eg, first letters of the name, date of birth, sex, and postal code), tumor characteristics (eg, date of incidence, topography, morphology, and stage), treatment, and follow-up data. All data are collected from the patient files in the hospital and are coded according to a national manual by trained registrars. This manual describes inclusion and exclusion criteria as well as definitions and coding of items. Topography and morphology are coded according to the International Classification of Diseases for Oncology.[14] The TNM classification is used for the staging of the tumors[15] and is the basis for the International Federation of Gynecology and Obstetrics (FIGO) staging. Stage "X" means "unknown stage," which is mostly due to insufficient information in the patient file to stage the tumor.

According to the national recommendations in 1990 for FIGO stages IB and IIA cervical cancer, primary surgery and radiotherapy were equal therapeutic options, the choice depending mainly on patient characteristics such as age and comorbidity.[16] For patients with FIGO stages IB2, IIB, and higher, radiotherapy was the treatment of first choice. However, since the publication of 5 clinical trials, which reported better survival rates after chemoradiation compared with radiotherapy only,[17–21] the revised national guideline recommends primary chemoradiation or radiotherapy combined with hyperthermia for patients with FIGO stages IB2, IIB, and higher. The treatment for patients with cervical cancer was classified as "surgery" (+/− radiotherapy and +/− chemotherapy), "radiotherapy" (+/− chemotherapy), "other" (palliative, lymph node dissection only, chemotherapy only, metastasectomy, and unknown therapy), or "none" (no therapy). According to the national guidelines, the most common treatment of vaginal tumors is radiotherapy combined with brachytherapy. Tumors localized in the proximal and middle one-third part of the vagina are treated as cervical tumors, tumors in the distal one-third part are treated as vulva tumors. The first group will therefore receive chemotherapy combined with radiotherapy, and the latter group will receive radiotherapy combined with hyperthermia. Small tumors in the proximal part of the vagina (FIGO stage I) can sometimes be treated with surgery. When the uterus is still in situ, surgery will be radical hysterectomy. However, because of registration practices, treatment for patients with vaginal cancer and CCAC was classified as "surgery" (+/− radiotherapy and +/− chemotherapy), "radiotherapy" (+/− chemotherapy), or "other/none" (palliative, lymph node dissection only, chemotherapy only, metastasectomy, unknown therapy, and no therapy). In situ tumors of the cervix are not registered in the NCR, and we therefore selected only all invasive cervical tumors (n = 10,570) and all in situ and invasive vaginal tumors (n = 778) diagnosed in the period 1989–2003 from the NCR. The histological subtypes that were described conform the classification of Blaustein, which is based on the classification of the World Health

Organization.[22] "Neoplasms not otherwise specified" were in our study classified as "other."

Statistical Analysis

The Statistical Package for Social Sciences (version 15.0) was used to perform the analyses. The age, stage at diagnosis, and treatment were described per histological subgroup to compare differences between common and uncommon tumors. Time trends in incidence were assessed by χ^2 analysis. $P < 0.05$ was considered to be significant: the chance that the difference that was found is due to coincidence is smaller than 5%.

Vital status was available up to January 1, 2006 for the patients from 4 of the 9 regional cancer registries (n = 6258 cervical cancers, n = 396 vaginal tumors, and n = 84 CCAC): Northwest, North, East, and South. Five-year relative survival rates were calculated separately for cervical tumors, vaginal tumors, and CCAC. For both cervical and vaginal cancers, patients with "other" histological types and histological subgroups with less than 20 patients were excluded from the survival analyses (n = 6153 cervical cancers and n = 330 vaginal cancers). Survival time was defined as the time from diagnosis to death or the end of the study (January 1, 2006). Relative survival was calculated as a measure of disease-specific survival using the Ederer II method in STATA version 9.2.[23] The relative survival is the ratio between crude and expected survival and is close to disease-specific survival. Because of the small number of different histological subgroups of cervical cancer and CCAC, relative survival was modeled multivariately only for vaginal cancer. In modeling relative survival, variables were considered confounders and included in the model when the regression coefficient of the variable of interest changed by more than 10%. Relative excess risks (RER) and 95% confidence intervals (CI) were calculated. $P < 0.05$ was considered to be significant. The RER describes the difference between the hazard of death in a given group and the hazard in the reference group, taking into account the risk of death in the Dutch population.

TABLE 5. Patient and tumor characteristics and relative survival of CCAC of the cervix and vagina, 1989–2003

Patient and Tumor Characteristics			5-Year Relative Survival			
Period 1989–2003, n = 159			Period 1989–2003, n = 84			
Factor	%	95% CI	Cases	5-Year %	95% CI	*P*
Localization						
Cervix	76	17–31	62	58	42–72	Ref
Vagina	24	70–83	22	58	30–79	0.3
Age group						
<25	6	3–10	6	80	20–97	0.9
25–49	38	30–45	35	72	52–86	Ref
50–74	36	28–43	27	47	24–68	0.03
75+	20	14–26	16	34	8–70	0.07
FIGO stage						
I	51	43–59	46	73	53–86	Ref
II	28	21–35	21	55	26–78	0.2
III+	18	12–24	12	11	1–38	<0.001
X	4	1–7	5	81	17–119	0.9
Treatment						
Surg	55	47–63	44	77	58–89	Ref
RT	38	31–46	34	40	19–62	0.1
Other/None	7	3–11	6	18	1–55	0.002

RESULTS

Cervix

Nearly all tumors diagnosed during the period 1989–2003 (n = 10,570) were carcinomas, 74% being of squamous cell origin, 16% of glandular origin, and 8% being classified as "other epithelial tumors" including adenosquamous carcinoma and small cell neuroendocrine carcinomas. Furthermore, 0.2% were leiomyosarcomas, 0.3% mixed epithelial and mesenchymal tumors like malignant mullerian mixed tumors, 0.3% lymphomas and melanomas, and 0.4% "other" tumors (Table 1). No time trends in incidence for the different histological subtypes were found.

Patients with papillary squamous cell carcinomas were older than patients with common tumors of squamous cell origin (73% were older than 50 years at diagnosis compared with 48%), and they most often received radiotherapy (73%). Thirteen of the 19 patients receiving radiotherapy had a diagnosis of FIGO stages IIB to IVA with only 1 receiving adjuvant chemotherapy. The guidelines for combined chemoradiotherapy were introduced only in 1999, and the condition of the 10 of these 13 patients was diagnosed before 1999.

Clear cell adenocarcinoma was the most frequent subtype within the adenocarcinoma group (1%). These tumors and endometrioid type adenocarcinomas were mainly found in patients older than 50 years (61% and 65%, older than 50 years, respectively). All patients whose condition was diagnosed as well-differentiated villoglandular carcinoma were below 50 years old, and 91% had a diagnosis of FIGO stages IA to IIA.

Adenosquamous tumors represented 3% of all cervical tumors, and this subtype was the most frequent within the group of "other epithelial tumors." Patients whose condition was diagnosed as small cell neuroendocrine carcinoma were older (19% diagnosed in patients aged 75 or older) and had a higher stage (30% had a diagnosis of FIGO stage IVB). Furthermore, this patient group was the only group showing a significantly worse prognosis compared with the patient group with squamous cell carcinomas (Table 2, $P < 0.001$).

Leiomyosarcoma was the most frequent malignant tumor of mesenchymal origin and most frequently diagnosed in age group 50 to 74 years (56%).

Patients with lymphoma were relatively old, 79% being older than 50 years, and they most often received chemotherapy (69%). Patients with melanoma most often received radiotherapy.

Of all cervical cancer patients, 25 patients (3%) subsequently developed a vaginal tumor (during 1989–2003) and 19 of these patients underwent surgery for their cervical cancer (76%). Four patients received resection of the vagina, 15 patients received radical hysterectomy. All of these patients had a diagnosis of FIGO stage I or with an in situ tumor. Five of these patients received adjuvant radiotherapy: 3 patients with FIGO stage I, 1 patient with FIGO stage III, and 1 patient with FIGO stage IVA.

Vagina

During the 15-year period, 1989–2003, seven hundred seventy-eight vaginal tumors (86 in situ carcinomas) were diagnosed, on average, 50 annually. No specific time trends in incidence were found, neither for age nor stage at diagnosis. Most patients were elderly with 38% being older than 75 years (Table 3). Squamous cell carcinoma was the most frequent histological subtype (67%). Patients whose condition was diagnosed as carcinoma in situ mostly received surgery (65%). Most women with FIGO stage I cancer received surgery (47%) or radiotherapy (48%). Women with FIGO stages II and higher most often received radiotherapy.

Few differences in age, stage, and treatment were found between the different histological subtypes of vaginal cancer. Patients with melanomas were mostly older than 75 years (51%) and most often underwent surgery (76%; Table 3).

Five-year survival was complete for 385 patients. Five-year relative survival was significantly worse for patients aged 50 to 74 years and 75 or older ($P = 0.001$ and $P < 0.001$, respectively), for patients with melanomas ($P < 0.001$), and for those who underwent surgery ($P = 0.002$; Table 4). Patients with a diagnosis of FIGO stages other than in situ tumors had a worse prognosis, but the difference between patients with a diagnosis of FIGO stages I to II and III to IVA was also remarkable (58% and 16%, respectively). In multivariate analysis, age, treatment, and histological type were independent prognostic factors, with independent significant worse survival for patients with age 50 to 74 years and 75 or older ($P = 0.006$ and $P < 0.001$, respectively), patients who underwent surgery ($P = 0.04$), and patients with melanoma ($P = 0.004$).

Clear Cell Adenocarcinoma

During the period 1989–2003, one hundred twenty-one patients with CCAC of the cervix and 38 patients with CCAC of the vagina were examined. Patients with CCAC were examined across all age categories with more than half of the patients having FIGO stage I (Table 5).

Surgery was the most frequently used therapy (55%), especially in FIGO stages I and II (77% and 48%, respectively), whereas radiotherapy was the treatment of choice in 61% of patients with FIGO stages III or higher. Older women tended to receive surgery in FIGO stage I less often compared with younger women: 84% in age group younger than 45 years versus 55% in age group 75 years or older ($P = 0.1$).

Although complete follow-up was only available for 69 patients, 5-year relative survival appeared significantly worse for patients aged 50 to 74 years ($P = 0.03$) and for patients who had a diagnosis of FIGO stages III or higher ($P < 0.001$; Table 5).

DISCUSSION

The less common histological types of cervical and vaginal cancers were clearly other entities than squamous cell carcinomas, which were reflected in differences in age at diagnosis and survival rates.

A good prognosis was exhibited for cervical cancer patients with "other epithelial tumors" and particularly poor prognosis for patients with small cell neuroendocrine tumors. In contrast to the literature, small cell neuroendocrine carcinomas only accounted for 0.6% in our study,[24] but with similar poor survival rates as indicated in the literature where small cell carcinomas are characterized by frequent and early nodal metastases and frequent vascular invasion.[24,25] In addition, the percentage of lymphomas was lower in this study than in the literature.[24] Because in the literature, the patients with lymphomas were mainly treated with combinations of radiotherapy and chemotherapy.[24,26]

Furthermore, we showed that patients with vaginal melanomas had a worse prognosis compared with other histological groups, which is in accordance with other reports.[27,28] It is clear that vaginal melanoma is mainly a disease of elderly women, who are often reluctant to see a physician and whose condition are therefore often diagnosed in late stages.[29,30]

Use of data from the population-based nationwide NCR allowed analysis of rare tumors, although many different pathologists are involved in diagnosing the tumors. There may be some problems with classifying and localizing the tumors. First, it may sometimes be hard to discern where the cervix uteri ends and the vagina begins. The size of the cervix decreases in the senium due to atrophy, and tumors that develop there might therefore occasionally incorrectly be regarded as vaginal tumors. Second, most of the carcinomas of the cervix uteri are squamous cell carcinomas; however, many also have invasive components of adenocarcinoma and could therefore be classified as adenosquamous carcinomas. In the literature, adenosquamous carcinomas account for 5% to 25% of all cervical cancers,[24,31] whereas, in this study, only 3% of all cervical cancers were classified as adenosquamous. Pathologists usually classify tumors according to the histological type, most prominent in the tissue. It is therefore not clear which part of the cervical tumors are true adenosquamous carcinomas. In our study, 77% of patients with adenosquamous carcinomas were alive after 5 years, whereas, in other studies, worse survival was reported for patients with these tumors.[32,33] Third, endometrioid type adenocarcinomas situated in the cervix uteri may in fact be endometrial carcinomas. A recent study concerning these endometrioid adenocarcinomas indicated that staining of vimentin and HPV detection may be helpful in distinguishing between true cervical carcinoma and endometrioid type adenocarcinoma developing in the uterus.[34]

Patients treated for a (pre)malignancy of the cervix may develop a vaginal carcinoma later in life.[35] In our study,

25 patients (3%) with cervical cancer subsequently developed a vaginal tumor (during 1989–2003), and 19 of these 25 patients underwent hysterectomy for their cervical cancer. When the uterus is removed by means of a hysterectomy, the vaginal top remains in situ and, if the transformation zone is still present in the vaginal top, then this is the predelicted site for tumors induced by high-risk HPV.

The treatment of vaginal carcinoma is a challenge because it is rare; on average, seen in any hospital once every 2 years. In this study, younger patients underwent surgery more often than older patients (data not shown, $P < 0.001$), and these patients showed significantly better survival compared with patients who received radiotherapy or other therapies who usually have a poorer general condition. Unfortunately, we did not have any data about comorbid conditions or performance status and were therefore not able to adjust for that.

Cervical and vaginal carcinomas share some etiologic features as they are both associated with high-risk HPV, and both develop at the transformation zone. However, vaginal cancers mainly develop in older patients, whereas cervical cancers are most frequent in younger patients. This might indicate that the vaginal tumors in younger patients, who are most likely to carry high-risk HPV, are comparable to cervical cancer.

Remarkably, in this study, patients with CCAC of the vagina and cervix were found across all age categories. It is known that DES-associated clear cell carcinomas mostly appear in young women, aged 15 to 29 years.[36] Moreover, one should bear in mind that CCAC of the vagina has already been described before the onset of the so-called DES era, and therefore most likely, not all CCAC found in this study are due to intrauterine DES exposure.[37] A study from the Netherlands found a bimodal age distribution of patients with CCAC at young age (mean, 26 years) and at older age (mean, 71 years). This bimodal age distribution still applied when the cases in whom DES exposure was reported had been excluded, suggesting a carcinogenesis-promoting role of menarche and menopause and/or the existence of a subpopulation with genetic risk factors or exogenous risk factors other than intrauterine exposure to DES.[38] The absence of a rise in the incidence of CCAC in this study could partly be explained by the investigated period. The incidence of CCAC, already rising since 1980, may now have reached a plateau.[11] The guidelines for the follow-up of DES daughters in the Netherlands are clear: initial examination of a DES daughter and yearly follow-up in case of vaginal adenosis or abnormal shape of the vagina or cervix.[39] From age 30 years onward, follow-up takes places by means of the national screening program in which DES daughters are also expected to participate. Despite the relatively favorable prognosis for patients with CCAC, periodical checks are not proven to be (cost-)effective and probably increase anxiety among patients.

In conclusion, patients with some uncommon cervical and vaginal tumors showed a worse prognosis compared with patients with the most common histological subtypes. By obtaining and spreading knowledge of effects of treatment of these uncommon tumors, the prognosis for these patients might increase. In evaluating the mass screening program for cervical cancer, vaginal carcinomas, mainly in younger patients, should be taken into consideration because of the comparability with cervical cancer.

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