

Original Contribution

Differing Age-Specific Cervical Cancer Incidence Between Different Types of Human Papillomavirus: Implications for Predicting the Impact of Elimination Programs

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The elimination of cervical cancer rests on high efficacy of human papillomavirus (HPV) vaccines. The HPV type distribution among cases of invasive cervical cancer (ICC) is used to make predictions about the impact of eliminating different types of HPV, but accumulating evidence of differences in age-specific cancer incidence by HPV type exists. We used one of the largest population-based series of HPV genotyping of ICCs ($n = 2,850$; Sweden, 2002–2011) to estimate age-specific ICC incidence by HPV type and obtain estimates of the cancer-protective impact of the removal of different HPV types. In the base case, the age-specific ICC incidence had 2 peaks, and the standardized lifetime risk (SLTR, the lifetime number of cases per birth cohort of 100,000 females) for HPV-positive ICC was 651 per 100,000 female births. In the absence of vaccine types HPV 16 and HPV 18, the SLTR for ICC was reduced to 157 per 100,000 female births (24% of HPV-positive SLTR). Elimination of all 9 types that can currently be vaccinated against reduced the remaining SLTR to 47 per 100,000 female births (7%), the remaining ICC incidence only slowly increasing with age. In conclusion, after elimination of vaccine-protected HPV types, very few cases of ICC will be left, especially among fertile, reproductive-age women.

age-specific cervical cancer incidence; cervical cancer; disease eradication; HPV vaccine; human papillomavirus; vaccination

Abbreviations: HPV, human papillomavirus; ICC, invasive cervical cancer; SLTR, standardized lifetime risk.

Editor's note: An invited commentary on this article appears on page 515.

Human papillomavirus (HPV) infection is virtually necessary for development of invasive cervical cancer (ICC) (1). Thirteen types of HPV have been established to be oncogenic, high-risk types, but a number of other mucosal types are also known to infect the genital tract (2). The incidence of ICC varies widely between populations, reflecting differences in both risk factors and cervical cancer screening policies (3).

There are 3 licensed prophylactic HPV vaccines that provide protection against HPV infection and its consequences,

all based on virus-like particles. The quadrivalent vaccine is constructed using virus-like particles specific to HPV types 6, 11, 16, and 18; the bivalent vaccine is specific to types 16 and 18; and the nonavalent vaccine is specific to types 6, 11, 16, 18, 31, 33, 45, 52, and 58. The vaccines are highly effective against infection with their respective HPV types (4–6). In addition, cross-protective efficacy has been demonstrated against HPV 31 for the quadrivalent vaccine and against HPVs 31, 33, 35, and 45 for the bivalent vaccine (7–9). Modeling studies predict that elimination of vaccine-protected HPV types from a vaccinated population is an achievable goal (10).

The HPV type distribution in ICC has been extensively studied. In a retrospective study (11) in which nearly 9,000

specimens were collected worldwide and analyzed for HPV, HPV 16 was the most common type, with 61% presence in ICCs, followed by HPV 18 (10%) and HPV 45 (6%). In a systematic review, Bzhalava et al. (12) found the corresponding proportions to be 56%, 14%, and 5%. However, an age-specific baseline HPV type distribution in ICC is needed to predict and monitor the public health benefits of vaccination programs accurately. For example, if nonvaccine HPV types are particularly common in ICCs of certain age groups, that would imply differences between age groups in the cancer-protective effectiveness of vaccination programs. Data on age-specific ICC incidence by HPV type have been collected from the prevaccination era and suggest differences between HPV types (13, 14). However, a very large data set is required to achieve adequate age-specific accuracy in ICC incidence by HPV type. Moreover, the requirement is difficult to fulfill by combining smaller data sets from different populations, because disentangling the between-type differences from the impacts of different risk factors and screening policies would then be a challenge.

Here we present estimates of the age-specific incidence of ICC by HPV type based on a very large, population-based series of HPV genotyping of ICCs carried out during a 10-year period (15). Moreover, to reveal the ultimate potential of successful HPV vaccination programs, eliminating vaccine-protected types, it is necessary to advance our perspective from existing ICC incidence to the incidence that would remain in the absence of vaccine-protected HPV types.

METHODS

Data

Details of this study have been previously published (15). Briefly, all invasive cervical carcinomas diagnosed in Sweden in 2002–2011 were retrieved from the Swedish Cancer Registry. A senior gynecologist (B.A.) reviewed the medical records of the cases to confirm primary, invasive, epithelial tumors of cervical origin—thus ruling out, for instance, noninvasive lesions (e.g., cervical intraepithelial neoplasia grade 3, adenocarcinoma in situ), sarcomas, metastases from other locations, and recurrences. All 4,253 confirmed ICC cases (i.e., squamous cell carcinomas, adenocarcinomas, and other rare carcinomas) were included in the analysis and linked to the register data on age and date at diagnosis and county (1 duplicate case was previously interpreted in a different way (15)). The number of woman-years for the Swedish female population in 2002–2011 was obtained from Statistics Sweden.

Diagnostic slides and formalin-fixed paraffin-embedded blocks of confirmed ICC cases were requested from local pathology laboratories. A senior pathologist reviewed the diagnostic slides to reconfirm the cases and to choose the block with the greatest ratio of tumor tissue to healthy tissue for sectioning. For contamination control, a blank block was sectioned in-between each case block. The first and last sections were put on slides and stained using hematoxylin and eosin. DNA was extracted by a validated method using

a Qiagen kit (QIAGEN N.V., Venlo, the Netherlands) with an extra heating step (16, 17). All samples were tested for both β -globin (to ensure the presence of human DNA) using real-time polymerase chain reaction and HPV type using modified general primer polymerase chain reaction (18) with primer target L1 and subsequent hybridization with HPV type-specific probes using Luminex (BioRad Laboratories B.V., Veenendaal, the Netherlands) (19). The cases with β -globin-negative results or with β -globin-positive blank blocks, indicating contamination, were excluded from HPV analyses. With Luminex, the HPV typing of each sample was determined for 13 high-risk HPV types (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) and a number of low-risk HPV types (types 6, 11, 26, 30, 40, 42, 43, 53, 54, 61, 66, 67, 69, 70, 73, 74, 81, 82, 83, 86, 87, 89, 90, and 91). In addition, the slides from sectioning, first and last, of the HPV-negative samples were rereviewed by the pathologist to confirm invasive tumor tissue in the tested sections. HPV-negative samples were further evaluated with real-time polymerase chain reaction for HPV 16 and HPV 18, targeting primers E7 and E6, respectively.

Valid HPV genotyping results were obtained for 2,850 cases. Of the 1,403 cases without HPV results, 639 cases were from 5 biobank archives that did not send their blocks for this study at all; 706 cases were from the other 20 biobanks which agreed to the study but may not have had sufficient tumor material available; and 58 cases had blocks that were excluded from the HPV analyses.

The nationwide HPV genotyping study was approved by the Regional Ethical Review Board in Stockholm, which determined that because of the population-based nature of the study, informed consent from the study participants was not required and collection of the samples for histology review and HPV typing was permitted.

Measures for HPV incidence

All age-specific measures were estimated in 5-year age groups ($j = \leq 4, 5-9, 10-14, 15-19, \dots, 80-84, \geq 85$ years). In age group j , the ICC incidence was estimated by $n(j)/N(j)$, where $n(j)$ is the number of ICC cases and $N(j)$ is the total number of woman-years, defined as 10 times the mean population in 2002–2011 within j . When estimating the type-specific incidence ($\text{inc}(j,t)$) in an age group j for HPV type t or grouped types t , we took into consideration that some ICC cases were without HPV results: We first estimated the proportion $\text{pos}(j,t)/k(j)$ of positive cases ($\text{pos}(j,t)$) for HPV type(s) t among cases with known HPV results ($k(j)$) and then attributed that proportion of ICC incidence to type(s) t to get

$$\text{inc}(j,t) = \frac{\text{pos}(j,t)}{k(j)} \times \frac{n(j)}{N(j)}.$$

When estimating the statistics for the type-specific incidence $\text{inc}(j,t)$, we assumed that the proportion and the ICC incidence were mutually independent (see the Web Appendix, available at <https://doi.org/10.1093/aje/kwaa121>).

As an age-standardized measure, we used the standardized lifetime risk (SLTR) (20) per 100,000 female births adjusted to the Swedish 2002–2011 female life tables (21). The SLTR per 100,000 female births equals the number of cases that would occur in a birth cohort of 100,000 females during their entire lifetime. In addition, for comparison purposes, we calculated the age-standardized incidence rates per 100,000 woman-years for the Swedish life-tables–based population and for the world (Segi 1960) (22) and European (1976) (23) standard populations (Web Table 1). Compared with the traditional standard population-based measures, the life-tables–based measures are favorable for long-term predictions of HPV vaccination. The standard populations reflect current populations, so they are more applicable for instantaneous comparisons. If a standard population is translated to a cohort, the corresponding mortality will be much higher than it currently is in Sweden and many other developed countries. In particular, the European standard population (24) from 2013 is not applicable for long-term predictions, because middle-aged groups are even larger than some younger age groups.

The measures were computed for individual HPV types and for any HPV, high-risk HPV, low-risk HPV, and HPV negativity. In addition, we studied the following groups of HPV types based on the available vaccines: HPV 16/18, HPV 16/18/31, HPV 16/18/45, HPV 6/11/16/18, HPV 6/11/16/18/31, HPV 16/18/31/33/35/45, and HPV 6/11/16/18/31/33/45/52/58, both for those type(s) alone and allowing for the presence of other HPV types. To demonstrate the impacts of potential elimination of a group of types, we estimated the remaining HPV-positive ICC incidence in the absence of these types—that is, group *t* in the above incidence formula consisted of the HPV types other than the listed types. Thus, a case with multiple HPV types remained if any HPV type remained, even if usually the classification of the remaining type was less oncogenic; this made the estimates conservative.

RESULTS

There were 4,253 confirmed ICC cases after 46 million woman-years of follow-up in Sweden in 2002–2011 (Table 1, Web Tables 2 and 3). HPV results were available for 2,850 ICC cases, of which 2,456 were HPV-positive. Figure 1 presents the distribution of ICC cases by age group and availability of HPV results. The proportion of cases without HPV results varied only slightly between different age groups (28%–35% above age 30 years), with no clear trend.

Age-specific ICC incidence had 2 peaks, the first at ages 30–45 years, after which the incidence decreased for 10–20 years, and the second at older ages (approximately 70–80 years) (Figure 2A, Web Table 4). The much lower HPV-negative and low-risk HPV-positive ICC incidence curves had different shapes and increased slowly with age. Among type-specific incidences, HPV 16 alone clearly had 2 peaks (Figure 2B, Web Tables 5 and 6). The next 2 most common types, HPV 18 and HPV 45, had only 1 wide peak, and the incidence decreased thereafter with age. The incidences of

Table 1. Human Papillomavirus Characteristics of Invasive Cervical Cancer Cases ($n = 4,253$), Sweden, 2002–2011^a

HPV Characteristic	No. of Cases	Proportion	
		%	95% CI
HPV status			
Known	2,850	67.0	65.6, 68.4
Unknown	1,403	33.0	31.6, 34.4
HPV result			
Positive	2,456	86.2	84.9, 87.4
Negative	394	13.8	12.6, 15.1

Abbreviations: CI, confidence interval; HPV, human papillomavirus.
^a 46.1 million woman-years of follow-up.

the other single HPV types were more occasional, mostly increasing slightly toward older ages.

The SLTR for all ICC was 759 per 100,000 female births using the Swedish 2002–2011 life tables (Table 2, Web Table 1). Age-standardized ICC incidence rates were 9.1, 6.6, and 8.2 per 100,000 woman-years using the Swedish population, the world population, and the European standard population, respectively—the difference originating mainly from a varying proportion of older women.

The SLTR for HPV-positive ICC was 651 per 100,000 female births, of which 630 per 100,000 (97% of HPV-positive SLTR) were attributable to high-risk HPVs (Table 2). In the absence of high-risk HPV types, the SLTR for low-risk HPV ICC was only 21 per 100,000 female births (3.2% of HPV-positive SLTR). The SLTR for HPV-negative ICC was 109 per 100,000 female births (14% of all ICC SLTR).

The SLTR for vaccine types HPV 16- and 18-positive ICC was 509 per 100,000 female births, with a 78% proportion of HPV-positive SLTR being attributable to those 2 types (Table 2, Figure 3). Without HPV 16/18, the remaining HPV-positive SLTR was 157 per 100,000 female births (24% of baseline HPV-positive SLTR). With additional inclusion of a single cross-protective type, HPV 31, in the analysis, the SLTR for HPV 16/18/31-positive ICC increased to 529 per 100,000 female births (81%), and without these types the remaining HPV-positive SLTR decreased to 137 per 100,000 (21%). These numbers were close to the results for HPV 6/11/16/18/31: an SLTR of 534 per 100,000 female births (82%) for the attribution and an SLTR of 130 per 100,000 (20%) for the remainder. In contrast, inclusion of a single cross-protective type, HPV 45, resulted in stronger changes, with an SLTR of 555 per 100,000 female births (85%) for HPV 16/18/45 and an SLTR of 109 per 100,000 (17%) for the remaining HPV-positive ICCs. For HPV 16/18/31/33/35/45, the attribution was SLTR 594 per 100,000 female births (91%) and SLTR 69 per 100,000 (11%) for the remainder; and numbers were improved still further for HPV 6/11/16/18/31/33/45/52/58: up to SLTR 610 per 100,000 (94%) for the attribution and down to SLTR 47 per 100,000 (7%) for the remainder.

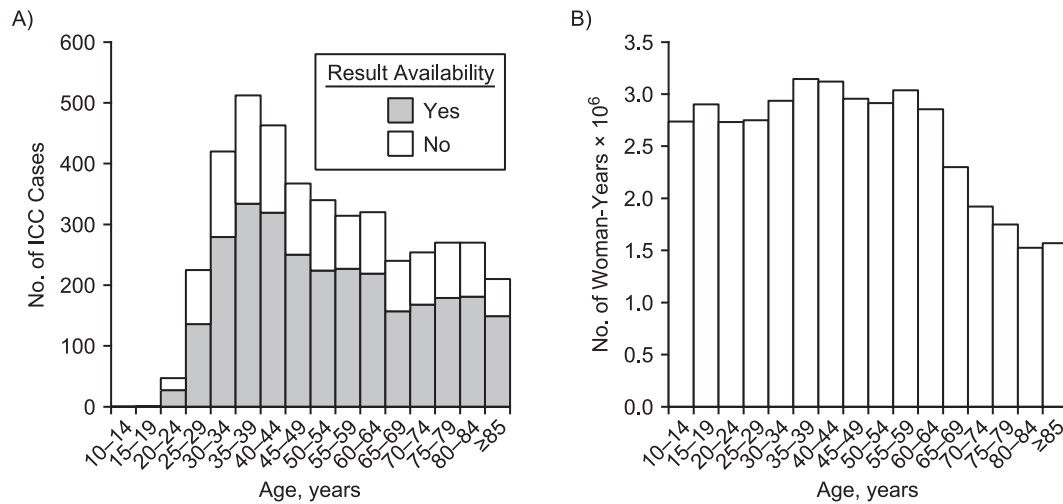


Figure 1. Numbers of invasive cervical cancer (ICC) cases by age and availability of human papillomavirus genotyping results (A) and numbers of woman-years of follow-up by age (B), Sweden, 2002–2011.

Figure 4 presents the remaining age-specific incidences of HPV-positive ICC in the absence of different vaccine-protected groups of HPV types. The first of the 2 peaks in the baseline ICC incidence curve practically disappeared from the remaining incidences. After elimination of HPV 16/18 and HPV 6/11/16/18/31 and, respectively, HPV 16/18/31/33/35/45 and HPV 6/11/16/18/31/33/45/52/58, the curves were close to each other.

Because some ICC cases were HPV-negative, the proportions of HPV group-associated SLTRs were lower among all ICCs than HPV-positive SLTRs (Table 2).

DISCUSSION

In this paper, we have presented estimates of age-specific ICC incidence attributed to different types of HPV, particularly in the absence of vaccine-protected HPV types. The estimates made without vaccine-protected HPV types correspond to the situation that would exist after elimination of these types. The age-specific ICC incidences for vaccine-protected HPV types peaked strongly in fertile, reproductive-age women when compared with the other HPV types. As a consequence, the cancer-protective effectiveness of the removal of the vaccine-protected HPV

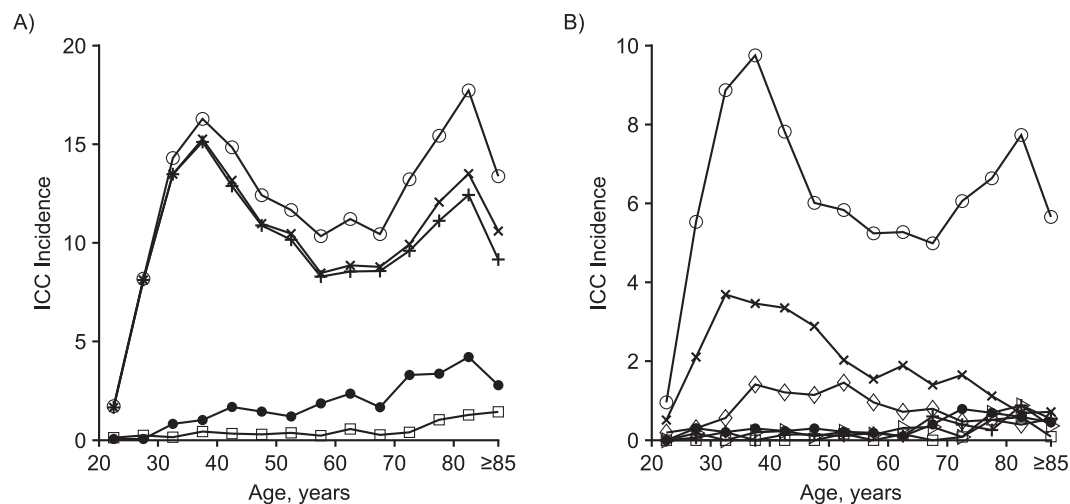


Figure 2. Age-specific incidence of invasive cervical cancer (ICC) per 100,000 woman-years by human papillomavirus (HPV) positivity, Sweden, 2002–2011. A) All ICC (○), HPV-positive ICC (×), HPV-negative ICC (●), high-risk HPV-positive ICC (+), and low-risk HPV-positive ICC (□). B) ICC positive for HPV 16 (○), HPV 18 (×), HPV 31 (●), HPV 33 (+), HPV 35 (□), HPV 45(◇), and HPV 52 (▷).

Table 2. Standardized Lifetime Risk of Invasive Cervical Cancer (per 100,000 Female Births) and Age-Standardized Incidence Rates of Invasive Cervical Cancer (per 100,000 Woman-Years) Associated With Groups of Human Papillomavirus Types and, in the Absence of Those Types, by Group of Human Papillomavirus Types, Sweden, 2002–2011

HPV Type(s)	SLTR per 100,000 Female Births (Sweden 2002–2011) ^c						Age-Standardized Incidence Rate per 100,000 Woman-Years					
	SLTR		Proportion of ICC SLTR ^a		Proportion of HPV-Positive SLTR ^b		Sweden 2002–2011 ^c		Europe 1976 ^d		World (Segi 1960) ^e	
	SLTR	95% CI	%	95% CI	%	95% CI	ASIR	95% CI	ASIR	95% CI	ASIR	95% CI
All ICC	759	736, 782	100.0				9.1	8.8, 9.4	8.2	7.9, 8.4	6.6	6.4, 6.8
HPV-positive ICC	651	629, 673	85.7	81.8, 89.5			7.8	7.5, 8.1	7.2	7.0, 7.5	5.9	5.7, 6.1
HPV-negative ICC	109	98, 119	14.3	12.9, 15.8			1.3	1.2, 1.4	1.0	0.9, 1.1	0.7	0.6, 0.8
High-risk HPV types (any) ^f	630	608, 652	82.9	79.1, 86.7	96.8	92.1, 100.0	7.6	7.3, 7.8	7.1	6.8, 7.3	5.8	5.6, 6.0
Only those types ^g	621	600, 643	81.8	78.0, 85.6	95.5	90.9, 99.4	7.5	7.2, 7.7	7.0	6.7, 7.2	5.7	5.5, 5.9
Remaining HPV-positive ICC ^h	29	24, 35	3.9	3.1, 4.7	4.5	3.6, 5.4	0.4	0.3, 0.4	0.2	0.2, 0.3	0.2	0.1, 0.2
Low-risk HPV types (any) ^f	29	24, 35	3.9	3.1, 4.7	4.5	3.6, 5.4	0.4	0.3, 0.4	0.2	0.2, 0.3	0.2	0.1, 0.2
Only those types ^g	21	16, 26	2.8	2.1, 3.4	3.2	2.5, 4.0	0.3	0.2, 0.3	0.1	0.1, 0.2	0.1	0.1, 0.1
Remaining HPV-positive ICC ^h	630	608, 652	82.9	79.1, 86.7	96.8	92.1, 100.0	7.6	7.3, 7.8	7.1	6.8, 7.3	5.8	5.6, 6.0
Type 16 (any) ^f	389	370, 407	51.2	48.3, 54.1	59.7	56.3, 63.2	4.7	4.4, 4.9	4.4	4.2, 4.6	3.6	3.4, 3.8
Only those types ^g	370	352, 388	48.8	46.0, 51.5	56.9	53.6, 60.2	4.4	4.2, 4.7	4.1	3.9, 4.4	3.4	3.2, 3.6
Remaining HPV-positive ICC ^h	281	265, 297	36.9	34.6, 39.3	43.1	40.3, 46.0	3.4	3.2, 3.6	3.1	2.9, 3.2	2.5	2.3, 2.6
Type 16 or 18 (any) ^f	509	489, 529	67.0	63.7, 70.4	78.2	74.2, 82.3	6.1	5.9, 6.3	5.9	5.6, 6.1	4.9	4.7, 5.1
Only those types ^g	494	474, 514	65.1	61.8, 68.4	75.9	72.0, 79.9	5.9	5.7, 6.2	5.7	5.5, 5.9	4.7	4.5, 4.9
Remaining HPV-positive ICC ^h	157	144, 169	20.6	18.9, 22.4	24.1	22.0, 26.2	1.9	1.7, 2.0	1.5	1.4, 1.6	1.2	1.1, 1.3
Type 16, 18, or 31 (any) ^f	529	508, 549	69.6	66.2, 73.0	81.2	77.1, 85.3	6.3	6.1, 6.6	6.0	5.8, 6.3	5.0	4.8, 5.2
Only those types ^g	514	494, 534	67.7	64.4, 71.1	79.0	74.9, 83.1	6.2	5.9, 6.4	5.9	5.7, 6.1	4.9	4.7, 5.1
Remaining HPV-positive ICC ^h	137	125, 148	18.0	16.4, 19.6	21.0	19.1, 22.9	1.6	1.5, 1.8	1.3	1.2, 1.4	1.0	0.9, 1.1
Type 16, 18, or 45 (any) ^f	555	534, 576	73.1	69.6, 76.6	85.3	81.0, 89.5	6.7	6.4, 6.9	6.4	6.2, 6.7	5.3	5.1, 5.5
Only those types ^g	541	521, 562	71.3	67.9, 74.8	83.2	79.0, 87.4	6.5	6.3, 6.7	6.3	6.0, 6.5	5.2	5.0, 5.4
Remaining HPV-positive ICC ^h	109	99, 120	14.4	12.9, 15.9	16.8	15.1, 18.5	1.3	1.2, 1.4	0.9	0.8, 1.0	0.7	0.6, 0.8
Type 6, 11, 16, 18, or 31 (any) ^f	534	514, 555	70.4	66.9, 73.8	82.1	77.9, 86.3	6.4	6.2, 6.7	6.1	5.9, 6.3	5.0	4.8, 5.2
Only those types ^g	521	501, 541	68.6	65.2, 72.0	80.1	75.9, 84.2	6.3	6.0, 6.5	5.9	5.7, 6.2	4.9	4.7, 5.1
Remaining HPV-positive ICC	130	118, 141	17.1	15.5, 18.7	19.9	18.1, 21.8	1.6	1.4, 1.7	1.3	1.1, 1.4	1.0	0.9, 1.1
Type 16, 18, 31, 33, 35, or 45 (any) ^f	594	573, 615	78.2	74.5, 81.9	91.3	86.8, 95.5	7.1	6.9, 7.4	6.7	6.5, 7.0	5.5	5.3, 5.8
Only those types ^g	581	560, 602	76.6	72.9, 80.2	89.3	84.9, 93.6	7.0	6.7, 7.2	6.6	6.4, 6.8	5.4	5.2, 5.6
Remaining HPV-positive ICC	69	61, 78	9.1	8.0, 10.3	10.7	9.3, 12.0	0.8	0.7, 0.9	0.6	0.5, 0.7	0.5	0.4, 0.5

Table continues

Table 2. Continued

HPV Type(s)	SLTR per 100,000 Female Births (Sweden 2002–2011) ^c			Age-Standardized Incidence Rate per 100,000 Woman-Years								
	SLTR		Proportion of ICC SLTR ^a	Proportion of HPV-Positive SLTR ^b		Sweden 2002–2011 ^c		Europe 1976 ^d		World (Segi 1960) ^e		
	SLTR	95% CI	%	%	95% CI	ASIR	95% CI	ASIR	95% CI	ASIR	95% CI	
Type 6, 11, 16, 18, 31, 33, 45, 52, or 58 (any) ^f	610	589, 632	80.4	76.6, 84.1	93.8	89.2, 97.9	7.3	7.1, 7.6	6.9	6.6, 7.1	5.6	5.4, 5.9
Only those types ^g	604	583, 625	79.5	75.8, 83.2	92.8	88.2, 97.0	7.2	7.0, 7.5	6.8	6.6, 7.1	5.6	5.4, 5.8
Remaining HPV-positive ICC ^h	47	40, 54	6.2	5.2, 7.1	7.2	6.1, 8.3	0.6	0.5, 0.6	0.4	0.3, 0.5	0.3	0.2, 0.3

Abbreviations: ASIR, age-standardized incidence rate; CI, confidence interval; HPV, human papillomavirus; ICC, invasive cervical cancer; SLTR, standardized lifetime risk.

^a SLTR per all ICC SLTR (759 per 100,000 female births).

^b SLTR per HPV-positive SLTR (651 per 100,000 female births).

^c ASIR for the Swedish 2002–2011 female life-tables-based population.

^d ASIR for the European 1976 standard population (23).

^e ASIR for the world standard population (22).

^f ICC positive for any HPV type in the group (other HPV types allowed).

^g ICC positive for any HPV type in that group only (negative for all other HPV types).

^h ICC positive for HPV but negative for all HPV types in that group.

types was not uniform over age, but highly beneficial for the reproductive-age women. The resulting postelimination ICC incidence was very low and increased only slowly with age.

Without the 2 vaccine types HPV 16 and HPV 18, which are common to all 3 HPV vaccines, the SLTR decreased from a baseline of 650 per 100,000 female births to 157 per 100,000—that is, the SLTR for the remaining HPV-positive ICCs was 24% of the original one. The incidence without the bivalent vaccine-targeted and cross-protected types, HPV 16/18/31/33/35/45, was similar to that of the nonavalent vaccine without types HPV 6/11/16/18/31/33/45/52/58, for which the SLTR was 47 per 100,000 female births for the remainder (only 7.2% of the original HPV-positive SLTR). Eliminating HPV 45 contributed to about half of the additional benefits compared with elimination of HPV 16/18.

Including ICC cases from the whole nationwide female population of Sweden in the study for a common 10-year study period enabled generation of stable age-specific results for a large number of analyzed HPV types. Through the comprehensive registration of cancer cases in Sweden (the Swedish Cancer Registry is estimated to be 96% complete (25)), practically all cases of cervical carcinoma were included in the analysis. Unfortunately, we were not able to analyze HPV type for all cases. However, the cases with missing blocks were distributed in age (and also between urban and semiurban regions) in a similar way as the cases with received blocks, implying that the received blocks were representative for all cases.

The study results were obtained from a country where the population is regularly screened, with high coverage (about 80%) (26). Future changes in screening might change the remaining HPV incidence curves. Furthermore, our 10-year study period was not able to catch very long-term trends in HPV type-specific ICC incidence.

The major roles of HPV 16 alone and HPV 16/18 together that we observed are in accordance with earlier observations about HPV type-specific fractions in ICC (11–14). Our accurate age-specific estimates of ICC incidence by HPV type also support and refine the earlier observations about ICC incidence peaks for vaccine-protected HPV types (13, 14). In addition, the strong attribution of HPV 45 among other types is in line with the above-mentioned studies, as well as with a finding of HPV 45 being the third most prevalent type in the last smears preceding ICC (27). However, in a Swedish study of HPV infection prevalence, HPV 45 was just among the top 10 most prevalent types (28). A combination of the results suggests that HPV 45 could have weaker-than-average transmission but entail a high chance of cancer progression if acquired. Other explanations are also possible.

The 14% proportion of SLTR for HPV-negative ICC was at a similar level as in a recent review (11). Even though the blocks with most tumor tissue were selected, HPV could have been more detectable elsewhere. In addition, some HPV-negative ICC cases may have been HPV-positive earlier. Indeed, there seems to be an age-related factor due to different shapes of HPV-positive and -negative incidence curves, for which an explanation might be the loss of detectable HPV positivity after a very long progression to cancer.

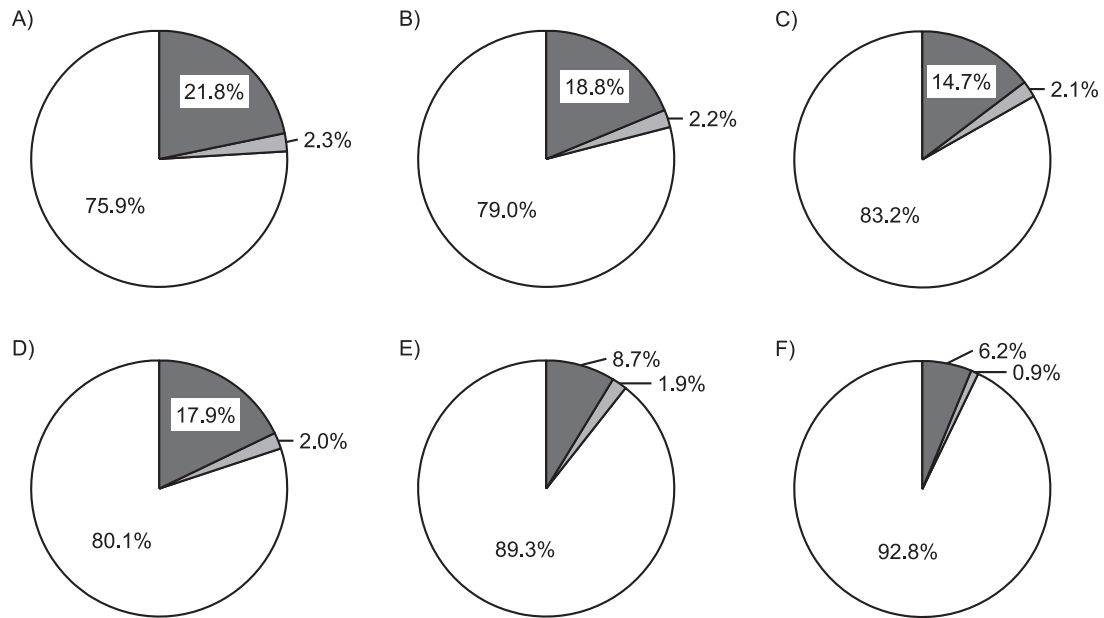


Figure 3. Proportions of invasive cervical cancer (ICC) cases attributable to human papillomavirus (HPV) types 16 and 18 (A); HPV types 16, 18, and 31 (B); HPV types 16, 18, and 45 (C); HPV types 6, 11, 16, 18, and 31 (D); HPV types 16, 18, 31, 35, and 45 (E); and HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 (F) in women’s standardized lifetime risk of HPV-positive ICC. White portion of circle: ICC positive for any HPV type in that group only and negative for all other HPV types; light gray: ICC positive for any HPV type in that group and for some other HPV type(s); dark gray: ICC positive for HPV but negative for all HPV types in that group.

Mathematical modeling studies provide timelines for how fast our register-based observations about ICC incidences without vaccine-protected HPV types could be realized under HPV vaccination programs. Because older, nonvaccinated cohorts benefit only a little from HPV vaccination, ICC incidence in the total population will remain high as

long as these cohorts still exist (29, 30). However, our estimates of remaining lifetime ICC risk apply to those vaccinated cohorts among which vaccine-protected HPV types have been eliminated. The first vaccinated cohorts will still experience the force of infection of vaccine-protected HPV types from the older, nonvaccinated cohorts (29–31),

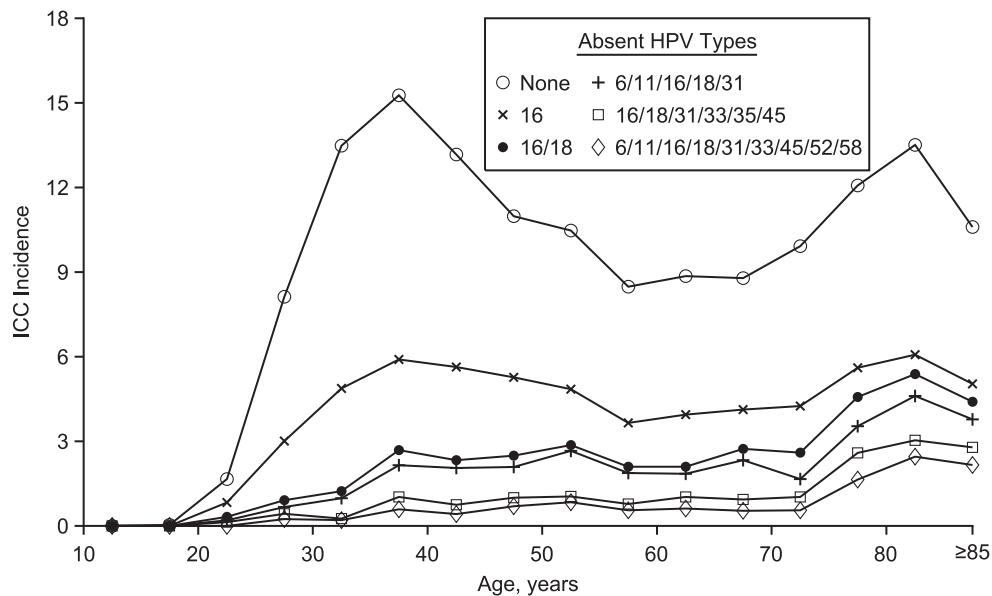


Figure 4. Remaining age-specific human papillomavirus (HPV)-positive incidence of invasive cervical cancer (ICC) per 100,000 woman-years in the absence of various groups of HPV types.

but when the first vaccinated cohorts have passed the ages of highest sexual activity and there are sufficiently vaccinated cohorts between nonvaccinated cohorts and new vaccinated cohorts, incidence of HPV infection in the new vaccinated cohorts will be close to the new steady state (29–31). In contrast, every birth cohort that missed HPV vaccination because of delays in program introduction would eventually miss the estimated reduction of 500–600 ICC cases per 100,000 female births, depending on the vaccine used. The numbers would be even higher for a less frequently screened population.

Our results demonstrate the preventive potential of optimal high-coverage vaccination programs, beyond the vaccine efficacies. The effectiveness of vaccination program depends on viral characteristics of each HPV type (32). Mathematical models suggest that the effective coverage of vaccination (efficacy times coverage) might have to be greater than 70% for both boys and girls to eliminate HPV 16, but the requirement for the other types is considerably lower (10, 32). Even though the vaccine protection is generally lower for cross-protected types than for vaccine-targeted types, the suboptimal vaccine efficacy of cross-protection may be improved by herd effects with optimally organized vaccination programs (33).

The full public health impacts of HPV vaccination will not consist of prevented cancer cases only; benefits will also arise from reducing precancerous screening findings and from optimizing cervical cancer screening. The comprehensive age-specific and type-specific ICC incidences presented here will help with the development of mathematical models assessing these benefits.

We have presented quantified age-specific estimates of remaining cervical cancer incidence in the absence of vaccine-protected HPV types in a population which has been screened intensively for decades. The very low numbers of cervical cancer cases projected to exist after elimination of vaccine-protected HPV types reflect the high cancer-preventive potential of effective vaccination programs, even among reproductive-age women, who are currently experiencing a peak in age-specific cervical cancer incidence.

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