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HPV infection in Europe

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ABSTRACT

In order to estimate the impact of primary cervical cancer screening with human papillomavirus (HPV) testing, and implementation of the current HPV vaccines, we have summarised the most recent and largest HPV studies in Europe. Eighteen studies including between 897 and 46,900 women from 14, mostly Northern and Western European, countries were included. Everywhere, high-risk (HR) HPV prevalence peaked before age 25 or 30 years with steady declines thereafter. For women in the 30–64-year age-range, for whom primary HPV testing is considered, age-adjusted HR HPV prevalence ranged from 2% in Spain to approximately 12% in Belgium and France, where sustained elevated levels were found in women aged ⩾35 years. HPV16 and 18, the two HR types prevented by current HPV vaccines, accounted for 30% (range 19–43%) and 12% (range 0–22%) of all HR HPV positives, respectively, and varied according to the presence of cervical lesions. Based on an updated meta-analysis of HPV type distribution in the whole of Europe, HPV16 and/or 18 are estimated to be present in 52%, 61% and 76% of cytologically detected high-grade squamous intraepithelial lesions, histologically confirmed cervical intraepithelial neoplasia grade 2/3, and invasive cervical carcinoma, respectively.

1. Introduction

Cervical cancer screening programmes based on cytological smears have been shown to be one of the most successful cancer prevention strategies with a decline of up to 80% in cervical cancer incidence in countries where organised screening programmes are in place.[1]

Important new methods of cervical cancer prevention have, however, been introduced or are being considered, notably primary prevention through prophylactic human papillomavirus (HPV) vaccination and secondary prevention through HPV testing. Knowledge of the level of type-specific high-risk (HR) HPV prevalence in the population, and in cervical lesions, is essential to predict the burden of positive test results if HPV testing were used in primary screening. It would also help to estimate the cost-effectiveness of a strategy that combines HPV vaccination and screening.

There is substantial evidence of variation in HPV prevalence in the general female population, between and within world regions.[2,3] Recently, a number of large studies and randomised trials on HPV testing as a primary screening test have become available.[4–14] It is mostly these studies that have greatly improved our knowledge on country- and age-specific HPV prevalence in European women and they will, therefore, be the principal subject of our present report.

2. Materials and methods

We did not try to include all information on the prevalence of HPV infection in Europe as in formal meta-analyses. Studies were selected instead on the basis of 'best available data' in each European country. Where several studies were available from the same country, the largest population- and screening-based studies and trials of HPV testing in primary screen-

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ing were chosen. Studies with less than 800 participants or based on clinically-selected populations were excluded. The PUBMED database was searched for reports on HPV prevalence published up to January 2009. The keywords used were 'papillomavirus' and country names, including the 27 member states of the European Union and Switzerland. Additional references from retrieved papers were also evaluated for inclusion. Only studies published in English and using either Hybrid Capture 2 (HC2) or HPV DNA PCR-based detection methodology were included, and if results from the same study were published in different papers, we retained the most recent or most complete publication. For some articles, additional information was requested from the authors, mostly regarding age-specific prevalence.[5–7,12–15]

The following data were extracted: study period, total sample size, age range and median age of the screened population, study design (randomised trials of HPV testing in primary screening and surveys of women participating in organised or opportunistic screening programmes), exclusion criteria, HPV testing methodology including PCR primers used, overall and age-specific HR HPV prevalence, and proportion of HPV16 and 18 among HR HPV-positive women. It was, however, impossible to separate HR HPV types from low-risk types in studies from Ireland and Greece, as only overall HPV prevalence was reported. Wherever possible, world-standardised HR HPV prevalence was calculated among women aged 30–64 years.

In order to assess HPV type distribution by severity of cervical lesions (low-grade squamous intraepithelial lesions [LSIL], high-grade squamous intraepithelial lesions [HSIL], squamous cell carcinoma, adenocarcinoma, and all invasive cervical carcinoma [ICC]) in Europe, we used updates of

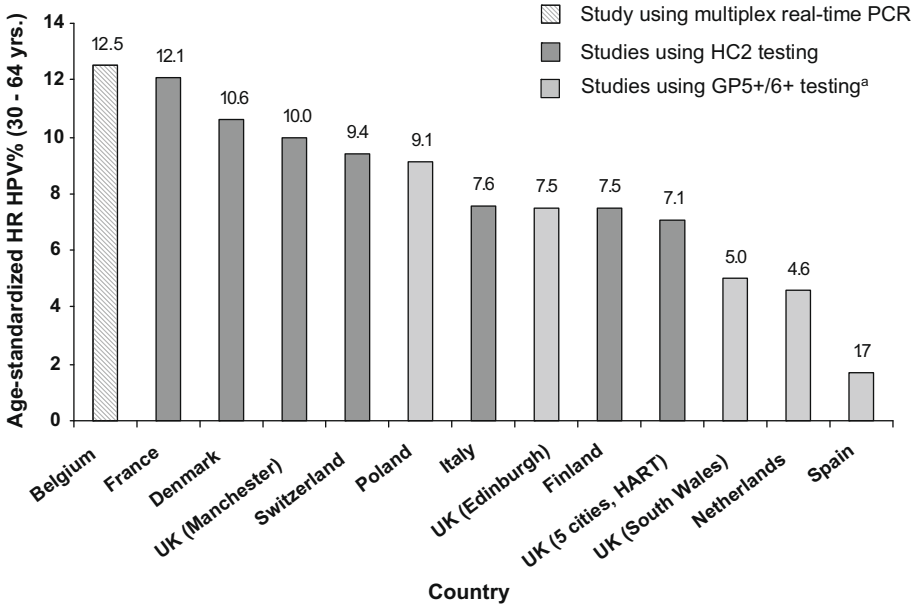

Fig. 1 – Age-standardised high-risk (HR) human papillomavirus (HPV) prevalence in 10 European Union countries and Switzerland, women aged 30–64 years. [a]HR HPV types only.

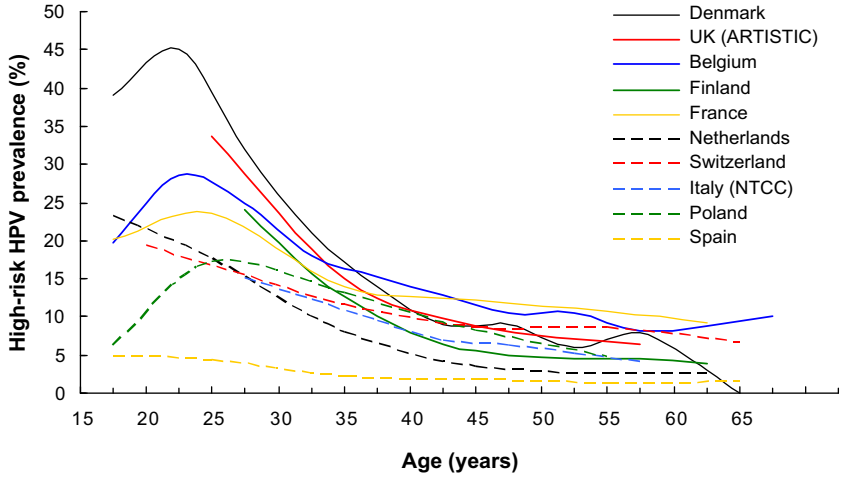

Fig. 2 – Age-specific HR HPV prevalence in nine European Union countries and Switzerland.

meta-analyses previously published by our Group.[16,17] The included studies were published between 1990 and May 2008, used DNA-PCR methodology and had no restrictions by age. At variance with our previous reports,[16,17] in this article we separated LSIL and HSIL from histologically confirmed cervical intraepithelial neoplasia (CIN) grades 1 and 2/3, respectively. The earlier published data on 4051 cytological LSIL or histological CIN1 by Clifford and colleagues[17] was updated and further separated into 3196 LSIL and 2144 CIN1 cases from 29 studies in total (Fig. 4). The data on 3494 HSIL or CIN2/3 previously published by Smith and colleagues[16] was updated and separated into 1061 cytological HSIL and 3272 histological CIN2/3 from 39 studies. Previously published HPV prevalence data on 4373 ICC[16] was updated to a total of 5538 ICC cases from 50 studies (all histological specimens) (Fig. 5).

3. Results

Eighteen papers from 14 countries were included in the assessment of HPV prevalence in the general female populations of the European Union (Table 1). Two studies used population-based sampling, seven were randomised trials of HPV testing in primary screening, three recruited women through organised screening programmes and six recruited from opportunistic screening programmes. Northern and Western Europe were best represented, followed by Southern Europe. Only one study from Eastern Europe fitted our eligibility criteria.

Crude HR HPV prevalence ranged between less than 3% in Spain and Greece to more than 15% in Denmark, the United Kingdom, Ireland, France and Belgium (Table 1), but this was partly dependent on the different age composition of the study populations. The proportion of HPV16 and 18 among HR HPV infections is shown for those studies that made information on HPV types available (Table 1). The average proportion of HPV16 and 18 among HR HPV-positive women was 29.8% (range 19–43%) and 12.0% (range 0–22%), respectively.

Age-standardised HR HPV prevalence rates (30–64 years) were calculated for all studies for which age-specific prevalence was published or provided (Fig. 1). Age-standardised HR HPV prevalence in women aged 30–64 years ranged from 1.7% (Spain) to 12.5% (Belgium). Some heterogeneity was noted within four studies from the United Kingdom, with prevalence ranging from 5.0% (South Wales) to 10.0% (Manchester, ARTISTIC study). Studies using HC2 reported on average a higher prevalence of HR HPV than studies using GP5+/6+ PCR detection methodology which reported HR types only.

Curves for age-specific HR HPV prevalence available in ten countries are shown in Fig. 2, based on the largest available study in each country. Especially high prevalence emerged in women aged 20–24 in Denmark (45%),[12] the United Kingdom (29%),[14] and Belgium (29%).[13] A steep decline after peak prevalence below age 25 or 30 years emerged everywhere. Prevalence of over 10% was, however, seen in two studies based on opportunistic screening from France and Belgium in middle-aged women (35–54 years).

The correlation between HR HPV prevalence and HSIL or worse (not standardised by age) in the 14 studies from Table 1 where the relevant information was available is shown in Fig. 3. A significant linear correlation emerged (Pearson correlation coefficient = 0.71; $p = 0.005$). The study from Edinburgh (UK) showed a HSIL prevalence that was higher than predictable on the basis of HR HPV prevalence.

Based on the update of the meta-analysis on cytological and histological abnormalities in Europe, the distribution of the eight HR HPV types most frequently found in ICC, and HPV6 and 11 by type of cervical precursor lesion, is shown in Fig. 4. A steady increase in the importance of HPV16, but not HPV18, was seen with the increase of lesion severity, and between cytologically detected and histologically confirmed lesions of a similar group (LSIL versus CIN1, HSIL versus CIN2/3). HPV16 or 18 was present in 33.3%, 29.4%, 51.7% and 61.4% of LSIL, CIN1, HSIL and CIN2/3, respectively.

Fig. 5 presents the prevalence of the same eight HR HPV types and HPV6 and 11 in ICC overall and by histological type (squamous cell carcinoma or adenocarcinoma) in the meta-

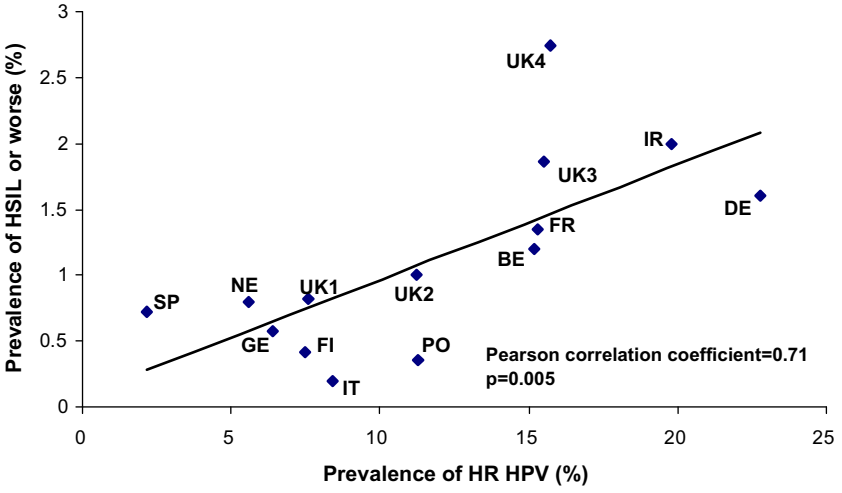

Fig. 3 – The correlation between the prevalence of HR HPV and high-grade squamous intraepithelial lesions (HSIL) or worse in 14 European studies. UK1: 5 cities (HART); UK2: South Wales; UK3: Manchester; and UK4: Edinburgh.

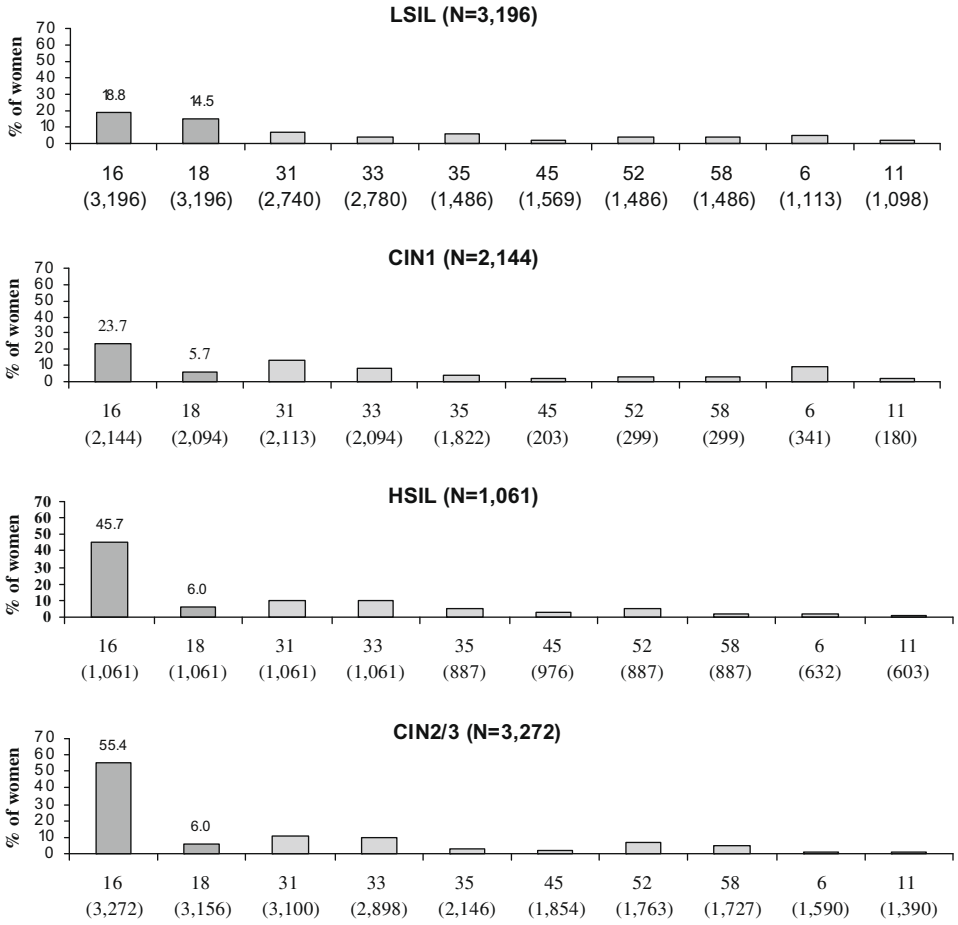

Fig. 4 – Prevalence of eight HR HPV types and HPV6 and 11 by presence of cytological (LSIL, HSIL) or histological (CIN1, CIN2/3) lesions in Europe. CIN: cervical intraepithelial neoplasia; LSIL: low-grade squamous intraepithelial lesions; HSIL: high-grade squamous intraepithelial lesions; N: number of cases tested for the given HPV type.

analysis. Compared to CIN2/3 (Fig. 4), HPV16 and 18 were further enriched in squamous cell carcinoma (64.5% and 11.0%, respectively). HPV16 and 18 were found with a similar frequency in adenocarcinoma (35.9% and 39.0%, respectively).

4. Discussion

We summarised the most recent cross-sectional data on HR HPV prevalence in Europe. Large screening trials or screening studies where women were actively invited and high-quality HPV testing was used were considered the best standard for evaluating the prevalence of infection at a population level. Such studies, including several with many thousands of women enrolled, were available for six European Union countries. Smaller but fairly population-representative studies were available for seven additional European Union countries and Switzerland, thus allowing us to confirm that the burden of HR HPV infection in the continent is low-to-intermediate on a worldwide scale.[2,3]

In agreement with the findings from many other high- or medium-resource countries in the Americas and Asia,[2,3] all European populations studied showed marked peaks of HPV prevalence among the youngest women, but, contrary to some populations in developing countries,[2,3] HPV prevalence was relatively low among middle-aged women.

The wide variation of HPV prevalence by age group makes findings from individual studies difficult to interpret without taking into account the age distribution of study women. Therefore, for practical and comparison purposes, the most useful information from our present report is the age-standardised prevalence among women aged 30–64 years, i.e. the groups in whom use of HPV testing as a primary screening test has been advocated.[1] The high prevalence of HR HPV in younger women represents an important challenge to offering HPV testing to women under the age of 30–35 years. Not only should we expect a high workload for confirmation of HPV-positive findings,[4] but we might also end up treating lesions that would have spontaneously regressed.[8] Although there is no clear cut-off point in age above which the presence of HR HPV is associated with a higher risk for future progressive disease, 30[18] to 35[4,8] years is recommended as the most appropriate age to start HPV-based primary screening in Europe.

Ten European Union countries and Switzerland contributed to age-standardised comparisons and showed that variations in HR HPV prevalence in Europe is substantial, but does not correspond strictly to the broad European regions (i.e. Northern Europe, Southern Europe, etc.) that are often used for descriptive purposes.[3] Relatively low prevalence (<5%) emerged, for instance, in Spain and Greece, but also in the

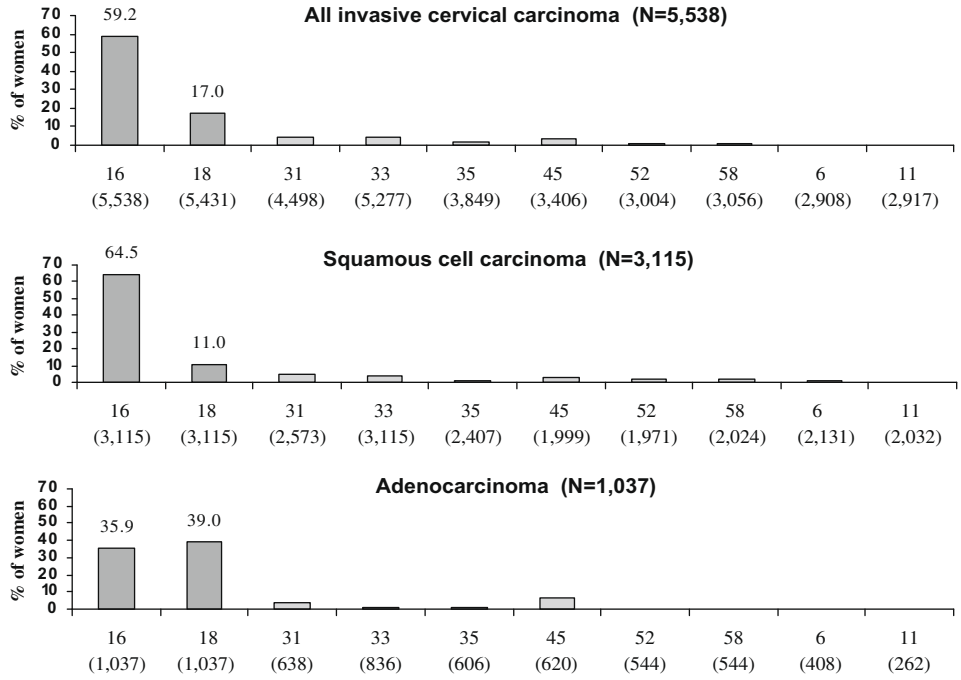

Fig. 5 – Prevalence of eight HR HPV types and HPV6 and 11 in invasive cervical carcinoma overall and by histological type in Europe. N: number of cases tested for the given HPV type.

Netherlands, whereas relatively high prevalence (>10%) was found in Denmark, the United Kingdom, France and Belgium. Substantial variation in age-adjusted HPV prevalence was also noted within a single country (e.g. the United Kingdom).

Such variation between European countries had not clearly emerged from HPV prevalence in a recent meta-analysis that was not adjusted by age.[3] On account of the many large HPV studies that have become available in the last few years, and the difference in inclusion criteria we used (>800 rather than >100 women), only three studies[15,19,20] were included in both our paper and the meta-analysis by de Sanjosé and colleagues.[3] We confirmed, however, their finding that HR HPV positivity is slightly higher using HC2, compared to PCR-based tests, likely due to some cross-reactivity of HC2 with low-risk HPV types, hence the presence of some false-positive results.[21] As expected, we showed a good correlation between the prevalence of HR HPV and HSIL across studies in different parts of Europe.

Elevated HR HPV prevalence in young women in Europe is compatible with rising trends of HPV infection, as already suggested by the continuing increase in CIN3 incidence in women below age 25 years (e.g. in the United Kingdom).[22] High HR HPV prevalence helps to explain the relatively high cervical cancer incidence in Poland, a country where, like most Eastern European countries, cervical cancer screening is still sub-optimal.[23] High HPV prevalence in middle-aged women is especially worrisome, as it has been reported to be strongly correlated with cervical cancer incidence rates in unscreened or inadequately screened populations in different continents.[24] However, evidence for the favourable role of screening is demonstrated by the low cervical cancer incidence found in certain countries like France or the United Kingdom[23] where HR HPV prevalence is relatively high even in middle-aged women. Additional evidence of a beneficial role of screening is also reported elsewhere in this Special Issue.[25,26]

In order to provide data more relevant to cervical cancer prevention, we chose to focus on HR HPV types only, although two of the studies we included (Table 1) did not allow us to separate HR from low-risk types. At variance with some previous work,[3,27] we did not exclude women with cytological abnormalities, but assumed that they represented a small and consistent fraction of women in population-based studies. Inclusion of cytological abnormalities may actually help to better estimate the HPV burden in the general female population.

We have also gathered substantial new information to expand previous meta-analyses[16,17] on the relative importance of HPV16 and 18 in women with different cytological or histological results. Such information derives from studies conducted in 24 European countries and is essential to predict the impact of currently available vaccines on cervical cancer prevention and screening cost reduction. The use of the present data for inference on the impact of HPV screening requires some caveats. The HPV type distribution in cervical lesions in our report derives from a broad range of studies and does not take into account possibly relevant information (e.g. women's age and whether lesions had been detected in screening programmes). In addition, the studies on HPV prevalence in our present report were carried out over a 15-year period. The prevalence of HR HPV tended to be higher in the most recent studies (e.g. Denmark, Belgium, Poland) than in the earliest studies,[28] possibly suggesting that the HPV burden in Europe has been increasing over the last decade.[12,29]

The inclusion of HPV vaccination into national immunisation schedules is high on the agenda of the EU member states, as is reported elsewhere in this Special Issue.[30] A vaccine against HPV16 and 18 would theoretically decrease by approx-

Table 1 – Selected characteristics of the largest studies of HPV prevalence from the European Union and Switzerland.

Country, study (Location)	Study period	Age range (mean age)	Population source (exclusion criteria)	Women screened (N)	HPV test	HPV prevalence		
						HR HPV %	HPV16 % of HR-pos	HPV18 % of HR-pos
United Kingdom, ARTISTIC (Manchester)[10]	2001–2003	20–64 (40)	Screening trial	24,470	HC2[b]	15.5	31.2	12.3
United Kingdom, HART (5 cities)[33]	1998–2001	30–60 (42)	Screening trial	10,358	HC2	7.6	–	–
United Kingdom (South Wales)[14]	2004	20–65 (38)	Organised screening	9079	GP5+/6+	11.2	31.4	21.7
United Kingdom (Edinburgh)[19]	2000	16–78 (37)	Organised screening	3444	GP5+/6+	15.7	41.1	14.3
Ireland (Dublin)[34]	2004–2005	16–72 (35)	Opportunistic screening	996	MY09/11	19.8[a]	–	–
Finland (nine municipalities)[6]	2003–2004	25–65 (45)	Screening trial	16,895	HC2	7.5	–	–
Denmark (Copenhagen)[9]	1991–1993	20–29/40–50	Screening trial	10,544/1,443	HC2[c]	17.9/4.4	29.0/19.0	11.9/0.0
Denmark (Copenhagen)[12]	2004–2005	15–93 (36)	Organised screening	11,600	HC2[c]	22.8	26.2	11.9
Sweden (five cities)[11–35]	1997	32–38	Screening trial	6089	GP5+/6+	7.1	30.9	8.5
Netherlands, POBASCAM (Amsterdam)[5]	1999–2002	18–65 (43)	Screening trial	45,362	GP5+/6+	5.6	32.5	9.9
Germany (Hannover/ Tubingen)[36]	1998–2000	>30 (42.7)	Opportunistic screening	8101	HC2[b]	6.4	31.4	9.0
France (Reims)[37]	1997–2001	15–76 (34 median)	Opportunistic screening	7932	HC2	15.3	–	–
Belgium (Antwerp)[13]	2006	14–97 (42)	Opportunistic screening	9297	Multiplex RT-PCR[d]	15.2	24.4	10.2
Switzerland (three cantons)[38]	2001–2002	13–96 (42)	Opportunistic screening	7254	HC2	11.4	–	–
Italy, NTCC (nine cities)[8]	2003–2004	25–60 (42 median)	Screening trial	46,900	HC2	8.4	–	–
Spain (Barcelona)[15]	1998–2000	14–74 (43 median)	Population-based sample	973	GP5+/6+	2.2	42.9	0.0
Greece (North)[20]	2000–2001	17–67 (43)	Opportunistic screening	1296	PGMY09/11	2.5[a]	18.7	–
Poland (Warsaw)[7]	2006	18–59	Population-based sample	897	GP5+/6+	11.3	33.0	6.4

a Overall HPV prevalence, as it was not possible to separate low-risk from high-risk HPV infections.
b Genotyping on all HC2-positive samples using PGMY09/11.
c As in footnote b., but with LIPA.
d Multiplex TaqMan-based real-time quantitative PCR; Abbreviations: CIN: cervical intraepithelial neoplasia; HC2: hybrid capture 2; HPV: human papillomavirus; HR: high-risk; pos: positive.

imately 40% the number of HR HPV-positive findings in screening programmes. It would prevent 52% of HSIL along with 61% of CIN2/3 and 76% of ICC (which is the highest estimate of all continents[16]). Whereas avoidance of HSIL would allow the saving of the cost of diagnostic management of abnormal cytological findings (e.g. colposcopical examinations and biopsies),[31,32] the HPV16/18 proportion in CIN2/3 gives an idea of additional savings in treatment costs.

In conclusion, our present findings show substantial differences in HPV burden between European countries and highlight the potential benefits from currently available HPV screening and/or vaccination methods. Although information on HPV burden is accumulating rapidly in many countries, the lack of data from several European Union countries, notably new member states, is of concern, especially when combined with a lack of high-quality statistics about cervical cancer incidence.[23] This knowledge gap may be an obstacle to the prioritisation of cervical cancer prevention programmes.

Conflict of interest statement

None declared.

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