EUROPEAN JOURNAL OF CANCER 45 (2009) 2640–2648

available at www.sciencedirect.com

journal homepage: www.ejconline.com

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*

ARTICLE INFO

Article history:
Received 25 February 2009
Received in revised form 5 March 2009
Accepted 22 July 2009
Available online 18 August 2009

Keywords:
Cervical cancer
Mortality
Trend analysis
Europe
European Union

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).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2009.07.018

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

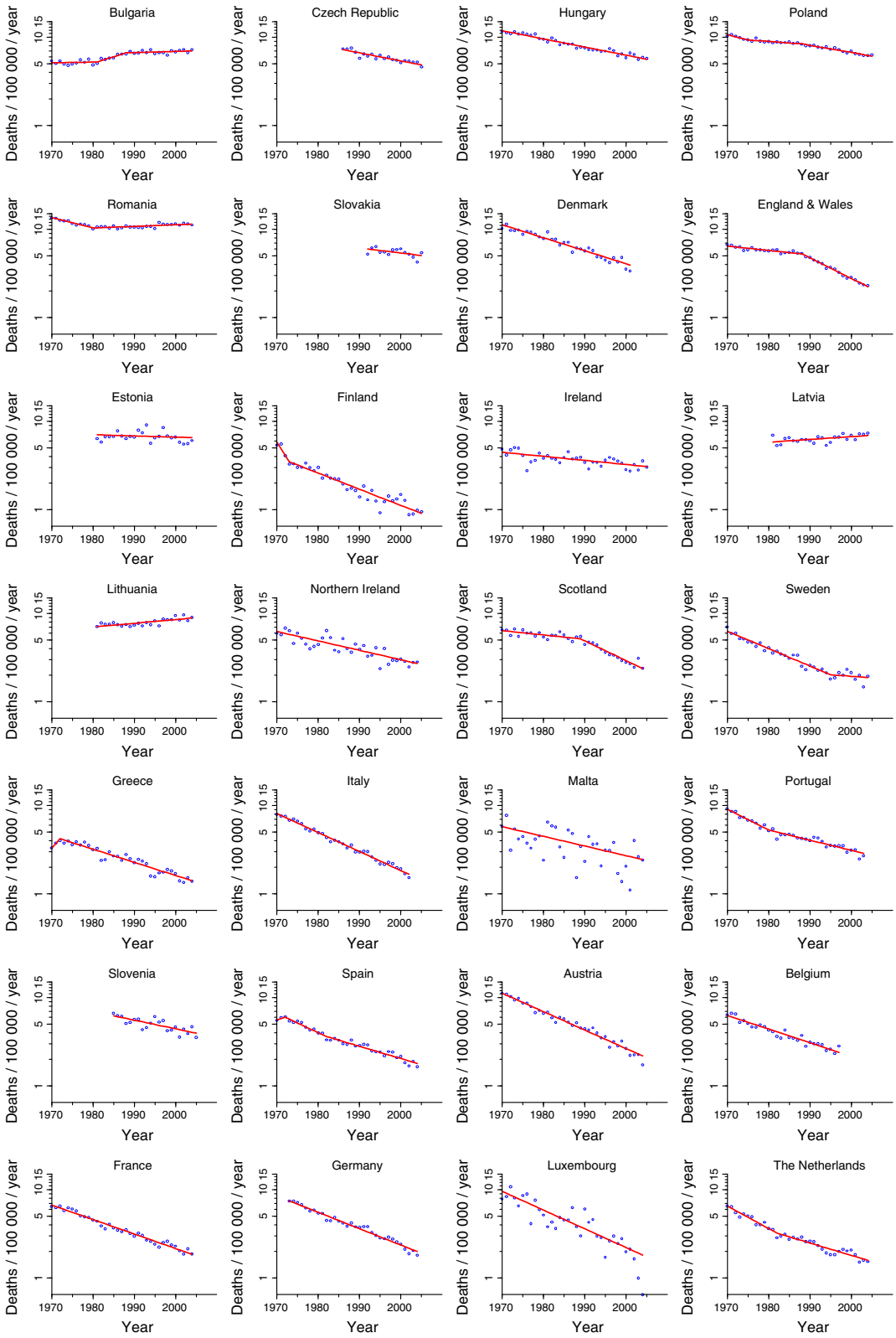

Fig. 1 – World-age-standardised mortality from cervical cancer, corrected for cause of death certification inaccuracies in 26 member states of the EU after 1970. Dots represent annual rates; lines represent linear trends obtained by joinpont regression. Countries are ranked by subcontinent: Eastern Europe: 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).

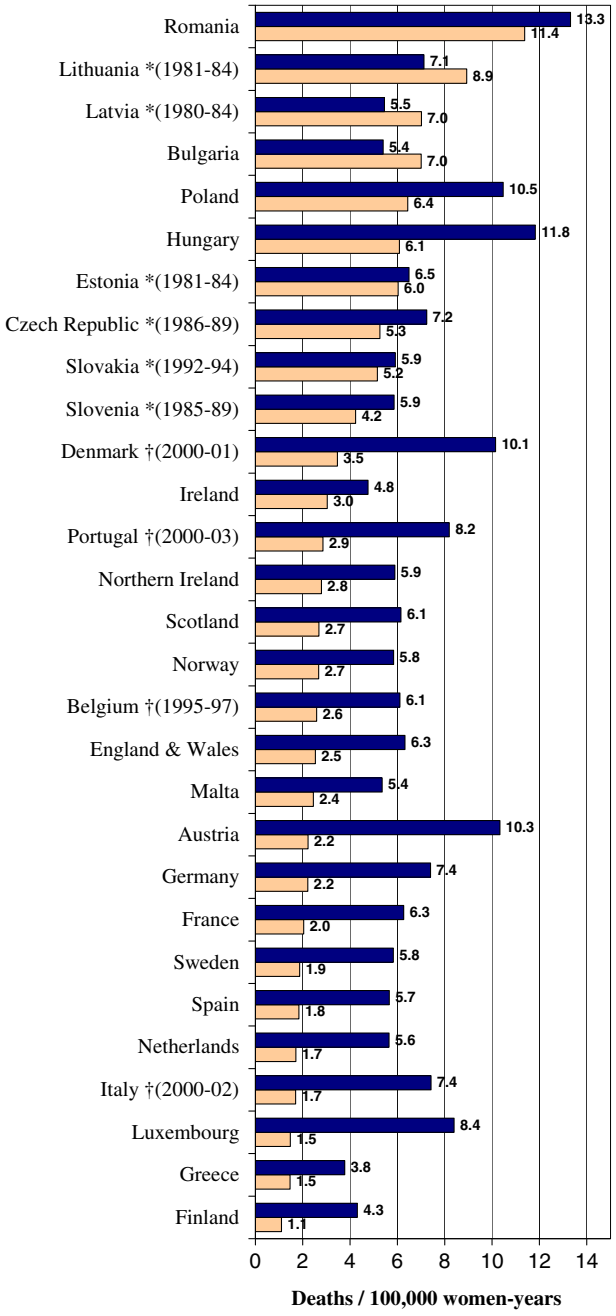

Fig. 2 – World-age-standardised rates of corrected cervical cancer mortality in 1970–1974 (blue bars) and 2000–2004 (orange bars) unless otherwise specified (see †/*). † (for countries where data were not available for 1970–1974, the earliest available period is indicated); * (for countries where data 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

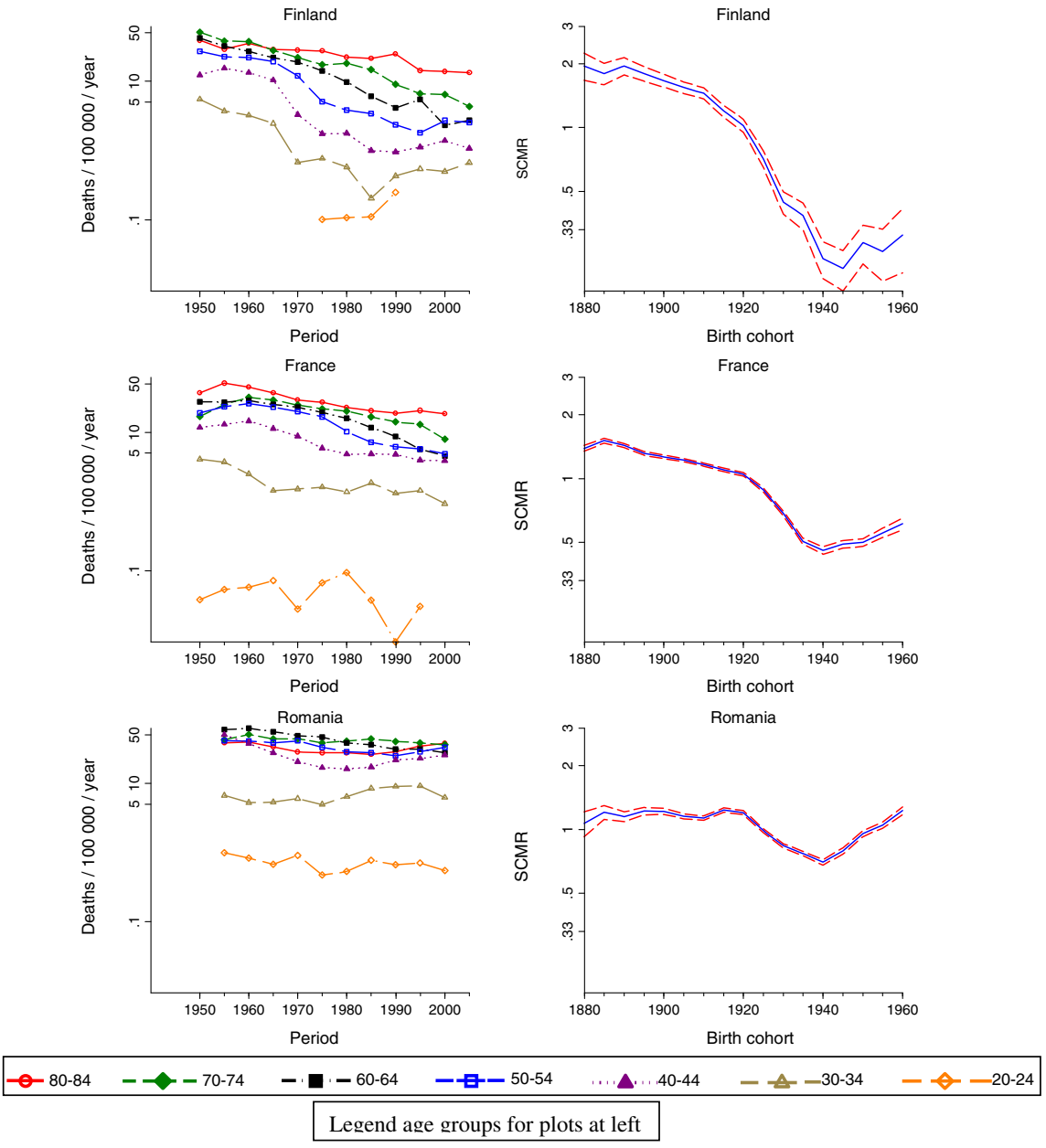

Fig. 3 – Mortality from cervical cancer corrected for certification problems. Left: age-specific* rate by 5-year period; right: standardised cohort mortality ratio (SCMR) by birth cohort with 95% confidence interval (interrupted line). Only the following age groups are displayed in the plots on the left: 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.

Acknowledgements

Financial support was received from (1) the European Commission (Directorate of SANCO, Luxembourg, Grand-Duchy of Luxembourg), through the European Network for Information on Cancer (IARC, Lyon, France) and through the EUROCHIP-3 Network (Istituto Nazionale dei Tumori, Milan, Italy); (2) *IWT* (Institute for the Promotion of Innovation by Science and Technology in Flanders, project number 060081); (3) National Cancer Plan, through the National Health Insurance Institute (Brussels, Belgium); (4) European Research Network of Excellence Cancer Control using Population Registries and Biobanking, funded by the 6th Framework programme (Brussels, Belgium) through the University of Lund (Malmö, Sweden).

REFERENCES

1. Arbyn M, Autier P, Ferlay J. Burden of cervical cancer in the 27 member states of the European Union: estimates for 2004. *Ann Oncol* 2007;**18**:1425–7.
2. IARC Monograph Working Group zur Hausen H, Arbyn M, Villa L, et al. *IARC Monographs on the evaluation of carcinogenic risks to humans. Human papillomaviruses*, vol. 90. Lyon: IARC Press; 2007.
3. IARC. *Cervix cancer screening. IARC Handbooks of Cancer Prevention*, vol. 10. Lyon: IARC Press; 2005.
4. Laara E, Day NE, Hakama M. Trends in mortality from cervical cancer in the Nordic countries: association with organised screening programmes. *Lancet* 1987;**1**:1247–9.
5. Bray F, Loos AH, McCarron P, et al. Trends in cervical squamous cell carcinoma incidence in 13 European countries: changing risk and the effects of screening. *Cancer Epidemiol Biomarkers Prev* 2005;**14**:677–86.
6. Arbyn M, Van Oyen H, Sartor F, Tibaldi F, Molenberghs G. Description of the influence of age, period and cohort effects on cervical cancer mortality by loglinear Poisson models (Belgium, 1955–94). *Arch Public Health* 2002;**60**:73–100.
7. Karim-Kos HE, de Vries E, Soerjomataram I, Lemmens V, Siesling S, Coebergh JW. Recent trends of cancer in Europe: A combined approach of incidence, survival and mortality for 17 cancer sites since the 1990s. *Eur J Cancer* 2008;**44**:1345–89.
8. Adami H-O, Ponten J, Sparen P, Bergstrom R. Survival trend after invasive cervical cancer diagnosis in sweden before and after cytologic screening. 1960–1984. *Cancer* 1994;**73**:140–7.
9. Anttila A, Laara E. Cervix cancer: geographical correlations. In: Sankila R, Demaret E, Hakama M, Lynge E, Schouten LJ, Parkin DM, editors. *Evaluation and monitoring of screening programmes*. Brussels, Luxemburg: Europe against Cancer Programme; 2000.
10. Arbyn M, Geys H. Trend of cervical cancer mortality in Belgium (1954–94): tentative solution for the certification problem of not specified uterine cancer. *Int J Cancer* 2002;**102**:649–54.
11. Loos AH, Bray F, McCarron P, Weiderpass E, Hakama M, Parkin DM. Sheep and goats: separating cervix and corpus uteri from imprecisely coded uterine cancer deaths, for studies of

geographical and temporal variations in mortality. *Eur J Cancer* 2004;**40**:2794–803.
12. Levi F, Lucchini F, Negri E, Franceschi S, La Vecchia C. Cervical cancer mortality among young women in Europe: patterns and trends. *Eur J Cancer* 2000;**36**:2266–71.
13. Jenssen OM, Estève J, Moller H, Renard H. Cancer in the European Community and its member states. *Eur J Cancer* 1990;**26**:1167–256.
14. Goldstein R. Sed10: Patterns of missing data. *Stata Technical Bulletin* 1996;**32**:12–3.
15. Little RJA, Rubin DB. *Statistical analysis with missing data*. 2nd ed. New York: Wiley; 2002.
16. Durrant GB. Imputation methods for handling item-nonresponse in the social sciences: a methodological review. University of Southampton, ESRC National Centre for Research Methods and Southampton Statistical Sciences Research Institute (S3RI), 2005.
17. Arbyn M, Raifu AO. *Trends of cervical cancer mortality in Europe*. Brussels: Scientific Institute of Public Health; 2009. IPH [Report Epidemiology No.:07].
18. Waterhouse JAH, Muir CS, Shanmugaratnam K. *Cancer incidence in five continents*. 4th ed. Lyon: International Agency for Research on Cancer; 1976.
19. Software produced by the Statistical Research and Application Branch, National Cancer Institute [computer program]. Silver Spring, US, 2008.
20. Lerman PM. Fitting segmented regression models by grid search. *Appl Stat* 1980;**29**:77–84.
21. Kim H-J, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. *Stat Med* 2000;**19**:335–51.
22. Devesa SS, Donaldson J, Fears T. Graphical presentation of trends in rates. *Am J Epidemiol* 1995;**141**:300–4.
23. Beral V. Cancer of the cervix: a sexually transmitted infection? *Lancet* 1974;**25**:1037–40.
24. Osmond C, Gardner MJ. Age, period and cohort models applied to cancer mortality rates. *Stat Med* 1982;**1**:245–59.
25. Arbyn M, Raifu AO, Autier P, Ferlay J. Burden of cervical cancer in Europe: estimates for 2004. *Ann Oncol* 2007;**18**:1708–15.
26. Llorca J, Prieto MD, Delgado-Rodr¡guez M. Increase in cervical cancer mortality in Spain, 1951–1991. *J Epidemiol Community Health* 1999;**53**:408–11.
27. Bosch FX. Trends in cervical cancer mortality. *J Epidemiol Community Health* 1999;**53**:392.
28. Llorca J, Rodriguez-Cundin P, Dierssen-Sotos T, Prieto-Salceda D. Cervical cancer mortality is increasing in Spanish women younger than 50. *Cancer Letters* 2006;**240**:36–40.
29. Zakelj MP, Kirn VP, Skrlec F, Selb J. Can we rely on cancer mortality data? Checking the validity of cervical cancer mortality data for Slovenia. *Radiol Oncol* 2002;**35**:243–7.
30. Suzan F, Séblain C, Boussac-Rarebska M, et al. Survey on the distribution of "uterus cancer, cervix corpus cancer and not otherwise specified cancer" among death certificates for cervix cancer and corpus uteri cancer, France. *Bull Epidémiol Hebdom* 2007;**9–10**:79–81.
31. Capocaccia R, Martina L, Inghelmann R, et al. A method to estimate mortality trends when death certificates are imprecisely coded: an application to cervical cancer in Italy. *Int J Cancer* 2009;**124**:1200–5.
32. Parkin DM, Bray FI, Devesa SS. Cancer burden in the year 2000. The global picture. *Eur J Cancer* 2001;**37**:4–66.
33. Laukkanen P, Koskela P, Pukkala E, et al. Time trends in incidence and prevalence of human papillomavirus type 6, 11 and 16 infections in Finland. *J Gen Virol* 2003;**84**:2105–9.
34. Lehtinen M, Kaasila M, Pasanen K, et al. Seroprevalence atlas of infections with oncogenic and non-oncogenic human papillomaviruses in Finland in the 1980s and 1990s. *Int J Cancer* 2006;**119**:2612–9.
35. De Vuyst H, Clifford G, Li N, Franceschi S. HPV infection in Europe. *Eur J Cancer* 2009;**45**(15):2632–9.
36. Arbyn M, Rebolj M, de Kok IM, Becker N, O'Reilly M, Andrae B. The challenges of organising cervical screening programmes in the 15 old member states of the European Union. *Eur J Cancer* 2009;**45**(15):2671–8.
37. Giard RWM, Coebergh JWW, Wijnen JA. Causes of low effectiveness of population screening for cervival cancer. *Ned Tijdschr Geneeskd* 1996;**141**:317–21.
38. Raffle AE. Deaths from cervical cancer began falling before screening programmes were established. *BMJ* 1997;**315**:953–4.
39. Anttila A, Nieminen P. Cervical cancer screening programme in Finland with an example on implementing alternative screening methods. *Coll Antropol* 2007;**31**(Suppl. 2):17–22.
40. Hristova L, Hakama M. Effect of screening for cancer in the Nordic countries on deaths, cost and quality of life up to the year 2017. *Acta Oncol* 1997;**36**(Suppl. 9):1–60.
41. Bielska-Lasota M, Inghelmann R, Poll-Franse L, Capocaccia R. Trends in cervical cancer survival in Europe, 1983–1994: a population-based study. *Gynecol Oncol* 2007;**105**:609–19.
42. Ronco G, Anttila A. Chapter 7: Summary table of key performance indicators. In: Arbyn M, Anttila A, Jordan J, et al., editors. *European guidelines for quality assurance in cervical cancer screening*. 2nd ed. Luxembourg: Office for Official Publications of the European Communities; 2008. p. 231–42.