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Editorial Comment

Cervical cancer screening in Europe – Changes over the last 9 years

Guglielmo Ronco[a], *Ahti Anttila*[b,*]

[a]*CPO Piemonte, Turin, Italy*
[b]*Mass Screening Registry of the Finnish Cancer Registry, Pieni Roobertinkatu 9, FIN-00130 Helsinki, Finland*

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The first studies showing a large impact of high-quality cervical cancer screening activity were published in the 1960s and 1970s and documented a decrease in the incidence of invasive squamous-cell carcinoma of the cervix uteri among women screened of up to about 90%, in comparison with those unscreened or the rates before screening.[1] It has been estimated that high quality screening can reduce cervical cancer incidence by 80% or possibly more in the whole screened population.[2] This large reduction, the relatively early age of occurrence of cervical cancer and the fact that cervical cancer screening prevents invasive cancer (with obvious impact on quality of life) give it high priority despite the fact that cervical cancer incidence, even before the advent of screening, was lower than that of other cancers subject for screening.

The first cervical cancer screening programmes in Europe were initiated in the 1950s and early 1960s. In the following years organised population-based programmes, or spontaneous (opportunistic) screening activities based on the Papanicolaou smear test, have developed in almost every European Union member country. In 2000, a first special issue of the *European Journal of Cancer* described the situation of cervical cancer screening in the European Union.[3]

Over the last years, cervical screening has been a field in rapid evolution and a further acceleration of these changes can be expected in the next few years. Knowledge on the role of Human Papillomavirus (HPV) as the causative agent of cervical cancer has resulted, on one hand, in the availability of prophylactic vaccines with high efficacy in reducing vaccine-type HPV infections and high-grade pre-cancerous lesions (reviewed in 4). On the other hand, new screening techniques, particularly those based on HPV detection, have been proposed and evaluated using severe pre-cancerous lesions as the outcome. The European contribution in this field has been relevant: randomised trials conducted in Sweden,[5] the Netherlands,[6] England,[7] Italy[8] and Finland[9] have concluded or are close to conclusion. Also, during these years, the European Union has expanded with the inclusion of countries from Eastern Europe. These countries share problems, different from those of the old members states, related to a different history of cervical screening, higher incidence and mortality from cervical cancer – frequently with increasing trends – and lower available resources. This special issue of the *European Journal of Cancer* aims at updating the situation in this new overall scenario.

The first two papers, reporting the available information on HPV infection[10] and on trends of cervical cancer mortality,[11] together with recently published data on cervical cancer incidence,[12,13] provide the background epidemiological information on the burden of cervical cancer and on its main risk factor. Unfortunately, lack of historical data on HPV prevalence

* *Corresponding author:* Tel.: +358 9135331; fax: +358 91355378.
E-mail address: ahti.anttila@cancer.fi (A. Anttila).

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limits the possibility of using such data to interpret mortality and incidence trends. The latter, however, provide elements for an evaluation of the historical impact of cervical screening practice.

High population coverage and high quality of the screening process are essential to achieve high effectiveness of screening at a population level. In addition, high screening quality is essential to avoid the potential side-effects of cervical screening. The European Union issued recommendations on cancer screening suggesting population-based organised programmes[14] and published related quality-assurance guidelines for cervix cancer screening.[15] Despite the long-lasting activities in most EU member countries, there are still few earlier reports monitoring these programmes and practically none comparing European countries regarding process performances of screening. This special issue includes summary data on the current cervical screening policies[16] and on monitoring and performance indicators,[17] based on the screening registers established thus far in the member countries and considering cytological screening, the screening technique currently largely adopted in Europe.

Given the high diversity of the status of cervical screening in European countries, it is, however, difficult to summarise it in a few quantitative parameters and it is important to underline the peculiarities of each country, also in order to allow a correct interpretation of summary results. Therefore, this special issue also presents brief descriptions of the current national situation of cervical cancer screening from all but one of the member states.[18] These papers include updated documentation of the most relevant publications. In addition, two summary papers discuss, separately, data on the challenges of organising cervical screening in the old[19] as well as the new member countries.[20]

As previously stated, it can be expected that cervical screening will be deeply changed over the next few years by the introduction of HPV vaccination (which several European Union member countries have already started to integrate in their vaccination programmes) and, possibly, by the adoption of new screening techniques. A specific paper reports information about decisions on the HPV vaccination.[21] This special issue ends with a discussion about the foreseeable future based on currently available data.[22]

The articles in this special issue show that the extension of population-based cervical screening programmes in the European Union has increased but still only includes approximately one third of the approximately 140 million women potential target population in the European Union.[23] As a result, screening coverage is still suboptimal despite a very high consumption of screening tests, and also because some countries adopt very intensive screening policies[16,17] associated with low cost-effectiveness.[24] In most member states the overall volume of screening tests is sufficient in order to invite women with 3- or 5-yearly intervals. The systematic registration of data to monitor the screening process has also increased but still includes a limited proportion of the European population[16] so that an evaluation of the quality of screening process is still not possible for the remaining women. Despite problems of comparability, due to different registration and classification systems, we observed a high variability in performance parameters between European countries.[17] These can only partly be explained by a different baseline risk[10,18] but seem largely related to differences in screening protocols, in variability of cytology interpretation and in the actual attendance to diagnostic work-up, suggesting important differences in the effectiveness and undesired effects of screening between European countries.

According to most recent estimates there are, every year, approximately 34,300 new incident cases of cervix cancer and 16,300 deaths from the disease in the whole European Union[12] (estimated among women aged 0–74 years); 22,700 incident cases and 9500 deaths in the old and 11,600 incident cases and 6800 deaths in the new member countries, respectively. There are annually almost 60,000 incident cases and 30,000 deaths in the whole of Europe.[25] Decreases of mortality were over 50% from 1970–74 to 2000–2004 in all the old EU member countries except Ireland.[11] If we assume that screening, from Arbyn and colleagues introduction, caused an approximate 60% average decrease, then possibly approximately 35,000 incident cases and 15,000 deaths are already prevented per year in these counties. However, compared to a potential reduction of over 80% with optimal screening, in most of these countries the current incidence and death rates could, however, still be largely reduced. The potential benefit in relative terms is even larger in the new member countries and in many non-member European countries, in most of which no similar historical decrease in the disease burden has taken place.

The new validated HPV-screening methods have shown clearly lower rates of severe pre-cancerous lesions after screening, compared with those after conventional cytology[5,6] and the absolute rate of severe lesions after a negative HPV test is almost negligible.[26] These findings make it likely that the overall impact against cervical cancers could increase from that of conventional cytology. Also, the screening intervals should become longer with consequences on quality of life and provision of new opportunities to increase coverage. Finally, the variability of screening quality due to subjectivity of cytology interpretation could be reduced. However, no relevant impact at a population level can be obtained in absence of high coverage. In addition, if not properly used, these new methods can add greatly to adverse effects and costs. Therefore, it is essential that they are integrated in organised screening programmes.

In conclusion, actions are needed to improve coverage and quality of cervical screening, through the implementation of well monitored population-based programmes and through the standardisation of registration systems between European countries.

Much of the newly-presented data has been collected in connection with the European Union funded European Network for Information on Cancer (EUNICE), coordinated by the International Agency for Research on Cancer, Lyon. A first report of the status of cancer screening programmes[23] has been published in collaboration, on cervical cancer screening, with the authors of the current special issue.

Conflict of interest statement

None declared.

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HPV infection in Europe

*Hugo De Vuyst, Gary Clifford, Ni Li, Silvia Franceschi**

International Agency for Research on Cancer, 150 cours Albert Thomas, 69372 Lyon cedex 08, France

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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-

* *Corresponding author:* Tel.: +33 472738402; fax: +33 472738345.
E-mail address: franceschi@iarc.fr (S. Franceschi).
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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

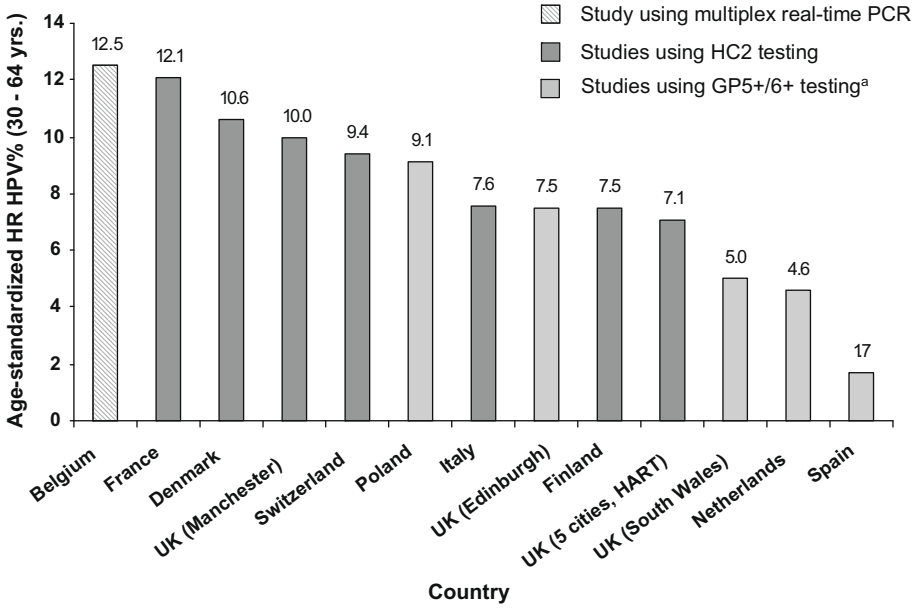

Fig. 1 – Age-standardised high-risk (HR) human papillomavirus (HPV) prevalence in 10 European Union countries and Switzerland, women aged 30–64 years. [a]HR HPV types only.

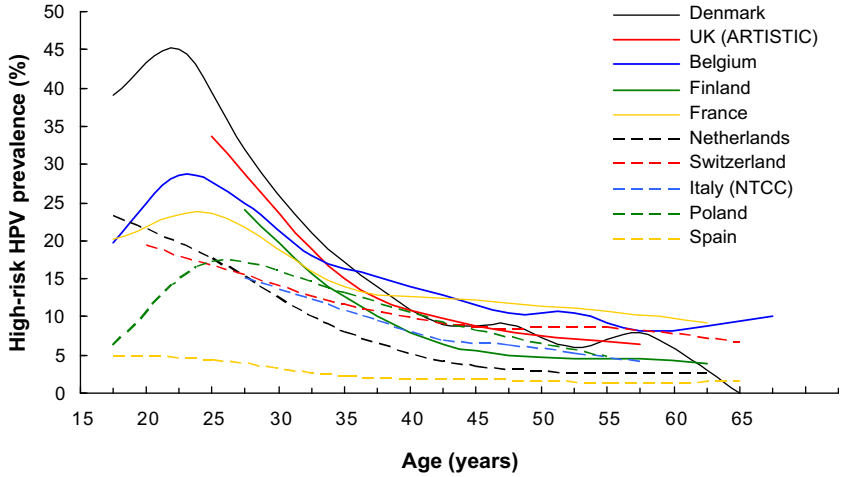

Fig. 2 – Age-specific HR HPV prevalence in nine European Union countries and Switzerland.

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-

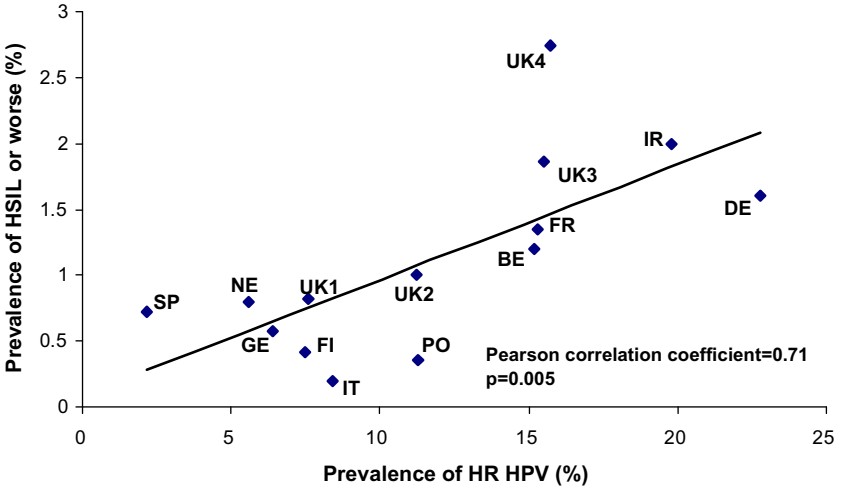

Fig. 3 – The correlation between the prevalence of HR HPV and high-grade squamous intraepithelial lesions (HSIL) or worse in 14 European studies. UK1: 5 cities (HART); UK2: South Wales; UK3: Manchester; and UK4: Edinburgh.

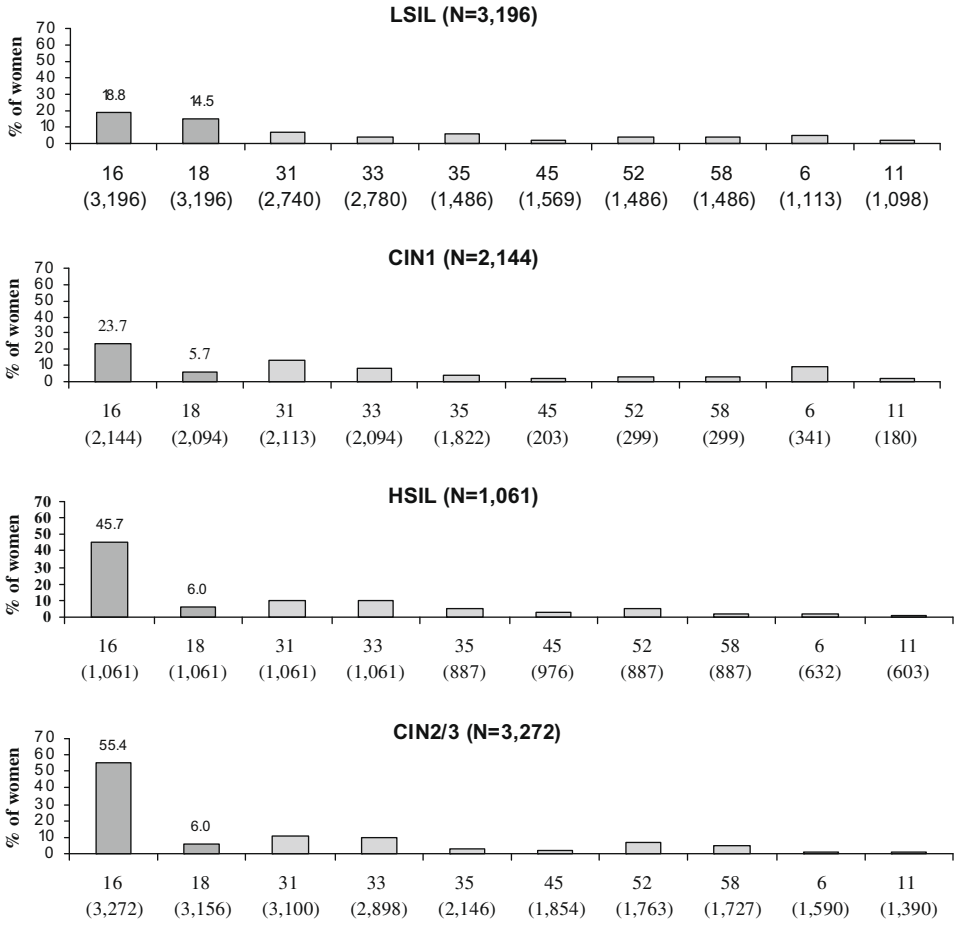

Fig. 4 – Prevalence of eight HR HPV types and HPV6 and 11 by presence of cytological (LSIL, HSIL) or histological (CIN1, CIN2/3) lesions in Europe. CIN: cervical intraepithelial neoplasia; LSIL: low-grade squamous intraepithelial lesions; HSIL: high-grade squamous intraepithelial lesions; *N*: number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

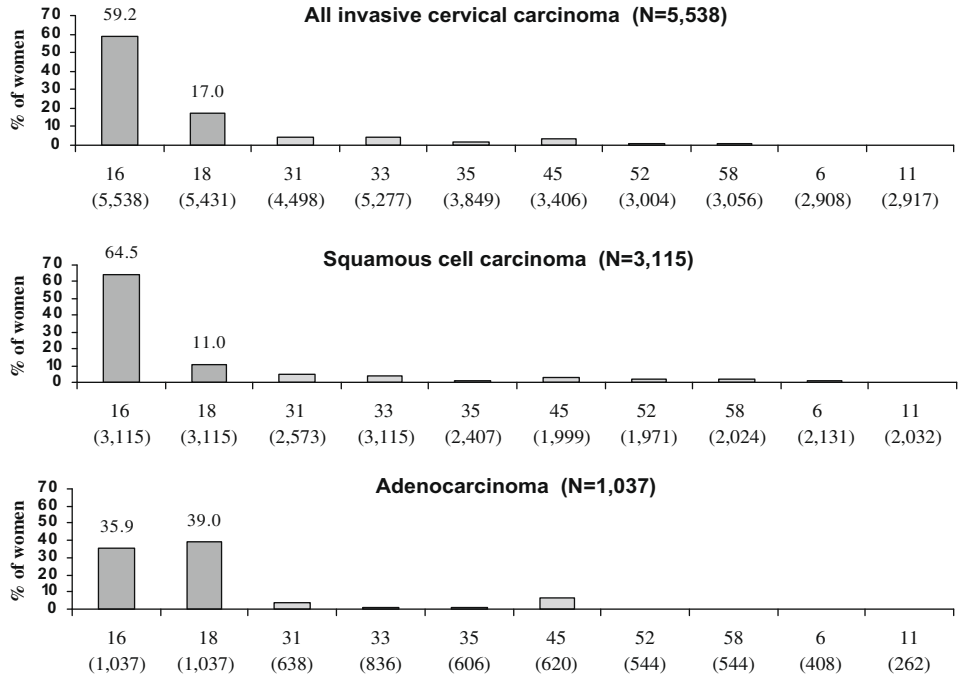

Fig. 5 – Prevalence of eight HR HPV types and HPV6 and 11 in invasive cervical carcinoma overall and by histological type in Europe. N: number of cases tested for the given HPV type.

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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Trends of cervical cancer mortality in the member states of the European Union

Marc Arbyn[a,*], *Amidu O. Raifu*[a], *Elisabete Weiderpass*[b,c,d,e], *Freddie Bray*[b,f], *Ahti Anttila*[g]

[a]*Unit of Cancer Epidemiology/Belgian Cancer Centre, Scientific Institute of Public Health, Brussels, Belgium*
[b]*Cancer Registry of Norway, Oslo, Norway*
[c]*Department of Genetic Epidemiology, Folkhälsan Research Centre, Helsinki, Finland*
[d]*Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden*
[e]*Institute of Community Medicine, University of Tromsø, Tromsø, Norway*
[f]*Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway*
[g]*The Finnish Cancer Registry, Helsinki, Finland*

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ABSTRACT

Background: Cervical cancer mortality can be avoided to a large extent by screening and treatment of screen-detected cervical lesions. However, in 2004, more than 16,000 women died from cervical cancer in the European Union (EU). In the current paper, we analyse cervical cancer mortality trends in the 27 member states since 1970 and, subsequently, try to explain how screening and other factors have driven changes.

Methods: Data on number of deaths from uterine cancers and overall female populations from EU member states were extracted from the World Health Organisation mortality database. Three different reallocation rules were applied to correct cervical cancer mortality for inaccuracies in certification of cause of death of not otherwise specified uterine cancer. Joinpoint regression was used to study annual variation of corrected cervical cancer mortality in all member states. We distinguished the 15 old from the 12 new member states, which acceded to the EU in 2004 or later. For Finland, France and Romania, age-specific trends by calendar period and the standardised cohort mortality ratios by birth cohort were analysed.

Results: Corrected age-standardised cervical cancer mortality rates have decreased significantly over the past decades in the old member states. Member states in Eastern Europe and also the Baltic states showed mortality rates that decreased at a lower intensity (Czech Republic, Poland), remained constant at a high rate (Estonia, Slovakia) or even increased (Bulgaria, Latvia, Lithuania, Romania). The standardised cohort mortality ratio indicated that mortality does not decrease further or even increase among women born after 1940.

Conclusion: Remarkable contrasts were observed on cervical cancer mortality, in particular, between the old and new member states of the EU, which might probably be explained by differences in preventive strategies. This contrast might increase in the future, unless adequate preventive measures are adopted.

* *Corresponding author:* Address: Unit of Cancer Epidemiology, J. Wytsmanstreet 14, B1050 Brussels, Belgium. Tel.: +32 2 642 50 21; fax: +32 2 642 54 10.
E-mail address: marc.arbyn@iph.fgov.be (M. Arbyn).
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1. Introduction

According to recent estimates for the year 2004, approximately 34,300 women in the European Union (EU) developed cervical cancer and about 16,300 died from the disease.[1] The main etiologic factor for cervical cancer is persistent infection with sexually transmittable high-risk human papillomaviruses.[2] By well organised screening and treatment of screen-detected high-grade cervical intraepithelial neoplasia (CIN) invasive cancer can be avoided.[3] Therefore, trends in incidence of cervical cancer largely reflect coverage and quality of screening, as well as changes in exposure to risk factors which are mainly related to sexual habits of successive cohorts.[4,5]

Mortality trends are determined by the incidence and case fatality rate. Survival (the complement of case fatality) is influenced by stage and age of diagnosis, and access to and effectiveness of cancer treatment.[4–7] Screening also plays a role in detecting invasive cancer at an early curable stage.[8] The study of incidence trends would be more pertinent to assess the impact of cervical cancer screening. However, incidence data reported by cancer registries are less comprehensive than mortality statistics, which have been compiled from nearly all European countries for several decades by the World Health Organisation (WHO). Furthermore, cancer incidence statistics from early periods in certain registries are inflated by inclusion of pre-invasive lesions, and cancer registries often do not separate micro-invasive (easily curable) from fully invasive cancer cases (resulting in substantial mortality).[9]

Trend analyses of cervical cancer mortality are often hampered by inaccuracies in certification of cause of death, since, in many countries, a substantial fraction of uterine cancer deaths are coded as cancer from the uterus not otherwise specified (NOS) where it is not determined whether the cancer originated form the cervix or the corpus uteri.[10,11] Moreover, in the 8th International Codification of Diseases, cancer of the corpus uteri or of the uterus NOS were grouped in one 3-digit code. In a previous special issue dedicated to cervical cancer screening in Europe, Levi et al. analysed the trend of mortality from cervical cancer in Europe.[12] No attempt was made to correct for inaccuracies in the certification of death by uterine cancers. As a proxy for cervical cancer mortality, cancer of all uterus cancers combined was studied among women aged younger than 45 years, since in this age group the large majority of uterine cancers originate from the cervix.[13] However, this age group may not enable assessment of the full population impact of screening, as the majority of deaths from cervix cancer occur after the age of 45 years. In the current study, an algorithm was developed to reallocate deaths from the uterus NOS or combined groups, building further on previously published methods.[10,11] Finally, the trends of the corrected rates are tentatively explained as a result of secondary prevention taking into account changes in exposure to risk factors and the impact of oncologic treatment on survival.

2. Materials and methods

2.1. Source of data

Data on number of deaths from uterine cancers and the size of the female population, aggregated by calendar year, 5-year age group (with the last category being $\geqslant$85 years) and country (current member states of the EU) was obtained from the WHO mortality database (http://www.who.int/whosis/mort/download/en/). We distinguished the 15 old (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Portugal, Spain, Sweden, The Netherlands and the United Kingdom) from the 12 new member states (Bulgaria, Cyprus, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Romania, Slovakia and Slovenia) which acceded to the EU in 2004 or later.

The following uterine cancers were distinguished: cervix uteri cancer (*CVX*), corpus uteri cancer (*CRP*), cancer from the uterus *not otherwise specified* (*NOS*) and some other very rare cancers such as placenta cancer (*OTH*). Separate International Codification of Diseases (ICD) codes were used to identify cervical cancer (180 in the 8th and 9th, and C53 in the 10th ICD edition). Corpus uteri cancer and uterus NOS cancer were codified separately in the 9th and 10th ICD edition (182 [ICD-9] and C54 [ICD-10] for corpus cancer; 179 [ICD-9] and C55 [ICD-10] for uterus NOS cancer). However, in the 8th edition, 182 was used for both corpus and uterus *NOS* cancer. The rare *other cancers of the uterus* were coded with 181 in the 8th and 9th editions and C57/C58 in the 10th edition.

2.2. Reallocation rules

The number of deaths from cervix uteri cancer (*corCVX*) can be estimated from the number of deaths certified as originating from cancer of the uterine cervix (*CVX*), the uterine corpus (*CRP*), the uterus not otherwise specified (*NOS*), or of combinations including *CRP* and *NOS* (*CRPNOS* or *CRPNOSOTH*) using three different reallocation rules.

According to Loos et al.[11], when the proportion of *NOS* of all uterus cancer was less then 25%, adjustments could be made using allocation rule 1, assuming that the *NOS* death certification was allocated at random:

$$corCVX_{ij} = CVX_{ij} + NOS^{*}_{ij}CVX_{ij}/(CVX_{ij} + CRP_{ij}),$$

where the indices *i* and *j* correspond with age group and year at death, respectively.

If allocation rule 1 could not be applied for certain periods (because pNOS>25% or because *NOS* was not available as a separate group but included in *CRPNOS* or *CRPNOSOTH*), allocation rule 2 was used. Rule 2 consisted of imputing[14–16] the age-specific proportion of corrected cervical cancer ($pcorCVX_{ij} = corCVX_{ij}/UT_{ij}$, [$UT_{ij}$ being the sum of the number of deaths from all parts of the uterus]) of a given country where reallocation rule 1 was applied (source period) to a relevant neighbouring target period, using a linear regression (containing an age * year interaction) as explained in a more comprehensive report.[17]

Certain countries, where reallocation rules 1 and 2 were applied, were used for reallocation in countries where conditions for allocation rules 1 and 2 could never be applied (allocation rule 3, see Table 1): $corCVX_{ijc} = UT_{ijc} * pcorCVX_{ijt}$, where *c* refers to a given country and *t* to its respective template country.

2.3. Presented trends

Age-standardisation was performed using the World standard population.[18] Due to the lack of available data, the last period

Table 1 – List of template countries used to correct data from countries where >25% of uterine cancer deaths were of unspecified origin (NOS) or were included in mixed code groups.

Template countries (*t*)	Countries (*c*) with >25% *NOS* or mixed codes (*CRPNOS*, *CRPNOSOTH*)
Finland	Sweden
Hungary	Bulgaria, Romania, Slovenia
Lithuania	Estonia, Latvia
The Netherlands	Austria, Belgium, France, Germany, Greece, Italy, Luxembourg, Malta, Portugal, Spain
England & Wales	Ireland, Northern Ireland, Scotland

did not always span 5 years. Certain newly founded states contributed data over a limited period: Estonia (⩾1981), Latvia (⩾1980), Lithuania (⩾1981), Slovenia (⩾1985), Czech Republic (⩾1986) and Slovakia (⩾1992). For Germany, data were added from East- and West-Germany from 1973 to 1989 and data from the unified Germany were used thereafter. For the United Kingdom (UK), we present separate data for England and Wales, Northern Ireland and Scotland. For Cyprus, no mortality data was available.

Joinpoint regression was used to analyse trends of the standardised corrected mortality rates, as a linear function of year at death, starting at 1970, for all member states with available data.[19] 1970 was chosen as the starting year for two reasons: (a) availability of data and (b) plausibility of the reallocation rules (see above), which are more questionable before 1970. Joinpoint regression identifies periods with distinct linear slopes that can be separated by *joinpoints*, where the slope of the trends changes significantly.[20,21] Joinpoint regression badly suits data with an autoregressive structure or periodic fluctuations, but is appropriate to identify abrupt or non-cyclic changes, which is the purpose of the current analysis. The maximum number of joinpoints was set at three. For each linear segment, the average annual percentage of change (APC) and corresponding 95% confidence intervals (CIs) were calculated. Trends were plotted on a logarithmically (log10) scaled Y-axis as proposed by Devesa.[22] Rates that change at a constant percentage every year are presented by a straight line on a log scale.

We selected three countries with data available over a longer period and representative for three typical situations: Finland (low burden of cervical cancer, well organised screening), France (low burden, non-organised but widespread screening) and Romania (high burden, low level of screening). For these countries we plotted age-specific trends by 5-year period and the standardised cohort mortality ratio (SCMR). The SCMR represents the relative risk of a certain cohort of dying from cervical cancer compared to the mean mortality rate of all generations together.[23,24] It consists of the ratio of the number of observed deaths in a given cohort, *k*, over the number of expected deaths if the average age-specific mortality rates are applied to the respective age segments of the population in cohort *k*.

3. Results

Fig. 1 shows the joinpoint regression plots for the age-standardised cervical cancer mortality corrected according to the three reallocation rules for all countries. The Y-axis is scaled equally in all graphs facilitating visual interpretation and comparison. Table 2 identifies the joinpoints and the annual percentage of change in each linear segment.

In Eastern Europe, standardised trends were localised above those observed in most other parts of Europe. The trends were decreasing in the Czech Republic, Hungary and Poland. In Slovakia, the trend did not differ significantly throughout the analysed period (APC = –1.3, 95% CI: –1.3 to 0.1%). In Bulgaria and Romania, mortality trends rose from the 1980s onwards (APC = 3.5% [95% CI: 1.2 to 5.7%] and 0.4% [95% CI: 0.2–0.6%], respectively). However, in Bulgaria, the increasing trend was not statistically significant after 1988.

In Northern Europe, trends were decreasing in Denmark, Finland, Sweden and the UK. In Finland, the negative slope of the trend was very steep in the first years (APC = –15.6%) of analysis but became less pronounced subsequently (APC = –4.7%). In Sweden, the APC did not differ from zero after 1995. England and Wales and Scotland showed a joinpoint near the end of the 1980s with a modest negative slope before and a steeper negative slope thereafter. Ireland showed a modest regularly decreasing trend (APC = –1.1% [–1.4 to –0.7%], no significant joinpoint). There was no statistically significant slope in Estonia, whereas in Latvia (APC = 0.7) and Lithuania (APC = 1.0) the trend was rising.

Decreasing trends in cervical cancer mortality were observed in Southern and Western Europe. In Portugal, Spain and the Netherlands, mortality rates showed one joinpoint and decreased less in recent periods. In the other countries, mortality rates dropped at a monotonous rate.

Fig. 2 compares the standardised rates of cervical cancer mortality in the periods 1970–1974 and 2000–2004, unless otherwise specified. Countries are ranked by decreasing mortality rate in the most recent period. All new member states of the EU, with the exception of Malta, rank highly. In all the old member states the ratio of the rate old/recent period was less than 0.5 with the exception of Ireland. In the new member states the contrast between recent and old periods was smaller (ratio > 0.60), with the exception of Hungary (ratio = 0.51). In Lithuania, Latvia and Bulgaria, age-standardised trends were higher in the most recent period (ratio > 1), whereas in Romania, Estonia and Slovakia differences were small (ratio > 0.85).

Fig. 3 shows the age-specific corrected cervical cancer mortality rates by 5-year period (on the left) and the standardised cohort mortality ratio by birth cohort (on the right) for the three selected countries. Finland and France show decreasing trends in age groups older than 30 years from

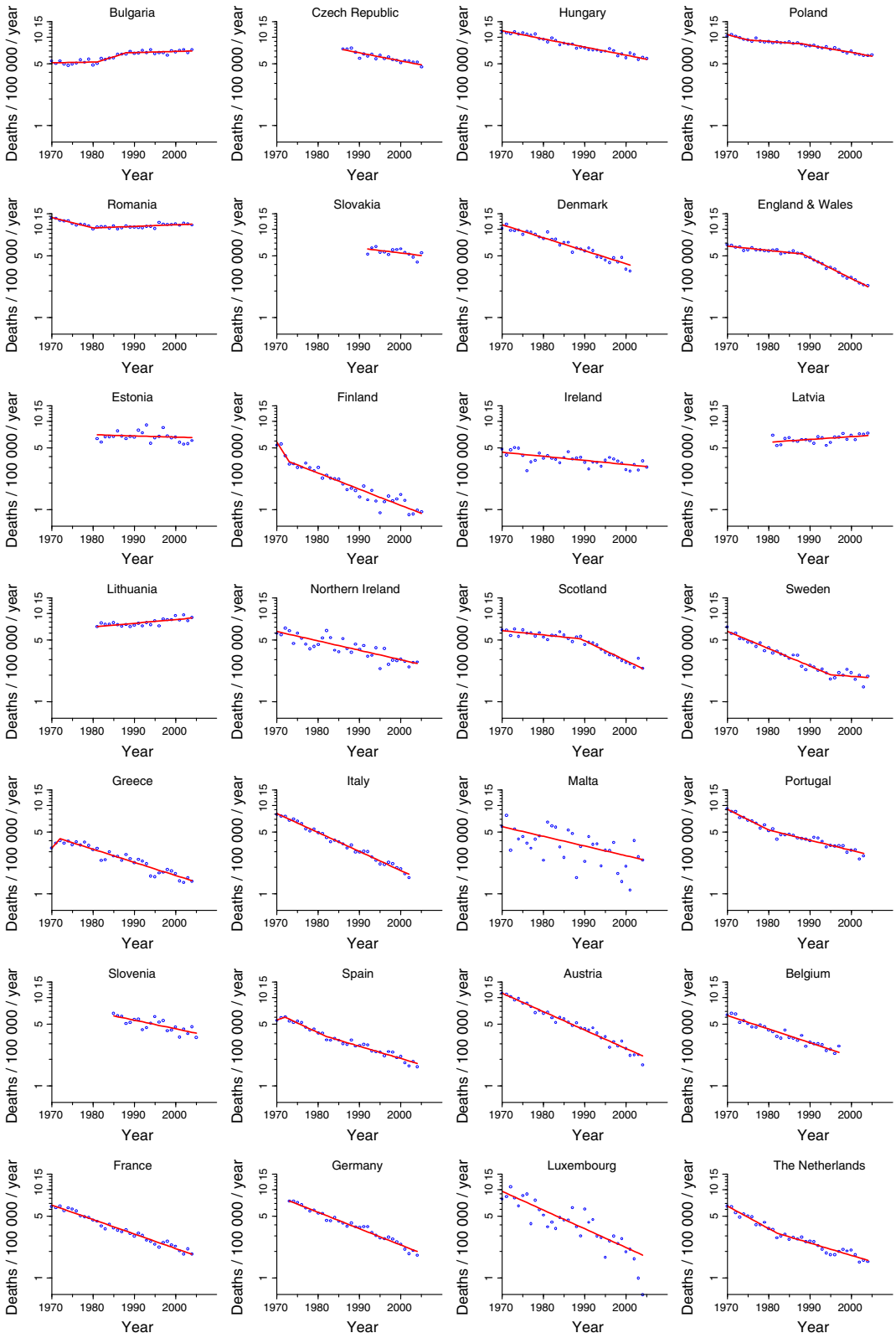

Fig. 1 – World-age-standardised mortality from cervical cancer, corrected for cause of death certification inaccuracies in 26 member states of the EU after 1970. Dots represent annual rates; lines represent linear trends obtained by joinpont regression. Countries are ranked by subcontinent: Eastern Europe: Bulgaria, Czech Republic, Hungary, Poland, Romania, Slovakia; Northern Europe: Denmark, Estonia, Finland, Ireland, Latvia, Lithuania, Sweden, UK (England & Wales, Northern Ireland, Scotland); Southern Europe: Greece, Italy, Malta, Portugal, Slovenia, Spain; Western Europe: Austria, Belgium, France, Germany, Luxembourg, The Netherlands.

Table 2 – Joinpoints, years where slopes of linear trends changed, (including 95% CI around this year), and magnitude of the annual percentage of change (APC) in each linear segment and its 95% CI.

Region	Country	Number joinpoints	Joinpoint (95% CI)	APC (95% CI)
Eastern Europe	Bulgaria	2	1981 (1972–1986) 1988 (1984–1994)	0.02 (–0.8 to 1.2) 3.5* (1.2 to 5.7) 0.3 (–0.2 to 0.8)
	Czech Rep.	0	–	–2.1* (–2.5 to –1.6)
	Hungary	0	–	–2.1* (–2.2 to –2.0)
	Poland	2	1975 (1972–1997) 1988 (1983–2003)	–2.7* (–4.4 to –1.0) –0.8* (–1.3 to –0.3) –1.8* (–2.1 to –1.6)
	Romania	1	1980 (1979–1983)	–2.7* (–3.3 to –2.0) 0.4* (0.2 to 0.6)
	Slovakia	0	–	–1.3 (–2.6 to 0.1)
Northern Europe	Denmark	0	–	–3.3* (–3.6 to –3.0)
	England & Wales	1	1988 (1986–1989)	–1.1* (–1.4 to –0.8) –5.2* (–5.6 to –4.8)
	Estonia	0	–	–0.3 (–1.1 to 0.5)
	Finland	1	1973 (1972–1976)	–15.6* (–25.7 to –4.0) –4.1* (–4.6 to –3.6)
	Ireland	0	–	–1.1* (–1.4 to –0.7)
	Latvia	0	–	0.7* (0.2 to 1.2)
	Lithuania	0	–	1.0* (0.6 to 1.4)
	N. Ireland	0	–	–2.4* (–2.9 to –1.9)
	Scotland	1	1989 (1985–1992)	–1.1* (–1.7 to –0.5) –5.0* (–6.0 to –4.0)
	Sweden	1	1995 (1987–1998)	–4.4* (–4.8 to 4.0) –0.8 (–3.4 to 1.9)
Southern Europe	Greece	1	1972 (1972–1980)	12.8 (–12.9 to 46.0) –3.4* (–3.7 to –3.0)
	Italy	0	–	–4.8* (–5.0 to –4.6)
	Malta	0	–	–2.5* (–3.6 to –1.4)
	Portugal	1	1980 (1976–1984)	–5.3* (–6.4 to –4.1) –2.6* (–3.1 to –2.2)
	Slovenia	0	–	–2.2* (–3.1 to –1.4)
	Spain	2	1972 (1972–1989) 1982 (1976–2002)	3.6 (–10.1 to 19.3) –4.9* (–6.2 to –3.6) –3.1* (–3.6 to –2.7)
Western Europe	Austria	0	–	–4.7* (–4.9 to –4.5)
	Belgium	0	–	–3.5* (–3.9 to –3.1)
	France	0	–	–3.7* (–3.9 to –3.5)
	Germany	0	–	–4.2* (–4.4 to –3.9)
	Luxembourg	0	–	–4.8* (–5.7 to –3.8)
	Netherlands	1	1982 (1979–1987)	–5.7* (–6.7 to –4.7) –3.2* (–3.7 to –2.7)

* Indicates that the magnitude of the APC is statistically significantly different from zero ($p < 0.05$).

the 1960s onwards. In Finland the slopes were steeper than in France in the age group 35–54 in the period 1965–1974. In Romania, rising trends are observed among women in the age range 25–60 in the more recent periods. For Finland and France a flattening in mortality trends could be distinguished for women younger than 50 years in the more recent periods. This flattening or rising tendency occurred progressively later in older age groups indicating a cohort effect. Indeed, as shown in the SCMR plots, all three countries show a breaking point at the 1940 birth cohort, after which trends become flat or start to rise. In Romania, the rising cohort effect is evident. Women belonging to the cohorts C_{1920}–C_{1935} had a progressively lower risk of dying from cervical cancer. For the oldest cohorts (C_{1890}–C_{1920}), we observed a steep, less steep and flat course of the SCMR for Finland, France and Romania, respectively.

4. Discussion

The current trend analyses confirm previous reports revealing the large contrasts in the burden of cervical mortality between the old and new member states of the EU.[1,25] Moreover, our study indicates that these contrasts will increase in the future since mortality rates continue to decrease in the western part of Europe, whereas in Eastern Europe and in the Baltic states they are either decreasing at a lower intensity (Czech Republic, Poland), remaining constant at a high rate (Estonia, Slovakia) or even increasing (Bulgaria, Latvia, Lithuania, Romania).

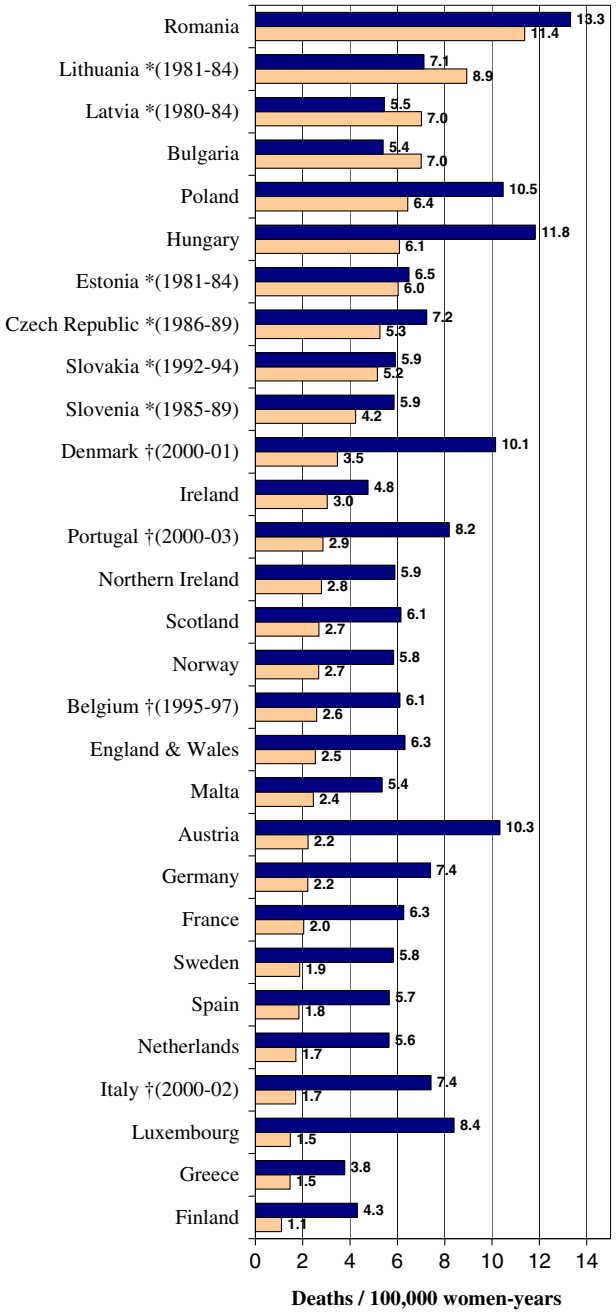

Fig. 2 – World-age-standardised rates of corrected cervical cancer mortality in 1970–1974 (blue bars) and 2000–2004 (orange bars) unless otherwise specified (see †/*). † (for countries where data were not available for 1970–1974, the earliest available period is indicated); * (for countries where data were not available for 2000–2004, the latest available period is indicated). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4.1. *Quality of data*

An important question is whether the applied correction for certification inaccuracies allows the study of the true rates of cervical cancer mortality. If the assumption of random allocation (applied in rule 1) is incorrect, the error would be limited since the rule is only applied when the proportion of NOS is rather small. For Finland, we compared our corrected cervical cancer mortality rate with that adjusted by linkage between the cause of death register and the cancer registry. Both corrected rates overlapped well, indicating that – at least in this example – reallocation rule 2 provided satisfactory results.[17] Less evidence of reliable correction can be found for reallocation rule 3. The assumption that the Lithuanian proportions are applicable to those of Estonia and Latvia look plausible given the common background risk and history of preventive health care. However, the application of proportions from the Netherlands to adjust data from different countries, such as Austria, France, Germany, Greece, Italy, Portugal or Spain, could be considered problematic. With alternative assumptions, it might be possible to obtain different patterns in the adjusted trends. Moreover, it is unclear whether cause-specific registration of deaths was accurate with respect to the uterus as a primary site or whether other errors may have affected data quality such as duplication of some disease groups due to the use of various coding rules. Concerning Spain, LLorca et al. concluded that the rate of cervical cancer mortality, based on certified cervix cancer deaths, was increasing.[26] This conclusion was considered as possibly spurious[27] since the proportion of uterus NOS cancer deaths progressively decreased (NOS_j/UT_j: 86% in the 1950s, 26% near the end of the 1990s). In a later study, cervical cancer mortality was corrected by considering fixed proportions of NOS as being of cervical origin.[28] The conclusion was that mortality was increasing among younger women. We found a nearly horizontal recent trend among young women in the Spanish data. We believe that corrections need to be age- and period-specific. Nevertheless, we are aware that such adjustments using a non-representative template country could also yield incorrect results. In order to find more reliable solutions to correct for NOS and CRPNOS cancer deaths, we propose further research, involving linkages between mortality and cancer registries.[29–31] These same procedures are required for producing current regular cancer statistics.

4.2. *Cohort effects*

Strong cohort effects could be discerned and some were common to nearly all European countries. The continuous decrease in cohorts born in the first decades of the 1900s, observed for Finland, France and many other countries but not for Romania, may be due to poorly understood etiological (co-) factors, linked to improved social conditions and access to health care.[32] Women born between 1920 and 1940 showed a progressively lower risk of dying from cervical cancer, whereas women born thereafter tended to have increasing risk. This cohort effect is most plausibly explained by changes in sexual behaviour resulting in higher rates of HPV infection in younger cohorts as shown from studies using serum Finnish biobanks.[33,34] Available data on HPV prevalence from other countries concern recent periods[35] but historical data are lacking. Therefore, it is impossible to use them to interpret trends. At most it can be noticed that Denmark had high mortality in the 1970s and also has a current high prevalence

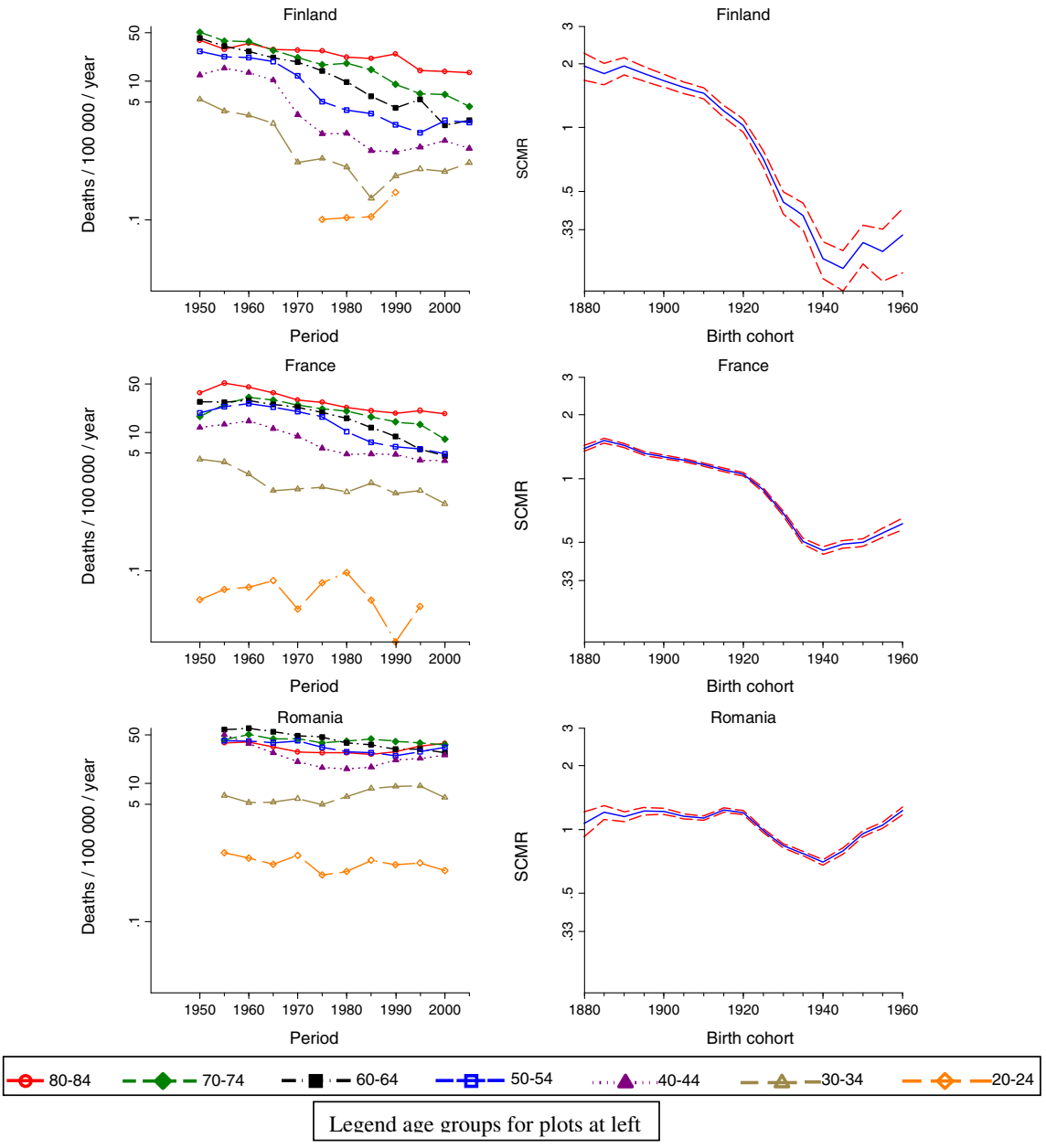

Fig. 3 – Mortality from cervical cancer corrected for certification problems. Left: age-specific* rate by 5-year period; right: standardised cohort mortality ratio (SCMR) by birth cohort with 95% confidence interval (interrupted line). Only the following age groups are displayed in the plots on the left: 20–24, 30–34, 40–44, 50–54, 60–64, 70–74, 80–84 (see legend); the in-between age groups are omitted for reasons of clarity.

of HPV suggesting that the background risk without screening is higher.

The increased frequency of smoking and oral contraception, both established risk factors for cervical cancer, may also have contributed to the recent rise of the SCMR. It is also possible that some other factors such as early diagnosis of invasive cancer among younger women due to increased access to gynaecological care may be responsible for cohort effects observed in the deaths rates.

In the future, the cohort effects will possibly be influenced by prophylactic HPV vaccination and further by screening practices in vaccinated cohorts.

4.3. *Screening effects*

In another paper, included in this issue of the *European Journal of Cancer*, we showed that substantial reductions in incidence and mortality, observed in several countries, correlated with the level of implementation of organised screening.[36] Opportunistic screening also resulted in a reduction of cervical cancer incidence and mortality in several other West-European countries.[5,12] Difference in coverage and quality of screening most plausibly explain the large differences between old and new member states.

The declining trend of cervical cancer mortality was initiated before screening became commonly practiced. The fact that increased coverage in the target population did not result in a further decrease in cervical cancer mortality has sometimes been suggested as evidence for a failure of screening.[37,38] However, this viewpoint ignores the strong recent cohort effects which we have illustrated for three countries. It seems that screening has counter-balanced the effect of increased exposure to etiologic factors in younger cohorts, by limiting the upward tendency of the SCMR. In countries without established screening programmes, the cohort effect was steeper (see Fig. 3 for Romania and the small differences between grey and black bars in several black and grey bars) than in countries with well organised screening.

The contrast between the 1970–74 and 2000–04 periods underestimates the effect of screening in Finland where organised screening was already established in the 1960s and where age-standardised corrected mortality rates have dropped by 80% over the last 45 years.[39] It was estimated from an age-period-cohort model that without screening, standardised cervical cancer mortality, in 2003–07 in Finland, would have been 6.5/10^5/year whereas observed rates were 0.7/10^5/year.[40]

The greatest contrasts over the studied 35-year span were observed in Austria and Luxembourg (ratios of 0.22 and 0.18, respectively). However, we cannot ascertain that these decreases should be explained exclusively as the effects of the intensive opportunistic screening existing in these countries.[36] Because of the particularly high rate of total uterus mortality in both countries in the earliest periods we cannot exclude that poor quality of historical data has driven these negative slopes.

4.4. *Improved survival*

A recent trend study of the 5-year survival from cervical cancer revealed a slow but steady improvement of about 2% per year among cancer patients diagnosed in the period 1983–94 in Europe.[41] No improvement was noted in the areas where survival was lowest (Central/Eastern Europe and the UK). Reduction of the case fatality can be expected by down staging through expansion of screening and by improved treatment. Unfortunately, there is no systematic data currently available on the quality of cervical cancer treatment in Europe.

Behind age-standardised trends, complex changes over time, age and birth cohort can be hidden which require more detailed analyses. We are currently performing age-period-cohort modelling of European mortality data and comparing incidence and mortality trends with the purpose of disentangling the separate effects of screening and exposure to risk factors. These studies provide indirect evidence of the effectiveness of preventive measures. Ideally, the evaluation of performance of secondary prevention should come from linkages of individual screening histories with cancer and mortality registries, as recently described in the 2nd edition of the European Guidelines for Quality Assurance in Cervical Cancer Screening.[42]

Conflict of interest statement

None declared.

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Cervical cancer screening policies and coverage in Europe

Ahti Anttila[a,*], *Lawrence von Karsa*[b], *Auni Aasmaa*[c], *Muriel Fender*[d], *Julietta Patnick*[e,f], *Matejka Rebolj*[g], *Florian Nicula*[h], *Laszlo Vass*[i], *Zdravka Valerianova*[j], *Lydia Voti*[k], *Catherine Sauvaget*[l], *Guglielmo Ronco*[m]

[a]*Mass Screening Registry, Finnish Cancer Registry, Pieni Roobertinkatu 9, FIN-00130 Helsinki, Finland*
[b]*Screening Quality Control Group, International Agency for Research on Cancer, Lyon, France*
[c]*Estonian Cancer Foundation, Tallinn, Estonia*
[d]*Association Eve, Strasbourg, France*
[e]*NHS Cancer Screening Programmes, Sheffield, UK*
[f]*Oxford University Cancer Screening Research Unit, Cancer Epidemiology Unit, University of Oxford, Oxford, UK*
[g]*Erasmus MC, Department of Public Health, Rotterdam, The Netherlands*
[h]*Institutul Oncologic 'I. Chiriuta', Cluj-Napoca, Romania*
[i]*Flór F. University Hospital, Kistarcsa, Hungary*
[j]*Bulgarian Cancer Registry, Sofia, Bulgaria*
[k]*Descriptive Epidemiology Group, International Agency for Research on Cancer, Lyon, France*
[l]*Screening Group, International Agency for Research on Cancer, Lyon, France*
[m]*Unit of Cancer Epidemiology, Centre for Cancer Epidemiology and Prevention (CPO), Turin, Italy*

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ABSTRACT

The aim of the study was to compare current policy, organisation and coverage of cervical cancer screening programmes in the European Union (EU) member states with European and other international recommendations. According to the questionnaire-based survey, there are large variations in cervical cancer screening policies and inadequacies in the key organisational elements of the programme such as registration and monitoring required for quality-assurance and fail-safe mechanisms. Based on data from available screening registers, coverage of the screening test taken within the population-based programme was below 80% in all programmes, ranging from 10% to 79%. The screening capacity is satisfactory in most EU member states, however, and there is even over-capacity in several countries. There are also countries which do not have an acceptable capacity yet. Control of proper capacity along with education, training and communication among women, medical professionals and authorities are required, accordingly. The study indicates that, despite substantial efforts, the recommendations of the Council of the EU on organised population-based screening for cervical cancer are not yet fulfilled. Decision-makers and health service providers should consider stronger measures or incentives in order to improve cervical cancer control in Europe.

* *Corresponding author:* Tel.: +358 9 135 331; fax: +358 9 135 5378.
E-mail address: ahti.anttila@cancer.fi (A. Anttila).
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1. Introduction

Organised screening programmes for cervical cancer, based on the conventional cytological screening test, have been shown to be effective in decreasing mortality and incidence from the disease.[1,2] Also, opportunistic, non-organised screening affects cervical cancer rates, although not to the same magnitude.[1–7] With non-organised activity, a considerable proportion of the population may be totally or partially under-screened, and at the same time there may be appreciable over-use of services among those served most actively.[5,8–11] There are concerns that adverse effects may become more common, if the clinical and diagnostic work-up of abnormal findings is not of a high quality. Hence these activities must be monitored and evaluated.[11–13]

The European Union (EU) currently recommends that cancer screening should only be offered in population-based, organised screening programmes, with quality assurance at all levels.[13,14] There are also some more detailed European recommendations and comprehensive guidelines describing the organisation and implementation, screening policies (recommended target age groups and screening intervals), as well as registration, evaluation and monitoring of organised cancer screening programmes.[13–15]

The aim of the current study was to assess the screening policy and the organisation of cervical cancer screening programmes in the EU member states, and to compare them with European and other international recommendations.

2. Materials and methods

The study is based on two questionnaire surveys. The first survey was performed within an expert network on cervical cancer screening registration and monitoring and the latter survey among respondents from the health authorities of the EU member states. In addition, materials from earlier published studies were searched and several interviews of experts and expert meetings were conducted in order to check and interpret data.

The first questionnaire survey was circulated between September 2005 and February 2008 among experts from 19 EU member states within a collaborative research project entitled 'Registration and monitoring of cervical cancer screening programmes in the European Union'. This project investigated whether organised cervical cancer screening programmes, or planning or piloting of them, were taking place, whether and how screening registration and monitoring was arranged and, finally, aimed to collect the monitoring results. This part of the work was done within the framework of the Cervical Cancer Screening Work Group of the European Network for Information on Cancer (EUNICE), financially supported by the EU. The overall network was coordinated by the International Agency for Research on Cancer (IARC), Lyon. Included in this project were those countries or regions for which the working group identified on-going screening registration, or where registration was being planned during the activity period.

The structured survey questionnaire along with the minimum data tables required for registration were the same as or corresponded closely with those published in the recently revised European quality assurance guideline for cervical cancer screening (Tables A and B of Appendix 2, Chapter 2, of Ref. [11]). A description of the screening data registration, screening policies, diagnostic work-up and characteristics of the programmes was included in the questionnaire. The screening findings together with further performance indicators, based mainly on the routine screening databases and regularly published statistics, and other summary characteristics of the programmes are reported elsewhere in this Special Issue.[16–23]

Emphasis on information collected on screening policy was on: targeted age range, screening interval with normal results, and number of lifetime tests recommended. Information on the target population, invitations and screening attendance (specifying whether after the invitation, or otherwise) were requested. Furthermore, it was requested whether the invitations and screening attendance were registered on an individual basis. One important structural aspect for screening registration and evaluation was to check availability of cancer registries. In this survey the data on cancer registries was collected from the most current edition of Cancer Incidence in Five Continents (CI5).[24] We also enquired with the expert group whether screening and cancer registry data could be linked with each other for evaluation and quality assurance purposes.

The second questionnaire was sent to the representatives of the national governments of the EU member states in Brussels and was designed to assess the status of cancer screening programmes in the EU.[25] It aimed to clarify broader aspects than screening policies alone, and information on other screening programmes than the cervix (e.g. breast, colo-rectum) was also solicited. Experience and definitions developed in the first survey were instrumental in developing the second questionnaire. The information collected on cervical cancer screening policies in this second survey was used in the current report. The information on screening policies was checked against the data obtained from the expert group of the first survey – who were mostly from countries with national cervical cancer screening coordination committees or national monitoring and evaluation units.

2.1. *Screening volume and coverage*

Different definitions affect the applicability of the concept of coverage.[11,26] Invitational coverage, defined as the proportion of target population invited during a screening round, is a meaningful measure among those programmes which invite all women in the target population or in the eligible target population. In addition, the proportion of women tested at least once within the recommended interval (women covered by the test) is a useful measure which can be computed on the basis of individual-level information from screening registries.

In addition to the smears taken within a programme, spontaneous or diagnostic smears were reported by a few centres. Due to a paucity of information, these could not be included in detail for all member states. For those countries which record all smears of any type, the proportion of women tested at least once during the recommended interval was

calculated from the register-based data or, respectively, on an annual basis. The current report includes coverage estimates as available from those screening registers which were able to convert their data into the requested guideline tables (Tables B1 and B2 of Ref. [11]). For those countries which record only the smears of the invitational programme, corresponding estimates can be derived from questionnaire studies among women, but reliability of that information was considered to be limited.

Information on the overall number of screening tests was also included in the second questionnaire. This information came from screening registries, if available, or from ad hoc databases. This was useful information in order to check completeness of screening registration. In addition, the overall volume of screening tests can be used to assess the screening capacity by comparing the number of tests performed with the number of women in the respective targeted populations. This assumes that the screening tests are evenly distributed within the target population during a screening round, which is, however, frequently not true.

Table 1 – Cervical cancer screening policy and programme features in the 27 European Union member states.

Country[a]	Type	Status	Eligible age in years[b]		Screening interval in years	Estimates number of tests in lifetime
			From	To		
Austria	Non-population-based	Nationwide	18+	Not specified	1	50+
Belgium	Non-population-based	Nationwide	25	64	3	14
Bulgaria	Non-population-based[c]	Nationwide	31	65	2	21
Cyprus	No programme	No programme	No data	No data	No data	No data
Czech Republic	Non-population-based	Nationwide	25	69	1	45
Denmark	Population-based	Nationwide	23	65[b]	3 in age 23–50; then 5[d]	Approx. 13
Estonia	Population-based	Nationwide, rollout ongoing	30	59	5	6
Finland	Population-based	Nationwide	(25) 30	60 (65)	5	7–9
France	Non-population-based	Nationwide	(20) 25	65	3	14
	Population-based	Local/Regional pilot	(20) 25 (50)	65 (74)	3	14 (9)
Germany	Non-population-based	Nationwide	20	Not specified	1	50+
Greece	Non-population-based	Natiowide	20	Not specified	1	50+
Hungary	Population-based	Nationwide	25	65	3	14
Ireland	Population-based	Regional; nationwide planning	25	60	3 in age 25–44; then 5	10
Italy	Population-based	Nationwide, rollout ongoing	25	64	3	14
Latvia	Non-population-based	Nationwide	20	70	3	17
Lithuania	Non-population-based	Nationwide	30	60	3	11
Luxembourg	Non-population-based	Nationwide	15	Not specified	1	50+
Malta	No programme	No programme	No data	Not specified	No data	Not specified
Netherlands	Population-based	Nationwide	30	60	5	7
Poland	Non-population-based	Nationwide	25	59	3	12
	Population-based	Local	25	59	3	12
Portugal	Population-based	Nationwide, planning	25	64	3	14
	Population-based	Regional, rollout ongoing	25	64	3	14
Romania	Population-based	Nationwide, piloting	25	65	5	9
Slovak Republic	Non-population-based	Nationwide	18	Not specified	1	50+
Slovenia	Population-based	Nationwide	20	64	3	15
Spain	Non-population-based	Regional	(18) 30 (35)	59 (65)	3 or 5[e]	5–15
	Population-based	Regional	(25) 30	(50) 65	3	9-15
Sweden	Population-based	Nationwide	23	60	3 in age 23 to 50; then 5	12
UK	Population-based	Nationwide	(20) 25	(60) 64	3 and 5[f]	12

Source: European Commission (DG SANCO); IARC (EUNICE and ECN projects, see Methods); and von Karsa et al.[25]

a Multiple entries for some countries due to dual implementation status.

b Regional variation within parentheses. Neither including age range of optional attendance after regular invitation ceases, nor age range of women especially invited or tested in some programmes because recent history of normal test results is lacking.

c Prophylactic activity on-going mainly among certain risk groups.

d From new national guidelines (31 December 2007); former guideline recommended screening every 3 year up to the age of 59 years.

e Regional variation also in the interval.

f Targeted age and screening interval vary by region: England 3-yearly screening in ages 25–49 and 5-yearly in ages 50–64; Northern Ireland 5-yearly in ages 20–64; Scotland 3-yearly in ages 20–60; and Wales 3-yearly in ages 20–64 years.

3. Results

3.1. Recommended age groups and screening intervals

Table 1 shows the screening policies in the EU member states. Cytology is largely the recommended primary screening test. Screening usually starts at an age between 20 and 30 years and stops at age 60 to 70. Austria, Luxembourg, Slovak Republic and Spain responded that they start screening at ages below 20 in all or some programmes. The activity was reported as non-population-based in these countries and it is likely that a similar screening activity, though not reported in detail, was also taking place in some other countries in the presence of population-based programmes.

Four countries (Estonia, Finland, The Netherlands and Romania) recommend a uniform 5-year interval for those screened negative. This results in approximately six to nine invitations during a lifetime, depending on the age of starting and stopping screening activities. In fourteen countries 3-yearly or a combination of 3- and 5-yearly intervals were recommended. The lifetime number of tests is then considerably higher, approximately 12–17. In nine countries the interval was less than 3 years or it was not specified.

The evident large variation in the lifetime number of screening tests between countries mainly reflects the opportunistic screening policy in several member states (for example, in Austria, Bulgaria, Cyprus, Czech Republic, Germany, Luxembourg, Malta, Slovak Republic). Recommendations in these countries usually permit a 1-year interval between negative tests. In several other countries with spontaneous screening the lifetime number of tests may have been underestimated, because of concurrent spontaneous screening activity.

3.2. Screening registration, evaluation and monitoring

Table 2 shows the available information on registration, monitoring and evaluation of cervical cancer screening. According to the data collected, in 15 out of the 27 member states, regular screening registration systems have been developed or are being developed, either nationally or regionally. Regular monitoring tables are routinely published in eight countries and they are under development in several other regions or countries. Planning or decisions to establish screening registration have also been forthcoming in several member states after collection of the currently reported data.

Validated regional or national cancer registration systems are already operating in 22 member states. Screening registry data, if existing, could in principle be linkable to cancer registries in most cases, providing a basis for comprehensive quality assurance and evaluation.

3.3. Screening volume and coverage

Table 3 shows the estimated numbers of women invited to screening and actually screened with respect to the number of women in the target population, as well as overall volume and average capacity compared with the policy recommended by the EU. The information was provided mainly by the national authorities in the second survey, and the table includes only those countries which reported numbers of screened women. Reported values are in most cases for the entire nation. The screening capacity is satisfactory in most member states and there is over-capacity in several of them. Nevertheless, in some countries the overall volume is still far from the level which would permit screening of the entire target population.

Invitational and screening coverage estimates were assessed from screening registers. Table 4 shows these data obtained by the expert network. Screening data were also reported for Estonia, Hungary and Poland, but were not included in the table, due to substantial numbers of smears performed outside the programme and not included in the register. Values refer to the target population of the respective areas. Therefore, denominators can differ from those in Table 3 that are nationwide in some cases. Invitational coverage approached 100% in Finland and England. Invitational coverage was low in some countries because only women who were not spontaneously screened were invited.

Coverage of the smear test was below 80% of the target population in all programmes, with the reported range from 10% to 79%. The documented smear test coverage was 70% or more in the programmes in five regions (Alsace, France, England, Finland, The Netherlands and Sweden). The estimates are not completely comparable, due to variations in the screening interval and inclusion of tests performed in opportunistic practice.

4. Discussion

The EU currently recommends that cancer screening should only be offered in population-based organised programmes with quality assurance at all levels.[13] The current study indicates that although a population-based policy for screening has been adopted by several EU member states, key elements of the comprehensive recommendations on programme implementation have yet to be fulfilled by many European countries.

The present study has been completed approximately 9 years after publication of a previous Special Issue of the *European Journal of Cancer,* in which the status of cervical cancer screening programmes in the EU15 was reported, and approximately 5 years after a similar study on screening policies published elsewhere.[27,28] Despite discernible progress in implementing organised, population-based cervical cancer screening in recent years, the extent to which the policies recommended by the Council of the EU have been adopted still leaves room for substantial improvement.

The most severe inadequacy relates to the continued unavailability of population-based, systematically organised screening programmes to women who may benefit from screening. There are also shortcomings in the registration, monitoring and evaluation required for systematic quality assurance and implementation of fail-safe mechanisms. In some member states, excessive numbers of smears are recommended in a lifetime due to short screening intervals and offering screening to young women. Neither of these policies are in agreement with the current edition of the European Guidelines for quality assurance in cervical cancer screening which recommend an age range beginning at

Table 2 – Monitoring of cervical cancer screening in the 27 European Union member states.

Country	Screening registration								Cancer registration	
	Screening registry available	Regular monitoring tables		Other data available	Available items included in reports				Available	Linkable with screening register
		Published	Pilot or developing		Invitations sent	Screening tests taken	Screening test results	Histology		
Austria	No	No		Yes	No	Yes	No	No	National	
Belgium	No	No		Yes	No	Yes	Yes	No	Regional	
Bulgaria	No	No		Yes	No	No	No	No	National	
Cyprus	No	No		No	No	No	No	No		
Czech Republic	No	No		Yes	No	Yes	No	No	National	
Denmark	National, under development	No	Yes	Yes	No	Yes	Yes	Yes	National	Yes
Estonia	National, under development	Yes		Yes	Yes	Yes	Yes	Yes	National	Yes
Finland	National	Yes		Yes	Yes	Yes	Yes	Yes	National	Yes
France	Local/regional, under development	No	Yes	Yes	No	Yes	Yes	Yes	Local/regional	Yes
Germany	No	No		Yes	No	Yes	Yes	Yes	Regional	
Greece	No	No		Yes	No	No	No	No	National	
Hungary	National	No		Yes	Yes	No	No	No		
Ireland	Regional, under development	No	Yes	Yes	Yes	Yes	Yes	Yes	National	Yes
Italy	Regional, under development	Yes		Yes	Yes	Yes	Yes	Yes	Regional	Yes
Latvia	No	No		Yes	No	No	No	No	National	
Lithuania	Yes, under development	No		Yes	No	Yes	Yes	Yes	National	
Luxembourg	No	Yes		Yes	Yes	Yes	Yes	No		
Malta	No	No		Yes	No	Yes	No	No	National	
Netherlands	National	Yes		Yes	No	Yes	Yes	Yes	National	Yes
Poland	Local; National under development	No	Yes	Yes	Yes	Yes	Yes	Yes	Local	Yes
Portugal	Regional, under development	No		Yes	No	No	No	No	Regional	Yes
Romania	Regional, under development	No	Yes	Yes	No	Yes	Yes	Yes		
Slovak Republic	No	No		Yes	No	No	No	No	National	
Slovenia	National	Yes		Yes	Yes	Yes	Yes	Yes	National	Yes
Spain	No	No		Yes	No	No	No	No	Regional	
Sweden	Regional, under development	Yes		Yes	No	Yes	Yes	Developing	National	Yes
UK	National	Yes		Yes	Yes	Yes	Yes	Yes	Regional	Yes

Source: EUNICE work group on screening registration and monitoring of cervical cancer screening; European Commission (DG SANCO); IARC (ECN project, see Methods); and von Karsa et al.[25]

Table 3 – Annual volume and capacity of cervical cancer screening in the EU – nationwide or regional estimates for 17 member states.

Country or region	Age-eligible national or regional population			Screening programme				Non-programme/all tests		
				Personally invited per year		Screened per year				
	Eligible age (years)	Women (×1000)	Screening interval (years)	Women (×1000)	% of Target population assuming the scheduled interval	Women (×1000)	% of Invited	Non-programme tests (×1000)	All tests (×1000)	Capacity (%) assuming the scheduled interval[a]
Bulgaria	31–65	1890	2	–	–	246	–	–	246	39
Denmark	23–59[b]	1310[b]	3[b]	–	–	300	–	–	451	103
Estonia	30–59	290	5	30	52	6	20	70	76	131
Finland	(25)30–60(65)	1290	5	270	105	190	70	–	460[c]	178
France	(20)25–65	16,300	3	–	–	4684[d]	–	–	4684[d]	90
Germany	20+	34,100	1	–	–	15,800	–	6000	21,800	192
Hungary	25–65	2950	3	690	70	45	7	960	1005	102
Ireland, regional	25–60	90	3 & 5	6	27	20	–	–	20	89[e]
Italy	25–64	16,500	3	2900	53	1120	39	4880	6000	109
Luxembourg	15+	200	1	–	–	230	–	–	230	345
Netherlands	30–60	3670	5	750	102	491	65	260	788	107
Poland	25–59	9740	3	–	–	370	–	–	370	11
Portugal except regional	25–64	2510	3	–	–	–	–	266	266	32
Portugal, regional	25–64	480	3	30	19	100	–	41	141	88
Romania	25–65	6080	5	–	–	8	–	28	36	3
Slovak Republic	18+	2180	1	–	–	–	–	679	679	93
Slovenia	20–64	630	3	90	43	200	–	–	200	95
Sweden	23–60	2240	3 & 5	–	–	390	–	315	705	126
UK[f]	(20)25–(60)64	14,970	3 & 5	4370	107	3400	78	634	4032	108

Source (unless otherwise specified): European Commission (DG SANCO); IARC (EUNICE and ECN projects, see Methods); Karsa et al.[25] and EUNICE work group on registration and monitoring of cervical cancer screening. Member states not shown, and other missing values (blanks) not shown for countries or columns for which data was not available to the authors.

a Estimated using the following equation: (number of tests × screening interval)/number of women in the target population. For Bulgaria, Germany, Luxembourg the capacity was estimated for screening once per 3 years and for Ireland, Sweden and UK once per 4 years. The capacity estimate within organised screening does not consider preferred screening attendance.

b Calculated for screening policy before 2007.

c *Reference*: Monto and Nieminen.[44]

d Number of smears with a re-imbursement (Ref. [45]).

e Does not include tests taken outside the programme, because the estimated number of all tests is not available.

f Excluding data for Scotland.

Table 4 – Coverage by invitation and by screening test of cervical cancer screening programmes in the EU – nationwide or regional estimates from screening registers from 12 member states, reported by the EUNICE working group.

Country or region	Resident women ×1000) [in target age group] (in years)	Screening interval (years)	Coverage by invitation (%)	Coverage by screening test (%)[a]	Comments on screening coverage
Denmark	1310 [23–59]	3	Not available	69	Target age range applicable in year of available data: 2006
Finland	1290 [30–60]	5	98	>70	70% Based on smears taken subsequent to invitation of targeted age groups, including 25–29 and 61–65 years in some regions. Questionnaire surveys suggest over 90% based on all smears
France, Alsace	483 [25–65]	3	33[b]	71	
Ireland South-Western region	89 [25–60]	5	68[c]	62	66% in Eligible target population
Italy active regional programmes	11,363 [25–64]	3	76	>59	Based on conservative estimate of non-programme smears, which account for at least one-half of all smears
Lithuania	750 [30–60]	3	68[d]	53	39% if only programme smears are considered
Netherlands	3670 [30–60]	5	Not available	77	
Portugal Central region	480 [25–64]	3	Not available	58	62% within the eligible target population
Romania Cluj region	355 [25–65]	5	Not available	10	
Slovenia	630 [20–64]	3	19[b]	68	
Sweden	2240 [23–60]	3 or 5	Not available	73	Overall coverage based on 3- or 5-yearly interval depending on target age group
England	13,600 [25–64]	3 or 5	Not available	74[e]	Estimated for 5-year interval; 79% in eligible target population

a Estimate based on smears taken inside or outside the programme for any reason.
b Invited only the women who had not taken the test within the recommended screening interval.
c With regionally variable invitational modes (e.g. invited all women in some regions and women without a recent smear in some regions).
d Invitation includes mainly informing women, the invitation system is decentralised.
e Invited all eligible women excluding those who have 'opted out'.

20–30 years and extending to 60–65 years, with a 3- or 5-year screening interval.[15] As pointed out elsewhere, adopting the recommended age ranges for cervical cancer screening in the respective programmes could avoid a considerable volume of unnecessary screening examinations. This, in turn, could improve the balance between harm and benefit, reduce the expenditure in human and financial resources, and increase the cost-effectiveness of screening.[25,26]

The disadvantages of cancer screening include psychosocial consequences among women screened positive or treated for cancer precursors, complications and risk of pre-term delivery among women treated for precursors, and also false reassurance or a delayed investigation or treatment among women with false negative test results or with non-compliance to confirmation and treatment.[11,29,30] Quality-of-life and potential adverse aspects should be investigated more thoroughly than done thus far and they should be taken into account when planning for screening policies. These issues are all the more relevant when considering that evidence on the validity of new test methods such as testing for Human Papillomaviruses (HPV) is accumulating, also in primary screening. For primary HPV screening, an organised approach to programme implementation including proper age group definitions and long screening intervals will be even more essential than for cytological screening.[15,22]

Incidence and mortality rates from cervical cancer can be reduced by up to 80% through well-organised cytological screening.[1,2] In the majority of European regions and countries, the age-adjusted historical decrease in the trends of cervical cancer are smaller, typically 40–70%.[2,11,18,31,32] There are also countries where no substantial decrease in the cervical cancer burden has occurred yet or where the rates are substantially increasing. There are no good historical data on screening intensity and quality or on differences in the background risk factors thereby making it difficult to assess the impact of screening in the trends. Substantial additional decreases in cervical cancer rates are still possible through the introduction of organised screening throughout the EU.

According to internationally recognised recommendations, screening with intervals from 3 to 5 years is acceptable among women with normal findings in cytological screening, and a shorter interval should be discouraged.[2,15] The duration of a pre-cancerous phase is usually quite long, averaging 10–12 years if progressing to cervical cancer. Within the above

recommended limits there is no major difference in programme effectiveness.[1,2,11] There is evidence of a substantial historical decrease in cervical cancer burden in countries with a 5-year interval recommended for screening and a high proportion of women actually tested.[33–36]

Concerning countries with opportunistic screening only, annual test coverage has been reported between 30% and 50% indicating a high level of over-use of services.[8,9,19,20,37–40] The proportion of underserved eligible women has been reported at 24% in Austria (women aged 20 to 69 years reported never to have had a smear in their lifetime), 18–30% in Malta (women aged 25–44 and 45–64 years, respectively, who never received a smear test), and 33% in Belgium (women of targeted age who had not had a smear during the previous 5-year period). In Belgium, which is lacking an organised, population-based screening programme, smear capacity is sufficient to cover more than 100% of the target population over the time span of a 3-year screening interval.[39] Our study suggests similar patterns of inefficient, non-organised screening activity in many affluent countries.

All of the new member states of the EU (Bulgaria, Cyprus, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Romania, Slovakia and Slovenia) have historically been without an organised screening programme. Several of these countries have a very high current burden of cervical cancer. Some of these countries have in recent years already started nationwide organised programmes (Estonia, Hungary, Poland and Slovenia), one country (Romania) responded as having started a pilot programme, and several other countries are planning for the activity.[20,23] In most instances a rather large number of screens per lifetime have already been recommended in piloting and early implementation phases. This, in turn, reflects financially and technically demanding programmes. One problem in such a policy seems to be that the actual number of tests taken in the organised programme, as well as the coverage, has remained low. In some of these countries the current capacity of the screening test also seems low (e.g. in Romania and Poland), whereas large-scale, non-population-based screening activities have often been on-going (Estonia, Hungary, Slovakia and the Czech Republic). The validity of the current diagnostic activity should be investigated further in these countries using register linkage studies.

Collaboration between member states, along with coordination and planning of capacity-building, education, training and communication among women, medical professionals and authorities is required to overcome the barriers to successful implementation of cervical cancer screening programmes. An essential recommendation for the healthcare systems in new EU member states is to plan and test the feasibility of population-based screening programmes in the initial phase of quality-controlled programme implementation. Given limited screening resources, programmes may be started with rather few age groups, provided that high coverage is being prioritised.[11] There is also a need to prioritise across potential screening and prevention programmes for various cancer sites, taking into account adequately evaluated cost-effectiveness and decision-making analyses. Pilot and demonstration studies should be subsequently started on a limited scale, in order to demonstrate that the programme works well enough in the respective context.[25] Quality-controlled rollout towards national implementation can take place gradually, keeping pace with appropriate development of professional and organisational training and infrastructure including programme managerial capacity. It is also important to assess in these countries whether screening efficacy can be improved by applying new technologies.

Information systems for organised screening are rapidly evolving. The EU can provide essential support by enhancing legislative frameworks in order to build-up these systems. Register-based evaluation and monitoring systems need to be established whenever screening tests are in use, irrespective of the programme type. Such systems should be an integral part of the accreditation and certification schemes and should include all elemental requirements as defined by the European quality assurance guidelines.[25] The same rigorous standards should be applied to monitoring and evaluating of existing programmes, or introduction of new screening or diagnostic techniques or other options for cervical cancer prevention.

The results of the presently reported surveys are consistent with recent resolutions of the European Parliament and conclusions of the Council of the EU adopted under the recent Slovenian EU Presidency.[41,42] These documents have emphasised the importance of further efforts to implement the Council Recommendation on cancer screening in the expanded EU. A recent report of the European Commission was based in part on data collected in the presently reported surveys.[43] The European Commission also emphasises the need for greater efforts to implement or improve population-based screening programmes. Substantial added value may be expected from support for such efforts.

In conclusion, despite the discernible, laudable efforts, the recommendations of the Council of the EU on cancer screening are not yet fulfilled in the EU. There are large variations in cervical cancer screening policies and in the organisation of existing programmes. In many member states, screening policies and registration and monitoring essential to quality assurance and fail-safe mechanisms throughout the entire screening process are still in need of substantial improvement. Decision-makers and health service providers should consider stronger measures or incentives than those adopted with current recommendations in order to improve successful cervical cancer control in Europe.

Conflict of interest statement

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Contributors

Helene Wiener, Austria; Marc Arbyn, Belgium; Zdravka Valerianova, Bulgaria; Myrto Azina-Chronides, Cyprus; Elsebeth Lynge, Denmark; Aunis Aasmaa and Piret Veerus, Estonia; Ahti Anttila, Laura Kotaniemi-Talonen and Nea Malila, Finland; Muriel Fender and Rosemary Ancelle-Park, France; Nikolaus Becker, Germany; Laszlo Vass, Lajos Döbrössy and Szilvia Madai, Hungary; Marian O'Reilly, Ireland; Guglielmo Ronco, Italy; Ilze Viberga, Latvia; Astrid Scharpantgen, Luxembourg; Juozas Kurtinaitis, Lithuania; Matejka Rebolj, Inge de Kok and Marjolein van Ballegooijen, The Netherlands; Arkadius Chil, Poland; Antonio Morais, Portugal; Florian Nicula and Ofelia Suteu, Romania; Ladislav Masak, Slovakia; Maja Zakelj, Slovenia; Silvia de Sanjose, Spain; Bengt Andrae and Pär Sparen, Sweden; Julietta Patnick and Lesz Lancucki, England, UK; Lawrence von Karsa, Max Parkin, Paola Pisani, Eva Steliarova-Foucher, Sandrine Montigny, Christian Hermann, Catherine Sauvaget, Lydia Voti and Philippe Autier, IARC, Lyon, France.

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Process performance of cervical screening programmes in Europe

Guglielmo Ronco[a,*], *Marjolein van Ballegooijen*[b], *Nikolaus Becker*[c], *Arkadiusz Chil*[d], *Muriel Fender*[e], *Pamela Giubilato*[a], *Juozas Kurtinaitis*[f,†], *Lesz Lancucki*[g], *Elsebeth Lynge*[h], *Antonio Morais*[i], *Marian O'Reilly*[j], *Pär Sparen*[k], *Ofelia Suteu*[l], *Matejka Rebolj*[b], *Piret Veerus*[m], *Maja Primic Žakelj*[n], *Ahti Anttila*[o]

[a]*Unit of Cancer Epidemiology, Centre for Cancer Prevention (CPO), Via San Francesco da Paola 31, 1023 Torino, Italy*
[b]*Department of Public Health, Erasmus MC Medical Centre, Rotterdam, The Netherlands*
[c]*Division of Cancer Epidemiology, German Cancer Research Centre, Heidelberg, Germany*
[d]*Regional Coordinating Office for Cervical Cancer Screening, Holycross Cancer Centre, Kielce, Poland*
[e]*Association EVE, Strasbourg, France*
[f]*Institute of Oncology, Vilnius University, Lithuania*
[g]*NHS Cancer Screening Programmes, Sheffield, UK*
[h]*Institute of Public Health, University of Copenhagen, Denmark*
[i]*Oncology Committee Coordination, Regional Health Administration of Central Portugal, Coimbra, Portugal*
[j]*CervicalCheck, The National Cervical Screening Programme, Limerick, Ireland*
[k]*Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden*
[l]*"Prof. Dr. I. Chiricuţă" Cancer Institute, Cluj-Napoca, Romania*
[m]*Department of Epidemiology and Biostatistics, National Institute for Health Development, Tallinn, Estonia*
[n]*Epidemiology and Cancer Registry, Institute of Oncology, Ljubljana, Slovenia*
[o]*Finnish Cancer Registry, Helsinki, Finland*

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ABSTRACT

Standardised tables of aggregated data were collected from 15 European national or regional cervical screening programmes and key performance indicators computed as reported in European Union (EU) Guidelines, 2nd edition.

Cytological results varied widely between countries both for the total proportion of abnormal tests (from 1.2% in Germany (Mecklenburg-Vorpommern) to 11.7% in Ireland-Midwest Region) and for their distribution by grade. Referral rates for repeat cytology (ranging from 2.9% of screened women in the Netherlands to 16.6% in Slovenia) or for colposcopy (ranging from 0.8% in Finland to 4.4% in Romania-Cluj) and the Positive Predictive Value (PPV) of colposcopic attendance (ranging from 8% in Romania-Cluj to 52% in Lithuania) were strongly influenced by management protocols, in particular for atypical squamous cells of undetermined significance (ASCUS) and low-grade squamous intraepithelial lesion (LSIL) cytology. However, cytology-specific PPV also showed remarkable variability. The detection rate of CIN2+ histology ranged from <0.1% of screened women in Poland to >1% in England and Denmark. Low attendance for colposcopy after referral was observed in some east-European countries.

These comparisons may be useful for improving the performance of cervical screening in general and more so if new screening technologies and vaccination for Human Papillomavi-

* *Corresponding author:* Tel.: +39 0116333850; fax: +39 016333861.
E-mail address: guglielmo.ronco@cpo.it (G. Ronco).
† Deceased.
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rus are introduced. Overall, quality was better in countries that have operated organised programmes for a longer time, plausibly as a result of long-lasting monitoring and quality assurance activities. Therefore, the availability of these data, the first comparing European countries, and the increased number of countries that can provide such data (only five in 2004) represent progress. Nevertheless, there is a clear need to standardise the cytological and histological classifications used in screening, as well as data registration systems across Europe.

1. Introduction

Cervical cancer screening is a complex activity involving different coordinated steps. It also involves a vulnerable balance between positive and negative effects and costs. These include anxiety and costs for unneeded diagnostic work-up and treatments, possible obstetric complications of treatment, and false reassurance by false negative tests. Direct evaluation of the impact of screening activities in terms of their final outcome – reduction of the incidence of and mortality from cervical cancer – is needed, such as auditing of the screening histories of women who developed cancer.[1] However, a continuous, ongoing evaluation of whether a programme is achieving its intermediate objectives is relevant in order to improve quality and reduce undesired effects, mainly those due to too high a referral for further actions. Monitoring screening process performance and making comparisons within countries provides feedback to help identify problems and is recommended by the recently published European Guidelines for Quality Assurance in Cervical Cancer Screening.[1,2]

Statistics for cervical screening have been regularly produced by a few European countries including England from 1989[3] (which also developed a set of indicators[4]), Scotland[5] from 1999, Wales from 2000,[6] Italy from 2002,[7] Slovenia from 2003,[8] the Netherlands from 2004[9] and Finland from 2005.[10] Performance data has also been published by the Estonian pilot[11] and French regional Alsace[12] programmes, as well as the distribution of cytology results for the Flemish region of Belgium.[13]

Comparing performance parameters between European screening programmes can provide important knowledge in order to improve their quality. However, the format of published data differs and comparisons are difficult. Some parameters from a few European countries were previously reported but comparisons could only be made between the recommended policies.[14,15] The new edition of the European Guidelines for Quality Assurance in Cervical Cancer Screening provides a set of standard tables[1] and parameters[2] for screening monitoring. In this paper we present the results of the EUNICE project, supported by the European Commission. In this framework we aimed at providing data as comparable as possible and to evaluate the applicability of the proposed tables and parameters.

2. Materials and methods

The members of EUNICE submitted tables of aggregated data based on those recommended by the European Guidelines for Quality Assurance in Cervical Cancer Screening.[1]

National data were reported whenever possible. If national data were not available we collected data for specific regions. The latter were, as a rule, from one single region in each country, except in Italy where data refer to organised programmes covering some 70% of the female population (further denoted as 'Italy – organised programmes'). Tables were completed on the basis of routine screening registration systems, except for the German Mecklenburg-Vorpommern region where they were based on cytology monitoring activity ([16] and Büttner HH, personal communication to NB).

Tables were checked for internal consistency and providers were contacted for clarifications. A single centre in Italy was responsible for computing some of the 'key performance indicators' reported by the European guidelines.[2] With the exceptions specified below, the instructions reported in the guidelines themselves were followed. In Italy not all data were available for all local screening programmes. Therefore, for each indicator the appropriate denominator, based on the programmes that had provided data for the numerator, was used. In Finland, 16,294 women who had had Human Papillomavirus (HPV) testing as primary screening were excluded.

Distribution of cytology results – for most countries cytological tests were the unit of information and all cytological results for a woman were considered. However, in England, Estonia, Finland, Germany, the Netherlands and Poland, women were the units of information and the worst result in case of repeated testing was considered. Smears taken during colposcopies were not considered. Usually we obtained data according to the Bethesda 2001 classification.[17] Abnormal results (i.e. $\geqslant$atypical squamous cells of undetermined significance (ASCUS)) were grouped as: (1) malignant cells, (2) high-grade squamous intraepithelial lesions (HSIL), (3) low-grade squamous intraepithelial lesions (LSIL) and (4) ASCUS + ASC-H + AGC. Here, AGC = atypical glandular cells and ASC-H = atypical squamous cells where high grade lesions cannot be excluded. Cytology results were provided already converted to the Bethesda system from England and Ireland (where they were originally reported according to the UK system) and from Denmark (where SNOMED codes are registered).

Finland, Germany and the Netherlands provided cytology reported using different (modified Pap) classifications, pregrouped as follows:

- The Netherlands (CISOE-A classification): Unsatisfactory, Pap1 (translated as Normal), Pap2/3a1 (which corresponds

to ASCUS, ASC-H, AGC and LSIL but was translated as LSIL for the purpose of this work) and ⩾Pap3a2 (translated as HSIL).[18]
- Finland (Papanicolaou Classification): Pap 1 (translated as Normal), Pap2 (which corresponds to ASCUS, ASC-H, AGC and LSIL but was translated as ASCUS for the purpose of this work), Pap3/4 (translated as HSIL).
- Germany, Mecklenburg-Vorpommern (Munich classification[19]): Group I/II (translated as Normal), Groups III and IIID (together translated as LSIL), Group IVa/IVb (translated as HSIL), Group V (translated as Malignant).

Referral rate for repeat cytology was computed as the number of screened women referred for repeat cytology at a shorter interval than routine in a given time period divided by the number of women screened in the same period.

In most countries the actual recommendation was not registered. Therefore, the number of women who should have repeated cytology according to local guidelines was the numerator. The actual recommendation was considered in Italy and England. Slovenia reported the number of women who were either registered as referred to repeat or should have repeated according to local guidelines. This was done because of the incompleteness of registration of recommendations.

Referral rate for colposcopy was computed as the number of screened women referred to colposcopy in a given time period divided by the number of women screened in the same period. We considered the actual recommendation in Italy, Portugal and Finland. Slovenia considered both the actual recommendation and the guidelines, similar to the criterion used for cytology repeat analysis. In the other countries the number of women who, given their cytology result, should have been referred to colposcopy according to local guidelines was noted. In Finland some referrals following borderline cytology may have been recommended outside the organised programme and may not have been recorded in the present data. Results were stratified by the last cytological diagnosis before referral.

The positive predictive value (PPV) for Cervical Intraepithelial Neoplasia grade 2 or more severe lesion (CIN2+) was calculated as the number of screened women with CIN2+ histology divided by the number of screened women who had attended for colposcopy. In Finland, Slovenia and Romania (Cluj county) the denominator was the number of women referred for colposcopy. In Denmark, Germany (Mecklenburg-Vorpommern) and the Netherlands the denominator was the number of women who should have had colposcopy according to the local protocol. In Lithuania only an audit sample of women who had both cytology and histology was available.

The *detection rate (DR) of CIN2* or more was calculated as the number of screened women with CIN2+ histology divided by the number of screened women. As the detection rate (DR) depends on the interval between screening rounds, for countries with a 3-year interval a rough estimate of the detection rates with a 5-year interval was obtained by multiplying the observed value by 5/3. This estimate was not calculated for Germany because of the high variability of the personal screening interval. In England a 5-year interval was assumed.

3. Results

Data from 15 countries could be obtained: national data from nine countries and regional cervical screening programme data from the other six countries. Details on the organisation and screening policies of the participating programmes are described in this special issue for each country[20] and in a summary report[21] which also reports coverage data. However, some information relevant for data interpretation, together with the list of parameters available for each country, is summarised in Table 1.

The proportion of women with cytology ⩾ASCUS (Table 2 and Fig. 1) was below 4% in Mecklenburg-Vorpommern (lowest at 1.2%), the Netherlands, Poland, and in Italian organised programmes while it was over 6% in Finland, England, Slovenia and Ireland-Midwest region (highest at 11.7%). Also, the distribution between the different grades of abnormality varied remarkably between countries. For example, women with HSIL represented less than 10% of all abnormal cytology in France-Alsace and in Italian organised programmes versus more than 25% in the Netherlands and in Ireland-Midwest region. However, there was not a clear relation between this distribution and the total percentage of abnormal cytology. In addition, the proportion of all screened women that was classified as HSIL ranged from values below 0.3% in Mecklenburg-Vorpommern, in Italian organised programmes and in France-Alsace to values above 1% in England, Slovenia, Denmark and Ireland-Midwest region (highest at 3.29%).

The proportion of women referred for repeat cytology (Fig. 2) varied from 2.9% in the Netherlands and 3.1% in France-Alsace to 16.6% in Slovenia. When considering the reasons for these referrals:

- The proportion of screened women advised to repeat cytology because of an unsatisfactory primary smear result was below 1% in Slovenia, France-Alsace and in the Netherlands while it reached 8.0% in England. The referral for a repeat cytology because of an unsatisfactory test could not be reported in Finland but is estimated to be very low.
- The proportion of screened women advised to have a repeat cytology because of a LSIL or ASC result was only 0.6% in Italian organised programmes and 1.1% in Poland while it was 5.9% in Ireland-Midwest Region and 7.9% in Slovenia.
- No woman was advised to repeat cytology for other reasons in England and the Netherlands while the 'other' component was very large in some countries (over 8% of screened women in Poland and Slovenia). These cases were not registered in France-Alsace.

The referral rate for colposcopy (Fig. 3) was below 1.5 % in Finland, Poland and the Netherlands while it was close to 4% in Ireland-Midwest Region and in Romania-Cluj. The referral rate because of HSIL or more severe cytology was below 0.5% in Italy, France-Alsace and Poland, between 0.5% and 1% in Portugal, Finland, the Netherlands, Romania-Cluj and England and over 1% in Slovenia and Ireland-Midwest region. Women with cytology less severe than HSIL represented only

Table 1 – Available data and selected features of the screening programmes included in the analysis.

Country	N screened women[a]	Period considered	Prevalence/incidence screening round	Target age[b]	Screening interval form (years)	Management of LSIL and ASCUS	Cervical cancer incidence[c]	Available parameters					
								Cytology distribution	Referral to repeat cytology	Referral to colposcopy	Compliance to colposcopy	PPV of colposcopy	Detection rate of CIN2+
Denmark	417,602	2006	Incidence	23–59	3	Repeat cytology or Colposcopy[e]	15.2					X	X
England	3,638,900	2004–2005	Incidence		3 or 5[d]	Repeat cytology	9.8	X	X	X	X	X	X
Estonia	6,249	2006	Prevalence	30–59	5	Colposcopy	20.3	X					X
Finland	176,507	2005	Incidence	30–60	5	Repeat cytology	4.9	X	X	X	X	X	X
Franlce Alsace	178,170	2004	Incidence	25–65	3	Colposcopy or repeat cytology or HPV triage[g]	11.7	X	X	X	X	X	X
Germany Mecklenburg-Vorpommern	378,291	2003–2005	Incidence	20+	1	Repeat cytology[h]	12.3	X				X	X
Ireland-Midwest Region	20,278	2006	Incidence	25–60	5	Repeat cytology	8.6	X	X	X	X	X	X
Italy Organised programmes	1,299,932	2006	Mixed, majority incidence		3	Mostly colposcopy	9.5	X	X	X	X	X	X
Lithuania	84,974	2006	Prevalence	30–60	3	Repeat cytology	20.1	X				X	X
The Netherlands	426,108	1999 and follow-up	Incidence	30–60	5	Repeat cytology	8.0		X	X	(X)[f]	X	X
Poland	682,805	2007	Prevalence	25–59	3	Mostly Colposcopy	19.2		X	X	X	X	X
Portugal, Central Region	110,516	2007	Prevalence	25–64	3	Repeat cytology, HPV triage	17.2		X	X			
Romania, Cluj County	7759	2005	Mainly Prevalence	25–65	5	Repeat cytology	24.5		X	X		X	X
Slovenia	205,036	2006	Prevalence	20–64	3 yrs (1 after first smear)	Repeat cytology	19.6		X	X		X	X
Sweden		2002	Prevalence	23–60	3 for age <50, 5 over 50	Repeat cytology	9.7						

a These numbers were used as denominators for computing the referral rate to cytology repeat (Fig. 2), referral rate to colposcopy (Fig. 3) and detection rate of CIN2+ (Fig. 4) except for Italy where the number of programmes that provided relevant data changes for different parameters (denominator reported in each figure).

b Most common, see Ref. [20] for details.

c Estimated national European age-standardised cervical cancer incidence rate per 100,000 women year in 2004. Source: Ref. [38].

d In England intervals are currently of 3 years up to age 49 and of 5 years over such an age. However, at the time of data collection these changes had not yet been implemented; instead, local programmes had a 3- or 5-year interval across all ages.

e Changes by administrative area.

f A minimum estimate, based on women who had biopsy available.

g The three options were possible on judgement of the gynaecologist for ASCUS. Only either colposcopy or repeat cytology was possible for LSIL.

h The gynaecologist could choose either colposcopy or repeat cytology. However, in most cases repeat cytology was recommended at the first ASCUS/LSIL test.

Table 2 – Distribution of abnormal cytological results in screening programmes from 15 European countries.

Country	N cytological exams	Total exams[a] with non-normal cytology (⩾ASCUS)		High grade intraepithelial lesion (HSIL) or invasive			Low grade intraepithelial lesion (LSIL)			ASCUS/ASC-H/AGC		
		N	% of all cytological exams	N	% of all cytological exams	% of exams with cytology ⩾ASCUS	N	% of all cytological exams	% of exams with cytology ⩾ASCUS	N	% of all cytological exams	% of exams with cytology ⩾ASCUS
Denmark	451,083	25,547	5.7	7765	1.72	30.4	6122	1.36	24.0	11,660	2.58	45.6
England	3,638,900	240,100	6.6	44600	1.23	18.6	71800	1.97	29.9	123,700	3.40	51.5
Estonia[b]	6153	346	5.6	77	1.25	22.3	47	0.76	13.6	222	3.61	64.2
Finland[c]	176,507	11,165	6.3	1244	0.70	11.1				9921	5.62	88.9
France-Alsace	187,484	8,719	4.7	563	0.30	6.5	2503	1.34	28.7	5653	3.02	64.8
Germany Mecklenburg-Vorpommern	378,291	4,439	1.2	615	0.16	13.9	3824	1.01	86.1			
Ireland-Midwest Region	20,995	2,452	11.7	690	3.29	28.1	945	4.50	38.5	817	3.89	33.3
Italy Organised programmes	1,384,034	37,824	2.7	2996	0.22	7.9	11,109	0.77	29.4	23,719	1.71	62.7
Lithuania	145,214	6927	4.8	1621	1.12	23.4	960	0.66	13.9	4346	2.99	62.7
The Netherlands[d]	426,108	11,779	2.8	3157	0.74	26.8	8622	2.02	73.2			
Poland	682,805	16,434	2.4	1934	0.28	11.8	4482	0.66	27.3	10,018	1.47	61.0
Portugal, Central Region	110,516	5819	5.3	663	0.60	11.4	1419	1.28	24.4	3737	3.38	64.2
Romania, Cluj County[e]	39,633	2362	6.0	447	1.13	18.9	902	2.28	38.2	1013	2.56	42.9
Slovenia	228,593	23,531	10.3	3167	1.40	13.5	7919	3.5	33.7	12,445	5.4	52.9
Sweden	702 716	32,120	4.6	6928	0.99	21.6	9762	1 39	30 4	15,430	2.20	48.0

a Units are women for England, Estonia, Finland, Germany, the Netherlands and Poland (see Materials and methods).
b Result unknown for 96 women.
c The The Pap2 category that corresponds to ASCUS, ASC-H, AGC and LSIL was translated as ASCUS for the purpose of this work.
d The Pap2/a1 category, that corresponds to ASCUS, ASC-H, AGC and LSIL was translated as LSIL for the purpose of this work.
e Results of tests performed in the years 2002–5 are considered.

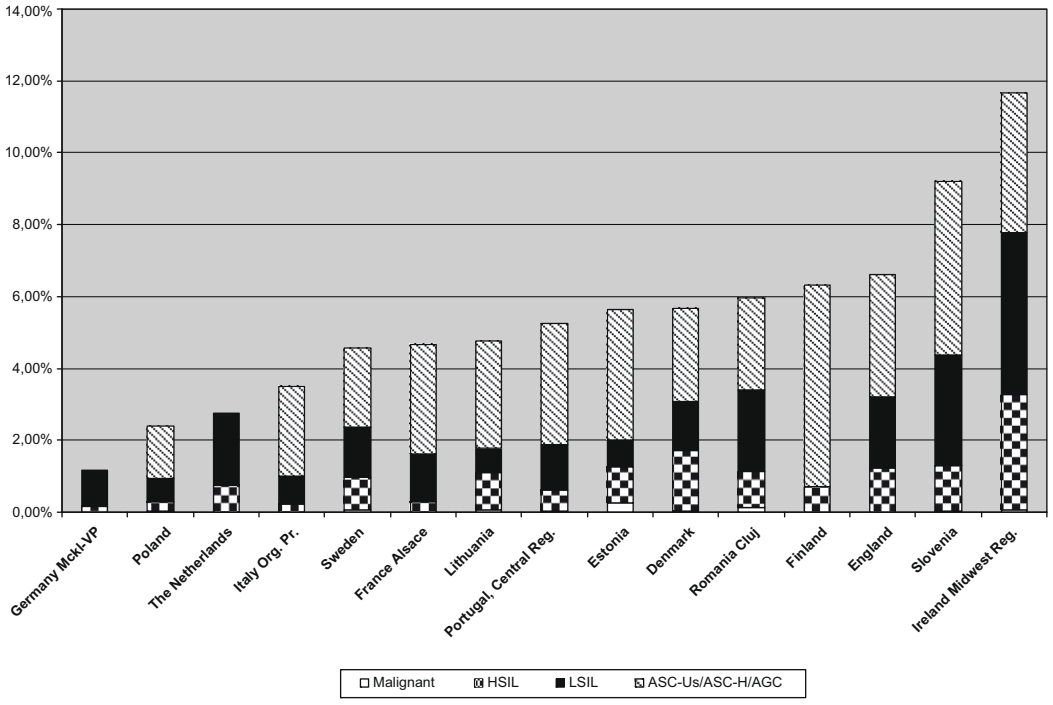
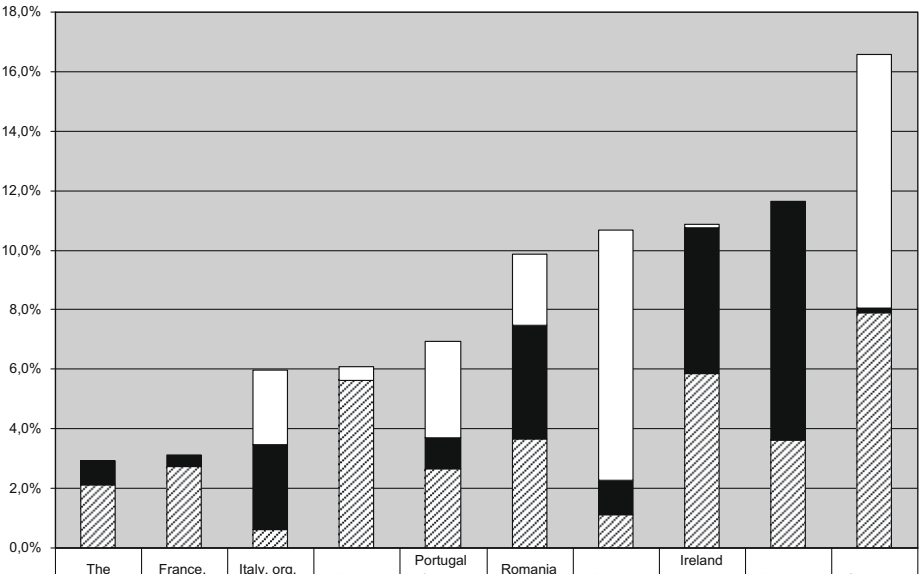


Fig. 1 – Proportion of screened women with abnormal cytology.



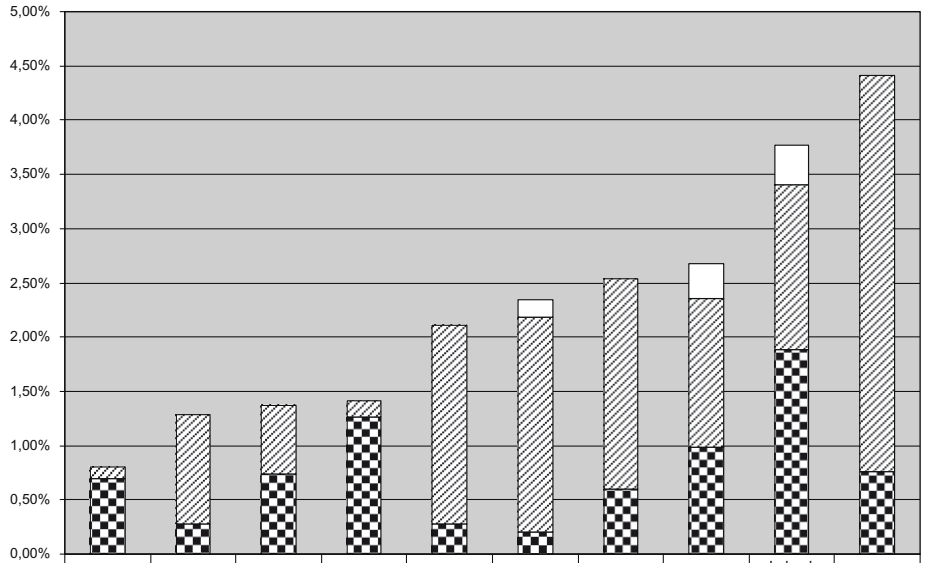
	The Netherlands	France, Alsace	Italy, org. progr.	Finland	Portugal Central Reg.	Romania Cluj	Poland	Ireland Midwest Reg.	England	Slovenia
other	0,0%	0,0%	2,5%	0,5%	3,3%	2,4%	8,4%	0,1%	0,0%	8,5%
unsatisfactory	0,8%	0,4%	2,9%		1,0%	3,8%	1,1%	4,9%	8,0%	0,2%
ASCUS/LSIL/AGC/ASC-H	2,1%	2,7%	0,6%	5,6%	2,7%	3,6%	1,1%	5,9%	3,6%	7,9%

Referrals for "other" are not registered in France-Alsace

Fig. 2 – Referral rate to repeat cytology by reason.

a small proportion of those referred to colposcopy in Slovenia (10%) and Finland (13%) while they were about half in the Netherlands (46%), Ireland (50%) and England (63%) and the large majority in Portugal-Central region (76%), Poland (78%), Romania-Cluj (83%), France-Alsace (87%) and Italy (91%).

The actual attendance to colposcopy after referral was available in only a few countries. It was over 80% in Finland (>99%), France-Alsace (84.5%), England (83.7%) and Italy (81.6%) and was 70.6% in Ireland-Midwest Region. It was at least 77% in the Netherlands and 72% in Slovenia (based on



	Finland	Poland	The Netherlands	Slovenia	France Alsace	Italy org. Prog.	Portugal Central reg.	England	Ireland Midwest Reg.	Romania Cluj
☐ Other	0,00%	0,00%	0,00%	0,00%	0,00%	0,16%	0,00%	0,32%	0,36%	0,00%
▨ ASC-US/ASC-H/AGC/LSIL	0,10%	1,00%	0,63%	0,15%	1,83%	1,98%	1,94%	1,37%	1,52%	3,65%
◧ HSIL+	0,70%	0,28%	0,74%	1,27%	0,28%	0,21%	0,60%	0,99%	1,89%	0,76%

Fig. 3 – Referral rate to colposcopy by reason.

the women with a histology report following referral). However, the registered attendance to colposcopy following referral was only 30.3% in Poland. Very low attendance was anecdotally reported, although it was impossible to measure it, in Romania-Cluj.

The overall positive predictive value (PPV) of referral to colposcopy for histologically confirmed CIN2+ varied widely between the observed programmes (Table 3), from values below 10% in Romania-Cluj to values close to 50% in the Netherlands, Slovenia and Lithuania. This overall PPV of referral to colposcopy was mainly related, with few exceptions, to the proportion of women with HSIL+ cytology among those referred to colposcopy. Variability was more reduced but still relevant when considering the specific PPV by cytology that caused the referral (Table 3).

The observed detection rate of CIN2+ histology per 1000 screened women (Fig. 4) was below 3 in Mecklenburg-Vorpommern, Finland, Poland and Italy, 3 to 4.5 in France-Alsace and Lithuania. On the other hand it was 6 to 7 in the Netherlands, Estonia and Romania-Cluj and approximately 10 in Ireland-Midwest Region, England, Slovenia and Denmark. When projecting the detection rate to 5 years, six out of 12 programmes had a DR between 4.5 and 7.5 per 1000 but outliers were still observed.

4. Discussion

Information on screening performance – either national or regional data – could be collected from 15 countries out of 27 European Union (EU) member states. Registration is however increasing: in a previous study, information on screening performance was available from only five member states.[15]

Due to the different registration systems, not all programmes could provide all the data required and there were clear differences in how the parameters were calculated for the different countries. A further difficulty was due to the use of different classifications for cytology. All classifications were converted to the Bethesda 2001 system but some classifications were only partly translatable. In addition, cytological results were received in pre-defined aggregations, which made it impossible to apply the existing tables of conversion.[22] Data required for calculating age-adjusted parameters were not available. Finally, some programmes were still at the prevalence screening phase while most of them conducted incidence screening rounds (see Table 1). As a result, great care is needed in the interpretation. On the other hand, the parameters calculated here are the most comparable produced so far.

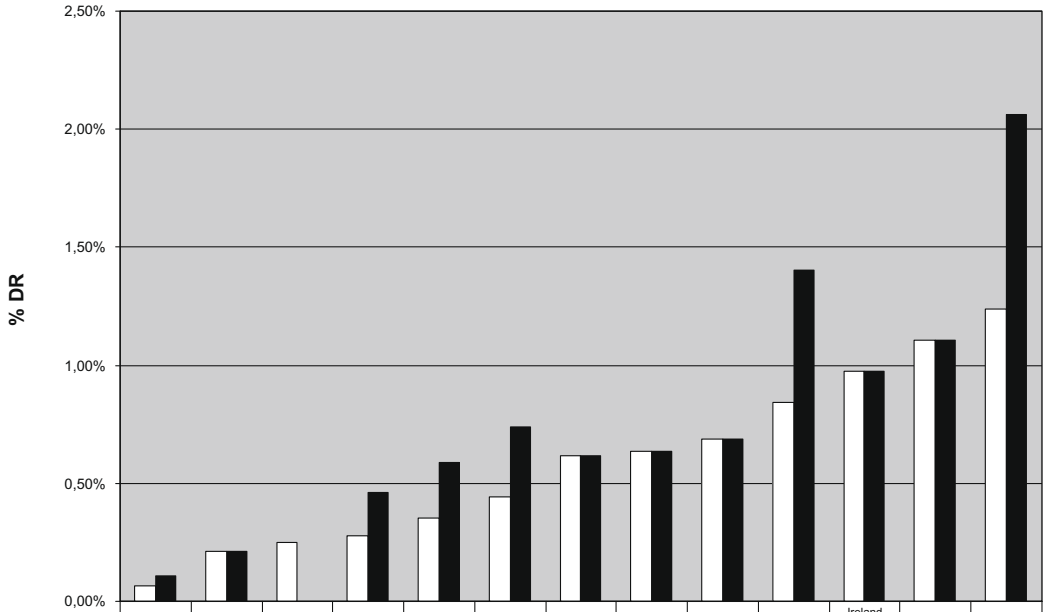
Differences in the proportion of women with abnormal cytology depend both on variations in the true frequency of abnormalities (that in turn is also affected by screening intervals and by either considering prevalence or incidence screening) and on differences in criteria for reporting cytology. The latter have as a result variability in the mix of different cytological grades among women with abnormalities. Remarkable variability in the interpretation of cytology was reported in the literature between centres in the same country, especially for lower grade abnormalities.[23–27] Additional differences between countries were previously observed in one study[26] but not in another study.[27]

Both referral rates for repeat cytology and for colposcopy were mainly determined by management protocols. Particularly, the fact that women with LSIL and ASC/AGC cytology were either referred for repeat cytology or directly for colposcopy was determinant. Women with LSIL/ASC/AGC cytology were a highly variable component of the referral rates for colposcopy and for repeat cytology and there was, in general, a balance between the two (referral for colposcopy increased

Table 3 – Positive predictive value (PPV) for CIN2 or more severe histology of referral to colposcopy and of cytology-specific PPV in different European cervical screening programmes.

Country	Reason for referral to colposcopy									
	All referrals				ASCUS, AGC, ASC-H or LSIL			HSIL+		
	With positive Histology	Denominator[a]	PPV (95% CI)	% with HSIL+ in denominator	With positive Histology	Denominator[a]	PPV (95% CI)	With positive Histology	Denominator[a]	PPV (95% CI)
Romania-Cluj	167	2197	7.6% (6.5–8.7)		ND	ND	ND	ND	ND	ND
Italy Organised programmes	3398	22414	15.2% (14.7–15.6)	19	1717	18071	9.5% (9.1–9.9)	1588	2230	71.2% (69.3–73.1)
Poland	441	2636	16.7% (15.3–18.2)	17	182	2179	8.4% (7.2–9.5)	259	457	56.7% (52.1–61.2)
France-Alsace	629	3163	19.9% (18.5–21.3)	14	304	2725	11.2% (10.0–12.3)	325	438	74.2% (70.1–78.3)
Denmark	5166	24750	20.9% (20.4–21.4)	78	1249	5531	22.6% (21.5–23.7)	3472	6063	57.3% (56.0–58.5)
Germany Mecklenburg-Vorpommern	946	4439	21.3% (20.1–22.5)	14	419	3824	11.0% (10.0–11.9)	557	615	90.6% (88.3–92.9)
Finland	374	1356	27.6% (25.2–30.0)	96	4	109	3.7% (0.1–7.2)	370	1244	29.7% (27.2–32.3)
Ireland-Midwest Region	198	540	36.7% (32.6–40.7)	62	26	207	12.6% (8.0–17.1)	171	293	58.4% (52.7–64.0)
England	40,200	95,400	42.1% (41.8–42.5)	42	9700	55,200	17.6% (17.3–17.9)	30,500	40,200	75.9% (75.5–76.3)
The Netherlands	2838	5829	48.7% (47.4–50.0)	54	483	2677	18.0% (16.6–19.5)	2355	3152	74.7% (73.2–76.2)
Slovenia	1462	2957	49.4% (47.6–51.2)	90	78	304	25.7% (20.7–30.6)	1384	2599	53.3% (51.3–55.2)
Lithuania	376	721	52.1% (48.5–55.8)	67	93	235	39.6% (33.3–45.8)	256	280	91.4% (88.1–94.7)

a See Materials and methods. The denominator is the number of women who had colposcopy (for England, France-Alsace, Ireland, Italy and Poland), who were referred to colposcopy (for Finland, Slovenia and Romania), and who should have had colposcopy according to the local protocol (for Denmark, Germany and the Netherlands). For Lithuania, data are based on an audit sample of women who had both cytology and histology.



	Poland	Finland	Germany, Mckl-VP	Italy Org. Progr.	France Alsace	Lithuania	Romania Cluj	The Netherlands	Estonia	Slovenia	Ireland Midwest Reg.	England	Denmark
□ Actual DR	0,06%	0,21%	0,25%	0,28%	0,35%	0,44%	0,61%	0,64%	0,69%	0,84%	0,98%	1,10%	1,24%
■ projected 5 years	0,11%	0,21%		0,46%	0,59%	0,74%	0,61%	0,64%	0,69%	1,40%	0,98%	1,10%	2,06%

Fig. 4 – Detection Rate of histologically confirmed CIN2 or more.

when referral to repeat cytology decreased). The overall proportion of women referred to either was quite stable, between 12% and 18% with the exception of Finland and the Netherlands, where it was below 8%.

Concerning repeat cytology, there was also a strong variability in criteria used to define a satisfactory smear. These were clearly stricter in England than in the other countries. Unfortunately, we had no data concerning the use of liquid-based cytology (LBC), which is associated with a lower proportion of unsatisfactory cytology.[28,29] In the UK, the switch to LBC has indeed resulted in a strong reduction of unsatisfactory rates. In most countries repeat cytology was also advised for other reasons, particularly so in Poland and Slovenia. These reasons include dystrophic or inflammatory changes in some Italian programmes, Slovenia and Poland.

The overall PPV of referral to colposcopy was mainly related to the cytology mix among referred women, and therefore, again, to referral criteria. Cytology-specific PPV also showed, however, variation between countries. The PPV of HSIL was low in Ireland and in Denmark where the proportion of screened women classified to have HSIL was high (which could reflect broader criteria in reporting) but also in Poland where this proportion was low. Part of this variability reflects problems in conversion of cytological classifications. This is plausibly the case for PPV of HSIL that was very high in Germany, low in Denmark and very low in Finland, where part of the Pap3 cytology included among HSIL is likely to correspond to LSIL. High values in Lithuania are plausibly due to selection, as only women who had a biopsy were considered in the denominator. Variations in PPV of LSIL/ASC/AGC cytology may partly depend on differences in the CIN2+ prevalence, as approximated by the corresponding DR (low in Germany, Italy, France-Alsace, Finland and Poland, high in Denmark and Slovenia). Another reason is that in some countries these women were directly referred to colposcopy following the first cytology result (e.g. in most Italian organised programmes). Instead, in other countries, they were referred only if this diagnosis was confirmed by a repeat cytology result. However, it is also possible that differences in criteria for reporting played a role. Indeed, the proportion of women with LSIL/ASC/AGC cytology among all those with abnormal cytology was very high in Italy, France-Alsace and Poland and PPV for the same category was low in these countries.

Detecting cytological abnormalities is clearly useless without treatment of intraepithelial lesions, based on assessment by colposcopy and biopsy. Therefore, high attendance at recommended colposcopies is crucial for screening to be effective in reducing incidence and mortality. Incomplete follow-up was shown to be the reason for a remarkable proportion of invasive cancers in some programmes.[30–34] Incompleteness of colposcopic assessment and of its registration seems to be a major problem in some east-European countries. Reasons are discussed elsewhere in this special issue.[35,20]

The DRs of histologically confirmed CIN2+ showed high variability. The DR depends on screening frequency. Indeed, most programmes with a low DR had a short recommended screening interval. However, remarkable exceptions are the low DR in Finland (5-year interval) and the high DR in Denmark and Slovenia (both with 3-year intervals). The projection to 5 years is, however, a very crude estimation that does not take into account regression of high grade lesions. The background risk is another obvious determinant of DR. For example, the population prevalence of HPV infection – the necessary cause of high grade CIN – was found to be high in England (although with heterogeneity between areas), Ireland and Denmark that also have high DRs of CIN2+.[36] Incidence of cervical cancer is reported in Table 1 for comparison, although it must be remembered that it re-

flects both the baseline risk and the effect of screening. In any case cervical cancer incidence was already high before screening in Denmark.[37] The population that participates in registered screening could also be selected differently regarding their baseline risk in different countries. DR was also expected to be higher in programmes that had just started their activity and where most women had not been screened previously. This was not always observed. Remarkably, low or intermediate DR was observed in some eastern European countries where screening had just started and where incidence and mortality from cervical cancer was high.[38,39] In Poland, Romania-Cluj and possibly in other countries the DR may have been greatly reduced by the reported low completeness of diagnostic follow-up. Unregistered opportunistic screening also possibly played a role. Indeed, the DR may have been reduced by unregistered CIN detection and treatment following opportunistic cytological tests performed between regular intervals. In fact, this is equivalent to reducing the screening interval. In Finland, when including the lesions treated outside the organised programme, the DR would be about double the observed one. The current recommendation is to include all screening tests and services in the registration systems.[1,2]

Finally, it is known from the literature that the reproducibility of interpretation of cervical histology is far from perfect, especially for CIN2.[25,40–43] Different criteria between countries could have been relevant in determining the observed differences in DR.

In conclusion, large differences in process performances were observed between European cervical cancer screening programmes. Some of these differences can have a remarkable impact on effectiveness, for example, the low attendance at recommended colposcopies observed in some east-European programmes. The observed large differences in referral rates for repeat cytology, colposcopy and in PPV have major consequences on costs, both economic and for women (e.g. loss of time and anxiety). Differences in cost-effectiveness would be even larger when cumulated over a long time period, considering that the lifetime recommended number of tests varies from seven to more than 50 in EU member states.[21] Referral rates to repeat cytology or to colposcopy are partly reciprocally balanced and result from different protocols, partly justified by different local costs and availability of colposcopy. Nevertheless, different quality in cytology interpretation and in organisation plays a relevant role. It is quite clear that the programmes that have been running for a longer period of time have better overall quality. This is plausibly the result of many years of monitoring and feedback and of quality assurance activities. The presence of a strong coordination also seems to be relevant. On the other hand, many East-European countries show problems. Most of these only started recently and have limited resources.

Reporting comparable monitoring data in EU countries is essential in order to improve quality. There is a clear need to standardise the cytological and histological classifications used in screening, as well as data registration systems across Europe. The data produced by current registration systems need to be improved and these data should be produced and compared on a regular basis. This will also help in providing reference values for the measured parameters, to be used as a benchmark. The relevance of monitoring would be even greater if HPV testing and vaccination were introduced, as discussed elsewhere in this special issue.[44,45]

Conflict of interest statement

- Guglielmo Ronco – Minor payment for participating in two internal scientific advisory meetings for GenProbe, a firm developing a test for HPV RNA. No conflict of interest since March 2008.
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The challenges of organising cervical screening programmes in the 15 old member states of the European Union

Marc Arbyn[a,*], *Matejka Rebolj*[b,c], *Inge M.C.M. De Kok*[b], *Murielle Fender*[d], *Nikolaus Becker*[e], *Marian O'Reilly*[f], *Bengt Andrae*[g]

[a]*Unit of Cancer Epidemiology and Belgian Cancer Centre, Scientific Institute of Public Health, Brussels, Belgium*
[b]*Department of Public Health, University Medical Centre, Erasmus MC, Rotterdam, The Netherlands*
[c]*Centre for Epidemiology and Screening, Institute of Public Health, University of Copenhagen, Copenhagen, Denmark*
[d]*Association EVE, Illkirch Graffenstaden, France*
[e]*Division of Cancer Epidemiology, German Cancer Research Centre, Heidelberg, Germany*
[f]*CervicalCheck – The National Cervical Screening Programme, Limerick, Ireland*
[g]*Gävle Hospital and the Centre for Research & Development, Uppsala University/County Council of Gävleborg, Sweden*

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ABSTRACT

Cervical cancer incidence and mortality can be reduced substantially by organised cytological screening at 3 to 5 year intervals, as was demonstrated in the Nordic countries, the United Kingdom, the Netherlands and parts of Italy. Opportunistic screening, often proposed at yearly schedules, has also reduced the burden of cervical cancer in some, but not all, of the other old member states (belonging to the European Union since 1995) but at a cost that is several times greater. Well organised screening programmes have the potential to achieve greater participation of the target population at regular intervals, equity of access and high quality.

Despite the consistent evidence that organised screening is more efficient than non-organised screening, and in spite of the Cancer Screening Recommendations of the European Council, health authorities of eight old member states (Austria, Belgium, France, Germany, Greece, Luxembourg, Portugal and Spain) have not yet started national organised implementation of screening for cervical cancer. A decision was made by the Irish government to extend their pilot programme nationally while new regional programmes commenced in Portugal and Spain.

Introduction of new methods of prevention, such as HPV screening and prophylactic HPV vaccination, can reduce the burden further, but this will require a high level of organisation with particular attention needed for the maximisation of population coverage, compliance with evidence-based guidelines, monitoring of data enabling continued evaluation and improvement of the preventive programmes.

1. Introduction

Among all malignant tumours, cervical cancer is the one which can be most effectively controlled by screening. Detection of cytological abnormalities by microscopic examination of Pap smears, and subsequent treatment of women with high-grade cervical intraepithelial neoplasia (CIN), avoids the development of cancer.[1] In 1986, the high effectiveness

* *Corresponding author:* Address: Unit of Cancer Epidemiology, J. Wytsmanstreet 14, B1050 Brussels, Belgium. Tel.: +32 2 642 50 21; fax: +32 2 642 54 10.
E-mail address: marc.arbyn@iph.fgov.be (M. Arbyn).
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of cervical cancer screening using Pap smears was established through the expert review of case-control and cohort studies as well as by comparisons between areas or periods with different population coverage.[2] Further evidence has been generated from more recent studies,[3–6] confirming the conclusion that well organised cytological screening, every 3 to 5 years in the age range 35–64 years reduces the incidence of cervical cancer by 80% or more among screened women.[7]

In 1993, when the European Union (EU) comprised 12 member states (Belgium, France, Germany, Greece, Ireland, Italy, Luxembourg, the Netherlands, Denmark, Portugal, Spain and the United Kingdom), the first edition of the European Guidelines for Cervical Cancer Screening was published in this journal.[8] Two years later, Austria, Finland and Sweden joined the Union. In the 1990s, cytological screening was well organised in only a few countries, such as the Nordic countries, the United Kingdom, the Netherlands and parts of Italy.[9] In the other countries, screening was mainly opportunistic, depending on the initiative of the individual woman or her doctor. The first edition of the European Guidelines for Quality Assurance in Cervical Cancer Screening established the principles of organised screening. It was pivotal in initiating some new pilot projects in Europe and pioneering in launching the concept of quality assurance.[10] Nevertheless, the 1993 version has had limited impact on opportunistic screening in countries with a 'liberal' health care system.[11] In 2003, the national ministers of health of all member states endorsed the European Council Recommendation on Cancer Screening and proposed that screening for breast, colorectal and cervical cancer should be offered only in organised settings.[12] In 2008, the European guidelines were updated in a 2nd edition, which corroborated the principles of organised screening and assessed the level of evidence regarding the effectiveness of new methods of cervical cancer prevention.[13]

In the current paper we demonstrate that well organised screening programmes have a greater impact than opportunistic screening because they have the potential to achieve greater participation of the target population at regular intervals, equity of access and high quality. In the second part, we discuss the challenges for health authorities and health professionals in implementing recommendations to organise screening where it is not yet standard. The current paper is restricted to screening in the 15 old member states of the EU in 1995, with some relevant references to Iceland and Norway, which are not EU members. Cervical cancer prevention in the new member states, where the burden of cervical cancer is of a higher order of magnitude,[14,15] is discussed separately.[16]

2. Evidence indicating greater effectiveness and efficiency of organised versus non-organised screening

2.1. *Trends in Nordic countries*

Trend analyses in Denmark, Finland, Iceland, Norway and Sweden have revealed a strong correlation between the decline in the burden of cervical cancer and the geographical extent and the population coverage of organised cytological screening.[17] In Norway, with only 5% of the population covered by organised screening, the cumulative mortality rates (0–74 years) fell by only 10% between the late 1950s and the early 1980s, whereas in Finland and Iceland, with nationwide implementation of organised screening, the reduction was 50% and 80%, respectively.[17]

In Finland, where a high level of organisation was reached (targeting women in the age range 30–60 years, screening interval of 5 years, 70% attendance, 98% invitational coverage), age-standardised incidence and mortality dropped by approximately 80%, between the start of the programme in 1963 and the 1990s.[18] A case-control study, comparing screening histories in women with and without cervical cancer in the Helsinki area, showed that the age-adjusted odds ratios (reflecting the relative risk of getting invasive cancer compared to non-screened women) were 0.25 (confidence interval [CI]: 0.13–0.48) for women participating exclusively in organised screening, 0.57 (CI: 0.30–1.06) for women participating in opportunistic screening only and 0.27 (CI: 0.15–0.49) for those attending both types of screening.[19] These results indicate that the decrease in incidence of invasive cervical cancer was mainly due to the organised mass screening programme.

In Denmark, cervical cancer screening is organised at a county level. In 1962, the first county set up a pilot screening programme, followed, in subsequent years, by several other counties. However, 30 years passed before screening was organised over the whole territory.[20] Incidence rates of cervical cancer were significantly higher in counties that started organised programmes later (after 1980) compared to those that had started earlier (1980 or before). In one county, the organised programme was interrupted between 1982 and 1994 resulting in a significant increase in the incidence of and mortality from cervical cancer. It was shown that contrasts in the burden of cervical cancer were mainly explained by differences in organised screening coverage.[20]

In 1995, Norway set up a national centralised system based on the integration of spontaneous and organised activities and comprising obligatory registration of all screen tests carried out in the organised, as well as in the opportunistic, setting. The 3-year coverage in the 25–67 year age group in the period 2001–2004 increased by about 7% compared to the period 1992–1995.[21] At the same time, the consumption of smears decreased by 7%. Also, the increase in coverage was accompanied by a decrease in the average number of yearly smears used (533,000 versus 494,000) and reached more older and high-risk women. Consequently, the incidence of invasive squamous cervical cancer, which was stable over the first half of the 1990s, dropped and was 22% lower in 1999–2000 compared to the 2-year period preceding the introduction of the programme.[21]

2.2. *United Kingdom, Netherlands and Italy*

Although cervical cancer screening in England and Wales started in 1964, it failed to achieve sufficient screening coverage and adequate follow-up of women with cytological lesions for over 20 years. The recognition that the incidence and even the mortality was rising among young cohorts[22] prompted health authorities to set up a national screening programme in 1988, involving financial incentives for general practitioners reaching 80% coverage and mandatory quality

assurance procedures.[23] The screening coverage rose from 42% in 1988 to 85% in 1994, and the incidence of invasive disease rapidly decreased by 35%.[24,25]

The Dutch nationwide screening programme started in 1989 for women aged 35–54 years with screening at 3 year intervals. Evaluation revealed suboptimal performance and, in 1996, the programme was restructured. It concerned the management and financing of the programme, organisation, target age ranges (30–60 years), a longer screening interval (5-years), follow-up of abnormal results, and evaluation.[26] As a result, the coverage increased substantially (currently around 80%) and the follow-up compliance among screen-positive women improved as well. Also, side effects of screening were reduced by a decrease of the test positivity rate from over 10% to approximately 2%.[27] In spite of the longer screening interval and the lower percentage of women under follow-up, no increased incidence of interval cancer was noted and the incidence of cervical cancer was maintained at a very low rate.[28–30]

In Italy, it was shown that through organised screening the incidence of cervical cancer can be reduced further in areas with pre-existing opportunistic screening.[31]

2.3. *Opportunistic screening in other countries*

In Austria, Belgium, France, Germany and Luxemburg, a substantial reduction in cervical cancer mortality has been observed.[32–35] In these countries, screening is mainly opportunistic, with the exception of a few isolated locally organised programmes. Opportunistic screening is characterised by too frequent testing, often performed by gynaecologists, and low coverage among older women, in socio-economically disadvantaged and high-risk categories, heterogeneous quality, uncontrolled introduction of new technologies and a poor level of monitoring.[16,11,36–38] All these elements result in poor cost-effectiveness.

For instance, in Belgium, approximately 1.2 million cervical samples are taken each year, whereas approximately 900,000 screening samples would be sufficient to cover the whole target population, if the recommended policy (one smear every 3 years for women in the 25–64 year age range) was adhered to.[39] In Germany, the quality of cytological screening has been reported to be poor, partially due to inadequate collection using cotton tip applicators, with low sensitivity for detection of high-grade CIN (less than 45% in certain settings).[40,41] In Germany, Luxembourg and Austria, yearly screening is still the official policy, despite evidence of its low cost-effectiveness.[36]

In Ireland, Spain and Portugal, increased mortality has been reported, which is explained most plausibly by the absence of a population-based screening programme or the low quality and coverage of present opportunistic screening.[32,42,43]

2.4. *Cost-effectiveness of different screening policies*

Fig. 1 shows the efficient cost-effectiveness frontier of optimal starting ages, number of scheduled examinations, and screening intervals, including cost-effectiveness of different screening policies in use in several old member states in the 1990s.[36] The costs and number of life-years gained were computed assuming 100% participation of the target population, absence of excess Pap smears, average sensitivity and natural history parameters.[36] When moving toward a more intensive policy (starting at a younger age and ending at an older age with a shorter interval), the incremental cost-effectiveness ratio increased because the incremental effects rapidly diminish. Screening policies from Finland and the Netherlands were remarkably close to the efficient frontier. Screening every year starting at young adult age without an upper age limit, as recommended in Austria, Germany and Luxembourg (>50 smears/lifetime), yielded a rather small additional gain in life years but at a cost that was dramatically high (Fig. 1). The costs per percentage reduction of life-years lost due to cervical cancer estimated for the German screening policy (yearly intervals, 50 smears per lifetime) were approximately five times greater than for the Finish or Dutch policy (5-yearly screening).[44]

3. Imperfections of organised programmes

Organised screening is more effective than non-organised screening but is not free from imperfections and achieved effects are not permanent if attention wanes. However, an intrinsic characteristic of organised screening is that imperfections come to the fore more easily and can be corrected in due time.

In England, since the year 2000, overall screening attendance has remained at a high level (80% screened <5 years ago, in the age group 25–64 years) but a continuing slow but steady fall-off has been observed among women under 50.[45] Similarly, in the Netherlands, the coverage among women in the youngest target age (30–34 years) has ceased to improve since 1999 and is currently lagging behind other age groups by about 10%.[16] Moreover, screening coverage is still lower in areas with low socioeconomic status, resulting in higher incidence rates of cervical cancer and more advanced staging at diagnosis.[46] In a Finnish area, poor performance observed in a cytology laboratory, characterised by low detection rates of cytological lesions, was accompanied by an increased incidence in the rate of cervical cancer.[47] In Denmark and Italy, where preventive health care is the responsibility of counties or provinces, extension of well organised screening has been slow.[20,48] A nationwide audit in Sweden detected regional differences in terminology and coding that hampered the straightforward pooling of data and highlighted the need for uniform methods of data collection.[6]

4. Challenges for the future

Despite evidence indicating greater effectiveness and cost-effectiveness of organised screening and in spite of the European Council Recommendation,[12] detection of cervical cancer precursors remains mainly opportunistic in eight of the 15 old member states. It should be considered as a compelling responsibility for national or regional health authorities of these countries to set up organised programmes preferably extending over the whole country in agreement with current European Guidelines for Quality Assurance for Cervical Cancer Screening.[13] Stakeholders and health professionals must understand that organised screening is not a question of

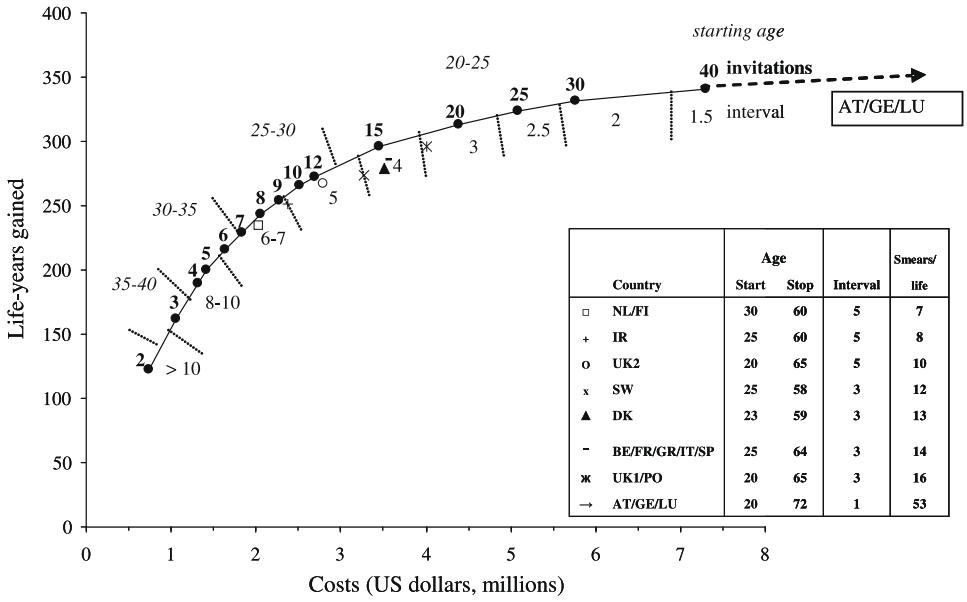

Fig. 1 – Schematic representation of the simulated efficient frontier showing the location of optimal starting ages, number of scheduled examinations, and screening intervals, including a comparison of the costs and effects for screening policies used in countries with a cervical screening programme or a programme recommended in national guidelines. The starting age ranges (in years), number of invitations and screening intervals (in years) are indicated above, on, or under the curve, respectively. The estimated life-years gained (per 1,000,000 screened women) and costs are shown for nine screening policies in place in EU member states in the 1990s (AT = Austria, BE = Belgium, DK = Denmark, FI = Finland, FR = France, GE = Germany, GR = Greece, IR = Ireland, IT = Italy, LU = Luxembourg, NL = The Netherlands, PO = Portugal, SW = Sweden, SP = Spain, and UK = United Kingdom) using a discount rate for costs and effects of 3% (adopted from Van den Akker et al.[36]).

economy to save resources for the public treasury but is, first of all, a question of optimising the effectiveness and minimising the adverse effects.

4.1. *Roll-out of pilot projects or local programmes to national implementation*

In Denmark, since 1996, and in Sweden, since 1977, all counties are covered by an organised programme.[20,49] In Italy, geographical coverage is rising progressively with 69% of the target population currently covered by an invitational system.[48]

Interesting pilot projects of organised screening have been set up over the past decades, for instance, in Bas-Rhin and Isère (France), the five Flemish provinces (Belgium),[50,51] in Vorarlberg (Austria)[52] and in Ormylla (Greece).[53] These local initiatives were more or less successful, but were never able to manage all the stages of an organised screening programme and were never extended to the national level. In the Bas-Rhin programme, all smears are recorded and under quality control whether the woman was invited or not. Three-yearly coverage in the 25–64 year age group reaches 71% (10% above the estimated coverage for the whole of France) and compliance to colposcopy is over 84%. Unfortunately, over-screening is still significant because health authorities do not limit reimbursement of unnecessary smears.[54] In France, national implementation of organised screening according to European guidelines, as successfully implemented in Bas-Rhin, has been proposed on several occasions without success. This was repeated very recently at a workshop organised at the Institut National du Cancer, by a group of national and European experts (Paris, 25 September 2008). The decision whether to implement this recommendation or not and the choice between cytology and HPV-based screening now rests in the hands of the French National Health Authority.

It is encouraging to note that the Irish Cervical Screening Programme Phase I which commenced in 2000, in Limerick, has been extended nationally since 1 September 2008.[16] A contract for the provision of smear taking services was issued directly to doctors in primary care settings. The Programme has signed a contract with Quest Diagnostics USA for the provision of cytology services to ensure volume capacity and turnaround time in an accredited facility. Colposcopy services are an integral part of the Irish programme. It is also encouraging to observe emerging pilot programmes in Spain and Portugal.[16] For regional screening programmes, it is crucial to evaluate the technical quality and population coverage, and to modify the programme appropriately before roll-out at the national level is considered.

4.2. *Integration of data collection from opportunistic screening activities*

In countries with organised screening systems, a substantial volume of opportunistic screening may co-exist with organised activities and this also consumes public resources. Screening could be further improved by extending data collection and evaluation procedures to include opportunistic screening activities such as is currently conceptualised in Sweden and Norway.

4.3. *Homogenisation of screening throughout the whole state or region*

In countries with decentralised responsibilities for preventive health care, the definition of screening policies, implementation of screening guidelines, data collection and evaluation should be homogenised. Funding should be made available to create a permanent team of highly skilled screening specialists to support health authorities and professionals workers involved in screening at the intermediate or local level. Such a team of specialists could also contribute to the training of health workers, establishing contacts with scientific societies, centralisation of data collection, analysis and statistical interpretation, organisation of the feedback at the peripheral level, scientific reporting, information to public and health authorities and coordination of screening activities.

As highlighted in the Swedish audit, and as a requirement for national and international comparison, it is of major importance to use common terminology and to develop uniform monitoring systems for screening and follow-up.[6] European guidelines allow proper national terminology systems which as a minimum should be perfectly translatable into the widely used *Bethesda System*[55] for reporting of cervical cytology. Information systems should be adapted whenever a new screening or triage method, such as HPV testing, is introduced. Regional screening programmes should use unique identifiers and procedures for data exchange between regions to allow completeness of data and to enable linkages between screening, follow-up and cancer registries.

4.4. *Reaching older women*

In organised screening, invitations cease at an upper age limit (59–65 years in the old 15 member states of the EU). It has been proposed that regularly screened women, aged 50 years or older, with successive negative cytology results have a very low-risk of cervical cancer precursors later in life and could be safely discharged from further screening.[56–58] This proposition has been challenged by recent data from the Netherlands showing that cumulative incidence of invasive cancer after three consecutive negative smears was similar in younger (30–44 years) and older women (45–54 years).[59] However, unscreened or insufficiently screened older women are still at considerable risk and could benefit from screening beyond the target age range.[6] Moreover, older women treated for high-grade CIN have a higher rate of recurrence or residual disease than younger women.[60] Women with a history of CIN treatment, in general, are at risk for subsequent cervical cancer that is 2–4 times higher than in the general population and this increased risk further rises by age at diagnosis.[61,62] A negative HPV at the age of 50 years or older or after treatment of CIN has been proposed as a criterion for ceasing screening or relaxing follow-up. Nevertheless, data are conflicting.[63,64] More research is needed regarding the choice of the age limit to stop screening, taking into account the screening and treatment history, the remaining healthy-life expectancy, the age-specific incidence of cervical cancer as well as age- and stage-specific survival.

4.5. *Monitoring of performance*

In order to be able to identify and act on problems, screening should be organised in such a way that the process, the impact, the side effects and the costs can be evaluated (invitation of the target population, response to invitation, overall attendance [organised + opportunistic], results of screen tests, proportion of unsatisfactory tests, compliance to follow-up or management according to guidelines, occurrence of interval cancers and auditing of all registered cancers).[65] Such a comprehensive evaluation requires population-wide individual linkages of routinely collected data, screening tests (laboratory results), follow-up (histology, treatment), cancer registry and mortality. Given evidence on obstetrical morbidity associated with prior surgical therapy of CIN, it is recommended to link treatment with maternity files.[66] Health authorities should create the legal and administrative framework, and services involved in data collection and processing must include adequate safeguards to preserve data safety and privacy. Where HPV vaccination is introduced (which should, preferentially, also be organised), vaccination registries linkable with the aforementioned data files must be set up as well.

A particularly interesting evaluation tool is the audit of screening histories of patients with cervical cancer selected from the cancer registry and matched with controls free of cancer, using a case-control study design.[3,6] Such case-control studies can be made even more informative by examining archived cervical cytology samples, allowing distinctions between screening and management errors. Cervical cytology biobank-based research is also a powerful tool to evaluate future screening methods and to answer pending questions on HPV vaccination (cross-protection, type replacement, duration of protection).[67,68] For instance, HPV testing using material scraped from stored smears of cancer cases and non-cancer controls could answer the question of whether interval cancers (previously Pap smear negative) could have been picked up by HPV screening.[67]

4.6. *Structural funding favouring the organised approach*

Health authorities and services defining tariff rates should direct public funding to the organised, quality-controlled, evidence-based and surveyed screening activities. The key to the success of the English programme involving payment of an additional fee for GPs reaching 80% coverage of their clients seems to be an effective template. Payment per individual screening act, independent of the screening interval or age, favours over-screening, which is cost-ineffective from an economical point of view but also results in over-diagnosis and over-treatment with associated adverse effects.[66,69] In Sweden, women not recently screened are invited to have a smear taken by a midwife. A visit to a doctor for a screening test is five times more expensive. In Stockholm, organised screening was free until 2003. Introduction of a fee (14€) resulted in a decline of attendance of 23%. When, in 2004, reimbursement for spontaneous screening visits to doctors was abolished and, in 2005, organised screening was rendered free again, attendance to organised screening rose to previous levels.[70] In the Netherlands, the issue of over-screening was

addressed in the national GP guidelines for cervical screening by abolishing payments for non-programme primary smears and by introducing special forms attached to the individual screening invitation, based on which payments are made (and not otherwise). However, in France, propositions to reduce payment for over-screening were not accepted by gynaecologists and lobbying from professional groups impeded resource reallocation favouring organised screening.[71]

4.7. *EU added value to improved cervical cancer screening in the member states*

The EU should offer a forum for discussion and exchange of experiences among national and regional experts who are mandated to manage or evaluate screening programmes. The EU should also continue to support international data collection using standardised aggregated datasets allowing calculation of comparable performance indicators as conceptualised within the European Network for Information of Cancer Epidemiology.[65] The EU could organise or at least actively support international efforts to assess and pool evidence of efficacy and effectiveness of new methods of cancer prevention.[72] Unbiased international systematic reviews of evidence are an important source in keeping guidelines updated. Finally, the EU should continue publishing guidelines taking into account actualised scientific evidence, cost-effectiveness and affordability.[13]

4.8. *Introduction of new methods of cervical cancer prevention*

European guidelines, updated according to evidence available in early 2007, recognised the clinical utility for high-risk HPV testing in the triage of women with atypical squamous cells of undetermined significance (ASCUS) and in the follow-up of women treated for high-grade CIN.[13,73,74] For a discussion of new evidence from randomised trials comparing HPV- and cytology-based screening, the triage of HPV-positive women, use of HPV self-sampling to reach non-participants at high-risk of cervical cancer, HPV vaccination and adaptation of screening policies for vaccinated cohorts, we refer to other sources.[72,75,76] It must be stressed that new strategies of cervical cancer prevention must be evaluated thoroughly before introduction, preferentially in an organised setting. Updated and evidence-based European guidelines on HPV screening and vaccination are currently being worked out and these should be ready by 2010. When new methods are introduced, information systems should be adapted accordingly, integrating all screening, triage and management data and allowing appropriate invitation of women (possibly at longer intervals), follow-up of screen positive subjects and evaluation of the modified policies.

5. Conclusions

The major take-home message for policy makers is that *screening must be well organised* with optimal screening coverage and follow-up of women with a positive screening test. The quality of screening should be assured and monitored at each stage of the screening process.

Achieving a high coverage for HPV vaccination is expected to reduce the burden of disease substantially which will require modification of screening policies, in the mid- to long-term. Meanwhile, cervical screening will need to be continued without change.

Conflict of interest statement

None declared.

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Challenges in starting organised screening programmes for cervical cancer in the new member states of the European Union

Florian Al. Nicula[a,*], *Ahti Anttila*[b], *Luciana Neamtiu*[a], *Maja Primic Žakelj*[c], *Ruth Tachezy*[d], *Arkadiusz Chil*[e], *Magdalena Grce*[f], *Vesna Kesić*[g]

[a]*Epidemiology and Biostatistics, Oncological Institute "I. Chiricuta", Cluj-Napoca, Romania*
[b]*Finnish Cancer Registry, Helsinki, Finland*
[c]*Epidemiology and Cancer Registry, Institute of Oncology, Ljubljana, Slovenia*
[d]*Institute of Haematology and Blood Transfusion, National Reference Laboratory for Papillomaviruses, Prague, Czech Republic*
[e]*Holycross Cancer Centre in Kielce, Regional Coordinating Office for Cervical Cancer Screening Programme, Kielce, Poland*
[f]*Rudjer Boskovic Institute, Division of Molecular Medicine, Zagreb, Croatia*
[g]*Department for Gynaecologic Diagnostics and Oncology, Institute of Obstetrics and Gynaecology, University Clinical Centre, Beograd, Serbia*

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ABSTRACT

Following the 2003 Recommendation of the Council of the European Union on cancer screening, equal access to organised cervical cancer screening is supposed to be ensured for all women at risk in all member states. However, the first IARC report on the implementation of the Council Recommendation suggests that a remarkable proportion of women in the new member states are not yet covered with the free Pap tests offered either in organised or opportunistic manners. Cervical cancer incidence and mortality rates in most of these countries are among the highest in Europe. The purpose of this paper is to identify some common challenges and make further proposals in organising and implementing quality-assured cervical cancer screening programmes in these countries. Based on the responses to a corresponding questionnaire, a summary on cervical cancer prevention policies was established for the seven new European Union member states, Czech Republic, Latvia, Lithuania, Poland, Romania, Slovakia and Slovenia, and two candidate states, Croatia and Serbia. In most of these countries there are a lot of challenges to overcome before achieving the level of preventive services as seen in Finland and the Netherlands nowadays.

1. Background

Cervical cancer incidence and mortality rates in the new member states of the European Union (EU) are still an important issue.[1–4] Available evidence on the efficacy of well organised screening programmes in decreasing cervical cancer incidence and mortality is sufficient for all these countries to implement population-based organised screening programmes.[5] Some of the new EU member states have already started large-scale, even though costly and apparently still relatively ineffective, activities whereas in some other countries no real screening activities are in action yet.[6,7]

* *Corresponding author:* Tel.: +40 744569898/722945245.
E-mail address: nicula@iocn.ro (F.Al. Nicula).
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Recently, efforts have been made to implement the Recommendation of the Council of the EU on cancer screening.[8] The Second Edition of European guidelines for quality assurance (QA) in cervical cancer screening was released in 2008, including comprehensive recommendations and suggestions to be considered in planning, organising and monitoring new programmes.[9] There is still a huge disparity between member states regarding not only the burden of the disease, but also access to quality-assured screening and related health-care services.

The aim of the current study is to assess the present status of cervical cancer screening in the new member states and two applicant countries, and discuss the challenges and obstacles in planning evidence-based and cost-effective organised screening activities. We also aim to develop new proposals based on these data, which will include the key points necessary for improvement of the overall situation of cervical cancer prevention in Europe.

2. Materials and methods

Data on screening implementation for the new member states were collected from the recently published status report of cancer screening programmes in the EU.[7] Further information on cervical cancer screening was collected through a questionnaire from each of the new member states and two applicant countries. The questionnaire included the following items: country, name and affiliation of responder, screening policy and target population, and coverage (national or regional; defined as the proportion of women in the target population screened at least once in the specified interval). Further questions included information on management and clinical resources; on population, cancer registry and screening database accessibility; and on implementation of the EU quality assurance guidelines,[9] and existence of national guidelines. The questionnaire was sent to 12 new member states (Bulgaria, Czech Republic, Cyprus, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Romania, Slovakia and Slovenia) and two non-member states (Croatia and Serbia). The seven responders for the new member states were: Dr. Ruth Tachezy for Czech Republic, Dr. Ilze Viberga for Latvia, Dr. Juozas Kurtinaitis for Lithuania, Dr. Arkadiusz Chil for Poland, Dr. Florian Nicula for Romania, Dr. Miloš Mlynček for Slovakia and Dr. Maja Primic Žakelj for Slovenia. Two candidate states, Croatia (Dr. Magdalena Grce) and Serbia (Dr. Vesna Kesić) also responded.

3. Results

3.1. Screening policies

Table 1 presents the current situation and the plans of new member states and two non-member states of the EU, based on the recent status report of cancer screening in the EU[7] and the questionnaire responses designed for this study. In addition, Table 1 shows data on the HPV vaccination policies and practices based on authors' personal communications and the recent report edited by the European Cervical Cancer Association (ECCA).[10]

The non-population based or opportunistic screening was still the only modality in place in Bulgaria, Croatia, Czech Republic, Cyprus, Latvia, Lithuania, Malta and Slovak Republic, while the population-based organised screening programme was implemented or piloted in the period from 2003 to 2008 in Estonia, Hungary, Poland, Romania, Serbia and Slovenia. In Croatia, Romania and Serbia regional pilots were ongoing together with the planning of national organised screening programmes. In Latvia, a population-based screening programme has been planned to be implemented in 2009. In the Czech Republic the state of the nationwide organised screening programme was officially announced in February 2008, after completion of the current data collection period. According to the responses to the questionnaire, quality assurance of cytology, national guidelines and/or recommendations, population database and cancer registries are available in each country. Gynaecologists are the main sample-takers in each responder country, and the screening tests were taken in connection with preventive gynaecological examinations or by opportunity. Invitational procedures or pilots were practiced in Poland, Romania and Slovenia. The proportion of women tested at least once during the screening interval was 24% for Poland, 30% for Latvia, 35% for Czech Republic, 62% for Serbia and 70% for Slovenia.

For the Czech Republic the estimate was for a 1-year interval only while for the rest it was a 3-year interval.

3.2. Organised national screening programmes

3.2.1. The situation in Slovenia

In Slovenia, opportunistic screening was introduced in regular gynaecological practice in 1960.[11] According to the data of the Cancer Registry of Slovenia there were no major changes in the incidence rates of cervical cancer from the late 1970s onwards, except that in 1994 the incidence rate started to increase again. This increase was ascribed to inefficiency of opportunistic screening in Slovenia and in 2003, after an initial pilot study, the organised screening programme was established. The programme has its legal basis in several regulations and recommendations.[12]

According to the new recommendations, each woman between ages 20 and 64 years is to be invited to undergo a preventive gynaecological examination together with the Pap smear once every 3 years (after two negative smears) either by her 'personal' gynaecologist, with whom she has already been registered, or by the Screening Registry in case she has not been registered yet.

Four years after the start of the national programme, 70% of women in the target age group (20–64 years) had at least one smear registered in the Screening Registry, located at the Institute of Oncology Ljubljana, Epidemiology and Cancer Registry Unit. The percentage is about 80% till the age of 45 and smaller among older women. According to the data from the Cancer Registry of Slovenia, the whole population-based incidence rate of cervical cancer has started to decrease, especially in the age group 35 to 49 years.

3.2.2. The situation in Poland

In Poland, at the beginning of 2007, an organised national cervical cancer screening programme started.[13] For management of

Table 1 – Cervical screening practice in Europe based on responses to the corresponding questionnaire and the recent report.

Countries	Cervical cancer rates		Cervical screening policy				HPV vaccination policy
	Incidence ASR(W)[a]	Mortality ASR(W)[a]	Organisation	Target population	Target age (years)	Screening interval	
Bulgaria	18.7	8.0	Non-population based	1.9 million	31–65	2-years	No
Croatia[b]	13.3	5.0	Non-population based, one pilot since 2006	1.2 million	25–64	3-years	Yes, a pilot programme since March 2009.
Czech Republic[c]	16.2	5.5	Non-population based	2.9 million	25–69	1-year	Yes, several insurance companies provide partial reimbursement.
Cyprus	11.6	5.3	Non-population based				NA
Estonia	15.5	6.6	Population-based, national since 2003	288,000	30–59	5-years	No
Hungary	15.7	6.7	Population-based, national since 2003	2.8 million	25–65	3-years	Yes, HPV vaccination has been included in the recommended vaccination.
Latvia	12.9	7.4	Population-based, nationwide from 2009	820,000	20–70	3-years	Yes, a pilot programme to vaccinate girls aged 12 is planned for 2010.
Lithuania	17.6	9.0	Non-population based	750,000	30–60	3-years	Yes, starting in 2012.
Malta	4.8	1.6	Non-population based				NA
Poland	18.4	7.8	Population-based, national since 2007	7.8 million	25–59	3-years	Yes, HPV vaccination has been included in the recommended vaccination list.
Romania	23.9	13.0	Population-based, regional pilot since 2002	6 million	25–64	5-years	Yes, since 2008.
Slovak Republic	18.5	6.1	Non-population based, national	2.2 million	>18	1-year	Yes, approximately 10% of the cost of vaccination is covered by compulsory medical insurance.
Slovenia	16.1	4.7	Population-based, national since 2003	630,000	20–64	3-years	Yes, starting in autumn 2009.
Serbia[d]	27.4	10.1	Population-based, pilot 2004–2006 national from 2008	2.3 million	25–69	3-years	No

NA: Data not available.

a Age Standardised Rate (World) according to GLOBOCAN 2002 (Ferlay et al., 2004[1]).

b Non-member states of the European Union, applicant countries; screening targeted within the age of 25–65 years and the 3-year interval is planned to be implemented in the future.

c Population-based since 2008, with the target age of 25–5 years and the 3-year interval is planned to be implemented in the future.

d Non-member states of the European Union, applicant countries.

the programme, coordinating offices were established by the Ministry of Health. About 8 million women aged 25–59 in 3-year intervals will receive invitations for cytology, which will be sent out by the National Health Fund. In order to collect the data of women participating in the organised screening, a computer database of prophylaxis was implemented. Detailed information of the anamnesis and enrolment data of invited women are recorded onto the computer database system including data from cytology laboratories, the outpatient clinics where the Pap smear was taken, and in the case of patients with an abnormal smear, on further diagnostic confirmation within the colposcopy clinics.

As the organised screening was introduced without well-designed pilot programmes, its shortcomings and the adverse impact of opportunistic screening on the organised programme became visible after the first few months. Women and gynaecologists were reluctant to participate in the programme. Therefore, at the beginning of 2008, significant modifications were introduced which aimed to facilitate access to the programme for women and to encourage gynaecologists to participate in the organised screening. Further corrections were also implemented which aimed to improve the invitational system and attendance of women with abnormal smears to colposcopy clinics working within the programme. As the organised programme in Poland is developing and the corrective changes are promptly applied on a large-scale without pilot programmes, there is still no clarity on which model, to organise these interventions, is well workable and efficient.

3.2.3. *The situation in Serbia*

Cervical cancer prevention in Serbia has relied on non-population based screening that is characterised by high coverage in

younger and low coverage in middle-aged and older women. Screening of selected groups of women employed in large companies is performed annually by many regional hospitals but this approach has little effect on morbidity and mortality. A number of pilot projects have been undertaken from 2002–2006 with the results being used for the development of a national programme for cervical cancer screening. In 2006, the Ministry of Health nominated an Expert Group to develop and implement a national cervical cancer screening programme. Work on the national programme was finalised in 2007.[14]

The Serbian Government approved the national programme for organised screening in May 2008, and it became an obligation for all subjects involved in the prevention of cervical cancer.

The target population is women aged 25–69 (approximately 2.3 million women), which will be screened by cytology every 3 years. The primary healthcare units conform to the basis of screening and the programme is run on an organised, even though decentralised, model. Serbia has 162 primary healthcare units, with more than 500 gynaecologists involved in the realisation of the national screening programme. Each primary healthcare unit is responsible for the population they cover and the organisation of invitations and collection of smears is adapted to local circumstances, regarding the available resources. Cytoscreening is performed on the primary level and all abnormal and 10% of all normal samples are referred to second level cytological laboratories to be reviewed by cytopathologists. The criteria for the second level (cytopathology) laboratories are strictly mandated by the programme. The coordination of all issues related to the work of Primary Health Care Units could be managed by a National Screening Centre, which could also collect the final data through the network of the Regional Public Health Institutes.

3.3. *Organised regional pilot and planning organised national programmes*

3.3.1. *The situation in Romania*

In Romania, a regionally organised, population-based pilot has been ongoing since 2002 and planning of a national programme started in 2008. The coverage of the regional pilot was 21% by the end of 2008.[15]

Difficulties appeared at almost all levels: first, in the organisation of the management unit and then subsequently in the implementation unit network, in training people in screening management, in setting standards and criteria, as well as in the protocols for the cytological laboratories, colposcopies and treatment units.

The screening database is connected to the regional cancer registry. Although the cytological results of the screening programme are registered at a rate of almost 100%, histology results and treatment and follow-up data are reported for less then 15% of the lesions found in the programme. The referral rate to colposcopy is high, but few are reported. This is the reason why, since 2008, new rules for data reporting and colposcopy registries were implemented.

Regional QA guidelines are used in line with the European recommendations (Arbyn et al., eds., 2008). Organising a national screening programme needs important EU guidance and assistance; for instance, at the level of screening management, only a few trained specialists are available regionally. The infrastructure of the screening network is insufficient; the estimated available quality assured resources represent less than 10% of the necessary resources.

3.3.2. *The situation in Croatia*

In Croatia, non-population based screening was introduced in 1968 and this was accompanied by decreasing cervical cancer incidence rates until the year 1991 but no further consistent decrease has been observed afterwards. The cervical cancer mortality rates remained at a low level during the entire period but no decrease was observed over the last decade. It is evident that even the opportunistic cervical cancer screening in Croatia had an impact on cervical cancer control. The number of Pap smears taken yearly is still increasing and reached more than 500,000 in 2005 in the whole country.[16] However, in the absence of an organised population-based programme, it is difficult to assess the efficacy of this screening approach and it is clear that a large proportion of the age-eligible target population still remains unscreened or under-screened. The only way to achieve further reductions in cervical cancer cases is through the introduction of an organised population-based cervical cancer screening programme. Following the elaborated 2003 proposals on prevention and early detection of breast, cervical, colorectal and prostate cancer of the Working Groups nominated by the Ministry of Health and Social Welfare of the Republic of Croatia, and the 2006–2011 National strategy on Health Development of the Republic of Croatia, which endorsed the 2003 Recommendations of the Council of the EU and the 2005 World Health Organisation Resolution on Cancer prevention and control,[17] the national programme of prevention and early detection of breast cancer and the national programme of early detection of colorectal cancer were implemented in 2006 and 2007, respectively. The national programme of prevention and early detection of cervical cancer was and still is the next programme planned to be implemented. The proposed programme comprises screening of all women aged 25–64 years every 3 years by conventional cytology in the first phase. In the second phase of the programme, in addition to conventional or liquid-based cytology (LBC), the human papillomavirus (HPV) test would be introduced for women aged 30–64, with 5-year screening intervals. The situation in the country was re-evaluated in 2007 and the consensus recommendation for the implementation of the organised cervical screening programme was established.[18] In 2006, a regional pilot started in the Southern-Western region of Croatia in the Primorsko-Goranska County, but further piloting in line with the proposed programme did not occur.

4. Discussion and conclusions

Despite a voluminous screening activity on-going nowadays in most of the studied applicant or new member states of the EU, the current cervical cancer burden is high compared with most of the old EU member states. Unfortunately, there is only little evidence from population-based incidence and mortality trend studies that the historical screening activity has been effective in those countries.[2,4,19] Evaluation using cohort study designs among screening populations – recommended in the

European QA guidelines for evaluation in the first place – are proceeding in some countries, but results are not available yet. It is not straightforward to assess yet in which degree the current screening activity will affect the cervical cancer burden in the future.

In all new member states, screening by the Pap test is primary method for early detection and prevention of cervical cancer. Despite the ongoing opportunistic or organised screening, a lot of women in those countries are still not covered by cervical screening. Some major barriers and challenges in organising cervical screening programmes are common for most of the new EU member states and for other countries of Central and South Eastern Europe:

- Coverage of invitations, as well as attendance based on invitations, are generally at a too low level for the programmes to be effective.
- Shortcomings in the information and awareness among women in the target population.
- Shortcomings in the management of organised population-based programmes, e.g. in identifying and inviting, in piloting, and in registration, monitoring and evaluation activities; all the necessary resources of epidemiological quality control are often not understood well enough by decision makers;
- The quality of the test is crucial: there are opportunistic practices which have been on-going for a long time with limited, or sometimes without any quality control, much more so than the organised screening activities in some of these countries. Some of these countries even have an over-capacity; often it has not yet been clarified in detail whether the screening methods are the same as the currently recommended standard methods and whether acceptable quality standards were adopted.[9,20]
- Inadequate understanding and involvement of all key medical groups and specialties of the population-based programmes; difficulties in reaching consent on decisions regarding the cost-effectiveness, population-based policy and organisation of the activity.
- Low application of colposcopy, treatment and follow-up protocols may also be a problem in some settings.
- Shortcomings in the availability of financial resources.

Building-up comprehensive quality-assured screening programmes from the identified target populations up to successful call-recall and fail-safe systems is still in a rather early phase in the herein analysed country situations. Systematic evaluation of activities of the whole screening chain are proceeding but only in a few settings and there are no systematic evaluation reports available yet based on the screening and cancer registry records and other related information sources.

How to respond to the barriers and draw-backs? Nowadays organised screening is still the only method that can be expected to timely reduce cervical cancer burden over the main age groups contracting the disease during the next few decades.[18] In contrast, non-population-based screening programmes have been shown to promote health inequalities and to be less effective, less efficient and to waste scarce healthcare money and resources.[5] How to define the screening chain optimally and how to share the various medical and population-based responsibilities, both at national and lower-level geographical units are still unsettled issues in the new EU member countries. Founding national screening coordination and evaluation centres with adequate resources and with appropriate institutional and legal backgrounds is one key. Intensive and coordinated education and training in all relevant fields for screening programmes and campaigning among populations at large and among decision makers and key medical groups are other key components. There is a need to support coordination between these centres at European level. Without these supportive mechanisms the current recommendation by the European Council is likely to be ineffective.

Most of the studies in Europe on new technologies in cervical cancer screening and prevention have been done in the old well-to-do member states, i.e. Finland, Netherlands and UK. These countries do not share similar characteristics with the new member countries in many important aspects. The disease burden is lower in the old member states of the EU and, at the same time, there are lots of resources and even wide overuse of resources, thereby having consequences on cost-effectiveness.[4,21–23] There are some benefits in the new member countries for evaluation purposes of new methods of cervical cancer screening, i.e. HPV DNA testing as primary screening with cytology triage of screen positives.[24] The disease burden is high in the new EU member states. This indicates not only a higher priority, but also the context and settings that need to be directly addressed in the evaluations. The systematic population and cancer registries and the linkage systems, which can be based on this, exist in almost all of the new EU member states. This enables very good possibilities for using convincing population-based evaluation methods.

The decision makers in public health at national level should recognise the benefit of population-based organised screening programmes and the importance of the screening management units; their existence, as well as a European School of Screening Management and related training programmes, is mandatory for the quality of all national screening programmes. Moreover, the future cervical screening programmes should take into consideration the primary prevention of cervical cancer by HPV vaccination and adapt the programmes according to the vaccination policies in respective countries. It could be speculated that in HPV vaccination high coverage populations, like in some old EU member states, cervical screening could be postponed till later on in life and be performed in wider intervals, while in those countries where the HPV vaccination coverage will be very low, like the new member states, i.e. Romania, cervical screening will still remain the main strategy for cervical cancer prevention.

Conflict of interest statement

Florian Al. Nicula – None declared; Ahti Anttila – None declared; Luciana Neamtiu – None declared; Maja Primic Žakelj – None declared; Ruth Tachezy – Membership of GSK advisory committee; Arkadiusz Chil – None declared; Magdalena Grce – None declared; Vesna Kesić – None declared.

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Description of the national situation of cervical cancer screening in the member states of the European Union ☆

Ahti Anttila[a,*], *Guglielmo Ronco*[b,*], *Working Group on the Registration and Monitoring of Cervical Cancer Screening Programmes in the European Union; within the European Network for Information on Cancer (EUNICE)*

[a]*Finnish Cancer Registry, Pieni Roobertinkatu 9, FIN-00130 Helsinki, Finland*
[b]*Unit of Cancer Epidemiology, Centre for Cancer Prevention (CPO), via San Francesco da Paola 31, 10123 Torino, Italy*

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ABSTRACT

This report up-dates information on the national situation of cervical cancer screening in the member states of the European Union. There is yet high diversity in the status of cervical screening, and rapid changes expected to occur in the situation in many countries. It is important to underline differences in the health care and other components in order to allow a proper interpretation of the summary results published elsewhere in this Special Issue. The brief national descriptions along with up-dated information on the recent references are available from all but one member states.

1. Introduction

This report up-dates information on the national situation of cervical cancer screening in the member states of the European Union. Given the high diversity of the status of cervical screening in European countries as well as rapid changes in the situation in many countries, it is difficult to summarise all essential aspects in a few quantitative parameters available for the summary papers among the member states.[1–6]

It is important to underline differences of the healthcare systems, in the action models and historical availability of organised screening, leading to peculiarities of each country in order to allow a correct interpretation of the summary results. Involvement and role of various medical disciplines (pathology, gynaecology, GP, epidemiology, public health) vary meaningfully between the programmes, affecting the organisation of the programmes. The data presented are also relevant for the national decision-making on screening. The brief national

☆ **Members of the group and co-authors**: HG Wiener, E Rasky, R Horvat (Austria), M Arbyn, L Annemans, A Vandenbroecke (Belgium), Y Panayotova, ILG Todorova, Z Valerianova (Bulgaria), M Azina-Chronides (Cyprus), R Tachezy, E Hamšíková, J Šmahelová, L Rob (Czech Republic), E Lynge, C Rygaard, B Bjerregaard (Denmark), P Veerus, A Aasmaa, T Raud (Estonia), M Leinonen, P Nieminen, A Anttila (Finland), M Fender, M Duport, R Ancelle-Park, JJ Baldauf (France), M Mund, J Knöpnadel, U Schenck, N Becker (Germany), L Vass, L Döbrössy (Hungary), M O'Reilly (Ireland), G Ronco, A Federici, M Zappa (Italy), I Viberga, L Engele (Latvia), J Kurtinaitis, A Armonaviciene, A Laurinavicius (Lithuania), A Scharpantgen, R Scheiden, C Wagener, U Knolle, A Wehenkel, W Dippel, C Capesius (Luxembourg), M Dalmas, R Busuttil (Malta), M Rebolj, M van Ballegooijen (Netherlands), A Chil, S Góźdź, J Starzewski, J Didkowska (Poland), A Morais (Portugal – Central Region), FA Nicula, O Șuteu. R Păiș, L Neamțiu (Romania), L Masak (Slovak Republic), M Primic-Žakelj, A Pogačnik, M Uršič-Vrščaj, V Zadnik (Slovenia), S de Sanjosé, R Ibañez, E Ferrer (Spain), B Andrae (Sweden), J Patnick, L Lancucki (United Kindom – England).

* *Corresponding authors:* Tel.: +358 9 135331; fax: +358 9 1355378 (A. Anttila), tel.: +39 011 6333850; fax: +39 011 6333861 (G. Ronco).
E-mail addresses: ahti.anttila@cancer.fi (A. Anttila), guglielmo.ronco@cpo.it (G. Ronco).

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descriptions along with up-dated information on the recent references are available from all but one member states.

Austria

Wiener HG[a], Rasky E[b], Horvat R[a]

[a] Klinisches Institut für Pathologie, Medizinische Universität Wien

[b] Institut für Sozialmedizin und Epidemiologie, Medizinische Universität Graz

Screening for cervical cancer started in Austria during the 1950s. Screening cytology on a larger scale followed during the 1970s.[7] Up to now the screening is opportunistic in eight of the nine Austrian federal states. In the Vorarlberg (4.3% of the female population), screening for cervical cancer is organised by one central institution. On the national level, screening is not population based as of yet. Smear taking is recommended annually, combined with a gynaecological examination. Expenses are covered by health insurances for women aged 19 years and older.[8] HPV-vaccination is recommended before the age of sexual activity.[9]

Recently, PAP screening data were collected from eight federal states. Based on information available from the social insurance company covering 98% of the population on a compulsory basis, data show differences due to the observation period chosen, region and age. Based on a single year observation (2003–2004), 27% of the target population used the opportunity of a gynaecocytological check. Within 3 years (observation period 2003–2006), 47% of the target female population had a PAP smear. Within the 3-year period the highest participation rate was 75%, seen in women 20–29 years of age. Only 57% of women aged between 50 and 59 years had a PAP smear within the same period.[10] Data on age dependence correspond to those given previously.[11]

Cervical smears are predominantly taken by gynaecologists but sometimes by general practitioners or medical doctors of outpatient clinics. The present screening situation results in about 1.5 million conventional smears, annually. Cytological evaluation of these smears is carried out in hospital and private laboratories. Licensed (cyto)-pathologists are responsible for the reports. The Austrian Societies of Cytology and of Pathology have published quality recommendations for structural conditions, processing features and the validation of results in laboratories for diagnostic cytology. The catalogue includes recommendations for the personal staff and the technical equipment.[12]

In 1998 a voluntary quality assurance programme was introduced by the Austrian Society of Cytology, based on comparison of the reports given by the participating laboratories. Collected data demonstrated that correlation with histology shows a low false positive rate, but adequacy of smears is inappropriate in a high percentage.[13] Now there are ongoing efforts to improve the quality of smears by the undertaking of an intensive search for those instruments which are best for the smear taker. Due to funding policy, liquid based cytology is not common in Austria.

Cervical cancer mortality rate has been reduced by about 50% since 1980 and to a third since 1960.[7] In 2004, 164 deaths from cervical cancer were documented (aged standardised rate 2.2).[14] At the beginning of 2008 an expert committee was established by the Austrian Federal Bureau of Health to find ways of improving the outcome of screening. There are plans to reach the underserved population by introducing an organised screening programme with a call-recall system and compulsory adherence of the labs to the quality assurance programme; efforts aim at establishing a nationwide basis for a screening programme in accordance with the European guidelines for quality assurance in cervical cancer screening.

Belgium

Arbyn M[a], Annemans L[b], Vandenbroecke A[c]

[a] Belgian Cancer Centre/Unit of Cancer Epidemiology, Scientific Institute of Public Health, Brussels

[b] Faculty of Medicine and Health Sciences, Department of Public Health, Ghent University, Ghent

[c] Centre Communautaire de Référence pour le dépistage du cancer du sein, Mont-Saint-Guibert

With an age-standardised incidence rate of 12/100,000 and a mortality rate of 5/100,000 (estimates for 2004, European reference population), cervical cancer in Belgium ranks in the middle group of the member states of the European Union.[15] In the 1950s, the standardised mortality rate (corrected for certification inaccuracy) was of the order of 15/100,000. Age-cohort-period analysis has revealed an increased risk of cervical cancer for cohorts born after 1940 that was counteracted partially by screening.[16,17]

In Belgium, the three Communities (Flemish, French and German Community) are responsible for the organisation of preventive health care, whereas financing of most medical acts mainly remains a matter for the Federal State. For instance, consultation of a gynaecologist or GP, taking and reading of a Pap smear are reimbursed by the National Health Insurance Institute. In 1993, the Flemish Community set up a screening programme, in collaboration with the five Flemish provinces, with two major aims: (a) inviting women aged between 25 and 64 years to have a Pap smear taken every 3 years and (b) promoting quality assurance regarding collection of Pap smears, uniform reporting of cytology results and follow-up of screen-positive women.[18] Currently, only two provinces (Antwerp and Flemish-Brabant) still maintain a residual activity of the original Flemish programme. The Flemish programme was successful in working out technical guidelines but failed in setting up a region-wide screening registry and in influencing clinical practice. The two main reasons for failure of the introduction of organised screening were: the lack of agreement between the Federal and Community authorities and the strict and conservative interpretation of the legislation on privacy protection. In spite of laudable efforts of provincial teams and several experts, cervical cancer screening in Belgium remains predominantly opportunistic.

Recently, a comprehensive data file was compiled containing all individual reimbursement claims for Pap smears, colposcopies, cervical biopsies and surgery on the cervix that took place in Belgium from 1996 to 2000.[19] The screening coverage in 2000, derived from this data and defined as the proportion of women aged 25–64 years with at least one Pap smear taken in the last 3 years, was 59% (57% in the Flemish region, 58% in the capital Brussels and 61% in the Walloon region). The increase in coverage (P_{2000}–P_{1996}) was 2%, 5% and

3% in the Flemish, Brussels and Walloon regions, respectively. The screening coverage declines by age. The modal screening interval is 1 year, meaning that many women are overscreened. The amount of used smears (1.2 million per year for a target population of 2.5 million) is theoretically sufficient to cover more than 100% of the target population at a 3-year interval. In 2000, 17% of all interpreted cervical cytology examinations were performed in women outside the target age range (10% in women aged less than 25 years old, 7% in women older than 64 years). Gynaecologists take most of the smears. The proportion taken by general practitioners varies substantially by region: 20%, 8% and 3%, in the Flemish, Brussels and Walloon regions respectively. An impressive amount of colposcopies are performed: on average, one colposcopic examination for every three Pap smears.

HPV testing is recommended for triage of women with ASCUS and after treatment of CIN, but not for primary screening.[20] However, hereto, HPV testing is not reimbursed.

The Federal High Council for Health recommends systematic prophylactic HPV vaccination of a 1-year cohort of girls aged 10–13 years.[21] Based on advice from the Flemish Health Council, the Flemish health authority has planned to offer such vaccination in the framework of school health including registration, linkable to a screening and cancer registry, and surveillance of effects.[22] Opportunistic vaccination with the quadrivalent or bivalent HPV vaccine is partially reimbursed for girls aged 12–15 years (co-payment by patient of ~10€/dose). Extension of reimbursement up to the age of 18 is currently considered.

To conclude, structural reduction of the overuse of Pap smears and other related diagnostic and therapeutic procedures and re-investment in coverage increase and quality improvement could potentially result in more life-years saved, without an increase in public funding. In Belgium, translation of European evidence-based guidelines into practice is a long and difficult process, due to the complex political decision making.

Bulgaria

Panayotova Y[a], Todorova ILG[a], Valerianova Z[b]

[a] Health Psychology Research Centre, Sofia

[b] Bulgarian National Cancer Registy, National Oncological Hospital, Sofia

In the last 20 years, the incidence and mortality from cervical cancer in Bulgaria have risen constantly, which is in sharp contrast to the steady decline in most European countries. Up to the late 1980s mortality rates from cervical cancer in Bulgaria were comparable to the rates of many EU countries. A dramatic increase in mortality rates has been observed during the political and socio-economic reforms of the last two decades.[25] Thus, in 2004, 1097 new cases of cervical cancer were registered with cervical cancer being responsible for 7.6% of all cancer cases in females, ranked after breast cancer, non-melanoma skin cancer and corpus uteri cancer.[24] Also, more than 30% of the new cervical cancer cases were in advanced (III + IV) stages[24], and this has not changed during the last 20 years. Moreover, cases of preinvasive cervix uteri cancer are only 20.4%, while invasive ones are 79.6%.

This situation of increasing incidence and mortality rates is due to the fact that the State funded health care system, existing before 1989, has been dismantled. The former health care model in Eastern Europe sought to mount comprehensive and well-organised prevention programmes such as universal childhood immunisations, screening for tuberculosis, sexually transmitted diseases and cervical cancer. Institutionally, the first official National Cervical Screening Programme in Bulgaria started in 1970.[23] For the period between 1970 and 1985, cervical cancer incidence and mortality rates remained relatively stable.

The reform of the health care system started in 1990 and is still ongoing. In 2000, a National Strategy and Programme for Oncological Screening in Bulgaria (2001–2006) was voted for by Parliament, aiming to institute a multifaceted programme of cervical cancer screening for women aged 20 to 60 years. It focused on cytological screening methods and proposed that cervical smears are taken at the primary care units (GPs or OBGYN practitioners) and analysed at specialised laboratories throughout the country. This programme was not implemented in practice in the way it was planned, and it expired at the end of 2006. Currently, Bulgaria has no national programme for cancer prevention; however, there are ongoing efforts to develop one. There are some local initiatives for free of charge preventive check-ups that are undertaken rarely and unsystematically.

As a result, the population based screening programme of the past has been replaced by opportunistic screening that requires a substantial personal initiative of both the providers and the clients.[26,27] The absence of institutionally structured preventive programmes creates significant barriers in access to regular smear tests. A study on psychosocial aspects of cervical cancer screening in Bulgaria has shown that the most important barriers women face are the unwillingness of doctors to offer and to perform Pap smears, the unpleasantness of the gynaecological visits, and the lack of information.[23]

There are no available data on prevalence of HPV infection in Bulgaria. HPV vaccination has now been available in the country for a year on a private basis. Although there were some promotional initiatives, the vaccine is not implemented as an institutional policy.

The challenge in starting an organised cervical screening programme in Bulgaria lies in proper organisation. The country has enough human and physical resources, but clear instructions for the organisation, management, and implementation of a screening programme are needed.

Cyprus

Azina-Chronides M. On behalf of the Director Medical and Public Health Services. M.A-Ch./d.pa

In Cyprus, the history of cervical cancer screening dates back to 1970 when the Ministry of Health identified the need for screening. Since then, Cypriot gynaecologists in the public and private sectors are recommending and applying Papanicolaou smear tests to all women in their fertile years.

This opportunistic screening does not cover women of older ages and no control exists in relation to the frequency of

screening, laboratory quality and follow-up mechanism. Unfortunately, no information on data collection is available for this opportunistic screening. Cervical cancer mortality rates are also not available. The incidence of the disease in Cyprus is 3.9 based on the data of the year 2004 of the Cyprus cancer registry.

Based on the political decision and commitment assigned by the Ministry of Health, the department of Medical and Public Health Services established an ad-hoc cervical screening committee in 2008. The aim of the committee is to prepare a proposal for the development and implementation of a National Screening Programme on Cervical Cancer.

According to the recommendations of the EU Council, Cyprus intends to implement a National Screening Programme on Cervical Cancer in 2009. The aim of the Programme is to reduce the incidence and mortality of cervical cancer by tracing it in the pre-clinical stage.

In cervical screening, one of the most important issues is the collection of a sample from the uterus cervix for cytological analysis. The method used is the Papanicolaou smear test. The smear will be taken by gynaecologists. At least two smears will be collected by using an endo-cervical brush and a spatula.

The ad hoc committee will propose that the target group for cervical cancer screening in Cyprus will be women in the age group from 30 to 60 years. They will be checked every 3 years. The number of Cypriot women in that age group is approximately 167,400. According to the population registry, a written invitation will be sent to every eligible woman. Every year about 57,000 women will be screened.

All Cypriot gynaecologists, in both the private and public sectors, will be involved. The smears will be examined by cytologists/histopathologists. The screening programme will come under the responsibility of the Department of the Medical and Public Health Services (MPHS) of the Ministry of Health of Cyprus. More specifically, MPHS will be responsible for the implementation, monitoring and evaluation of the whole programme. The Medical and Public Health Services in coordination with the Information and Technology Department will also develop a computerised system which will be used for data collection and analysis.

The ad hoc committee intends to propose a follow-up system which will be performed in cooperation with the cancer registry (health monitoring unit). It will be based on a call system and a follow-up form will be developed:

(1) Women who should have a normal smear will be informed (in writing) of their results and the date of their next smear.
(2) If the smear should be insufficient or slightly abnormal, women will be contacted by phone and a new appointment, after 3 months, will be arranged.
(3) If the smear should be abnormal, women should also be informed by phone and should be referred to the gynaecologist for colposcopy/colposcopy directed biopsy or other diagnostic procedures, if necessary.

Over the computerised network system, the Ministry of Health will be able to follow-up further steps.

The Government of Cyprus will fund the whole screening programme. Our target is to achieve coverage of at least 80% of the targeted population. The high response of the eligible women will be achieved mainly by the dissemination of information and by a successful health education campaign involving mass media. In addition, the awareness of health professionals will be raised. After the implementation of the National Screening Programme, the HPV vaccination will be introduced for a certain age group of adolescent girls, possibly at the age of 13–14, through school Health Services.

Summary and conclusion: A National Screening Programme for Cervical Cancer will decrease the incidence and mortality of the disease. Cyprus intends to establish a screening programme on cervical cancer in the near future. Women in the age group of 30–60 years will be examined using the Papanicolaou smear test. The Programme will be funded by the Ministry of Health of Cyprus. The Medical and Public Health Services are responsible for the implementation, the coordination, and quality control of the programme. The aim of the programme is to achieve coverage of at least 80% of the targeted population.

Czech Republic

Tachezy R[a], Hamšíková E[a], Šmahelová J[a], Rob L[b]

[a] Department of Experimental Virology, National Reference Laboratory for Papillomaviruses, Institute of Haematology and Blood Transfusion, Prague

[b] Department of Oncogynaecology, Obstetrics and Gynaecology Clinic, Second Medical Faculty, Charles University, Prague

Though lower than in the 1960s, the incidence rates of cervical cancer in the Czech Republic (CR) remain high despite opportunistic screening. In 2005, the incidence was 19.1 and mortality 6.5 per 100,000 women and world standardised rates were 13.5 and 3.9, respectively.[28] The Czech National Health Law from 1966 is still valid and it is the basis for opportunistic screening in the CR today where all women (no age is specified) are entitled to a free preventive gynaecological examination once per year. This prevention visit includes basic colposcopy and a Pap test. All gynaecologists can perform basic colposcopy in their office and it is paid for by the compulsory health insurance. Expert colposcopy is performed only by those specialists who are certified.

Incidence and specific mortality are calculated from data of the National Cancer Registry of the Czech Republic (NCR) (Institute of Health Information and Statistics, Ministry of Health CR) which was established in 1976. Information about cause of death from the Death Certificates is also collected in the NCR database. In the CR, there are 5.2 million women in total and 2.9 million women in the screening age (25–65 years of age).

For the cytological analyses of cervical smears in the CR, there are about 50 laboratories. For the evaluation of cytological slides, the 2001 Bethesda system is used. The data about coverage as well as about the number of annual smears comes from the National Health Insurance Fund. The coverage in women aged younger than 30 years is 33%, 35% in women aged 30–59 years and 17% in women older than 60 years

(period of 3 years). The annual number of cytological smears is approximately 1.5–2 million.

In February 2008, the Ministry of Health of the CR announced the onset of an organised screening programme. The press report announced the following information: (1) The process of the accreditation of the cytological laboratories is to be based on strict criteria. (2) Insurance companies will invite women 25–60 years of age who have not had a cervical smear taken within the last 2 years. Should they not respond, they will be invited again the following year. In 2008, three out of 12 insurance companies sent out the invitation and it is expected that others will follow in the near future. 3. A new screening code for cervicovaginal screening smear has been defined and it is planned that the expected increase in the volume of cervicovaginal smears performed once the organised programme starts will be reimbursed. 4. The cytological laboratories are obligated to keep evidence of the analyses of the screening smears. While these steps are certainly crucial, without the national screening registry, evaluation of the programme performance will not be possible. Nevertheless, the decision of establishment of the registry has been made. Despite EU recommendations, the screening interval in the Czech guidelines is still 1-year but it is planned that if the cytological smear of a woman is normal in two consequent annual examinations, the screening interval will than be extended to 3 years (personal communication).[29,30]

HPV detection is recommended in the Ministry of Health guidelines only for the triage of borderline findings up to 4% of the volume of Pap smears for each laboratory.[30] Even though HPV detection is reimbursed by the insurance companies the test is expensive and therefore not widely used by gynaecologists. On the other hand, there are 30 routine laboratories performing HPV detection which regularly participate in the External Quality Assurance (EQA) programme. The EQA in medical microbiology in the Czech Republic is well organised. It is coordinated by the Accreditation Department of the Centre of Epidemiology and Microbiology of the National Institute of Public Health in Prague. EQA for HPV has been available in the Czech Republic since 2000 and it is prepared by the National Reference Laboratory for Papillomaviruses (NRL PV).[31]

In 2006, deputies of all medical societies, with the exception of the representatives of the Czech Gynaecological and Obstetrical society (CGOS), agreed on the need to implement routine vaccination for girls at the age of 13 years. The CGOS, however, would recommend routine vaccination in girls 15 years old and only on the condition that an organised screening programme in the Czech Republic is established.[32] This recommendation was sent to the Ministry of Health in December 2006 but, so far, there has been no response. Several insurance companies provide partial reimbursement (18–107 EUR; the price of the three doses is approximately 375 EUR) for the vaccination of girls from 12–13 to 15–18 years of age. Several other recommendations for vaccination against HPV were issued by other professional associations.[33,34]

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Denmark

Lynge E, Rygaard C, Bjerregaard B

Institute of Public Health, University of Copenhagen

Denmark has been a high risk country for cervical cancer. When cancer registration started in 1943, the national age-standardised rate (World Standard Population) was 25 per 100,000. Health care in Denmark is tax-paid and organised by regional authorities. Cervical cancer screening started in the 1960s with population-based, organised screening programmes in some counties and a nationwide agreement in 1969 for payment of general practitioners for the taking of opportunistic smears. Two parallel screening systems thus developed, and this led to a high consumption of smears, being 630,000 in 1983 in a population of five million people.

National screening recommendations were issued in 1986 recommending a screening interval of 3 years for women aged 23 to 59 years. An integrated model was implemented, where all cervical smears in Denmark were centrally registered, and screening invitations were sent only to women not already registered with a cervical cytology within the last 3 years. These recommendations were gradually implemented and only reached national coverage by January 1st 2006, where the last of 14 counties extended a previous programme targeting women aged 25 to 45 to also include the younger and older recommended age groups. The integrated system has considerably reduced the number of cervical smears taken, being 425,000 in 2006.

In 2007, the National Board of Health issued a new programme for cervical cancer screening in Denmark recommending screening every third year for women aged 23 to 50, and every fifth year from age 50 to 65 if the latest two smears within the last 10 years were negative. The programme stills builds on the integrated model where women without a registered cervical cytology within the last 3 years are personally invited to have a smear taken free of charge by their general practitioner. Cervical cytology reading is recommended to be concentrated to pathology departments reading a minimum of 15,000 cervical smears per year. No recommendation is made as to the use of conventional or liquid-based cytology. In 2006, liquid-based cytology was used for 44% of the cervical smears in 2006, and computer-assisted reading was used for 51%. All pathology departments are recommended to use the Bethesda-classification. Human papillomavirus (HPV)-testing is recommended for women with ASCUS and as control after treatment for cervical intraepithelial neoplasia (CIN) 2/3. Use of HPV-DNA or HPV-RNA testing is optional. Where HPV-RNA testing is used, this is also recommended for women with LSIL. Women with other types of abnormal cells are referred to colposcopy. Denmark was, by 1st January 2007, administratively restructured into five regions, and it is up to these regions to implement the new recommendations. A nationwide monitoring with ten quality indicators will be implemented, and the results will be validated both by region and nationwide. HPV-vaccination of girls aged 12 with a catch up programme for girls aged 13–15 has been recommended by the National Board of Health.[35] The proposal is currently being negotiated in the Danish Parliament.

Estonia

Veerus P[a], Aasmaa A[b], Raud T[c]

[a] National Institute for Health Development, Tallinn

[b] Cancer Screening Foundation, Tallinn

[c] Tartu University Women's Clinic, Tartu

Estonia has a population of about 1.3 million (Statistics Estonia, 2007). Reliable cancer incidence data is available for Estonia from 1968 when the cancer registration became centralised. All malignant neoplasms and *in situ* cancers have to be reported to the Estonian Cancer Registry (ECR) by physicians and pathologists.[36] Since 2000, the reported incidence and mortality are affected by the data protection act that prevents linkage of the ECR database with the death certificate database.[40]

In the year 2000, the age standardised (world) incidence rate of cervical cancer was 15.5 per 100,000 women-years in Estonia[38] with 162 new cervical cancer cases being detected. In 2004, the world age standardised incidence rate for cervical cancer was 17.5 per 100,000 women with 181 primarily detected cases (ECR unpublished data, 2007).[41] The age standardised (European) mortality rate of cervical cancer in Estonia was 8.1 per 100,000 women-years in 2000. The incidence and mortality rates are about fourfold higher in Estonia than those in neighbouring Finland.[37]

In the year 2006, nationwide organised cervical cancer screening was started in Estonia. According to the National Cancer Strategy, personal invitations to cervical cancer screening have to be mailed to all insured women in the age group of 30 to 59 years with a 5-year interval after a negative test. In 2006, women in the age cohorts of 30, 35, 40, 45, 50 and 55 years were invited to attend cervical cancer screening. Conventional Pap-smear is used for the screening test. Women diagnosed with cervical cancer, without health insurance and having had a Pap-smear in the past 12 months are excluded from the list of invitees.

Pap-smears are taken at 19 clinics by specially educated midwives. Cytological investigations are performed in seven labs. Women have to contact the clinic themselves to be informed about the test result.[39] Gynaecologists treat pathological findings according to the guidelines approved by the Estonian Gynaecologists' Association.[42]

Cervical cancer screening is funded by the Estonian Health Insurance Fund and the National Cancer Strategy. The technical work (mailing of personal invitations and reminders, statistics on attendance rates at different clinics, test results, possible additional investigations) is carried out in cooperation with the Cancer Screening Foundation. To promote participation and increase the awareness of cervical cancer prevention, the Estonian Cancer Society started annual media campaigns in 2007. Human papillomavirus (HPV) vaccination is recommended by the Estonian Gynaecologists' Association, but has not been implemented in Estonia as a national programme.

As the nationwide screening programme started in 2006, only an *ad hoc* audit to check the quality of tests performed in different labs was carried out in 2007.

The unacceptably low population coverage of cervical cancer screening is a major problem to be solved. There is an urgent need for establishing a central electronic screening registry to facilitate the data collection on attendance and test results, and to follow-up women with an abnormal smear. Under-funding and division of work tasks between many parties are main obstacles for improving the efficacy of cervical cancer screening in Estonia.

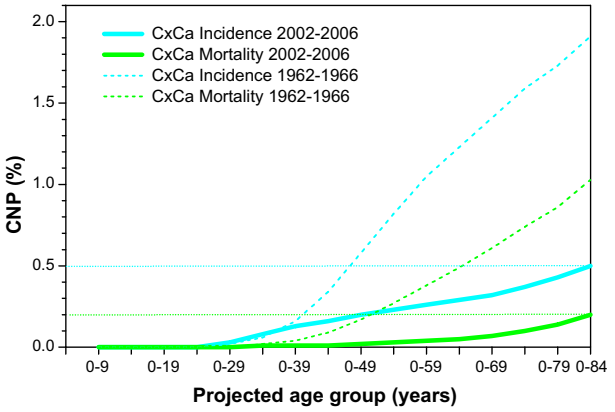

Fig. 1 – Cumulative net probability (%) of cervix carcinoma by age in Finland, 1962–1966 versus 2002–2006 (Finnish Cancer Registry, 2008).

Finland

Leinonen M[a], Nieminen P[b], Anttila A[a]

[a] Mass Screening Registry, Finnish Cancer Registry, Helsinki

[b] Department of Obstetrics and Gynaecology, Helsinki University Central Hospital, Helsinki

In Finland (population 5 million), the nationwide organised cervical cancer screening programme has been in action since the early 1960s and has reduced the cervical cancer burden by 80%.[43] The age-adjusted incidence rate of cervical cancer is nowadays 4 and mortality rate 1 per 100,000 woman-years in our country.[44] The cumulative lifetime probability for cervical cancer in Finland is 0.5% and for death from the disease 0.2% (Fig. 1).

Women aged 30 to 60 years are actively invited to screening using information from the National Population Registry. Attending is free of charge, screening is provided by municipalities from the primary health care budget. The screening interval is 5 years if normal screening results. Some municipalities also invite women aged 25 and/or 65 years. Over 35 years, the registered screening invitational coverage has been almost complete within the centrally targeted screening ages. In 2005, invitational coverage was 98% with about 270,000 invitations and 190,000 screening visits in the programme. The attendance rate per one invitational round is 71% but it varies across ages being lowest among the youngest screening ages.[43,44] Detection rates of any histologically confirmed CIN and invasive cancer within the programme is about 0.4% and 0.01%, respectively.

Samples are taken by trained nurses or midwives in local healthcare centres. Sample quality is under continuous internal control by cytology laboratories of the programme. Confirmation and treatment are an integral part of the routine healthcare system. The invitational and screening results, including histologically confirmed diagnosis, are registered at the Finnish Cancer Registry.[45,46]

Conventionally, screening has been based on Pap-smears. However, novel technological alternatives have been introduced as screening tests with an aim to assess screening effectiveness.[46] Approximately 860,000 women have been allocated to automation-assisted cytology (since 1999), human papillomavirus (HPV) DNA testing (since 2003), or to conventional cytology within the organised programme.[47] In the HPV arm, a sole primary HPV test is done and those who test positive initially are tested with cytology (triage). In each arm, women with cytology equal to low-grade squamous intraepithelial lesion (LSIL) or worse are referred for colposcopy.

The detection rates as well as cross-sectional specificity estimates in automation-assisted screening are very similar to conventional screening.[48] There is variation between laboratories in the performance of both conventional and automation-assisted cytology which does not reflect on effectiveness but may affect cost-effectiveness.[49] Initial results from HPV screening suggest slightly increased positivity rates, follow-up screening recommendations and referral rates compared to conventional cytology.[50]

Only small additional impacts on cervical cancer prevention can be expected from any new technologies. However, results on subsequent cervical cancers and screen-detected pre-cancers are needed for planning optimal screening policies for various tests in the future.[47]

Improving screening attendance and compliance into the organised programme, especially among women 25 to 39 years of age, is a key to further prevent cervical cancer in our country. Interventions to achieve better attendance are needed. Reminding (by letter or phone) women initially non-responding is an option. We are also piloting the self-sampling test instead of re-invitation.

In parallel with improving efforts, the stopping of unnecessary actions should also take place. There are wide and wild testing practises outside the screening programme. Unfortunately, we do not have, as of yet, data to study the magnitude and trends in the use of opportunistic screening. Efforts are needed to avoid overuse of services due to spontaneous screening and, hence, to decrease potential adverse effects and improve overall cost-effectiveness.

Currently, HPV vaccines are not included in the Finnish vaccination programme. A cost-effectiveness evaluation on control of HPV-related disease burden is proceeding up to autumn 2010.

France

Fender M[a], Duport M[b], Ancelle-Park R[c], BALDAUF JJ[d]

[a] Association EVE 69 route du Rhin, 67400 Illkirch Graffenstaden

[b] DMCT – Unité Cancer – Unité transversale Institut de Veille Sanitaire, 12 rue du Val d'Osne, 94415 Saint-Maurice Cedex

[c] Responsable Dépistage des cancers, Bureau MC3, Direction générale de la santé, 14 Avenue Duquesne, 75350 Paris 07 SP

[d] Département de Gynécologie et d'Obstétrique, Hôpital de Hautepierre, Hopitaux Universitaires de Strasbourg, 67098 Strasbourg Cedex

In 2005, the French estimated world age-standardised incidence rate of cervical cancer was 7.1, and the mortality rate reached 1.9 for 100,000 women. Between 1980 and 2000, incidence rates have been regularly declining by 2.9% a year[51,52]; the decrease was smaller between 2000 and 2005 (1.8%). Cervical cancer screening remains mostly opportunistic. Despite over 6 million smears performed each year, only about 57% of the target population is screened within 3 years[53] but among them 45.5% get their second smear between 1 and 2 years.[54]

Nevertheless, since 2003, when the National plan against cancer was launched, several measures have been taken to improve cervical cancer screening. In 2006, the National Committee on Cervical Cancer Screening established Guidelines for organised cervical cancer screening[55] and advised ongoing pilot projects to follow them.

In 2007, the National Institute against Cancer published an update of the cervical screening status, focusing on available data, medical access, local organised initiatives and psychological barriers.[56] In the same year, HPV vaccination guidelines using the quadrivalent vaccine were set,[57,58] recommending vaccination for girls aged 14 and a catch up for girls between 15 and 23 if sexual activity had begun less than 1 year before. It was stated in the document that cervical screening had to be maintained and should be organised. At the moment, a commission on cervical cancer screening is working on how to improve cervical cancer prevention.

Nowadays, only three regional cervical cancer screening programmes are ongoing, financed by National and local grants. One takes place in Martinique, one in Isère and the last one in the Alsace region[59] (the Doubs programme stopped in 2004). These programmes cover about 4% of the French target population (aged 25 to 65 years). At the moment, data are not comparable[60] but starting from 2009 the three programmes will follow the same Guidelines.[55] Two or three new sites should begin organised screening by the end of the year.

Only data from Alsace are presented here. This programme[61] is based on a screening register where all smears taken in the target population are recorded whether the women were invited or not. Almost all smears (95%) are performed by gynaecologists but general practitioners are also involved.

Invitations are sent using the Health insurance lists to women without a smear in the last 3 years. No appointment is given; the choice of the physician is theirs. All smears, opportunistic and organised, are under quality control. Follow-up of abnormal tests is done by contact with the clinicians. Since 2007, a pathology register of all cervical sampling completes the screening register. Interval cancers are known through the two local population-based cancer registers.

Coverage of screening at 3 years reaches 70.6% which is about 10 points above estimated coverage of opportunistic screening in France[53] and quite a good rate in Europe. The overall Positive Predictive Value of colposcopy is low (19.9%) due to the fact that in France, as in Italy, colposcopy is widely available and reimbursed by the health insurance system so that direct referral to colposcopy is a common and recommended attitude for ASC-US and low-grade smears. On the other hand, Positive Predictive Value for col-

poscopy for high grade smears is quite high. Detection rate of CIN2+, projected at 5 years, ranges in the middle values found in the EU.

The Alsatian experience confirms that organising cervical cancer screening in France is possible. The health authorities are still thinking of the best integrated strategy for cervical cancer prevention, including vaccination, screening and treatment of precancerous lesions.

Germany

Mund M[a], Knöpnadel J[a], Schenck U[b], Becker N[c]

[a] National Association of Statutory Health Insurances Physicians, Herbert-Lewin-Platz 2, D-10623 Berlin

[b] Institute of Pathology, Technische Universität München, Ismaningerstrasse 22, D-81675 München

[c] German Cancer Research Centre, Division of Cancer Epidemiology, Im Neuenheimer Feld 280, D-69120 Heidelberg

In the 1960s, cervical cancer was the second most frequent cancer site after breast cancer in both parts of Germany.[62] In the past 50 years, incidence and mortality fell by about 75%, whereby the decrease was lower in East than in West Germany[63] (Fig. 2). Today, with an estimated 6200 new cases and 1660 deaths,[64] cervical cancer has become a relatively rare cancer site.

In West Germany, cervical cancer screening started with the *statutory cervical screening programme* launched in 1971. From the age of 20 and without an upper age limit, statutory health insured women (around 90% of the population) are offered a screening programme without personal invitation including a yearly gynaecological check-up with a conventional PAP smear. Women with private health insurance have equal access to screening. Thus, more than 95% of German women have access to annual screening.[65] The programme is opportunistic and based on self-referral. Currently, 9500 office-based gynaecologists and 1200 cytology laboratories take part in the programme covering 34 million women.

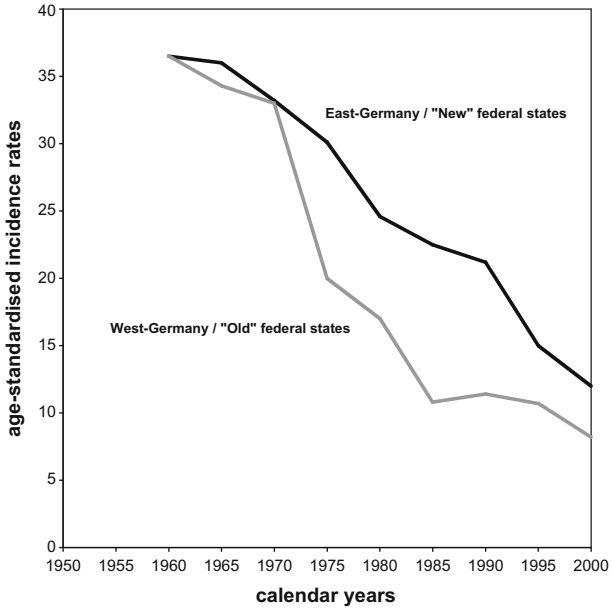

Fig. 2 – Age-standardised incidence rates (world standard) in Germany 1961–2000 (modified from Becker 2003).

Table 1 – Cervical cancer screening in Denmark.

Deaths, 2005	137
Invasive cancer cases, 2003	408
Invasive cancer cases, max. count in 1966	964
Treatment of dysplasia, estimate 2003	5000
Non-negative smears, 2006	38,181
Smears, 2006	424,799

In East Germany, screening for cervical cancer also started in the 1970s; however, full population coverage was not achieved so that the slower decrease of cervical cancer incidence and mortality was largely due to the slower implementation of screening. After the German reunification in 1990, the West German programme was extended to East Germany.

In the past, nationwide regulations for cytology laboratories included standards for qualifications and proficiency testing of the physicians in charge. As from October 2007, additional quality assurance measures have been implemented by the authorities, including maximum workloads for screeners (10 per hour), and standards for re- (or pre-) screening procedures. Furthermore, regular random sample checking of slides for technical quality and correct documentation, as well as mandatory annual statistics on cytological results according to the *Munich* II *classification*, and correlation of abnormal PAP smear findings with histopathological results are part of the regulations. Adherence is controlled by the regional Associations of Statutory Health Insurance Physicians (KV), and non-adherence is sanctioned by withdrawal of the licence to settle accounts.[66]

The interpretation of the smears is based on the *Munich II classification* which deviates in some aspects from the Bethesda system.[67] The main difference is the assignment of moderate dysplasias. In Germany, these abnormalities fall into the category of Group IIID (mild to moderate dysplasia), whereas in the Bethesda system they are assigned to a higher category comprising severe dysplasia and carcinoma *in situ*. Translatability to the WHO system of histological CIN 1–3 classes is limited since categories are partially overlapping[68]; see also Table 1 in Petry et al.[69].

Recommendations for the management of abnormal PAP smears are published in national guidelines[70] in line with international recommendations comprising early recall after about 6 months in case of mild or moderate dysplasia. For repeated abnormal findings (Group IIID, cytology of mild or moderate dysplasia) or higher abnormalities, colposcopic assessment is recommended. For hospitals (including in and out patients), the Federal Office of Quality Assurance defines a low rate of conisations without histological signs of (pre) malignancy as a quality indicator for gynaecological surgery, and publishes annual results at regular intervals.[71] Similar measures for office-based gynaecological surgery are currently lacking.

According to current evaluations based on billing procedures, participation rates are highly variable in different age groups: 80% of women aged from 20 to 40 receive at least one PAP smear within 3 years. From ages 40 to 65, this rate continuously declines to 60%. Thus, the non-attendance rate is 20–40% in the above named age ranges. Only 25% of women

aged under 50 receive PAP smears in yearly intervals[72] (for data based on specific evaluations see[73–76]).

Hungary

Vass L[a], Döbrössy L[b]

[a] Flór F. Hospital of Pest County, Kistarcsa, Semmelweis tér 1

[b] Screening Coordination Department of the National Public Health Institute

The history of *opportunistic* cervical screening in the country goes back to the mid 1950s. It was quite extensive: in the 1980s the annual number of smears taken and analysed exceeded 1 million, the clinical stages of detected cervical abnormalities were favourably shifted, but the mortality levelled off at a rather high level (10 per 100,000 population). It was admitted that the programme had failed, due to the lack of organisation, i.e. personal identification of women screened.

In the early 2000s, a nationwide *organised screening programme* was established in the frame of the National Public Health Programme.[77] Screening strategy is as follows: '*after one negative smear, once in every three years, full gynaecological examination, comprising both colposcopy and cytology, of women between 25 and 64 years of age*'. Since 2004, the cancer screening has been in operation.

The task of the organisation, coordination, monitoring, quality control and evaluation has been delegated by law to the Office of the Chief Medical Officer (CMO). A Screening Coordination Department has been set up which supervises the screening Coordinating Units in the 20 administrative areas (regions, counties), being responsible for management of the implementation. Most importantly, a Central Screening Registry has been established to serve the programme which receives a population list from the database of Health Insurance Fund Administration (HIF), which comprises *personal identification data (name, date of birth, place of birth, mother's name, address), including a social security number (TAJ),* and covers virtually the entire Hungarian population, with the exception of those hysterectomised, those diagnosed and treated with cervical cancer, and those who had received a *screening examination for any reasons outside the programme over the last 3- year period ('quasi organised screening')*.

The established procedure: the 'list' is broken down by counties and sent to the particular primary care physician for *validation* (migration, deceased etc.). It is then sent back to the Coordination Department and used as a *notification list*. A *personal invitation letter* (with a perforated 'slip') is centrally issued. The 'gatekeepers' of the screening are – traditionally – the gynaecologists. The test comprises a complete gynaecological examination including colposcopy; and a smear for cytology, taken by a gynaecologist, analysed by cytologists. Some 40 cytology labs are contracted by the Health Insurance Fund Administration (approximately half of the existing ones where cytological exams are regularly done). The contracted cytology labs are to report back monthly and quarterly, to the Central Screening Registry, data of those who presented themselves for screening. *The rest of the cytology labs not contracted are not obliged to report*. Data collected are the following: the social security number (TAJ) and age of women eligible for screening, the place and date of smear-taking, and cytology examination, and the test results of those smears analysed and classified as '*negative*', '*non-negative*' *and* '*unsatisfactory*'. The *Bethesda categories* – though widely used by cytologists – are *not reported to the Screening Registry.* The test result can be reported *in aggregate* only, and cannot be linked to an individual, because *any data referring to an individual's health status in a way that it might be linked to an individual to communicate to the Screening Registry is strictly forbidden by the data protection law.* The same applies to the confirmatory histology.

So far, some 2 million invitation letters have been sent out but less than 5% of those invited have been registered as screened. In the same time, according to the estimate by HIF, approximately 60% of eligible women attended screening in or outside the programme.[78,79]

Consequences: The difficulties of the transition from extensive opportunistic to organised screening are being reflected in the current problems of population screening:[80]

- The gynaecologists working in private clinics do not report the activity even though they are estimated to screen about 30% of eligible women.
- The gynaecologists do perform a colposcopy 'screening' before every single smear taking action – hence colposcopy does not play any role in the screening process.[81]
- Due to the partially unregulated privatisations both in the field of the gynaecologist and the cytopathologist (outsourcing activities and real privatisations) most of the data are produced outside the organised programme.

There are attempts to break through by

- Educating alternative health care professionals, e.g. midwives (non MDs) as smear takers.
- Finding, establishing and introducing the proper use of colposcopy in the screening process (e.g. follow-up of those with non-negative test results).
- Establishing a centralised database of all histology proven cervical abnormalities, using the above database to trace back the cytodiagnostic history of the woman by linking histology with previous test results ('pathobank').

The insistence of the gynaecological community on their 'historical role' seems to be the major impediment to carrying out an effective screening programme.

There is a long way to go until a 'state-of-the-art' cervical screening programme can be delivered in Hungary because 'old habits die hard'.

Ireland

O'Reilly M

The National Cancer Screening Service, St Joseph's Hospital, Mulgrave St, Limerick

The publication of *A Strategy for Cancer Control in Ireland* 2006 advocates a comprehensive cancer control policy programme in Ireland with cancer screening managed by one organisation. Following this *The National Cancer Screening Service* was established.

A national population based Cervical Screening Programme was introduced in Ireland in autumn 2008. The Na-

tional Cancer Screening Service Board provides governance for the Irish Cervical Screening Programme since January 2007. The Board has introduced a contractual model to include the following:

(1) Contracts with medical practitioners in primary care for smear taking.
(2) A contract for the provision of cytology services with an accredited laboratory following a procurement process and
(3) Service level agreements with colposcopy services.

Arrangements will be made for primary treatment of cervical cancers. The Board is committed to delivering a quality assured service for women for smear taking, analysis and diagnosis. The National Cancer Registry of Ireland reports that on average there are 200 cases of cervical cancer per year and 72 recorded deaths. The average age at diagnosis is 46 years and at death 56 years (Women and Cancer in Ireland 1994–2001 NCRI and Women's Health Council February 2006).

Gynae-Cytology laboratory services have been provided in Ireland since the late 1960s on an opportunistic basis. The Irish Cervical Screening Programme Phase One has offered free smear tests through organised cervical screening to women in the Midwest aged 25–60 years since October 2000.

Planning for a National Cervical Screening Programme. Census data from the Irish Central Statistics Office in 2006 indicate that there are over one million women aged between 25 and 60. With an intended 80% uptake rate for the Programme to be successful, and allowing current policy, then the annual number of smears will amount to 300,000 per annum nationally on a call-recall basis.

The Programme Process. Women aged 25–44 in the target screening population are invited for screening every 3 years and women aged 45–60 are invited every 5 years. Eligible women can join the Programme by invitation from the central office based on the screening register or directly at the discretion of their medical practitioner or by self-registration.

A central office administers the Cervical Screening Register information system that maintains call and recall and manages the computerised Clinical Result Register which records women's cytology, colposcopy, cervical histology and hysterectomy status. This organised approach ensures that appropriate follow-up care is provided.

The smear takers are doctors or nurses that are contracted and/or registered with the Programme. An accredited smear taker training programme is available from a number of Irish institutions in partnership with the Programme. The single test in use in all of Ireland is the liquid-based cytology preparation and kits are provided by the Programme.

In preparation for the national Programme a quality assurance framework was established in 2007 and is reviewing the standards and performance indicators to be launched in 2009. The establishment of multi-disciplinary teams in managing women and the monitoring of quality assurance measures are recommendations that will be addressed.

HPV Vaccine. A Health Technology Assessment (June 2008) on the role of vaccination against HPV in reducing the risk of cervical cancer in Ireland shows that universal HPV vaccination of 12-year-old females would be cost-effective in Ireland. The report also recommends a one-off vaccination programme for 13–15-year-old females. The Minister for Health and Children announced on 5th August, 2008, the preparation and submission of a plan for the introduction of a HPV vaccination programme for 12-year-old girls. This has been delayed due to the current economic climate.

Italy

Ronco G[a], Federici A[b], Zappa M[c]
[a] CPO, Turin
[b] Ministry of Welfare, Rome
[c] ISPO, Florence

In Italy, where the health service is managed by regions, the implementation of organised screening programmes for cervical cancer, with active invitation every third year of women aged 25 to 64 years, was recommended in 1996.

At the end of 1997 only 13% of Italian women 25–64 years old were included in the target populations of organised programmes. In 2007 the corresponding proportion was increased to 72%. Incompleteness is due to implementation still in progress in southern Italy, where start was mostly delayed, and by absent or minimal activity in a few regions.

A set of process indicators for monitoring and standardised tables of aggregated data from which indicators are computed was agreed within the association of organised cervical screening programmes (GISCi, Gruppo Italiano Screening Cervicale). This allowed national surveys that were first conducted by GISCi itself and then by the Osservatorio Nazionale Screening on behalf of the Ministry of Health (now of Welfare). Yearly reports have been published from 2002[82]; an English version is available from 2006.[83–88]

Most organised programmes invite all women independently of their spontaneous activity but some only invite women not screened spontaneously. In 2006, invitational coverage was 75%, suggesting problems in performing all the activities needed for full implementation. There is a systematic registration of invitation, smears, colposcopy, histology and, frequently, also of treatment. However, this is true for what is performed within the organised programmes but little is known about spontaneous activity. This is the main limitation of the Italian system. Compliance to invitation was 38.5% in 2005, with a North to South decreasing trend, leading to a projected 29% of the target population screened in 3 years. However, even in areas where organised programmes are active, a large number of women are screened spontaneously, so that the overall coverage is plausibly at least double.

The detection rate of histologically confirmed high-grade lesions shows a decreasing trend from North to South and in northern Italy from East to West. However, the detection rate within organised programmes is a plausible underestimate of the overall one in the screened population, due to the fact that some women have tests both in and outside the organised programmes. The most widely applied protocol, as a result of colposcopy being widely available and relatively inexpensive, is direct referral to colposcopy of all women with ASC-US or more severe cytology, although in the case of ASC-US some programmes repeat cytology and a few have started triage by HPV testing. This results in a low Positive Predictive

Value (PPV) of cytology referral. PPV values, however, have increased over the past years despite the start of many new programmes, while in a previous period the start of new, less experienced, programmes had led to a decreasing trend for many years. This is plausibly also the result of intensive quality assurance programmes conducted by GISCi.

Implementation of organised screening resulted in a 20% reduction of cancer incidence in Turin.[89] Estimation of the impact at a national level is being performed.

The current Italian guidelines, released in 2006, recommend primary screening by cytology, and are awaiting the results of large randomised trials on HPV testing, one of which, the NTCC study, is being conducted in Italy.[90–93] A review is planned. In the meantime, large demonstration projects are starting.

A programme of prophylactic HPV vaccination, with active invitation of women at age 12 recently started in all regions. Some regions also vaccinated other birth cohorts (16 years and in a few 18 and 25 years).

Latvia

Viberga I[a], Engele L[b]

[a] Riga Stradins University

[b] Latvian Oncology Centre of Riga East Clinical University Hospital

In the 1960s, cytological testing played an important role in the decrease of cervical cancer incidence in Latvia. From 1970 to 1978, 2.5 million women had been cytologically tested and cervical cancer crude incidence rates decreased from 31.7 per 100,000 women in 1963 to 8.9 in 1989. Until the end of the 1980s, the extent of preventive examinations was increasing. Starting from 1983, preventive gynaecological examinations with cytological testing were available for all women aged 18 and over. In 1984, cytological screening was recommended as a compulsory part of the system for the prevention and treatment of disease for all inhabitants. In 1989, due to political and economical changes in the country, the compulsory preventive examinations were terminated. From the mid-1990s, when the number of women's preventive examinations and, therefore, also the amount of cytological testing was rapidly decreasing, the incidence rates rose again (Fig. 3).

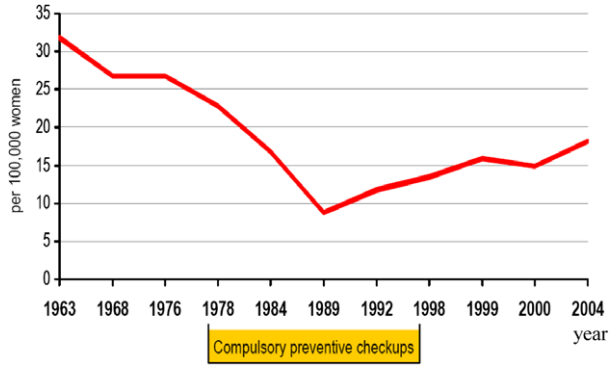

Fig. 3 – The dynamics of the cervical cancer incidence crude rates in Latvia, 1963–2004.

Unfortunately, the last 15–20 years have brought negative changes on the health care system in Latvia. Currently, the cervical cancer incidence and mortality rates in Latvia are very adverse phenomenon (Table 2).

Year 2005 was the date of the reintroduction in Latvia of *cervical cancer screening examinations*. For women aged between 20 and 35, a cytological smear is done once a year, and, if the findings are normal, the smear is repeated every 3 years. In women between the ages of 35 and 70, a cytological smear is done once a year. The entire responsibility for organising and performing the screening examinations is delegated to the general practitioners. A centralised database for the screening register and collecting the results was not created. The screening model, implemented in Latvia, was opportunistic screening with two target population groups.

From 2007, the cancer screening programme was revised in compliance with the European Parliament recommendations on one target age group: 25 – 70 with repeated cytological smears every 3 years. It also provided a role for gynaecologists/obstetricians in the programme. These most recent regulations from 2007 do not contain any specific reference regarding the organisation of the screening programme. This type of screening is considered an ineffective use of funds. The financial incentives without changes in the organisational principles of the screening did not bring the expected results, because cooperation of the population in the screening activities was and is very low. The small numbers of preventive screening examinations over the first 2 years confirm the idea that the decentralised or opportunistic screening can not guarantee the achievement of goals required. However, it should be noted that the above information refers only to the services paid by the state; it is not possible to obtain accurate information about preventive examinations paid for by individuals. The inactivity and unawareness of people, the insufficient availability of services, the overloaded general practitioners, the lack of involvement of gynaecologists who have private outpatient practices in the programme, and the non-existence of a comprehensive implementation programme of screening are unconquerable obstacles in applying screening as a tool to decrease cervical cancer morbidity and mortality.

Table 2 – Crude cervical cancer incidence and mortality per 100,000 women in Latvia, 1999–2005.

	1999	2000	2001	2002	2003	2004	2005
Morbidity	16.4	15.4	14.6	16.6	16.5	18.3	17.7
Mortality	8.3	10.9	9.7	8.7	9.5	10.7	9.9

Currently, in Latvia, there is no management, coordination, and control of cancer, including cervical screening programmes. There is no institution that would collect and store data on the clinical results of examinations (either paid for by the state or by the patient), or which would control the quality of screening examinations – cytological tests, or indeed which would generalise data about the impact of the screening programme on the oncology morbidity rates, the actual improvement of early diagnostics and the decline of mortality. Up to now, no assessment has been made as to the capacity of human resources and technologies in proportion to the required coverage of screening.

As the opportunistic cervical cancer screening initiated in Latvia in 2005 is ineffective, it should be transformed into an organised national cervical cancer screening programme. Now, Latvia is at the stage of needed preliminary activities and preparations prior to implementing the organised cervical cancer screening from 2009.

Lithuania

Kurtinaitis J[a,*], Armonaviciene A[b], Laurinavicius A[c]

[a] Vilnius University Institute of Oncology

[b] Ministry of Health, Lithuania

[c] National Centre of Pathology and Vilnius University, Vilnius

In Lithuania, in 2001–2003, before the onset of the national cervical cancer screening programme, there were high cervical cancer incidence and mortality rates, a low prevalence of early detected cancer and a low detection rate of precancerous lesions. Cervical cancer represented more than 5% of new malignancies among women, and less than 50% of cases were detected at early stages. In 2004, the Ministry of Health adopted the population-based cervical cancer screening programme with a screening interval of 3 years, targeting women at the age of 30–60 years – 750,000 in the country (since 2008 the age interval was increased to 25–60 years). The primary health care centres – more than 350 around the country – were invited to join the screening programme and to implement the screening procedures.

According to the guidelines, the primary health care centre is responsible for the invitation of the women and PAP smear taking. Although general guidance on the invitation procedure has been provided by the programme, much of the practical details were left to be decided by the primary care providers. This led to variation in invitation methods – from verbal communication during a primary care visit to written invitation. A formal individual invitation letter with necessary details to attend is still a rare practice. The visit of the woman to a health care centre in Lithuania is free of charge if she is registered on the list of the centre. It is the responsibility of the GP or a member of the team to provide information to the woman about the screening programme. Each GP is supposed to serve 1500–2500 women of the target population. The funds for cervical cancer screening are allocated at the State Patient Fund (SPF) which is responsible for providing reimbursement for the services. The management of services is enforced by the information system at the SPF and does not allow simultaneous registrations of a woman at different centres. Ten pathology laboratories around the country were certified to assess the conventional PAP smears. Results are reported by the Bethesda system and are stored at the SPF database.

The implementation of nationwide organised cervical screening along the state insurance based health care system was the new and reasonable approach for cervical cancer screening in a country having relatively low health economy resources. The lack of a population-based invitation system is seen as the weakness of the programme. The first year experience has shown that the programme still carries opportunistic features: it was strongly dependent on the frequency of visits of the woman to the GP, the activity of the GP and experience of the PAP smear takers at each centre. The programme has made an evident impact on the rates of detection of the premalignant lesions (carcinoma *in situ*) and increases the number of cases detected at early stages. Major events (invitation, smear taking, PAP test result, visit to the GP for the test result) of the programme are registered in the IS of the SPF and are monitored and evaluated by the SPF along with the Coordinating Committee at the Ministry of Health. Primary care centres are incentivised for increasing the coverage of the population and detection of precancerous lesions and early stages of cervical cancer.

Luxembourg

Scharpantgen A[a], Scheiden R[b,c,d], Wagener C[b], Knolle U[b], Wehenkel A[d], Dippel W[d], Capesius C[d]

[a] Ministry of Health, National Health Directory

[b] Division of Clinical Cytology, National Health Laboratory

[c] Division of Anatomic Pathology, National Health Laboratory

[d] Morphology Tumour Registry, Grand-Duchy of Luxembourg

In 1962, a non-systematic National Cervical Cancer Screening Programme (NCCSP) was established in the Grand-Duchy of Luxembourg. The target population is women aged 15 years and above. Demographic data for the female population are obtained from the annual report of the Central Department for Statistics and Economics Studies (STATEC).

The programme is based on the collaboration of the general practitioners (GPs) and gynaecologists and not on a system of sending out invitations to every woman.[94]

In 1980, the NCCSP was 'institutionalised' by introducing one central division of clinical cytology within the National Health Laboratory responsible for the smear interpretations and the programme administration. In 1990, the second version of the Munich classification, modified by Soost and the recommendations by the Bethesda System, was applied at the national laboratory.[95–97] All materials needed to take the smears are handed out to the doctors involved. The doctors are paid by a system of bonuses given by the Government and a reimbursement by the Health Fund. The number of all doctors taking smears increased from 68 to 105 and the number of gynaecologists increased from 19 (with 28% of smears taken by gynaecologists) to 52 (with 50% of smears taken by gynaecologists).[94] The annual cervical smear is free of charge for every woman. The participation of the women targeted by the programme has increased by approximately 50%

every decade from the early 1970s increasing from 10,950 in 1972 to 70,441 in 1999. Between 1980 and 1999, the number of women at risk taking part in the programme increased from 10.80% to 38.92%.[94,98] The mortality rate has decreased continuously from 6.1/100,000 in 1990 to 0.86/100,000 in 2005.[99]

The success of the Luxembourgish model programme of early diagnosis of cervical cancer is not based on sending out invitations to the target population, but on the principle of one centralised laboratory where all smear interpretation takes place. The strength of this set-up is that the administrative part is reduced to a minimum. The direct collaboration of the three centralised departments (i.e. divisions of cytology and anatomical pathology and the Morphological Tumour Registry) allows an evaluation of each individual case ad hoc. Through a network of closed collaboration between the Department of Preventive Medicine of the National Health Direction and the associations of medical doctors, the programme has improved over time. The target population is informed about the importance of cervical cancer early detection by regular pap smears through the media and through the Family Planning Foundation and the Luxembourgish Foundation against Cancer.

Since March 2008, the HPV vaccination is free of charge for young women aged between 12 and 18 years. Only 12-year-old girls are invited by personal letter. The vaccine is paid for by the Ministry of Health. The principles of this programme have been defined by a contract between the National Health Fund and the Luxembourgish Government.[100]

Malta

Dalmas M[a], Busuttil R[b]

[a] Strategy and Sustainability Division, Ministry of Social Policy, Valletta

[b] Cytology Laboratory, Pathology Department, Mater Dei Hospital, Msida

At present in Malta, there is no organised National Cervical Screening Programme. Since 1978, the public health care centres, St. Luke's Hospital and Mater Dei Hospital, have offered a free cervical cytology screening service. Furthermore, most of the private laboratories on the islands provide a similar service for payment. Consequently, all cancer screening activity in Malta is opportunistic in nature.

Incidence and mortality rates of invasive cervical cancer in the last 36 years have maintained a steady trend, with minor fluctuations, in spite of the fact that screening has become more available over these last decades.[101] A review of the smear history of women diagnosed with invasive cervical cancer between 1992 and 2002 has shown that 44% of these women did not have any reported smears prior to the diagnosis of the invasive lesion, and that 46% of women diagnosed with cancer had rare smears whilst only 10% had regular smears (once every 3 years).[102]

The Eurochip-2 study,[103] funded by the European Commission, allowed for the first time the quantification of the amount of cervical cytology examinations performed on the Maltese islands. Data were collected from seven laboratories (one public and six private) which perform all the cervical screening activity on the islands. Data collected was limited to cervical cytology examinations performed by each laboratory from 2003 – 2005 (3 years).[104]

The data revealed that on average 30,000 smears are performed annually. Organised cervical screening programmes usually cover women between 20 and 69 years of age. In population estimates based on mid-2004, the number of women in this age group was 132,473.[105–107] If an organised screening programme is implemented in the near future, and women in the 20–69 year age group are invited for screening every 3 years, the annual volume of activity can be estimated to amount to about 44,000 smears per year. Currently, with the opportunistic screening scenario prevalent in Malta, only 29,000 smears in this age group are being done annually and at face value this amounts to 66% of the target population.[104] However, the opportunistic screening activity is actually resulting in some women being over-screened while others (who may or may not be more at risk for the disease) are excluded from the potential benefits of the screening process.

The data also revealed a number of interesting findings in the distribution of cytological examination by age. Smear taking peaked between the ages of 25 and 49 years. The activity started to slow down from age 50 years, followed by an even sharper drop in the 6th and 7th decades of life. The highest smear taking rates were between the ages of 30 and 49 years, with corresponding lower rates for the 20–29 age group as well as for women older than 50 years.

Most of the smears are still taken using the conventional spatula/brush methods. Only recently has a private laboratory introduced the liquid based technique. At present, no standardised system in the reporting of smears in Malta is in place. The dyskaryosis/cervical intraepithelial neoplasia (CIN) classification is still very much in use whilst the Bethesda system which provides more detailed information about smear results and better criteria for smear suitability is not applied in every laboratory. HPV typing has been introduced by a number of private laboratories, but not as yet by the public laboratory. The Bethesda system together with HPV typing would definitely improve patient management policies, since management would focus on women with high risk HPV lesions.[102]

Following the recent results of the Maltese action for Eurochip-2 project, one can for the first time analyse the situation of cervical screening activity on the islands. This can be used to assess the current situation so as to identify problems of attendance in specific age groups and to estimate the need of healthcare services for establishing the organised cervical cancer screening programme in the future. This should eventually lead to a number of proposed changes which should improve the uptake of cervical screening on the islands.

Netherlands

Rebolj M, van Ballegooijen M

Erasmus MC, Department of Public Health, Rotterdam

By 2003, the cervical cancer incidence and mortality rates in the Netherlands decreased to 6.2 and 2.0 per 100,000 (European standardised rate), respectively,[108] and were among the lowest in the world. Since 1996, all women aged 30–60 receive an individual invitation every 5 years to have a conventional

Pap smear taken free of charge. The basis for invitations is the population registry. Pap smears are taken by general practitioners (GP) or trained GP assistants.[109] Practice guidelines concerning cervical cancer screening for GPs, pathologists and gynaecologists were published.[110–112] Smears are classified according to the Dutch CISOE-A classification which can be translated into other classifications.[113] While the screening programme is implemented regionally with a complete national coverage, it is financed by central earmarked funds, and is coordinated by a central governmental body. The requirements for the certification of the programme are described in the law on organised screening programmes.

Regular monitoring and evaluation at the regional and the national level are done continuously. Each region appoints a coordinating pathologist who is in charge of the quality control and assurance. This includes providing laboratory-specific feedback. The data used for regional programme monitoring is a combination of information from the organisation in charge of the invitations and that from the regional laboratories, including the linkage to the follow-up data for screened women stored in the computerised national registry of histo- and cytopathology (PALGA). The latter registry is also the basis of the national-level effectiveness evaluation. National evaluation includes programme as well as non-programme screening and its follow-up, and all cancers, screen-detected or not. In PALGA, the woman is identified based on at least her birth date and the first four letters of her maiden name. This registry achieved national coverage in 1990, and the quality of the registration has been improving since.

In 2003, 77% of women aged 30–64 at risk (i.e. with a cervix) had at least one smear in the past 5 years, whereas the response to the screening invitations was 65%.[114] The majority (>50%) of women with cervical cancer are those who were not screened regularly.[115] Whereas the coverage rates among the youngest invited women (30–34 years) improved substantially immediately after 1996, these have not shown any improvement since 1999, and are still lagging behind the rest of the target group by about 10 percentage points. Among the oldest invited women, however, the coverage rate is still increasing. After changes were made to the recommended follow-up (i.e. cessation of follow-up to non-dysplastic smears with inflammatory signs, and those lacking endo-cervical cells), the proportion of primary programme smears requiring any follow-up dropped from 19% to 3% per screening round.[114] This significantly increased the positive predictive value of an abnormal smear. A recent cost-effectiveness analysis estimated that these improvements helped decrease the cost per life-year gained from €15,000 before 1996 to €9000 thereafter.[116]

While at present a conventional Pap smear is the recommended screening tool, much research is also carried out into screening with liquid-based cytology, automated screening, the Human Papillomavirus (HPV) test, and HPV self-sampling. In March 2008, the Health Council advised implementation of the HPV vaccination in 12-year-old girls, and catch-up vaccination for girls aged up to 16 years.[117]

In summary, the 1996 changes helped improve the Dutch cervical cancer screening programme insofar that the uptake of screening within the target age group has increased, whereas the side effects have been considerably limited. Depending on the outcomes of on-going research on incorporating HPV testing and vaccination, the programme may in the future undergo several important changes.

Poland

Chil A[a], Góźdź S[a], Starzewski J[a], Didkowska J[b]

[a] Holycross Cancer Centre, Regional Coordinating Office for Cervical Cancer Screening Programme, Kielce

[b] National Cancer Registry, The Maria Sklodowska-Curie Memorial Cancer Centre, Warszawa

At the beginning of 2007 the organised nationwide cervical cancer screening programme started in Poland. For administrative and logistic help of the programme, coordinating offices were established by the Ministry of Health. There is one central office and 16 regional offices coordinating the Programme. Each Regional Coordinating Office has a contract with the Ministry of Health for conducting and coordinating the programme in its voivodeship. The Central Coordinating Office has a contract with the Ministry of Health for monitoring the effects of the Programme in Poland. About 8 million women aged 25–59 in 3-year intervals will receive invitations for cytology sent out by the National Health Fund (NHF). In order to collect the data of women participating in organised screening, a computer database of prophylaxis was started. The computer database is hosted in central servers and is available across the whole country. Each participant (e.g. ambulatory, colposcopy clinic, regional coordinating offices) has access to the database online and can enter the clinical data into it. Details of screened women are entered into a computer system which consists of three levels. The first level is filled by the out-patient clinic the moment the Pap smear is taken. The second level is filled by the cytology lab when the smear is evaluated. The last one is filled out in the colposcopy clinic if the cytological smear is abnormal and further diagnostic is necessary. In the database, personal and clinical information of invited patients can be registered. After the first months of screening implementation, the following problems occurred:

(1) Most women in Poland had a Pap test taken in an opportunistic screening setting, which was better paid by the NHF, rather than cytology done within the programme.
(2) Gynaecologists were reluctant to enter details of patients into the database system. Moreover, they had to finance computer equipment and access to the internet themselves. Therefore, a very low number of out-patient clinics decided to participate in the Programme.
(3) Very few women attended the colposcopy clinics paticipating in the programme (actually less than 10% of women with abnormal results of their cytology).

Therefore, the data gathered were insufficient and diagnostic and treatment indicators were unreliable.

(1) A large number of invitations sent out in a short time (5.5 million in 3 months) caused, in some regions, a long waiting time for cytological examination.

(2) Low compliance to invitation (about 10%).
(3) No central guidelines on management of abnormal Pap smears.

As a consequence, the NHF decided to change assumptions of the programme and at the beginning of 2008 the following modifications took place:

(A) All gynaecological out-patient clinics which declared an intention to participate in the Programme were accredited by the NHF.
(B) Details of patients could be entered into the database system in cytologic labs (on the basis of questionnaires filled in by out-patient clinics).
(C) Doctors for Pap smears taken within the Programme are better paid by the NHF than for Pap smears taken in the opportunistic screening setting.

In summary, the screening programme in Poland is still developing and resolution of the following problems seems to be most important: (a) Access to out-patient clinics where Pap smears are taken should continue to be improved. (b) More efforts are needed to ensure that all screening smears are assessed in well equipped labs with specialised personnel (for example, reimbursement for smears evaluated in labs not complying with standards of equipment, staff qualifications and skills should be stopped). (c) Appropriate financial support should be provided for colposcopy clinics complying with programme standards. Also, only colposcopic clinics participating in the programme should be reimbursed for follow-up of women with abnormal smears. (d) Initiatives should be taken to ensure that Pap smears taken outside the programme are registered in the central database in order to effectively monitor efforts to increase attendance and to reduce the volume of non-programme smears from women eligible to attend screening e) More efforts should be made to inform women about cervical cancer screening and these should be coordinated with improvements in the invitational system.

Portugal – Central Region

Morais A
Oncology Committee Coordination, Regional Health Administration of Central Portugal, Coimbra

Mortality from cervical cancer in the central region of Portugal has been experiencing a marked decrease since the introduction of cervical cancer screening in 1990; from 6.3 per 100,000 to 2.7 per 100,000 in 2005. This mortality is somewhat lower than those of the rest of the mainland, 7.1 per 100,000 in 1990 and 3 per 100,000 in 2005, and this difference is statistically significant – SMR = 0.70 xi2 = 4.5, $p < 0.05$.[118,119]

The incidence of cervical cancer before the beginning of the screening programme in the Portuguese Central Region was 19.6 per 100,000 in 1989, and rose progressively to 28.4 per 100,000 in 1995. Since then it has decreased progressively.

In Portugal, cervical cancer screening had been kept as an opportunistic action for many years, in almost the entire country. However, at the Central Region in the mainland, a population based cervical cancer screening programme started in 1990.[120] As of June 2006, the coverage attained all of the 109 municipalities of the Central Region.

In 2007, the Southern Region (Alentejo) began the implementation of a cervical cancer screening pilot in 44 municipalities, aiming at launching a national programme in 2009.

The Portuguese Ministry of Health set the goal of covering all of the mainland health regions by the end of 2009 - according to the National Oncologic Plan 2007/2010.[121,122]

In October 2008 the National Directorate of Health began HPV quadrivalent vaccination (covering 6, 11, 16 and 18 types) in young girls aged 13 years, according to the new national vaccination schedule.[123]

The Central Region has a target population of 476,000 women (aged between 25 and 64 years), and approximately 448,000 as eligible population (after removing the women who meet the exclusion criteria). The screening has had a formal centralised organisation since 2005.

The women registered on a health database (each one with a national health number), receives a personal invitation (considering the exclusion criteria) every 3 years. This invitation is issued by the local health centres, providing a specific date to perform the test.

The programme uses conventional Papanicolaou Smear as a primary screening test, performed at local health centres by family doctors. The introduction of liquid-based cytology (routinely used in the Southern Region's pilot) is under evaluation, and it may be adopted in 2010, thereby enlarging the screening interval from 3 to 5 years. The screening is free of cost for women.

Two cytopathology laboratories, with quality assurance methodology, provide support to the screening at the Central Region. Bethesda 2001 classification is used for reporting the smear results. The procedures to maximise quality assurance in these two laboratories include: double registration of results; re-evaluation by a 3rd experienced cytopathologist in case of disagreement; review of previous screening smears for positive cases; review of false positive smears after anatomo-pathological diagnosis; review of negative smears on randomised samples in a fixed periodicity, and cito-histological correlation.

These laboratories have a permanent linkage with the local health centres (feedback of smear results) and with the nine Cervical Pathologic Units (referral centres for gynaecological diagnosis and treatment).

Between 1990 and 2005, this regional programme only had a database system monitoring cytopathologic laboratories. During 2005–2006, a new database system was developed which monitors all interactive modules (family physician/GP, cytopathology laboratory, cervical pathologic units and epidemiologic monitoring, with linkage to the Regional Cancer Registry). This database system still has some difficulties concerning the above mentioned linkages.[124]

Data from 2005 showed a standardised incidence ratio of 14.4 per 100,000 (5.5 per 100,000 of *in situ* cancer, and 8.9 per 100,000 of invasive cancer).[125] These regional data are lower than those of the rest of the mainland; however, we are slightly above the average in the EC.

Before the onset of cervical cancer screening in the Central Region, the staging analysis of cervical cancers in a Central Oncologic Hospital revision (1985) showed that less than

30% of lesions were diagnosed as stage 0–I, and over 50% of lesions were stage III and IV. With the screening implementation, the same authors, in 1997 and 2001 and in the same hospital, found that 89.5% of lesions correspond to stage 0–I, and only 5.9% were advanced cancers (stage III–IV).[126]

Romania

Nicula FA, Şuteu O, Păiş R, Neamţiu L

"Prof. Dr. I. Chiricuţă" Cancer Institute, Cluj-Napoca

With an age standardised mortality rate of 10.64% in 2005, Romania reports the highest mortality from cervical cancer in Europe.[127,128] From 1927, when Aurel Babeş used cervical cytology for diagnosis of cervical cancer,[129] until now, opportunistic screening has been in practice in our country. However, a low number of tests performed with an extremely low coverage of the target population and lack of quality control in diagnosis, treatment and follow-up[130] has taken us to the situation that Romania has the highest incidence and mortality rate of cervical cancer in Europe.[131]

In 2002, the Ministry of Public Health (MPH) took the decision to finance a regional pilot screening programme, using conventional smear, organised by the "Prof. Dr. Ion Chiricuţă" Cancer Institute from Cluj-Napoca.[132] For the rest of the country, opportunistic screening activities were financed too. The pilot programme is population based, targeting 195,000 women aged 25–64 years (3% from the whole of the female target population in Romania).[133] From 2004, the programme was extended regionally to five counties, representing administrative North-West European development regions of the country.

Starting in 2006, the set of indicators for monitoring and standardised tables of aggregated data, proposed by the EUNICE-ECN network, was used to evaluate the regional screening programme. In the first round of the organised screening programme, 16.23% from the target population were tested, due to limited financial resources provided by the MPH. Difficulties appeared first in organising the management unit and then in the implementation unit network, in training people in screening management, in setting standards and criteria, as well as in the protocols for the cytological laboratories, colposcopies and treatment units. There were also problems in financing.[132,134]

The invitational system consists of a limited number of letters of invitation - personal invitations performed by the general practitioners, mediators from nongovernmental organisations, city-halls and churches. At the beginning, opportunistic screening was also enrolled in the programme.[134,135]

The screening database is connected to the regional cancer registry, which has been a member of ECNR from 2003. Although the cytological results of the screening programme are registered 100%, the histology and treatment data include less than 10%. The referral rate to colposcopy is high, but few are reported,[134] which explains the extremely low positive predictive value of the referral to colposcopy CIN2+. This is the reason why, since 2008, we are implementing new data reporting rules (colposcopy registries).

Quality control guidelines used are regional, according to the European recommendations.[134,136,137] National guidelines are a part of the planning for a potential rollout of the regional programme to the national level, started in 2007, and the national strategy is based on eight regional management units for screening programmes, corresponding to the administrative European development of new regions of Romania.

Organising a national screening programme needs important EU assistance. At the level of screening management, no regional resources are in place. The infrastructure of the screening network is insufficient; the estimated resources available are less than 10% of the necessary amount of resources. It is an urgent necessity to organise a complex project of training, certification and accreditation, as well as some criteria for training centres, management units and implementation units. We also consider less labour-intensive HPV primary screening as a useful new method.

Decision makers in public health at the national and European level do not seem to understand the importance of the screening management units. Their existence, as well as a European School of Screening Management, is mandatory for the quality of all national screening programmes.

Slovak Republic

Masak L

Cancer Institute St.Elizabeth, Bratislava

The Section of Gynaecological Oncology and Section of Colposcopy and Cervical Pathology, as part of the Slovak Gynaecological and Obstetrics Society, recently prepared proposals oriented to the realisation of systematic cervical cancer screening across the whole territory of Slovakia. This proposal was accepted by members of the Slovak parliament and is now a law, No. 661/2007 (since January 1st 2008).

According to this law, cervical cancer screening in Slovakia will be organised from one central point which has the working name 'Reference centre'. The Reference centre will be a governmental institution. The Slovak Ministry of Health Care is responsible for constituting the centre. This centre has been designed to facilitate the written invitation of women to cytological examination and for the monitoring and feedback of the entire cervical cancer screening process.

The screening test is via conventional cytology. Screening starts for women at the age of 23 years and finishes at the age of 64 years if the three previously performed tests have been negative. During the first 2 years of screening we apply 1 year examination intervals. If the first two smears are negative the next examinations should be performed at 3-year intervals. If the woman starts screening later than age 23 years the schedule is the same.

The smears should be evaluated in accredited cytological laboratories which are able to apply and respect the principles accepted by European Union. The results should be evaluated and formulated according to the Bethesda classification.

The detection of HPV is not at the present time a part of screening due to the high price of this test. Health insurance companies are obliged to pay for the detection of HPV for women with cytological confirmation of ASCUS and for women 6 months after conisation for dysplasia using the method HC2.

Of great importance in the introduction of systematic screening is the health education of the female population,

oriented to information on the importance and advantages of screening and its performance and positive consequences.

In our country, the vaccines Cervarix and Silgard (Gardasil) are accepted and have been available since 2007. Both vaccines could be used for girls from the age of 9–10 years and for women under 25–26 years of age. Vaccination is not covered by health insurance companies. Health insurance companies reimburse 10% of the price of the vaccine to girls aged 12 years.

Slovenia

Primic–Žakelj M, Pogačnik A, Uršič–Vrščaj M, Zadnik V
Institute of Oncology, Ljubljana

In Slovenia, opportunistic screening was introduced in regular gynaecological practice in 1960. According to the data of the Cancer Registry of Slovenia, the crude incidence rate of invasive cervical cancer increased from 22.5/100,000 in 1950 to 34/100,000 in 1962 and then decreased to 14/100,000 in 1979, when the incidence was the lowest.[138] Since then, till 1993, there were no major changes, but in 1994 the incidence rate started to increase again and reached 20/100,000 in 2000.[139] Cervical cancer mortality, however, has never been as high in Slovenia as in some Eastern European Countries, though the official cervical cancer mortality is underestimated for about 20%; on the basis of death certificates it is not always possible to distinguish between cervix, corpus and unspecified uterine cancer deaths.[140] The increase in cervical cancer incidence rates in the 1990s was ascribed to the inefficiency of opportunistic screening in Slovenia and in 2003 (after the initial pilot study) the organised screening programme was established.[141] It has its legal basis in several regulations: the Screening Registry with its database on all smear reports and histology reports was included in the Act on Databases in Health Care.[142] The special regulation with standards for cytopathology laboratories was published by the Ministry of Health and laboratories have been reviewed to evaluate whether they comply with these standards.[143] The screening policy was defined with the ministry's recommendation on preventive examinations in primary reproductive health care.[144] National guidelines for quality assurance and control of all procedures involved in cervical cancer screening and treatment of intraepithelial lesions and of cervical cancer were published at the beginning of the programme[145–147] and reviewed in the following years.[148–150] All of these guidelines are available at the web–site of the programme also (http://www.onko-i.si/zora/), but currently in Slovenian language only.

According to the new recommendations, each woman between ages 20 and 64 is to be invited to perform a preventive gynaecological examination together with a PAP smear once every 3 years (after two negative smears) – either by her 'personal' gynaecologist with whom she has already been registered or from the Screening Registry in case she has not been registered yet.[142] All smear reports (in electronic form) from all cytological laboratories are gathered in the central database of the Screening Registry which is linked to the central Population Registry.[142] The Screening Registry also enables the sending of invitations to women whose smear has not been registered in the past 4 years.

Data from the Screening Registry at the Institute of Oncology in Ljubljana also serve to monitor coverage and compliance with screening together with other screening performance indicators. The condition for establishing such an information system was uniform smear reports and standardisation of work in cytopathology laboratories and was introduced during the pilot stage.[143] The National Board nominated by the Ministry of Health supervises the results of the programme.[151]

Four years after the start of the national programme, 70% of women in the target age group (20–64 years) had at least one smear registered in the Screening Registry. The percentage is about 80% till the age of 45 and smaller among older women.[151] In 2006, 228,593 smears have been registered from 205,036 women aged 20–64; 6.1% of screening smears were less adequate or inadequate and in 10.3% some cell abnormality has been found. In 71.8% of women with high grade intraepithelial lesions, the pathology report revealed CIN2 or worse lesions (positive predictive value). In 2006, 160 new cervical cancer patients were registered in the Cancer Registry of Slovenia. The linkage of their data with the Screening Registry enables us to review their screening history; nearly three quarters of these patients did not attend for regular screening. According to the data from the Cancer Registry of Slovenia, the incidence rate of cervical cancer started to decrease, especially in the age group from 35 to 49 years.[151]

Spain

de Sanjosé S[a,b], Ibañez R[a], Ferrer E [a]
[a] Unit of Infections and Cancer, Cancer Epidemiology Research Programme, Institut Català d' Oncologia, Idibell
[b] CIBERESP

Incidence and mortality from cervical cancer (CC) in Spain are in the lower end of the world rankings, similar to those observed in the USA and Canada but double that of Finland. The age-standardised incidence and mortality rates for 100,000 women are 7.6 and 2.2, respectively.[152] These relatively low rates prevented Spanish health authorities from prioritising a population-based screening programme against cervical cancer.

Spain is divided into 17 autonomous communities and each is responsible for its own health policy and management. There is not a unified health data collection system but there are 13 population-based cancer registries that provide good quality data and some also collect information on pre-neoplasic cervical lesions. Spain has a universal Health System and women can access gynaecological clinics free of charge.

All regions have progressively adapted cervical cancer screening recommendations from scientific organisations, especially those issued by the European Union leading to an overall 14 regions with established protocols. Most programmes target women sexually active between 25 and 65 years of age. Over the last decades, opportunistic screening has been the prevalent preventive intervention throughout the different communities. More recently, La Rioja and Castilla & Leon have initiated an organised screening programme while in all other communities there exist organised strategies with limited call-recall systems and monitoring.[153,154]

Currently, cytology is the reference method for cervical screening. Sample collection is performed by gynaecologists and/or midwives in both reproductive and primary health care centres. Colposcopy is widely available and is often performed as a complementary evaluation. Cytologies are to be performed on a 3 yearly basis after two consecutive negative ones. In some regions there is an active educational effort to inform women on cervical cancer prevention activities.[154]

HPV DNA testing is starting to be included as a novel detection and triage tool in Spain. Catalonia is the first region that has included HPV DNA testing in the publicly financed screening protocol and introduced it as a tool in clinical management algorithms of screened women. Women with inadequate screening (aged over 40 years and with no Pap in the previous 5 years), those with atypical squamous abnormalities with unknown significance and those who underwent surgical conisation are eligible for this testing. This new programme was fully implemented during 2007 and first results are expected for 2009. Castilla & Leon is using HPV testing among women over age 34 as an adjuvant to cytology. Extremadura and Andalusia are likely to follow suit and include HPV DNA as a triage tool for abnormal results.

Each community actively evaluates screening coverage and access as well as sexual behaviour through surveys. All communities participate in the 'Encuesta Nacional de Salud' carried out every 2–3 years by the National Office of Statistics. Other sources of information are specific surveys aimed at evaluating screening coverage at a national level.[155,156] Global overall coverage data (% of those female respondents aged 18–69 who self-reported receiving a past smear during the last 3 years) ranges from 50% to 69%.[155–158] In the most recent survey, younger women (30–39 years) reached a coverage of 67%, while women aged 60–69 only 35%.[157] Women in the richest income quintile reached a screening coverage of 65% while among those most disadvantaged only 32% women are screened.[157] Despite general recommendations, many women are often overscreened with annual cytologies. Of the total women screened, approximately 30% undergo cytologies with their private health insurance companies.

Both commercially available HPV vaccines have been authorised in 2006 and 2007 and will be implemented in the immunisation schedules free of charge for one cohort of girls aged between 10 and 14 years in all communities before 2010.[159]

Sweden

Andrae B

Swedish Society of Obstetrics and Gynaecology and the Centre for Research & Development, Uppsala University/ County Council of Gävleborg, Sweden

The Swedish screening programme has been in action since the end of the 1960s. There are National recommendations, the latest revision in 1998, but the 21 counties are autonomous in providing health care and the implementation is therefore regional.[160]

Age limits and intervals for invitation to cervical cancer screening are every 3 years for ages 23–50 years and every 5 years for ages 51 to 60 (with one or two exceptions). Invitations are issued by the laboratories except in Stockholm where there is a special screening office covering several laboratories in the metropolitan area.[161]

Invitations are sent to women who have not had a smear registered in the morphology database for 3 (or 5) years. Fees for a cytological smear differ between 0 and 200SEK (approx. 20€). In some counties a specific time and place for the test is issued in the invitation, while in others, women need to make their own reservations at the antenatal centres.

In Sweden, routine smear taking is performed by midwives at antenatal centres supervised by gynaecologists. The screening invitation usually gives an appointment to such a clinic, but if the woman prefers to go to a doctor on her own initiative, that test is registered and the next invitation is postponed. This is what we call integration of opportunistic and organised screening. Smears outside the programme are usually taken by private gynaecologists, whereas GPs are seldom involved. Coverage is higher in the rural areas where organised screening dominates and personal invitations to screening are the rule.

Computer systems linking cytology registers and invitation have been in action since the 1960s. Today, there are two different database systems used. Terminology for diagnosing cervical cytology varies slightly between laboratories. Since about 2000, a common terminology with only 14 SNOMED codes is recommended but there are still variations regarding the interpretation of ASCUS (atypical squamous cells of undetermined significance).[162]

Sweden has a national population register and every individual has a Personal Identification Number used in all contexts of health care from birth throughout life. This makes is possible to collect and compare health data from registers. A National Cancer Registry has been in practice since 1958 and it is mandatory for all laboratories and clinicians to report all cases of invasive cancers as well as Cancer *in situ*/CIN3 by location (T83) and by the SNOMED classification code. Since 2004 all gynaecological tumours have also been classified by FIGO stage.[163]

There is a list of quality indicators, the most important being coverage of testing within the recommended screening interval in the screening ages.[164] A nationwide audit of cervical screening was performed in connection to the establishment of a national register for the quality control of cervical cancer screening. The screening history of all cervical cancer cases in 1999–2001 could be related to that of population based controls. This audit was published in 2008.[165]

Recent development – a professional network for the coordination of the regional screening programmes is formed in order to optimise the computer systems. The national board of health and welfare and its national registries cooperates with this network in developing standards for mandatory reports of morphology and HPV data concerning all HPV related cases of disease to the central registers.

The responsibility of long term follow-up after diagnosis and treatment of atypical smears is being moved from individual clinics to the screening invitation systems, taking advantage of the computerised call and recall and the use of trained midwives to take the tests. HPV-testing data are to be registered in a detailed standardised format that can be integrated in the screening registers to facilitate the flow of the screening algorithms.

Strengths – Good registers with possibilities of complete linkage allow for good monitoring. Coverage is 79% in the screening ages, Total cervical cancer incidence is 6.6 per 100,000 women (world standard rate).[166]

Drawbacks – Decentralisation has slowed down the coordination necessary for the integration of novel technologies into cervical cancer prevention.

United Kingdom – England

Patnick J[a,b], Lancucki L[a]

[a] NHS Cervical Screening Programme, Sheffield

[b] Oxford University Cancer Screening Research Unit, Cancer Epidemiology Unit, University of Oxford, Oxford

Currently, the NHS Cervical Screening Programme screens 3.4 million women of all ages in England each year.[167] Coverage has dropped to 79.2% of women having been screened in the last 5 years and this is a matter of some concern, particularly as younger women now are less likely to attend for screening than their counterparts in previous generations.[168] Cervical screening coverage rates were maintained at over 80% for a number of years and cervical cancer rates fell from 15 per 100,000 population in 1986 (just before the national screening programme was introduced) to 8.7 per 100,000 in 2005.

In 1988 the organisation of call and recall signalled the official beginning of the NHS Cervical Screening Programme. Screening was targeted at women aged 20 to 64 and performed at least 5 yearly. Smears were largely taken by doctors in general practice and in 1990 a system of payments for General Practitioners (GPs) depending on coverage rates was introduced. Over the next few years coverage rose to over 80% of eligible women having been screened in the previous 5 years.

Quality Assurance (QA) was introduced to the programme in 1994 with the introduction of regional teams which monitor the service locally. They also validate statistical reports produced by the service and ensure services work to national minimum standards. Regular QA visits are carried out for all parts of the service with recommendations for improvement made where needed and followed up as appropriate.

The biggest changes to the screening programme have come in the last 5 years. The requirement for women to be screened 'at least every 5 years' had resulted in a mix of screening frequencies around the country. As a result of an independent audit in 2003 screening intervals were standardised at 3 yearly for women aged 25–49 and 5 yearly for women aged 50–64.[169] The same audit led to the policy decision to raise the age of first invitation to 25. The decision was also made in the same year to convert to Liquid Based Cytology (LBC).[170]

Conversion to LBC is now complete. The latest year's figures from the screening indicate that the proportion of inadequate smears had dropped to 2.9% whereas it had been consistently over 9% since reporting began 10 years earlier.[167] Other benefits of LBC conversion include test results being available sooner for women, with 49% reported within 2 weeks compared with 34% in 2 years previously. Two-week turnaround in laboratories was not even reported before conversion to LBC began.

Over 100,000 women per year are referred to hospital colposcopy clinics for investigation of abnormal cytology following a non-negative screening result.[167] Information systems in cervical screening are not all-encompassing and obtaining timely and accurate information on colposcopy outcome, including histology where appropriate, is difficult and time-consuming. The regional quality assurance teams are a key feature in effective monitoring of colposcopy and histology.

The next few years see a number of challenges ahead for the cervical screening programme in England. Automation of cytology reporting is the subject of a major trial,[171] as is primary HPV testing.[172] Six sentinel sites have implemented HPV triage of borderline and mild abnormalities (equivalent to ASCUS and LSIL) with a view to eventual national roll out.[173]

The Department of Health announced the introduction in September 2008 of an HPV immunisation programme to routinely vaccinate girls 12–13 years of age, with a catch-up for girls up to age 18 years over the next 2 years.[172] This is not expected to have any impact on the screening programme for some years, but may assist in addressing the danger of increasing incidence caused by falling coverage in younger women.

The NHS Cervical Screening Programme is estimated to be saving currently around 3000 lives each year in England.[174] It has been hugely successful in controlling cervical cancer. Over the next few years new technologies will be the topic of much debate and could possibly lead to a redesign of the Programme. However, the basic issue of recruiting women to be screened remains of the highest importance.

Conflict of interest statement

None declared.

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The current state of introduction of HPV vaccination into national immunisation schedules in Europe: Results of the VENICE 2008 survey ☆

D. Lévy-Bruhl[a,], V. Bousquet[a], L.A. King[a], D. O'Flanagan[b], S. Bacci[c], P.L. Lopalco[d], S. Salmaso[c], the country specific VENICE gate keepers and contact points [e]*

[a]*Institut de Veille Sanitaire, Saint-Maurice, France*
[b]*Health Protection Surveillance Centre, Dublin, Ireland*
[c]*Istituto Superiore di Sanita, Rome, Italy*
[d]*European Centre for Disease Prevention and Control, Stockholm, Sweden*

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ABSTRACT

Three surveys have been undertaken in European Union (EU) member states since January 2007, within the European Commission funded Vaccine European New Integrated Collaboration Effort (VENICE) project, to monitor the decision status regarding the introduction of human papillomavirus (HPV) vaccination into national immunisation schedules. A web-based questionnaire was developed and completed online by the 28 countries participating in VENICE. According to the last update (31st December 2008), 15 countries have decided to introduce HPV vaccination into their national immunisation schedule, while another six have started the decision-making process with a recommendation favouring introduction. Varying target populations have been selected by the countries which have introduced vaccination. The number of countries which have made a decision or recommendation has increased from 12 to 21 between October 2007 and December 2008. This survey demonstrates the rapidly evolving nature of HPV vaccine introduction in Europe. A further update should be available in the second half of 2009.

1. Introduction

Two vaccines protecting against human papillomavirus (HPV) infections have recently been licensed in the European Union (EU): a quadrivalent vaccine (Gardasil®), in September 2006, and a bivalent vaccine (Cervarix®), in September 2007. Both vaccines have a prophylactic indication and aim to prevent pre-cancer lesions (CIN II+) and cancers due to persistent infection with HPVs 16 and 18 in women who have not been previously infected with these HPV types. HPV 16 and 18 have been estimated to cause 73–76% of cases of cervical cancer in Europe.[1,2] The quadrivalent vaccine also prevents infection with HPV 6 and 11, viruses responsible for 80–90% of genital warts.[3]

Despite the high efficacy of these two vaccines, the decision to introduce HPV vaccination into a national immunisation schedule is complex and requires thorough epidemiological and economical analyses. Many factors must be considered, for example, the high vaccine cost and the added benefit of vaccination over an effective cervical cancer screening programme.[4]

☆ Vaccine European New Integrated Collaboration Effort.

* *Corresponding author:* Tel.: +33 141796874; fax: +33 141796872.
E-mail address: d.levybruhl@invs.sante.fr (D. Lévy-Bruhl).

[e] See list at http://venice.cineca.org.

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No mechanism allowing the monitoring of decisions taken by each individual country exists in Europe and the vaccine industry represented, up til now, the almost exclusive source of information regarding the status of a newly licensed vaccine in various countries. Within the framework of the VENICE project, we set up a mechanism to gather such information for both the rotavirus and HPV vaccines. Venice was a 3-years European Commission (DG SANCO) sponsored project launched in January 2006 to which 28 European countries participate, 26 EU member states (MS) (all except Malta) and two European Economic Area/European Free Trade Association countries (Iceland and Norway). It aimed to create an EU vaccination network capable of collecting and collating information on MS vaccination programmes and to encourage a rational approach to vaccination policy decision-making.[5] Three surveys were conducted during the project in all Venice participating countries regarding the status of the decision regarding HPV introduction in national immunisation schedules, in early and late 2007[6,7] and in late 2008. For this last round, a shorter version of the questionnaire was developed, aiming at allowing bi-annual updating of the situation, based on a questionnaire of acceptable length. We present the results collected in November and December 2008 through this revised version of the questionnaire. We have tried in the analysis to correlate the decision status regarding HPV vaccination introduction with the data presented in this current issue of the *European Journal of Cancer* regarding national screening policies and coverage as well as cervical cancer mortality data.

2. Materials and methods

2.1. Questionnaire

A web-based questionnaire to explore the decision-making process for the introduction of HPV vaccination was posted on the VENICE website in November 2008. The questionnaire was filled in by the national VENICE project gatekeeper, or a designated contact point, in each participating country, using the dedicated web-based VENICE platform and stored on a secure domain of the website. The questionnaire focused on the current status of the decision regarding HPV vaccination integration into national (or if applicable regional) immunisation schedules and on the undertaking and current status of supporting studies for the introduction decision (disease burden studies, mathematical modelling, economic analysis). Only the results regarding the integration of the vaccination into the immunisation programmes are presented here.

2.2. Data analysis

Data were analysed using Microsoft Excel® and Stata v8®.

3. Results

Completed questionnaires were received from all 28 participating countries. The analysis performed was validated by the participants in January 2009.

3.1. Status of countries concerning the introduction of HPV vaccination (Fig. 1)

The process of introducing a new vaccine into the national immunisation schedule in European countries occurs in two steps: firstly, a recommendation is made by a national vaccine advisory body; secondly, an official decision is taken by the national health authorities. As of the end of December 2008, the advisory bodies in 21 countries (75%) had made a recommendation (in all cases positive) regarding the introduction of HPV vaccination into their national immunisation schedules. The national health authorities in 15 of these countries (54% of the 28 participating countries) subsequently took the decision to introduce HPV vaccination into their national immunisation schedule (Austria, Belgium, Denmark, France, Germany, Greece, Italy, Ireland, Luxembourg, Norway, Portugal, Romania, Spain, The Netherlands and the United Kingdom). These countries are, in the majority, located in the Western part of Europe. No recommendation has been made so far in the remaining seven countries. There was no distinction made in the questionnaire regarding the nature of the HPV vaccine (bivalent or quadrivalent) to be used in the national immunisation schedule.

3.2. Vaccination strategy in countries where HPV vaccination was introduced

The available information is detailed in Tables 1a and 1b. Countries have been grouped according to their decision regarding the implementation or not of an initial catch-up vaccination strategy. In each of the two groups, they have been ranked according to the date of the decision of introduction. The most striking feature is the heterogeneity of the target populations chosen by the different countries for the routine vaccination. Almost half of the countries (7/15) have chosen to target a single year of age, ranging between 12 and 14 years. In the other eight countries in which a multi-cohort age range has been identified as the target for routine vaccination, the lower bound varies between 10 and 12 years of age and the age range involved between 2 and 5 years. Only one country has included in the recommendation the vaccination of boys/young males (Austria). The population targeted by the initial catch-up vaccination activities also varies within the six countries having decided such a strategy at the national level. The lower bound is dependant on the target age for routine vaccination. The upper bound does not, in all countries except one (France), exceed 18 years of age. Only Italy anticipated different catch-up policies across the country, and as such a decision is taken at the regional level.

Regarding who bears the cost of the vaccine, 12 countries have answered that the HPV vaccine was offered free of charge or reimbursed for the target population (Belgium, Denmark, France, Germany, Greece, Italy, Luxembourg, Norway, Portugal, Spain, The Netherlands and the UK). Romania has answered that the vaccine was offered free of charge from the National Cancer Programme and Austria that it was partly paid for by some federal counties. In Sweden, the vaccine will be offered free as of 2010, but is already reimbursed to 12- to 18-years-old adolescent girls through insurance. In Ireland,

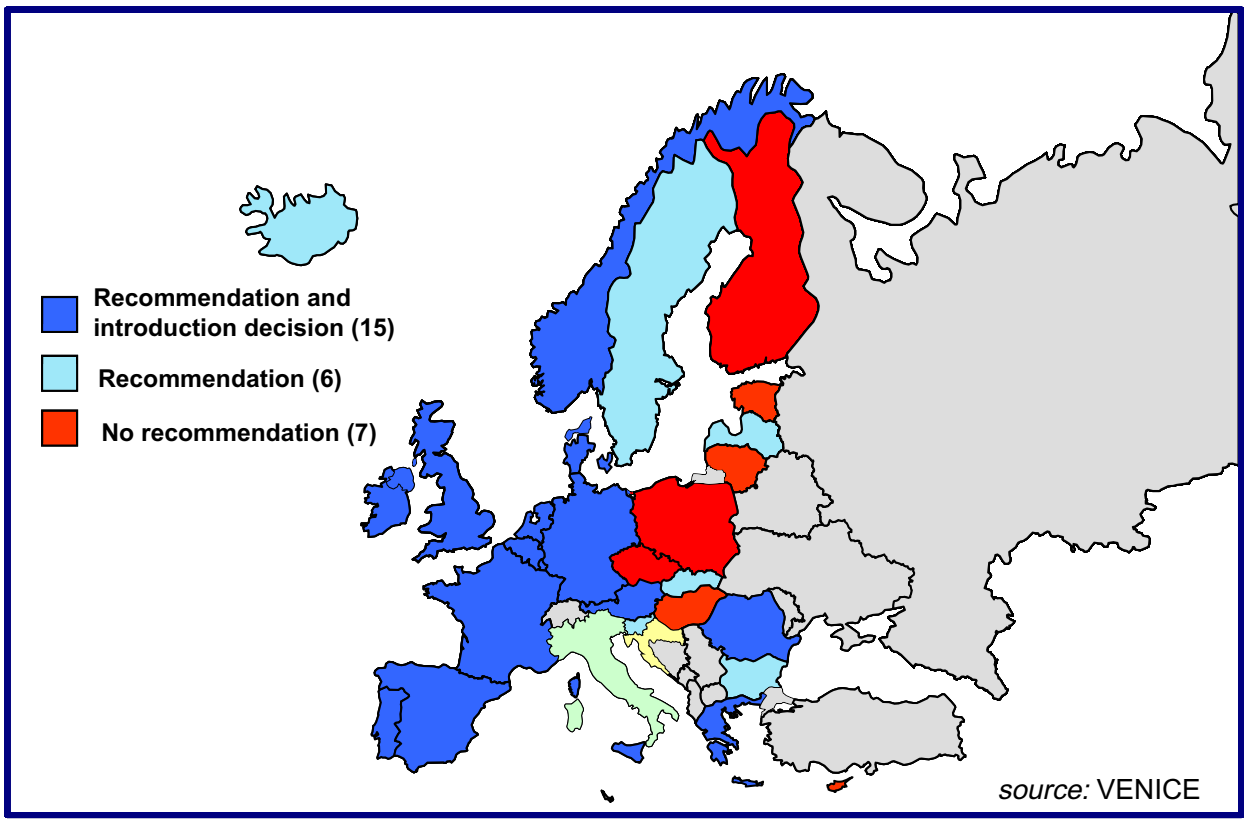

Fig. 1 – Status of HPV introduction decision making process in Europe – Data as of the end of 2008.

Table 1a – Details of HPV vaccination introduction to immunisation schedules (countries with catch-up vaccination).

Countries	Date of decision	Target group for routine vaccination		Catch-up
		Gender	Age	
France	March 2007	Female	14 y	15–23 y (or having started sexual life < 1y ago)
United Kingdom	October 2007	Female	12–13 y	13–18 y
Portugal	November 2007	Female	13 y	17 y (2009–2011)
Italy	December 2007	Female	11 y	According to regions
Denmark	January 2008	Female	12–14 y	F born in 1993–1995 (13–15 y in 2008) October 2008/end 2010
Luxembourg	March 2008	Female	12 y	13–18 y
Netherlands	November	Female	12 y	13–16 y

the actual implementation of the programme has been postponed as, in the context of the financial crisis, the government has not been able to fund it in 2009.

4. Discussion

This study is the first documentation of the status of European countries regarding HPV vaccination. The very high participation rate in this study indicates the high level of interest in this issue among European countries and the effectiveness of the VENICE network as a means of collecting and sharing vaccination information at a European level.

In a little more than 2 years (up to the end of 2008) after the European licensing of the first HPV vaccine, Gardasil®, the national health authorities of 15 MS decided to introduce HPV vaccination into their national immunisation schedules, while another six countries have started the decision-making process with a recommendation favouring introduction. It is noteworthy that all advisory bodies that made a recommendation advised the introduction of the HPV vaccine and all national health authorities that made a decision opted for the integration of the HPV vaccination into their national immunisation programmes. These results represent very significant increases as compared with those of the previous

Table 1b – Details of HPV vaccination introduction to immunisation schedules (countries without catch-up vaccination).

Countries	Date of decision	Target group for routine vaccination	
		Gender	Age
Austria	November 2006	Both	Females before sexually actives; boys, young males
Germany	March 2007	Female	12–17 y
Spain	October 2007	Female	1 Cohort between 11 and 14 y differing according to region
Belgium	November 2007	Female	10–13 y
Greece	January 2008	Female	12–15 y
Ireland	August 2008	Female	12–13 y
Norway	December 2008	Female	12 y
Romania	2008	Female	10–11 y

survey conducted in Autumn 2007. At that time, the advisory bodies in 12 countries (44%) had made a recommendation regarding the introduction of HPV vaccination into their national immunisation schedules and the national health authorities in five of these countries (Austria, Germany, France, Italy and the UK) had subsequently taken the decision to introduce HPV vaccination into their national immunisation schedules. This suggests a high public health priority given to HPV vaccination which probably reflects the high expected gain from a vaccine that can prevent cancer.

This contrasts with the situation regarding the rotavirus vaccination. Although the two rotavirus vaccines were licensed a few months before Gardasil®, a similar survey to the one described here for HPV vaccination has shown that out of the 23 countries who provided information at the end of 2008, only nine have made a recommendation regarding the inclusion or not of this vaccination in their immunisation schedules.

The survey results show that the countries which decided to introduce HPV vaccination adopted varying vaccination policies. This is particularly evident in terms of target ages and catch-up campaigns. Such a result is not unexpected considering the variety in national immunisation programme delivery services and diversity of health service infrastructures in European countries. Our short version of the questionnaire did not allow us to further document the anticipated or current modalities of delivery of the vaccine. Regardless of the vaccination policy adopted, all but two countries out of the 15 countries with an effective integration into national immunisation schedules have chosen to offer the vaccine free or to reimburse it. The data collected in the survey do not allow us to be sure that in all countries with a reimbursement policy, the cost of the vaccine will be fully reimbursed.

Our data suggests that there may be two different profiles within the 13 countries which have not, at least as of early 2009, introduced HPV vaccination. The first category would include countries with a very effective control of cervical cancer through a high coverage of the screening programme, making routine HPV vaccination cost-effectiveness questionable. This category includes three countries, located in the Northern part of Europe, Finland, Sweden and Iceland. All three have a nationwide screening policy with coverage of at least 70% of the target population.[8,9] Their standardised incidence rates of cervical cancer were below 10 for 100,000 women-years and their mortality rates below 1 for 100,000 women-years in 2004.[10] The second category would include countries which have, for the vast majority, a lower performance of the screening programme. In the remaining 10 countries which have not yet integrated HPV vaccination into their national immunisation schedules, all situated in the Eastern part of Europe, only three (Estonia, Slovenia and Hungary) have a nationwide screening policy.[8] Within the nine countries for which cervical cancer incidence data are available (all but Bulgaria), they all have an incidence above 10 per 100,000 women-years and seven have an incidence of 18 per 100,000 women-years or above.[10] The nine countries for which cervical cancer mortality rates are presented in this current issue of the *European Journal of Cancer* (all but Cyprus) show values above 4 per 100,000 women-years and, even more strikingly, they rank second to tenth when countries are graded by decreasing mortality rates.[11] This situation may at least partly reflect the insufficient financial resources to fund a comprehensive screening programme in those countries, a situation which may also hamper the inclusion of the expensive HPV vaccine into their routine immunisation schedules. The comparison of the national per capita gross domestic product (GDP) of the 21 countries where a recommendation of introduction has been made (20,600 €) with one of the seven countries with no recommendation so far (13,140 €) could indeed reflect a financial barrier to the decision, although these two groups of countries may differ for other reasons that also contribute to the decision making process. It therefore appears from this analysis that, at least as of early 2009, the countries which have not yet introduced the vaccine into their national immunisation schedules are, in the vast majority, those where the impact of the vaccination is expected to be the highest due to the high epidemiological burden of cervical cancer and the insufficient implementation of screening activities. The postponing of the implementation of the vaccination programme in Ireland for financial reasons is a source of concern for the sustainability of HPV vaccination programmes in the EU.

A new update will be launched in the second half of 2009. It should allow the assessment of the changes that have occurred in 2009. It will be carried out within the VENICE 2 project, funded by the European Centre for Disease Prevention and Control, which took over VENICE in early 2009. It will encompass additional aspects of HPV vaccination programmes such as vaccination delivery strategies and monitoring activities which were not covered in the 2008 survey. Thanks to VENICE 2, this first experience of close monitoring

of the vaccination decision making process and of regular exchanges of information between member states regarding decisions taken will be maintained and extended to HPV vaccination implementation and evaluation strategies and to other vaccines.

Conflict of interest statement

None declared.

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What's next? Perspectives and future needs of cervical screening in Europe in the era of molecular testing and vaccination

Elsebeth Lynge[a,*], *Ahti Antilla*[b], *Marc Arbyn*[c], *Nereo Segnan*[d], *Guglielmo Ronco*[d]

[a]*Institute of Public Health, University of Copenhagen, Østre Farimagsgade 5, DK 1014 København K, Denmark*
[b]*Finnish Cancer Registry, Helsinki, Finland*
[c]*Scientific Institute of Public Health, Brussels, Belgium*
[d]*Centro per la Prevenzione Oncologica, Torino, Italy*

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ABSTRACT

Aim: To outline the perspectives for future control of cervical cancer in Europe.
Methods: Review of current status for major cervical cancer control tools. The review was based on PubMed searches for cervical cancer prevention, Human Papillomavirus, HPV-test, HPV-vaccination, and treatment with large loop excision of the transformation zone, LLETZ.
Results: Recent studies suggest that condom use offers some but not complete protection against HPV-infection. High quality cytology screening with good population coverage reduces the incidence and mortality of cervical cancer. Randomised controlled trials have found HPV-testing to increase the detection rate of cervical intraepithelial neoplasia grade 2+, CIN2+, compared with cytology. Two studies found a decreased detection rate of CIN3+ in the HPV-testing arm at the subsequent screening. Randomised controlled trials found that women not infected with vaccine HPV-types at vaccination are well protected against CIN2+ from these HPV-types, but the vaccine does not protect against CIN2+ from other HPV-types and neither does it protect already HPV infected women. There is an increased risk of adverse obstetric outcomes following excisional treatment.
Conclusions: The future of cervical cancer control may become a diversified strategy, one for non-vaccinated birth cohorts and another for vaccinated cohorts. It will take another 50 years before the non-vaccinated cohorts have passed the screening age. With the current uncertainty concerning the long term protection from HPV-vaccination it will furthermore be precautionary to continue screening practice for the first cohorts of HPV-vaccinated women. Organised vaccination and screening programmes with good record keeping are necessary to optimise the future control of cervical cancer.

1. Introduction

The control of cervical cancer has a long and relatively successful history in countries with adequate resources and infrastructure. Surgical treatment of uterine cancer started in the 1890s, and radium treatment was added in the 1920s. However, control of cervical cancer took a new turn in the 1950s when Pap smears started to be used for screening of

* *Corresponding author:* Tel.: +45 35 32 76 35; fax: +45 35 32 73 83.
E-mail address: elsebeth@pubhealth.ku.dk (E. Lynge).
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the cervical mucosa for precursor lesions. Cervical cancer screening is a well established practice in Europe, as documented in the European Guidelines for Quality Assurance in Cervical Cancer Screening.[1–3] In the 1990s, the identification of human papillomavirus (HPV) infection as a necessary step in the development of cervical cancer further expanded the possibilities for disease control. Public health authorities are now faced with the question of how to optimise disease control given the extended battery of tools. It is the purpose of this paper to discuss the future of cervical cancer control in Europe.

2. Biology of cervical cancer

The cervix uteri is only 2–3 cm long, but this small organ nevertheless harbours the second most common cancer in women.[4] At present, cervical cancer constitutes 15% of female cancers in developing countries, and 3.6% in developed countries. In the pre-screening era of the Nordic countries, cervical cancer constituted 10% of female cancers.[5] Cervical cancer originates in the mucosal layer, mainly in the transformation zone, starting with formation of dysplastic cells along the basal membrane, spreading to the entire depth of the mucosal layer, and finally invading the underlying tissue. Dysplasia, or cervical intraepithelial neoplasia, CIN, is an unstable condition which can both progress to invasive cancer, and regress to normal mucosa. CIN3 is supposed to be the last stage before invasion. In a recent 30 year follow-up study, one third of untreated CIN3 cases had progressed to invasive cervical cancer.[6]

It has been known for a long time that the risk of cervical cancer varies both geographically and by socio-economic status. The disease is common in prostitutes and rare in nuns, and the risk increases with number of sexual partners, with age at first intercourse, and with other aspects of sexual life. It is, however, only with the understanding of the essential role of HPV-infection in the disease aetiology that cervical cancer has been named a sexually transmitted disease.

In 1985, zur Hausen et al.[7] found DNA sequences of human papillomavirus in cervical carcinoma cells. In 1992, Muñoz et al.[8] published the first of a series of case–control studies showing HPV-infection to be an overwhelmingly strong risk factor for development of cervical cancer. In 1995, Bosch et al.[9] found that high risk types of HPV were present in virtually all specimens of cervical cancer collected from around the world. These findings formed the key elements when the International Agency for Research on Cancer in 1995 concluded that HPV 16 and 18 were carcinogenic to humans.[10] In 2007 this list was extended to include HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 66.[11] Studies of the prevalence of HPV-infection show that a large proportion of young women in the early phase of their sexual life carry an HPV-infection. However, the majority of these women clear their infection, and the prevalence decreases after the age of 30.[12] Cervical cancer will originate primarily in women with a persistent high risk HPV-infection, but only a fraction of these women will develop cancer. Persistent infection with high risk types of human papillomavirus is therefore a necessary, but not a sufficient, cause of cervical cancer. These aspects of the disease aetiology have to be taken into account in deciding on the optimal control of cervical cancer.

In the following text, the presently available cervical cancer control tools, see Fig. 1, will be described briefly, and thereafter the future combination of these tools as a public health policy in Europe will be discussed.

3. Primary prevention

The high risk types of HPV are sexually transmitted, and the question therefore arises whether transmission can be avoided or limited. While postponement of marriage age or age of onset of sexual activity may be considered in some parts of the world, the relevant tool in the European context is use of condoms.

A meta-analysis of cross-sectional studies using broad measures of condom use found condoms not to protect against infection with HPV.[13] A recent prospective study from the Unites States following 18 to 22-year-old undergraduate women at the start of their sexual life found, however, that incident HPV-infections decreased with increasing condom use by partners. Incident HPV-infection was 70% lower among those always using condoms compared with those using condoms in less than 5% of intercourses, hazard ratio 0.3 (95% confidence interval [CI] 0.1–0.6).[14] These data are supported by a randomised controlled trial undertaken in women attending a colposcopy clinic in the Netherlands. Included were women with an abnormal cervical smear and/or colposcopy and/or histology confirmed CIN, grade unspecified. Excluded were women surgically treated for their lesion and with regular condom use at baseline. Willing couples were randomised to condom use for at least 3 months or to controls. Women were followed up by colposcopy, HPV-testing, and cervical smears. The 2-year cumulative regression rate of CIN was 53% in the condom group versus 35% in the noncondom group ($p = 0.03$), and the 2-year cumulative rate of HPV clearance was 23% in the condom group versus 4% in the noncondom group ($p = 0.02$). The study thus showed that condom use promoted regression of CIN and clearance of HPV.[15] Condom use thus seems to be a method for limiting the risk of HPV-infection, and it may in this way serve as a supplementary tool for primary prevention of cervical cancer.

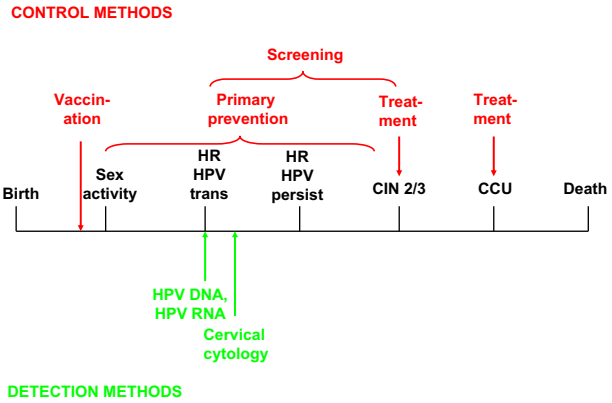

Fig. 1 – Natural history of cervical cancer. Control and detection methods at the various steps.

4. Secondary prevention (screening)

Cervical cancer screening aims at decreasing the incidence of, and the mortality from, cervical cancer by detection of abnormal cells/HPV-infection indicative of dysplasia in the cervical mucosa. Suspected findings are assessed by repeated testing and/or colposcopy, and biopsy confirmed lesions are treated. With surgical removal or destruction of the dysplasia, the potential progression towards invasive cervical cancer can be stopped. Based on follow-up studies of women with negative screening tests, it has been estimated that high quality screening with good population coverage reduces cervical cancer incidence by 80% or more.[16]

4.1. *Cytology testing*

Exfoliated cells are collected from the ecto- and endocervical mucosa. For the traditional Pap smear, cervical cells are directly fixated on a glass. For liquid based cytology, the cells are suspended in a liquid medium and cleaned before being fixated on a glass in a monolayer. Up until recently, all screening was done manually. Now, computer-assisted screening is possible. Normally a cut-off point is used where e.g. 25% of the specimens are automatically classified as normal and not further examined, whereas the remaining specimens are read manually often with the most abnormal areas highlighted by the computer. Liquid based cytology, LBC, specimens can also be handled with computer-assisted reading. Over time different classification systems have been used for cytology specimens. The systems though have two elements in common. Specimens are classified into satisfactory and unsatisfactory, and the satisfactory specimens are graded. In the presently used Bethesda 2001 classification, satisfactory specimens are for squamous cells divided into the following main groups: normal, atypical squamous cells of undetermined significance (ASC-US), low grade squamous intraepithelial lesions (LSIL), and high-grade squamous intraepithelial lesion (HSIL), and a parallel classification is used for endocervical cells.[17] LBC in general yields a lower proportion of unsatisfactory specimens than traditional Pap smears. A meta-analysis did not show significant differences in sensitivity and specificity between the two methods.[18] However, LBC with computer-assisted interpretation was recently found to have higher sensitivity than conventional cytology.[19]

4.2. *HPV-testing*

As virtually all cervical cancer cases are now known to originate from persistent high risk (hr) HPV-infections it has also become a possibility to use viral tests in the screening and management of cervical lesions. Both HPV-DNA and HPV-mRNA can be detected in exfoliated cells.

The Hybrid Capture 2, HC2, test is the most widely used HPV-DNA test. It screens for the presence of HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68. The result is expressed as the ratio of the sample's light emission compared with the mean of three concurrently tested controls of 1 pg/ml HPV-DNA. Normally, 1 pg/ml is used as the cut-off point for a positive test. The presence of high risk types of HPV-DNA can also be tested for by using polymerase chain reaction (PCR)-enzyme immunoassay, using general primers GP5+ and GP6+ that detect the same HPV-types as listed above plus HPV 66. Pretect HPV-Proofer is an mRNA test able to detect the presence of E6 mRNA from HPV 16 and/or E7 mRNA from HPV 18, 31, 33 and 45. These are some of the most widely used tests, but a number of other HPV tests are available.[20] However, only validated tests should be used, especially in order to have sufficient specificity and to avoid over-referral for further work-up.[21]

4.3. *HPV-testing used in triage in cytology screening*

Screening programmes have applied various policies for women with ASC-US. In some settings, all women with ASC-US are referred to colposcopy, whereas these women in other settings are referred to repeat cytology in 6 or 12 months. Combined data from trials of women with ASC-US cytology show that triage with HPV-DNA is more sensitive and equally specific as triage with cytology, when CIN2+ detection rate is used as the outcome measure.[22] Triage of ASC-US findings with HPV-DNA testing has therefore been introduced in many screening programmes. Specificity of HPV-testing is low in the triage of LSIL. In one study, specificity increased with increasing age and was shown to be acceptable in women over age 35,[23] but further data are warranted. In a recent testing of 953 women referred to colposcopy, the sensitivity and specificity for CIN3+ were 99.5% and 25.4%, respectively, when HC2 testing was used, and 82.2% and 70.4%, respectively, when Pretect HPV-proofer testing was used.[24] In some labs, for instance in Denmark, triage of both ASC-US and LSIL is undertaken using HPV-mRNA testing.

4.4. *HPV-test as the primary screening test*

In order to avoid cervical cancer it is desirable that a screening test has a high sensitivity for progressive CIN lesions. However, it is at the same time necessary to ensure a high specificity, and to avoid treatment of low grade lesions which would have regressed to normal if untreated. A meta-analysis of 25 non-randomised studies compared the sensitivity and specificity of HC2, PCR and cytology using CIN2+ as the disease cut-off point. HC2 had the highest sensitivity and the lowest specificity, and cytology with LSIL as the cut-off point for a positive test had the lowest sensitivity and the highest specificity.[25] A recent, pooled analysis of European studies using CIN3+ as the disease cut-off point and ASC-US+ as the cytology cut-off point found an overall sensitivity of 0.599 for cytology and 0.896 for HPV-testing. The specificity was 0.954 and 0.893, respectively. Both differences diminished with age.[26] In the United States, HPV-testing is accepted as an adjunct to cytology testing for women over the age of 30. This policy has not been adopted in the European guidelines since higher CIN2+detection with HPV-testing, as observed in cross-sectional studies, does not prove that these detected lesions would have progressed to invasive cancer if untreated.

The long term effect of HPV-testing is currently under study in six randomised controlled trials in Europe and one in Canada.[27] In five of these trials, the performance of HPV-testing combined with cytology testing is compared with cytology testing alone. In two trials, HPV-testing as a

stand alone test is compared with cytology testing. The control arms in the trials are offered the standard screening regime with conventional Pap smears or LBC. An overview of the design of European trials has previously been published.[28] Data from the baseline screening round have been published from five of these trials. Although the design varies slightly across the trials, the results unanimously show a higher detection rate of CIN2+ lesions in the HPV-testing arm than in the standard screening arm. In the trials with combined HPV and cytology testing the relative risks were 1.51 in Sweden[29] (age 32–38; HPV positive only: repeat HPV after 12 months, if continued HPV-type specific positive then referral to colposcopy), 1.56 (relative risk calculated from published absolute numbers) in the Netherlands[30] (age 30–60; HPV positive only: repeat both tests after 6 and 18 months and referral if cytology becomes positive or infection persists at 18 months), 1.61 for women below the age of 35 in Italy[31] (HPV positive only: repeat both tests after 12 months and referral if either are positive), and 1.47 for women at age 35 and above in Italy[32] (with direct referral to colposcopy of all HPV positives). In the trials with HPV alone testing, the relative risks were 1.44 (relative risk calculated from published absolute numbers) in Finland[33] (women age 30+, cytological triage), 1.92 for women at age 35 and above and 3.50 for women below the age of 35 (both with direct referral of all HPV positives to colposcopy) in Italy.[34] The latter result suggests that among younger women, HPV-testing with direct referral to colposcopy of all positives plausibly results in the detection of regressive lesions and should therefore be avoided. In the Netherlands with combined testing and referral of HPV positive women only if cytology was also positive or infection was persistent, the positive predictive value of the HPV-test was similar to that of cytology,[35] while the positive predictive value of the HPV-test was remarkably reduced for women over the age of 35 in Italy, where all women with a positive HPV-test were referred directly to colposcopy.[34] These results overall underline the need for adopting appropriate protocols of management of HPV positive women, in order to avoid both over-referral to colposcopy and overtreatment of regressive lesions.

As a very long term follow-up is needed in order to measure the effect of a new screening modality on the incidence of invasive cervical cancer, the effect on the detection rate of CIN3+ at the subsequent screening round has been used as a surrogate endpoint.[26] Data from the trials in Sweden and the Netherlands found HPV-testing to be associated with a reduction in CIN3+ detection at the subsequent screening round, the relative risks being 0.53 (95% CI 0.29–0.98) in Sweden,[29] and 0.45 (95% CI 0.28–0.72) in the Netherlands.[30] The reduction was particularly strong when comparing women who, at the previous screening round, were HPV-negative to those who had normal cytology. This suggests that prolonged screening intervals can be applied in HPV-negative women.

It remains to be seen whether similar results will come out from the other trials. Especially interesting are the trials using HPV-testing as a stand alone test, as a single test is a more attractive screening modality than combined testing. The trial data also need to be reported and analysed from the point of view of the cumulated burden of follow-up testing and treatment in the two trial arms.

5. Vaccination

As cervical cancer only develops in women with persistent hrHPV-infection, cervical cancer could in principle be controlled by prevention and/or treatment of persistent hrHVP-infections. So far, no therapeutic vaccine or other anti-viral treatment is available. Two types of prophylactic HPV-vaccines are available. One is the Gardasil vaccine from Merck, which protects against HPV 16, 18, 6 and 11, of which 16 and 18 are high risk types, and 6 and 11 are the types causing genital warts and benign condylomas.[35,36] The second is the Cervarix vaccine from GSK protecting against HPV 16 and 18.[37] About 70% of invasive cervical cancers derive from infection with HPV 16 and/or 18. Randomised controlled trials show consistently that women who are hrHPV-naive at vaccination are well protected against development of CIN2+ from vaccine-type HPV, the efficacy being nearly 100% for women who have followed the treatment protocol (Table 1). For the total of randomised women, i.e. including those who were vaccine-type HPV positive at entry, the efficacy for CIN2+ from vaccine-type HPV is only at the level of 44–55%, and at the level of 17–20% for CIN2+ from all HPV-types. For women being both HPV16 and 18 naive at entry, the efficacy for CIN2+ from all HPV-types was only 27%. With the presently available prophylactic HPV-vaccines, women therefore have to be vaccinated at an age where they are expected to be hrHPV-naive, this means before sexual life is normally commenced.

So far, trial results represent short term follow-up. The long term surveillance will have to clarify questions concerning the need for booster vaccinations, possible cross protection or further spread of infection with non-vaccine HPV-types. It should be noted that the trial control groups have been vaccinated later, and the trials will therefore provide limited information on the effect of vaccination on cervical cancer incidence and mortality. An official decision to include HPV-vaccination in the national immunisation schedule has been taken in some EU countries, with quite different approaches. However, the situation is rapidly evolving.[38]

6. Treatment

The treatment options for CIN have changed over time. Total hysterectomy was considered the proper treatment of detected precancerous lesions in the early era of cervical cancer screening in the 1960s, though this method was quickly replaced by the uterus-preserving cold knife conisation. Nowadays, the much more conservative treatment with large loop excision of the transformation zone, LLETZ, is the recommended and most commonly used procedure. This treatment method is also known as loop electrosurgical excision procedure, LEEP.

Cold knife conisation has been known for some time to be associated with increased risks of preterm delivery and low birth weight in subsequent pregnancies,[39,40] and the risk of these side-effects was a major reason for the transition to the more conservative treatment. However, a recent meta-analysis found that all excisional treatment procedures were associated with significantly increased risk of adverse obstetrical outcomes.[41] Serious obstetrical outcomes, perinatal mortality and extreme preterm delivery, were only associated

Table 1 – H8V-vaccination protection against CIN2+.

Study	Inclusion criteria	Outcome group	Definition	Vaccine	Placebo	CIN2+ protection Efficacy in % (95%CI)	
				N	N	HPV 16 or 18	All HPV
Future I, Gardasil[35]	16–24 y, ⩽4 sex partners, not pregnant, no history of genital wards or abnormal cytology	Per protocol	Sero and DNA negative for HPV 16 or 18 at enrolment, remained similar for 7 months, no protocol violation	2241	2258	100 (94–100)	NR
	Mean follow- up: 36 months	Unrestricted	Sero and DNA negative for HPV 16 or 18 at enrolment	2667	2684	98 (92–100)	NR
		Intention	Randomised	2723	2732	55 (40–66)	20 (8–31)
Future II, Gardasil[36]	15–26 y, ⩽4 sex partners, not pregnant, no history of abnormal cytology	Per protocol	Sero and DNA negative for HPV 16 or 18 at enrolment, remained similar for 7 months, no protocol violation	5305	5260	98 (86–100)	NR
	Mean follow-up: 36 months	Unrestricted	Sero and DNA negative for HPV 16 or 18 at enrolment	5865	5863	95 (85–99)	NR
		Unrestricted	Sero and DNA negative for HPV 16 and 18 at enrolment	4693	4703	NR	27 (4-–44)
		Intention	Randomised	6087	6080	44 (26–58)	17 (1–31)
PATRICIA Cervarix[37]	15–25 y, ⩽6 sex partners, used contraceptives, had intact cervix Mean follow-up: 14.8 months	Unrestricted	Sero and DNA negative for HPV 16 or 18 at enrolment, with follow-up	7788	7838	90 (53–99)	NR

with cold knife conisation though, while moderately, non statistically significant, elevated risks of serious side-effects were observed after LLETZ: 1.17 (95%CI 0.74–1.87) for perinatal mortality, and 1.20 (95%CI 0.50–2.89) for preterm delivery in weeks 32/34.[42] Because of possible obstetrical side-effects, it is therefore necessary to carefully monitor the treatment burden associated with different screening modalities. Gynaecologists should tailor the management of young women to minimise both residual disease and possible adverse obstetric outcomes.

The result from the Dutch trial on condom use for women with cervical dysplasia suggests the possibility for considering condom use for some months as an alternative first-line treatment in the management of women with CIN,[15] where surgery could then be reserved for persistent lesions. Larger trials on this topic are strongly recommended. Intervention on smoking cessation is also recommended, as a long term follow-up study found an excess risk of smoking related cancers in CIN-patients.[43]

7. Future cervical cancer control

All preventive measures have to be seen in a long term perspective, because a preventive intervention at one point in time will – in most instances – only affect the disease occurrence some years later. This is certainly true for cervical cancer control, and here the time perspective has been radically expanded over time. The naturally occurring incidence of cervical cancer peaks around the age of 50. When organised cervical cancer screening programmes started in the 1960s, many programmes therefore focused on screening women age 40–50. Nowadays, screening starts at a much lower age, for example at age 30 in the Netherlands, at age 25 in the UK, and at age 20 in Iceland. With the implementation of HPV-vaccination, control of cervical cancer will already start at the age of 12. The longer the time interval between costs and benefits of cervical cancer control, the more difficult the long term planning. With HPV-vaccination starting at the age of 12, and screening starting at the age of 25, it will take 13 years before the first HPV-vaccinated cohorts reach screening age, and much progress in the understanding of both cervical cancer aetiology and control is expected in the meantime. However, the length of the interval depends on the catch-up policy, and it will in some countries be much shorter than 13 years.[38]

The long time perspective also implies that a diversified strategy has to be followed in future cervical cancer control. It is common in Europe to offer cervical screening up to the age of 65. This means that if HPV-vaccination at the age of 12 is introduced now, screening of unvaccinated cohorts still has to continue for another 53 years (Fig. 2). Furthermore, vaccination coverage can not be expected to be 100% complete in the targeted cohorts. On the other hand, some sexually inactive girls above the standard vaccination age will certainly also seek HPV-vaccination, as will some sexually active

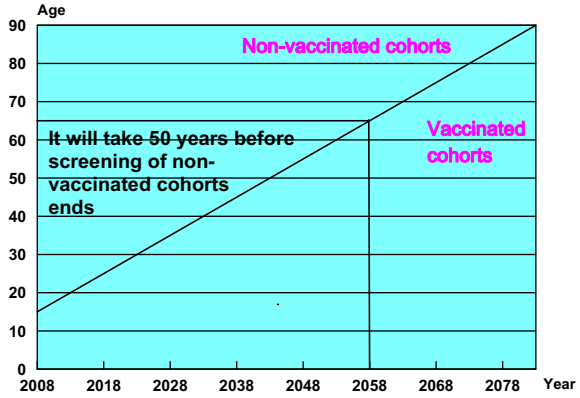

Fig. 2 – Birth cohorts by HPV-vaccination status in Denmark. *Note*: Danish cut-off points used, where girls <15 years by October 2008 will be vaccinated, and where screening stops at age 65.

women attracted by advertisements, etc. The future European population will consequently be divided into four parts: the vaccinated and non-vaccinated women in the birth cohorts targeted by vaccination, and the same two groups in birth cohorts not targeted by vaccination.

7.1. *Non-vaccinated women*

Non-vaccinated women should continue to be screened and monitored following the procedures presently established in the European guidelines for quality assurance in cervical cancer screening.[1] The same is true for women who have been vaccinated after they start sexual life. Screening is, however, as described above, a rapidly developing field. A switch to HPV-testing as the primary screening test is likely, if the screening trials unanimously point to a reduction in CIN3+ detection rates at the subsequent screening round, and if the new modality, by appropriate triage of HPV-positive women, does not increase the burden of follow-up and treatment for participating women.

Policies for HPV-testing in terms of age at start and stop of screening, screening interval, and triage of women with a positive HPV-test will have to be defined. An updated version of the European guidelines,[1] taking the long term trial results into account, are expected to be released in 2010. Further research on the optimal management of HPV positive women, including the use of biomarkers, is ongoing and is a priority.[44] Applying adequate policies will be crucial, also in order to avoid over-referral and overtreatment. The possibility of prolonged screening intervals is attractive as it might be possible in this way to reach a higher coverage. Trials are warranted to follow-up on the Dutch results on alternative strategies to the presently used surgical treatment of CIN.

To ensure optimal screening, organised programmes with good registration, with monitoring, and with quality assurance should be implemented. New parameters and standards for monitoring need to be defined. On the other hand, spontaneous screening is typically associated with overconsumption of screening and less rigorous management of screen-positive subjects. Education of professionals and of women is also an important need.

7.2. *Vaccinated women, short term policy*

'In countries with effective screening programmes with high coverage ... the benefit of adding vaccination to the screening programme will be relatively small in terms of further reducing cervical cancer related mortality'.[45] To maximise the benefit of adding vaccination, a high coverage should therefore be aimed at, in particular of subgroups with low screening participation. An active offer of the vaccine is expected to result in a higher coverage than a reimbursement policy, where there is a risk that the women who are screened will not be vaccinated either.[46]

Vaccinated women should undergo some screening in the future to protect them against lesions developing from the hrHPV infections not prevented by vaccines, and to offer a safety net for those who might not have been HPV-naive at vaccination. Screening will serve as a real life testing of the impact of vaccination in terms of reduction of high-grade CIN. Here, it should be taken into account that the trial participants were followed up much more frequently than normally recommended in screening programmes, where the intervals are of 3 to 5 years. If screening is to be based on HPV-testing it will also allow monitoring of the effect of vaccination in terms of reduction of the infections by vaccine HPV-types and of possible replacement by other types. This, however, will be feasible only in the presence of comprehensive screening registration. On the other hand, good registration of

Table 2 – Future cervical cancer control in Europe.

	HPV-vaccination status	
	Not vaccinated	Vaccinated
Birth cohort offered HPV-vaccination		
Yes	Minority born ⩾ 1993	Majority born ⩾ 1993
No	Majority born < 1993	Minority born < 1993
Screening policy		
Short term	As previously	As previously
Long term	As previously	Monitoring/research topic

Note: Danish cut-off point used, where girls born ⩾1993 will be vaccinated. Girls aged 13–15 years will be vaccinated October–December 2008, and future generations of girls will be vaccinated at the age of 12. However, it should be noted that the cut-off points will vary considerably across European countries depending on the adapted vaccination policy.

vaccination will be essential in order to allow different screening policies among vaccinated and unvaccinated women.

Even if changes of screening schedules will be plausibly appropriate in vaccinated women, the first birth cohorts of vaccinated women should preferably undergo the same screening as the previously unvaccinated birth cohorts. The European guidelines state that 'current evidence does not justify modification of the current guideline recommendations on the age groups and interval for cervical cancer screening in women who have been vaccinated for HPV'.[1] A similar statement comes from the European Centre for Disease Prevention and Control saying that 'in countries where international standards are already applied (starting screening at 25 years old and every 3 or 5 years) the screening strategy should not be changed in the short term'.[45] If this policy is followed, the standard schedule of screening will be offered to all women for approximately the next 15 years or so, i.e. 13 years before the first vaccinated cohorts reach screening age, and 5 years as a monitoring period, where the disease outcome is followed in the first vaccinated birth cohorts (Table 2). The length of this time window depends, however, very much on the chosen catch-up vaccination policy.

7.3. *Vaccinated women, long term policy*

In the long term, HPV-vaccination is, however, expected to reduce the risk of cervical cancer and high-grade CIN. This will reduce the need for screening-induced treatments. However, the detection of cytological abnormalities will be reduced much less than the detection of high-grade CIN, and this will result in a strongly decreased positive predictive value of cytological screening.[46,47] Also, the positive predictive value of HPV-testing will be reduced, as the transition from HPV-infection to high-grade lesions is lower in women infected with non-16/18 HPV-types than in those infected with 16/18 HPV-types.[47,48] This will need adequate management of screen-positive women in order to avoid over-referral and subsequent over-treatment,[49] making the need for organised programmes even more urgent.

To plan for the screening schedule of future generations, the time is shorter than it looks and research in this field is a priority. Because the incidence of high-grade CIN is lower with non-16/18 HPV-infection,[48] the interval free of high-grade lesions after a HPV negative test is expected to be longer in vaccinated than in unvaccinated women. This could allow for a further prolongation of the interval between screens with HPV tests in vaccinated women. However, population based studies are necessary to follow the rates of positive screening tests, the detection rates of CIN2+, and the incidence rates of invasive cervical cancer, in women for whom both the vaccination status and the screening histories are known. Only organised vaccination and screening programmes with systematic record keeping will allow for such studies. The aim is to avoid invasive cervical cancer and at the same time to minimise the negative side-effects such as overtreatment. The extended battery of tools may allow for longer screening intervals and for individualised control of cervical cancer, policies which can only be effectively implemented within organised and well documented programmes.

Conflict of interest statement

Elsebeth Lynge – none declared.

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