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Original paper

# A cross-sectional, multicentre, epidemiological study on human papillomavirus (HPV) type distribution in adult women diagnosed with invasive cervical cancer in Belgium

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## *Abstract*

***Objective:*** **Despite an advanced national cervical cancer screening and vaccination programme cervical cancer is still the third most frequent diagnosed gynaecological tumour in Belgium. The goal of this study is to present the Belgian data of a cross-sectional, multicentre, epidemiological study on human papillomavirus (HPV) type distribution in adult women diagnosed with invasive cervical cancer (ICC) conducted in 12 European countries.**

***Material and Methods:*** **Centres in four major Belgian cities (Antwerp, Brussels, Ghent and Liège) participated in this study. Tissue samples from women with ICC were collected from the period 2001 - 2008. All slides were centrally reviewed and analysed for HPV. The total enrolled cohort included 278 subjects.**

***Results:*** **The histologically eligible cohort comprised of 255 patients (mean age 51.3 ± 15.1 years) and 237 were confirmed HPV positive (mean age 50.6 ± 14.9 years). A single HPV infection was present in 95.8%. The five most frequent HPV types were HPV 16 (68.7%), HPV18 (12.3%), HPV 31 (6.2%), HPV 33 (5.3%) and HPV 45 (1.8%). Multiple HPV types were present in 3.4%, with two HPV types in 2.5% and three HPV types in 0.8%. In the various HPV type combinations observed in multiple infected women, HPV 31 (62.5%) and HPV 33 (50.0%) were the most frequent. The ratio of adenocarcinoma (ADC) versus squamous cell carcinoma (SCC) cases in the histologically eligible cohort was 1:8. Compared to the pooled European data the Belgium HPV 16 is 1.1, HPV 33 is 1.2 and HPV 31 is 1.7 higher and the HPV 18 is 0.8 and HPV 45 is 0.34 lower.**

***Conclusion:*** **The 5 most frequent HPV types in Belgium are the same as in the rest of Europe, but the distribution is different. Cervical cancer screening should therefore be HPV type specific and HPV prophylactic vaccination should also focus on other types then HPV 16 and HPV 18. A national registry is needed in order to follow the trends of HPV types in the society and to measure the impact of prevention, for which the data presented in this study can be an important basis.**

***Key words:*** **Human papillomavirus, HPV, epidemiology, cervical cancer, cervical intraepithelial neoplasia, CIN, screening, prevention, vaccination.**

## Introduction

The crude incidence and mortality rates of cervical cancer in Belgium are 11.8 and 3.4 per 100.000, respectively (Cancer incidence in Belgium, 2008). This leads to a cervical cancer diagnosis in two women each day and one woman dies of the disease every second day (Cancer incidence in Belgium, 2008; Tjalma, 2014). The 5-years survival regardless of stage for the period 2004-2008 was 70%. Unfortunately this result is a bias as 65% of the patient data are missing (Van Hoof et al., 2012). Despite advances in screening and prevention, cervical cancer is still the 3rd most frequently diagnosed gynaecological tumour in Belgium, while it should actually be a historical disease. The last ten years no significant changes have occurred in the incidence and the mortality rates linked to this disease (Tjalma, 2014).

Secondary prevention is based on the European Guidelines that advises one Pap smear or liquid-based cytology sample for women of 25 to 64 years of age at a three-year interval (Coleman et al., 1993; Council of the European Union, 2003; European Commission, 2008; Arbyn et al., 2009). Implementation of cervical cancer screening programs is different across Belgium, as it was introduced in the Flemish region in 1994 but not yet in the Walloon region (Coleman et al., 1993; Arbyn et al., 2000; Hulstaert et al., 2006). Based on the current evidence it is to be expected that the national screening practices will soon change from cytology to HPV screening (Tjalma, 2014). The primary prevention based on the two currently available HPV vaccines, *Gardasil*™ (Merck & Co. Inc, USA) and *Cervarix*® (GSK, Belgium), is different across Belgium. In the Flemish region an organized HPV vaccination started in September 2010 with *Gardasil*™ for girls aged 12 years. In 2014 this was changed into *Cervarix*®. In the Walloon region the organized HPV vaccination started in September 2011 with *Cervarix*® for girls 13 years of age. The school-based program is free of charge in both regions.

We recently presented the HPV type distribution across a large number of European countries (Tjalma et al., 2013), but the details regarding histology, occurrence of single or multiple infections, and type distribution by age and year was not presented and is still not well characterized in Belgium. Understanding the HPV type distribution is important for tailoring national screening programs, both for current reflex HPV testing and in the near future for primary HPV screening. Furthermore, describing the baseline HPV type distribution before the introduction of vaccination programs facilitates future estimations of the impact of these HPV vaccines. Belgium presents an interesting case for studying the future vaccination impact, given the regional differences in choice of screening and vaccination described above. Therefore, the objective of this study is to assess the HPV type distribution in Belgian women with an invasive cervical cancer, prior to the introduction of vaccination.

## Material and methods

Present study (GSK study identifier: 108288) was part of a cross-sectional, multicentre study conducted in 12 European countries (Belgium, Czech Republic, Denmark, Germany, Greece, Hungary, Norway, Poland, Portugal, Romania and Scotland and Wales, both in the United Kingdom). This study was named SCALE, which stands for **S**tudy on cervical **CA**ncer **L**esions in **E**urope. The HPV type distribution was determined in subjects with ICC (SCC, ADC and other types) using standardized HPV deoxyribonucleic acid (DNA) detection and typing on archived, formalin-fixed, paraffin-embedded cervical specimen and excision specimens. The study design required that Belgian centres provided 290 cases of invasive cervical cancer. The investigators retrospectively collected invasive cervical cancers specimens from their archives, starting in 2001 until 290 cases of invasive cervical cancers were included. Belgium provided 290 cases of ICC. The inclusion criteria were women aged 18 or above at the time of collection of cervical/excision specimens, diagnosed with ICC (SCC, ADC and other types) from 2001 onwards. Tissue blocks (cervical biopsy or excision specimen) on which the diagnosis was made prior to any chemotherapy or radiotherapy had to be available (the ones including only invasive cancer and the ones including the highest proportion of relevant lesions). The study design, the procedures and the European data were recently published (Tjalma et al., 2013). The study was approved by the Independent Ethics Committee or Institutional Review Board of each participating country and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

## Study objective

The primary objectives were to assess the HPV type distribution of the most frequent types, namely HPV 16, 18, 31, 33, 35, 45, 52 and 58, in women with HPV positive ICC and SCC. The secondary objective was to report on the proportion of SCC versus ADC and other types of invasive cancer.

## Statistics

Approximately 290 women with a diagnosis of ICC were to be included in the study with an estimated 260 cases of SCC, 30 cases of ADC and a small number of other histological subtypes. The expected proportion of different HPV types may have varied between participating countries but the calculations were based on European pooled figures (Clifford et al., 2003). The sample size estimation for each participating country was based on the available epidemiologic data and practical considerations. Considering that the HPV testing method used has a sensitivity of 95% in buffered formalin-fixed and paraffin-embedded specimen samples, 221 women with a confirmed diagnosis of ICC had to be recruited in order to reach 210 HPV positive women. Considering also that the original histological diagnosis of ICC would have been confirmed for 85% of the cases, 260 women had to be included in the study.

As the two co-primary endpoints were based one on the ICC and the other one on the SCC diagnosed women, and because women diagnosed with SCC represented a subset of women diagnosed with ICC, the enrolment was based on 260 SCC diagnosed women to reach the expected precision for both co-primary endpoints.

Based on the literature, expected ratio of ADC versus SCC was approximately 1:9, an estimated 30 cases of ADC and a small number of other cancer types were therefore expected to be recruited.

## Study cohorts

Three sub-divisions were defined for the final analyses: Total enrolled cohort, Histologically eligible cohort and the Histologically eligible HPV positive cohort.

The Total enrolled cohort included all women enrolled in the study i.e. all women who met the inclusion criteria and for whom there was at least one biopsy shipped. The Histologically eligible cohort included all women from the Total enrolled cohort for whom the diagnoses were assessed by DDL Diagnostic Laboratory were eligible for the study, concordant and for which the PCR test for HPV DNA was done. The Histologically eligible HPV positive cohort (HPV+ cohort) included all women from the Histologically eligible cohort presenting any HPV type infection (i.e. for whom the PCR test for HPV DNA was positive).

## Results

Centres in four major cities in Belgium participated in this study. The centres were located in Antwerp, Brussels, Ghent and Liège. All cervical specimens were collected between 2001 and 2008. The total number of screened subjects was 306 (Fig. 1). Since 28 subjects had no blocks shipped (20 did not have adequate biopsies and 8 had shipping information missing), they were not selected. Therefore the population "All subjects" included 278 subjects. There were no subjects failing on inclusion criterion, leaving all 278 subjects as the Total enrolled cohort. The Histologically eligible cohort included all women from the Total enrolled cohort for whom the diagnoses assessed by DDL Diagnostic Laboratory were eligible for the study, were concordant and for which the PCR test for HPV DNA was done. No subject from the Total enrolled cohort had a discordant "H&E (Haematoxylin & Eosin) before" and "H&E after" diagnosis. For three subjects, a diagnosis could not be determined (non diagnostic sample), thus these subjects were excluded from the Histologically eligible cohort. PCR testing was done for all subjects with a diagnostic sample. Twenty subjects presented a non-eligible diagnosis, and they were also excluded from the Histologically eligible cohort. Therefore the Histologically eligible cohort was composed of 255 subjects (91.7% of the Total enrolled cohort).

The Histologically eligible HPV positive cohort (HPV+ cohort) included all women from the Histologically eligible cohort presenting any HPV type infection (i.e. for whom the PCR test for HPV DNA was positive). Eighteen subjects were excluded from the HPV+ cohort because they had negative PCR results for HPV. Therefore the HPV+ cohort was composed of 237 subjects (85.3% of the Total enrolled cohort). The data collection is summarized in the flow chart (Fig. 1).

The demographic data of all three cohorts is given in Table I. All cohorts were comparable in terms of age, with a higher percentage of women between 36 and 55 years of age and over 55 years. The majority of cases were staged as to be expected in an industrialized country FIGO I (Fig. 2). The most frequent diagnosis was SCC in the histological eligible cohort (82.7%) and HPV + cohort (85.7%) (Table II). The proportion of ADC in the histologically eligible cohort and the HPV+ cohort was 11.0% and 8.9%, respectively (Table II). The ratio ADC versus SCC was approximately 1:8 in the histologically eligible cohort.

In ICC 95.8% of the women were infected by one HPV type. In SCC and ADC 96.6% and 90.5%, respectively were infected by one HPV type (Table III). The five most frequent HPV infections were HPV 16, HPV 18, HPV 31, HPV 33 and HPV 45. Remarkable was the higher prevalence of HPV 18 in ADC compared to SCC. Figure 3 presents the

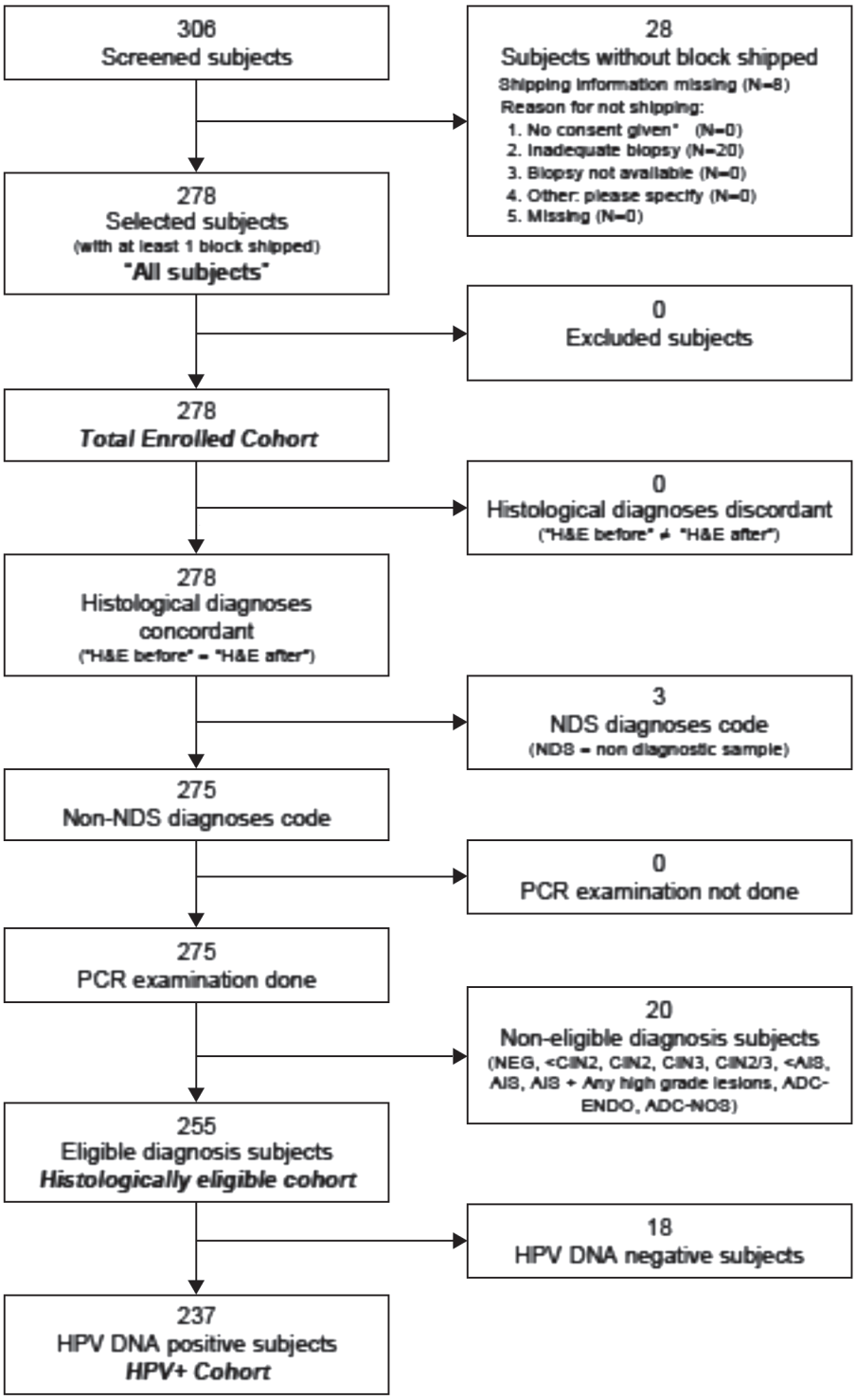


***Fig. 1.*** — Flow chart of study cohorts.

HPV type distribution in single infected women with ICC, SCC and ADC are given. A total of 8 (3.4%) women with ICC were infected with multiple HPV types: 2.5% by two types and 0.8% by three types. The most frequent combinations in ICC included HPV 31 and HPV 33, which occurred in 62.5% and 50.0%, respectively. Given this low number and the various combinations no conclusions can be drawn for multiple infections.

## Discussion

The results of this study are largely comparable to the pooled results from the international SCALE study, showing that HPV16, 18, 31, 33, and 45 are the five most common types in ICC (Tjalma, 2013). However, on top of the pooled data previously presented, the study results also shed light on the age distribution and histological diagnosis of

**Table I.** — Demographic data.

| | Total enrolled cohort | | Histologically eligible cohort | | HPV + cohort | |
|---|---|---|---|---|---|---|
| N | 278 | | 255 | | 237 | |
| % | 100 | | 91.7 | | 85.3 | |
| **Age (years)** | | | | | | |
| Mean and SD | 51.2 ± 15.0 | | 51.3 ± 15.1 | | 50.6 ± 14.9 | |
| Median | 49.0 | | 49.0 | | 48.0 | |
| Minimum | 24 | | 24 | | 24 | |
| Maximum | 94 | | 94 | | 94 | |
| Percentage | | | | | | |
| 36-55 years | 54.3% | | 54.1% | | 55.7% | |
| > 55 years | 33.8% | | 34.1% | | 32.1% | |
| **Age class (years)** | | | | | | |
| ≤ 20 | 0 | | 0 | | 0 | |
| 20-25 | 3 | 1.1% | 3 | 1.2% | 2 | 0.8% |
| 25-30 | 12 | 4.3% | 12 | 4.7% | 12 | 5.1% |
| 30-35 | 18 | 6.5% | 15 | 5.9% | 15 | 6.3% |
| 35-40 | 45 | 16.2% | 40 | 15.7% | 39 | 16.5% |
| 40-45 | 45 | 16.2% | 41 | 16.1% | 40 | 16.9% |
| 45-50 | 27 | 9.7% | 26 | 10.2% | 25 | 10.5% |
| 50-55 | 34 | 12.2% | 31 | 12.2% | 28 | 11.8% |
| > 55 | 94 | 33.8% | 87 | 34.1% | 76 | 32.1% |
| **Year of collection** | | | | | | |
| 2001 | 17 | 6.1% | 16 | 6.3% | 15 | 6.3% |
| 2002 | 36 | 12.9% | 34 | 13.3% | 32 | 13.5% |
| 2003 | 47 | 16.9% | 43 | 16.9% | 40 | 16.9% |
| 2004 | 42 | 15.1% | 38 | 14.9% | 37 | 15.6% |
| 2005 | 49 | 17.6% | 44 | 17.3% | 43 | 18.1% |
| 2006 | 41 | 14.7% | 37 | 14.5% | 34 | 14.3% |
| 2007 | 44 | 15.8% | 41 | 16.1% | 35 | 14.8% |
| 2008 | 2 | 0.7% | 2 | 0.8% | 1 | 0.4% |

cervical cancer in Belgium during the pre-vaccine era, which can help build the foundation for future vaccine impact studies.

The strengths of this study include the representativeness of the samples selected, the standardized methods of HPV PCR testing and the careful central histopathological review of all samples. Therefore, misclassification of disease was limited and is not expected to have an important impact on the results. Potential limitations can

**Table II.** — Histological diagnosis distribution.

| | | Histologically eligible cohort | | HPV + cohort | |
|---|---|---|---|---|---|
| ICC | | 255 | | 237 | |
| SCC | | 211 | 82.7% | 203 | 85.7% |
| ADC | | 28 | 11.0% | 21 | 8.9% |
| | ADC-CX | 25 | 9.8% | 21 | 8.9% |
| | ADC-CC | 2 | 0.8% | 0 | 0.0% |
| | ADC-SER | 0 | 0.0% | 0 | 0.0% |
| | ADC-MIN | 1 | 0.4% | 0 | 0.0% |
| ASC | | 6 | 2.4% | 5 | 2.1% |
| Other diagnosis | | 10 | 3.9% | 8 | 3.4% |

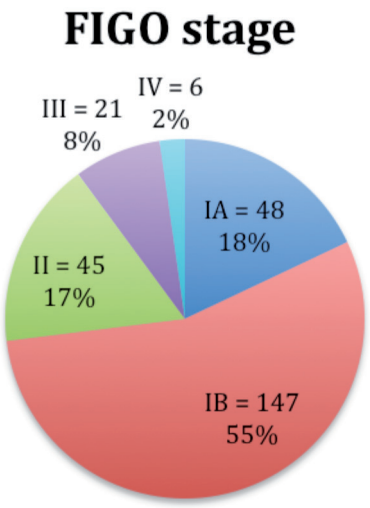


***Fig. 2.*** — Stage distribution according to FIGO.

mainly be referred to the cross-sectional study design with no reference group included, hampering the possibilities to study outcomes following diagnosis or any other longitudinal effects. Selection bias cannot be ruled out, but given the descriptive nature of this study and the way that the women were selected from existing archives, suggest that this would not have any important impact on the results.

There is only one previous study that reported HPV data in Belgian women with cervical cancer before 2000 (Tjalma et al., 2001). This study showed that 67% of the women with ICC were HPV 16 positive, 11% HPV 18, 3% HPV 31, 0% HPV 33, 0% HPV 45, 0% HPV 52, 0% HPV 68, 6% unknown HPV type(s) and that 13% were HPV "negative". The present study, including the period 2001-2008, showed infections rates for HPV 16, HPV 18, HPV 31, HPV 33, HPV 45, HPV 52, HPV 68, unknown HPV type(s) and HPV "negative" of 61.6%, 11.4%, 7.5%, 6.3%, 2.0%, 1.6%, 1.6%, 0.8%, and 7.1% respectively. The lower frequency of unknown HPV types and in the numbers of HPV negative cancers may reflect the improvements in the technology used for HPV detection. Interesting is the increase in HPV 31 tumours and the appearance of HPV 33, HPV 45, HPV 52 and HPV 68. Compared to the pooled European data (Tjalma et al., 2013) the Belgium figures for HPV 16 is 1.1, HPV 33 is 1.2 and HPV 31 is 1.7 higher and the HPV 18 is 0.8 and HPV 45 is 0.34 lower. The present study demonstrates that other HPV types besides the well-known HPV 16 and HPV 18 are gaining significance in Belgium. Whether this points to a true shift to more and other high-risk HPV types or that other high-risk HPV types are less aggressive is difficult to tell at this moment.

Since the results presented here represent a period before the HPV vaccination era it is expected that HPV 16 and HPV 18 will decline following the introduction of HPV vaccination. Due to cross-protection associated with the vaccines it is expected that there will also be a decline in other HPV types. This cross protection is different for each vaccine (Tjalma, 2012). Thus, due to the direct effect of vaccination in combination with cross-protection, a decline is expected for HPV 16, 18, and 31 in the Flemish region where *Gardasil*™ is being used, while in the Walloon region, where *Cervarix*® is used a decline can be expected for HPV16, 18, 31, 33, 35, 45 as well as 51 and 56 (Tjalma, 2015). For the Flemish region the latter can also be expected for the cohort vaccinated in 2014, because *Cervarix*® substituted *Gardasil*™ in September 2014.

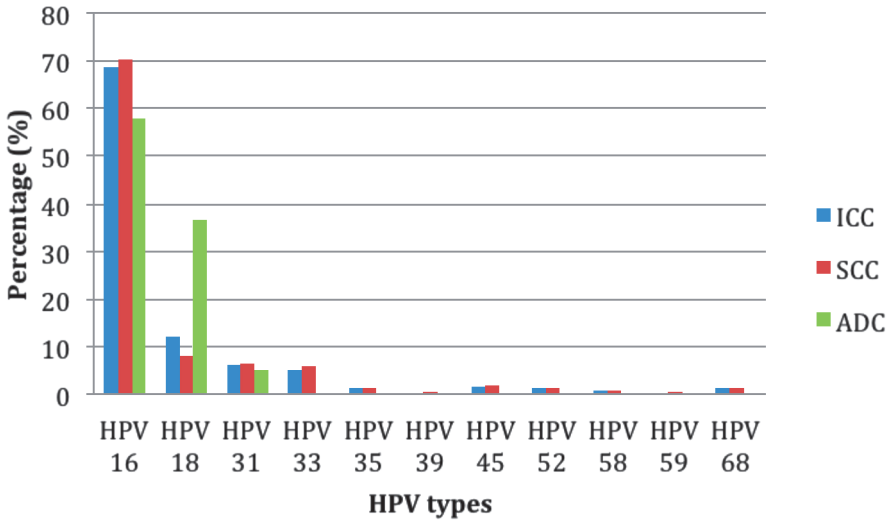


***Fig. 3.*** — HPV type distribution in single infected women with ICC, SCC and ADC.

**Table III.** — The number of HPV type infections stratified by histological diagnosis in the histologically eligible cohort and the HPV+ cohort.

| Histological diagnosis | Number of HPV type infections | Histologically eligible cohort | | | HPV + cohort | | |
|---|---|---|---|---|---|---|---|
| | | n | % | 95% CI | n | % | 95 % CI |
| ICC | All (N) | 255 | – | – | – | – | – |
| | HPV negative | 18 | 7.1 | 4.2-10.9 | – | – | – |
| | HPV positive | 237 | 92.9 | 89.1-95.8 | 237 | – | – |
| | – Single HPV infection | 227 | 89.0 | 84.5-92.6 | 227 | 95.8 | 92.4-98.0 |
| | – Multiple HPV infections | 8 | 3.1 | 1.4-6.1 | 8 | 3.4 | 1.5-6.5 |
| | ❍ 2 | 6 | 2.4 | 0.9-5.1 | 6 | 2.5 | 0.9-5.4 |
| | ❍ 3 | 2 | 0.8 | 0.1-2.8 | 2 | 0.8 | 0.1-3.0 |
| | ❍ 4 and more | 0 | | | | | |
| | – Unknown HPV type(s) | 2 | 0.8 | 0.1-2.8 | 2 | 0.8 | 0.1-3.0 |
| SCC | All (N) | 211 | – | – | – | – | – |
| | HPV negative | 8 | 3.8 | 1.7-7.3 | – | – | – |
| | HPV positive | 203 | 96.2 | 92.7-98.3 | 203 | – | – |
| | – Single HPV infection | 196 | 92.9 | 88.5-96.0 | 196 | 96.6 | 93.0-98.6 |
| | – Multiple HPV infections | 6 | 2.8 | 1.1-6.1 | 6 | 3.0 | 1.1-6.3 |
| | ❍ 2 | 5 | 2.4 | 0.8-5.4 | 5 | 2.5 | 0.8-5.7 |
| | ❍ 3 | 1 | 0.5 | 0.0-2.6 | 1 | 0.5 | 0.0-2.7 |
| | ❍ 4 and more | 0 | | 0 | | | |
| | – Unknown HPV type(s) | 1 | 0.5 | 0.0-2.6 | 1 | 0.5 | 0.0-2.7 |
| ADC | All (N) | 28 | – | – | – | – | – |
| | HPV negative | 7 | 25.0 | 10.7-44.9 | – | – | – |
| | HPV positive | 21 | 75.0 | 55.1-89.3 | 21 | – | – |
| | – Single HPV infection | 19 | 67.9 | 47.6-84.1 | 19 | 90.5 | 69.6-98.8 |
| | – Multiple HPV infections | 1 | 3.6 | 0.1-18.3 | 1 | 4.8 | 0.1-23.8 |
| | ❍ 2 | 0 | | | 0 | | |
| | ❍ 3 | 1 | 3.6 | 0.1-18.3 | 1 | 4.8 | 0.1-23.8 |
| | ❍ 4 and more | 0 | | | | | |
| | – Unknown HPV type(s) | 1 | 3.6 | 0.1-18.3 | 1 | 4.8 | 0.1-23.8 |

It can also be expected that other HPV types become more prominent following the introduction of the HPV vaccines. Cervical cancer screening will shift from cytological testing first followed by reflex HPV typing in case of ASCUS to HPV screening followed by cytology in case of HPV positivity. The HPV screening should be type specific in order to follow the shift in HPV types and the prophylactic vaccination must be as broad as possible as other HPV types then 16 and 18 will become more important. Furthermore, a national registry is needed in order to follow the trends of HPV types in the society and to measure the impact of prevention, for which the data presented in this study can be an important basis.

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compensation related to the development of the manuscript. We would like to dedicate this article to all women with cervical cancer and hope that in the future cervical cancer will become a historical disease.
*Gardasil*™ is a trademark of Merck & Co. Inc.
*Cervarix*® is a registered trademark of the GSK group of companies.

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