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ORIGINAL ARTICLE

Prevalence of human papillomavirus (HPV) types 16 and 18 in cervical cancer in Stockholm, Sweden during 2019–2023 compared to 2003–2008

Lars Sivars[a], Stefan Holzhauser[c], Torbjörn Ramqvist[c], Emma Tham[a,b], Kristina Hellman[d,e]* and Tina Dalianis[c]*

[a]Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden; [b]Department of Clinical Genetics, Karolinska University Hospital, Stockholm, Sweden; [c]Department of Oncology-Pathology Karolinska Institutet, Karolinska University Hospital Solna, Stockholm, Sweden; [d]Department of Women's and Children's Health, Karolinska Institutet, Stockholm Sweden; [e]Department of Gynecologic Cancer, Theme Cancer, Karolinska University Hospital, Stockholm, Sweden

ABSTRACT

Background: The prevalence of different HPV types, especially HPV16 and 18 in cervical cancer in patients diagnosed 2019–2023 in Stockholm was compared to corresponding data from 2003–2008 before the introduction of HPV vaccination in Sweden.

Material and Methods: Cervical cancer samples from 125 patients diagnosed 2019–2023 in Stockholm were analysed for 27 HPV types by multiplex assay and the HPV type prevalence data was compared to data obtained in 154 cervical samples from 2003–2008.

Results: Patient median age was higher 2019–2023 compared to 2003–2008 (55-years vs. 42-years, $p = 0.046$). Overall HPV prevalence was 93.6%, HPV16 and 18 accounted for 62.2% of all squamous cell carcinoma cases (SCC) and 63.6% of all adenocarcinoma cases (ADC) vs. 92.9%, 69.7% and 88.6% respectively 2003–2008.

Conclusion: The joint prevalence of HPV16 and 18 in SCC and ADC tended to be slightly lower in 2019–2023 as compared to 2003–2008, but the difference was not statistically significant.

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Introduction

Cancer of the uterine cervix is a common cancer among women [1]. However, due to differences in screening and vaccination against human papillomavirus (HPV) its incidence varies worldwide [1]. In the Nordic countries, a decrease in the number of cases was demonstrated after the start of organized screening in the mid-1960s, but the past decade in e.g., Sweden an increasing number of annual cases have been reported [2,3].

Most cervical cancer cases are squamous cell carcinomas (SCC), followed by adenocarcinomas (ADC) in addition to some rare cancer types [4,5]. The well-known cause of cervical cancer is persistent infection with various high-risk human papillomavirus (HPV) types, with some variations in which high-risk HPV types are more frequent in different parts of the world [6,7]. HPV16 is generally responsible for about half of all cervical cancer cases, followed by HPV18, and together they contribute to 70–76% of all invasive cervical cancers [6,7].

In 2012 the tetravalent Gardasil vaccine targeting high-risk types HPV16 and 18 and low-risk types HPV6 and 11 was introduced into the Swedish school-based HPV-vaccination programme for girls aged 10–12 years [8,9]. Subsequently, catch-up HPV vaccination was offered to women up to 26 years of age. In 2014, the tetra-valent Gardasil vaccine was gradually replaced by Gardasil-9, targeting high-risk HPV16, 18, 31, 33, 45, 52, 58 and low-risk HPV6 and 11, and since 2020, boys aged 10–12 years have been included in the school-based HPV vaccination program [9].

There are several reports, and especially a systematic review and meta-analysis showing that the incidence of genital HPV16, 18 and 6 and 11 infections and pre-cancerous lesions are decreasing [10]. However, to our knowledge there are no reports of HPV type changes in invasive cervical cancer. Nevertheless, in 2020, it was reported that the frequency of cervical cancer had decreased in HPV vaccinated as compared to non-HPV vaccinated younger women in Sweden [11].

Noteworthy, in 2011, before the school-based HPV vaccination program was introduced in Sweden, to obtain a base line of HPV types present and especially of HPV16 and 18 in SCC and ADC diagnosed 2003–2008, in the Stockholm region we completed a retrospective study [12].

To determine whether changes in HPV prevalence and especially HPV16 and 18 in cervical cancer have already occurred after the introduction of the HPV vaccine, we here performed a follow up study. We assayed for the presence of 27 HPV types in cervical samples collected 2019–2023 and compared the obtained data to data attained 2003–2008 with the same assay.

CONTACT Lars Sivars lars.sivars@ki.se Department of Molecular Medicine and Surgery, Karolinska Institutet, 171 76Stockholm, Sweden; Tina Dalianis tina.dalianis@ki.se Department of Oncology-Pathology, Karolinska Institutet, Bioclinicum J6:60, 17164 Stockholm, Sweden
*These authors are contributed equally to this work

Material and methods

Patients and tumour samples

In total, 125 patients with locally advanced cervical cancer (LACC) diagnosed between March 2019 and February 2023 at the Karolinska University Hospital, Stockholm, Sweden, were included in the study. Biopsies were taken during examination under anesthesia and stored at −20 °C until HPV prevalence analysis.

HPV prevalence data determined from the samples of the above patients were compared to corresponding data in our retrospective study from 2003–2008 [12].

The latter retrospective study included data from 154 patients with samples verified to have sufficient paraffin embedded formalin fixed tumor material for DNA extraction and further analysis, with experimental details described in detail before [12]. Of these 119 were SCC, and 35 were ADC, and of these 111/119 (93.3%) and 32/35 (91.4%) resp. were shown to be HPV positive [12].

The study was conducted according to ethical permissions 2008/813–31/2, 2016/2–31/1, 2017/599–32/1, and 2018/1472–32/1 from the Ethical Committee at Karolinska Institutet and the Regional ethical review board in Stockholm, respectively.

Extraction of HPV DNA and HPV-typing

DNA was extracted from cervical cancer biopsies using the EZ1 DNA Tissue Kit (Qiagen, Hilden, Germany) according to the manufacturers' instructions and stored in −20 °C, until further analysis. HPV typing was then performed by a bead-based multiplex assay (Luminex) on a Magpix (Luminex corp, Genk, Belgium) analyzing 27 HPV types. The latter included all 15 high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82), 3 putative high-risk types (26, 53 and 66) and 6 low-risk types (6, 11, 42, 43, 44 and 70), as previously described [12,13]. If HPV-negative by this method, the biopsies were also tested by digital droplet PCR (ddPCR) for HPV16, 18 and 45 as previously described [13].

Statistical methods

Fischer's exact t-test was used to examine for significant differences in HPV type prevalence and median age between patients diagnosed between 2003–2008 and 2019–2023.

Results

Patient characteristics

The age range and median age of patients with samples 2019–2023, including all CCs, thereby both the SCC and ADC groups, was 29–84 years and 55 years respectively (Table 1). More specifically, the age range and median age of all 106 SCC patients diagnosed 2019–2023 was 29–84 years and 54 years of age while the 11 ADC patients ranged between 39–76 years with median of 61 years of age.

In the retrospective study 2003–2008, the age range for patients with available samples was 23–88 years in SCC group (119 cases) and 25–81 years in ADC group (35 cases) with a median age of 42 years for both SCC and ADC patients [12].

Table 1. Histological sub-types of the cervix uteri in patients diagnosed 2019–2023.

	Patients ($n = 125$)
Type, n (%)	
Squamous cell	106 (84.8)
Adenocarcinoma	11 (8.8)
Clear cell	1 (0.8)
Sarcomatoid	1 (0.8)
Adenosquamous	1 (0.8)
Adenocystic	1 (0.8)
Adenocarcinoma of gastric type	2 (1.6)
Adenocarcinoma of mesonephric type	1 (0.8)
Neuroendocrine	1 (0.8)

There was a significant difference in median age between the cohorts of patients diagnosed 2019–2023 and those diagnosed 2003–2008 year i.e., 55 years of age vs. 42 years of age, $p = 0.046$. This was also the case when comparing the corresponding ADC cohorts, with median ages 61 years of age vs. 42 years of age respectively, $p = 0.0001$, but not the corresponding SCC cohorts 54 years of age vs. 42 years of age respectively $p = 0.1448$.

Prevalence of different HPV types in cervix cancer including both SCC and ADC types

All 125 cervical cancer samples obtained 2019–2023 demonstrated PCR amplifiable DNA since they all tested positive for the presence of the beta-globin gene. Analysis of the HPV-negative samples by ddPCR discovered two additional HPV18-positive biopsies noted just below the cut-off used in the multiplex assay.

In total, 117/125 (93.6%) of the samples were HPV positive while 8/125 (6.4%) were HPV-negative, where the latter consisted of two SCC, two ADC, two ADC of gastric type, one ADC of mesonephric type and one neuroendocrine tumor. Consequently, the overall high HPV-prevalence 2019–2023 was similar to that in 2003–2008 (93.6% vs. 92.9% respectively, p = ns) [12].

During 2019–2023, of the HPV-positive biopsies, 60/117 (51.3%) were positive for HPV16, and 17/117 (14.5%) positive for HPV18, with HPV16 and HPV18 together contributing to 77/117 (65.8%) of the cases, while the remaining 40/117 (34.2%) were positive for other HPV-types, with HPV45 (7%), 31 and 39 both (6%) and 33 (5%) being the most frequently occurring ones (Table 2).

In comparison, during 2003–2008, HPV16 and HPV18 explained 90/154 (58.4%) and 29/154 (18.8%) respectively of all samples, but since HPV16 and HPV18 also occurred together, they contributed to 114/154 (74.0%) cases and were responsible for 114/143 (79.7%) of all HPV positive cases. Most common thereafter were three high-risk types also occurring 2019–2023, i.e., HPV33, 31 and 45 contributing to 4.5%, 3.2% and 3.2% respectively of all samples [12].

Considering the proportion of HPV16 and/or HPV18 positive samples among all HPV positive cases during 2003–2008 and 2019–2023, they contributed to 114/143 (79.7%) and 77/117 (65.8%) of the cases respectively. This indicated a trend of a decrease over time, but the difference was not statistically significant ($p = 0.3369$).

Table 2. Human papillomavirus type distribution in squamous cell carcinoma, adenocarcinoma and other histological sub-types of the cervix uteri in patients diagnosed 2019–2023.

	Squamous carcinomas		Adenocarcinomas		Other		Total	
	HPV-positive cases (*n*)	HPV prevalence (%)	HPV-positive cases (*n*)	HPV prevalence (%)	HPV-positive cases (*n*)	HPV prevalence (%)	HPV-positive cases (*n*)	HPV prevalence (%)
All	104/106	98.1	9/11	81.8	4/8	50.0	117/125	93.6
Age (year)								
20–39	20/20	100	1/1	100	1/1	100	22/22	100
40–59	47/48	97.9	4/4	100	2/5	40.0	52/54	96.3
60+	37/38	97.4	4/6	66.7	1/2	50.0	43/49	87.8
Mean	54		57		62		55	
Median	54		61		65		55	
HPV type								
HPV16	57	53.8	1	9.1	2	25.0	60	48.0
HPV18	9	8.5	6	54.5	2	25.0	17	13.6
HPV30	1	.9	0	0	0	0	1	.8
HPV31	5	4.7	1	9.1	0	0	6	4.8
HPV31&52	1	.9	0	0	0	0	1	.8
HPV33	5	4.7	0	0	0	0	5	4.0
HPV35	1	.9	0	0	0	0	1	.8
HPV39	6	5.7	0	0	0	0	6	4.8
HPV45	6	5.7	1	9.1	0	0	7	5.6
HPV52	2	1.9	0	0	0	0	2	1.6
HPV56	3	2.8	0	0	0	0	3	2.4
HPV58	2	1.9	0	0	0	0	2	1.6
HPV59	1	.9	0	0	0	0	1	.8
HPV66	1	.9	0	0	0	0	1	.8
HPV73	4	3.8	0	0	0	0	4	3.2
Negative	2	1.9	2	18.2	4	50.0	8	6.4
HPV16 or HPV18								
Of all	66	62.2	7	63.6	4	50.0	77	61.6
Of HPV-positive	66	63.5	7	77.8	4	100	77	65.8

The contribution of HPV16 and HPV18 in SCC and ADC was also investigated.

During 2019–2023, among HPV-positive SCC samples, 57/104 (54.8%) were HPV16 positive and 9/104 (8.7%) HPV 18 positive (i.e., together in total 66/104 (63.5%) (Table 2). Among HPV positive ADC samples, 6/9 (66.7%) were HPV18 positive and 1/9 (11.1%) HPV16 positive, i.e., together in total 7/9 (77.8%) (Table 2).

Between 2003–2008, HPV16 and HPV18 were found in 76/119 (63.9%) and 12/119 (10.1%) of the SCC cases respectively, with the overall distribution of HPV16 and 18 being 83/119 (69.7%) and more specifically 83/111 (74.8%) of the HPV positive cases, due to double infections between HPV16 and 18 [12]. Corresponding figures 2003–2008 for ADC, were in total for HPV16 and HPV18 14/35 (40%) and 17/35 (48.6%) respectively and for the respective HPV positive cases, 14/32 (43.8%) and 17/32 (53.1%), with an overall distribution of HPV16 and 18 in 31/35 (88.6%) of all, and 31/32 (96.6%) of the HPV positive cases [12].

There were thereby no statistically significant changes in the proportion of HPV16 and 18 among the HPV positive cases in SCC between 2019–2023 and 2003–2008 (66/104 (63.5%) vs. 83/111(74%), $p = 0.4564$). Neither was the tendency of a lower frequency of HPV16 and HPV18 prevalence during 2019–2023 compared to 2003–2008), in HPV positive ADC samples (i.e., 7/9 (77.8%) vs. 31/32 (96.9%) $p = 0.78$) statistically significant ($p = 0.78$).

Discussion

In this report, >10 years after introducing school-based HPV vaccination in Sweden, we disclose a high prevalence of HPV (93.6%) in cervical cancer samples obtained from 125 patients diagnosed between 2019–2023 in the Stockholm region. In addition, we found that HPV16 and/or 18 was present in 65.8% of the HPV positive tumour samples, while 34.2% samples were positive for other HPV types, with HPV45, 31, 33 and 39 the most frequent.

We then compared the obtained HPV prevalence data from these 125 patients to corresponding data from 154 cervical cancer patients diagnosed 2003–2008 in Stockholm, and found that the overall HPV prevalence was similar and high in both studies [12]. The proportion HPV16/18 among the HPV positive tumours was slightly lower 2019–2023 compared to 2003–2008 (65.8% vs. 79.7%, respectively) but this difference was not statistically significant, neither in the whole cohort or when SCC or ADC were analysed separately. Moreover, infections with HPV45, 31, 39 and 33 were the most common ones after HPV16 and 18 showing similarity between commonly occurring HPV types during both periods of investigation.

The median age in the 2019–2023 group was 55 years of age as compared to a median age of 42 years, in the 2003–2008 group, possibly due to that most patients in this study had LACC [14, 15]. However, when comparing SCC and ADC, the difference in median age between the two time periods was only significant for the ADC cohorts, where limited numbers of patients were included, so the data should be interpreted with caution. Nonetheless, our data could still be in in line with a previous report where the incidence of invasive cervical cancer in 1,672,983 girls and women who were 10 to 30 years of age from 2006 through 2017 was investigated [11]. In that report, the incidence of cervical cancer was reduced in women that had been HPV vaccinated as compared to those that had not been HPV vaccinated (19 cases

vs. 538 cases) [11]. Moreover, after adjustments for covariates, the incidence rate ratio was 0.12 (95% CI, 0.00 to 0.34) among women who had been vaccinated <17 years of age and 0.47 (95% CI, 0.27 to 0.75) among women who had been vaccinated at the age of 17–30 years [11]. However, in that study they did not examine the prevalence of HPV type [11].

There are some limitations in our study. First the time period for diagnosis was limited to 2019–2023, preventing the study of larger natural fluctuations in the prevalence of HPV types over time. Furthermore, although we had the benefit of attaining fresh cancer biopsies, we did not explore all cases 2019–2023 in the Stockholm region through the Swedish Cancer Registry.

Furthermore, the proportion of patients aged 20–39 years in this study was lower than among those in 2003–2008, although the proportion of younger patients has not changed considerably between the two periods according to the Swedish Cancer Registry. Notably, in contrast, in 2003–2008, the available samples were from patients with a median age slightly below that of the median age of the whole group, due insufficient material in biopsies from the elderly patients [12].

In summary, we describe a maintained high prevalence of HPV, including HPV16 and 18 in SCC and ADC in the Stockholm region, which is comparable to many European studies [16–19] and emphasize the urgency to continue HPV vaccination in Sweden.

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Disclosure statement

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ORCID

Kristina Hellman http://orcid.org/0000-0002-5124-7412

Data availability statement

Data supporting this study are included within the article and in reference [12].

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