Tumori, 96: 517-523, 2010

Trends in cervical cancer incidence and mortality in Bulgaria, Estonia, Latvia, Lithuania and Romania

Marc Arbyn[1], Jerome Antoine[1], Zdravka Valerianova[2], Margit Mägi[3], Aivars Stengrevics[4], Giedre Smailyte[5], Ofelia Suteu[6,7], and Andrea Micheli[8]

[1]Unit of Cancer Epidemiology, Scientific Institute of Public Health, Brussels, Belgium; [2]Bulgarian Cancer Registry, Sofia, Bulgaria; [3]Estonian Cancer Registry, Tallinn, Estonia; [4]Latvian Cancer Registry, Riga, Latvia; [5]Lithuanian Cancer Registry, Vilnius, Lithuania; [6]I. Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania; [7]Institute of Oncology, Cluj, Romania; [8]Descriptive Studies and Health Planning Unit, Fondazione IRCCS "Istituto Nazionale dei Tumori", Milan, Italy

ABSTRACT

Objective. The burden of cervical cancer varies considerably in the European Union. In this paper, we describe trends in incidence of and mortality from this cancer in the five most affected member states.

Methods. Data on number of deaths from uterine cancers and the size of the female population of Estonia, Latvia, Lithuania, Bulgaria and Romania were extracted from the WHO mortality database. Mortality rates were corrected for inaccuracies in the death certification of not otherwise specified uterine cancer. Incidence data were obtained from the national cancer registries. Joinpoint regression was used to study the annual variation of corrected and standardized incidence and mortality rates. Changes by birth cohort were assessed for specific age groups and subsequently synthesized by computing standardized cohort incidence/mortality ratios.

Results. Joinpoint regression revealed rising trends of incidence (in Lithuania, Bulgaria and Romania) and of mortality (in Latvia, Lithuania, Bulgaria and Romania). In Estonia, rates were rather stable. Women born between 1940 and 1960 were at continuously increasing risk of both incidence of and mortality from cervical cancer.

Conclusions. Rising trends of cervical cancer in the most affected EU member states reveal a worrying pattern that warrants urgent introduction of effective preventive actions as described in the European guidelines. Free full text available at www.tumorionline.it

Key words: cervical cancer, incidence, mortality, trend analysis, Bulgaria, Estonia, Latvia, Lithuania, Romania, Europe.

Acknowledgments: Financial support was received from: (1) European Commission, Health and Consumer Protection Directorate-General, through the EUROCHIP-3 project (Fondazione IRCCS "Istituto Nazionale dei Tumori", Milan, Italy) and through the European Network for Information on Cancer (IARC, Lyon, France); (2) 7th Framework Program of DG Research of the European Commission through the EUROCOURSE project (Optimization of the Use of Registries for Scientific Excellence in research, Comprehensive Cancer Centre South, Eindhoven, the Netherlands); (3) IWT (Institute for the Promotion of Innovation by Science and Technology in Flanders, project number 060081), Brussels, Belgium.

Correspondence to: Marc Arbyn , Unit of Cancer Epidemiology, Scientific Institute of Public Health, J. Wytsmanstreet 14, B1050 Brussels, Belgium.
Tel +32 26425021;
fax +32 26425410;
e-mail marc.arbyn@wiv-isp.be

Introduction

The burden of cervical cancer varies widely among the member states of the European Union (EU)[1]. The world-age standardized incidence rate for 2004 was estimated to be 10 (expressed per 100,000 women-years) in the 15 older member states, situated in West and South Europe, but was 17 among the ten new member states that joined the Union in this year and that are predominantly situated in Central or Eastern Europe[2]. Moreover, in Bulgaria and Romania, the two newest member states that acceded to the EU in 2007, rates were still higher (age-standardized incidence [2004] of respectively 20 and 22 per 100,000). The incidence of and mortality from cervical cancer in Romania was approximately five and twelve times higher compared to Finland, the country in Europe with lowest cervical cancer burden at present. In Eastern Europe, cervical cancer is now the gynecological cancer associated with the highest incidence and mortality[3].

We assessed trends of cervical cancer incidence and mortality in the five countries of the EU with the highest mortality from cervical cancer: in the North-East of the EU (Estonia, Latvia and Lithuania) and two countries in South-East Europe (Bulgaria and Romania). These five countries currently receive support from the European Commission through the EUROCHIP-3 Network to assess the situation and to increase adherence to organized cervical screening in accordance to European guidelines[4-6].

In the current paper, we summarize findings from more comprehensive trend analyses which describe in more detail how cancer cases of and deaths from cancer originating from the uterus not otherwise specified (NOS) can be reallocated to obtain corrected rates for cervix uteri cancer[7,8]. We subsequently describe variations in incidence and mortality over time and try to relate these to historical changes in exposure to risk factors, implementation of screening and treatment of invasive cancer.

Materials and methods

Data sources and reallocation of uterus cancers

Data on the number of deaths from uterine cancers and the size of the female population, aggregated by calendar year, 5-year age group and country were extracted from the World Health Organization (WHO) mortality database (http://www.who.int/whosis/mort/download/en/) for Bulgaria, Estonia, Latvia, Lithuania and Romania[7].

The cancer registries of these five countries provided data files containing the number of newly diagnosed cancer cases originating from the same anatomical localizations, by 5 year-age group for available calendar years. The period-range of the obtained data is shown in Table 1. The ranges of incidence data received from the cancer registries was larger than those included in the volumes of Cancer in 5 Continents (http://www-dep.iarc.fr/data/), which are submitted to systematic quality control (Table 1).

Algorithms, described previously, were applied to reallocate deaths ascribed to cancer of the uterus, where the exact origin (cervix uteri or corpus uteri) was not specified[7]. Shortly, good quality data from Lithuania for the period 1993-2004 (<25% NOS among all uterus cancer deaths) were imputed to older periods of Lithuania and used to reallocate uterus NOS cancer deaths from Estonia and Latvia. The period- and age-specific proportions of cervix over total uterus deaths, derived for Hungary, were used to adjust mortality rates in Bulgaria and Romania[7,9].

The proportion of uterus NOS cancers among all uterine cancers was small (<25%) in all the registries. Therefore, a simple correction formula (random allocation) could be applied to correct incidence rates based on the age- and country-specific repartition of certified cervix and corpus uteri cancer cases[7].

Table 1 - Period range of incidence and mortality data obtained and availability of incidence data in Cancer in 5 continents (CI5) (source: http://www-dep.iarc.fr/data/)

		Included in current trend analysis	
Country	Inclusion in CI5	Incidence	Mortality
Bulgaria*	1998-2002*	1980-2006	1964-2004
Estonia	1968-2002	1968-2006	1968-2004
Latvia	1983-2002	1980-2004	1980-2004
Lithuania	1998-2002	1978-2007	1990-2004
Romania	None	1982-2004	1959-2004

*Low % of histological verified cases.

Time trends

Age-standardized rates were computed using the world standard population as reference[10]. Joinpoint regression was used to analyze time trends of the standardized corrected incidence or mortality rates, as a linear function of year of cancer incidence or death[11]. Joinpoint regression identifies periods with distinct linear slopes that can be separated by *joinpoints*, where the slope of the trends changes significantly[12,13]. For each linear segment, the average annual percentage of change (APC) and corresponding 95% confidence intervals were calculated. Trends were plotted on a logarithmically (log10) scaled Y-axis, where rates changing at a constant percentage over time are presented as a straight line[14].

Age-specific trends were analyzed by 5-year calendar period and by 10-year birth cohort. Five-year periods were defined using years ending with zero or five as starting year. According to availability of data, first and last periods did not always span five years. Birth cohorts (k = calendar period – age) were identified by the median year within each category[15]. Standardized cohort mortality (SCMR) or incidence (SCIR) ratios were computed to assess birth cohort effects. 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[16,17].

Results

Age standardized incidence and mortality

Age-standardized incidence trends increased linearly in Bulgaria and Romania and, in Lithuania between 1992 and 2004 (ACP statistically significantly >0, Figure 1). The incidence was initially decreasing, in Estonia and Latvia, but became stable since the early 1980s. The rates, expressed per 100,000 women-years, observed in the latest available years, were respectively: 12.3 in

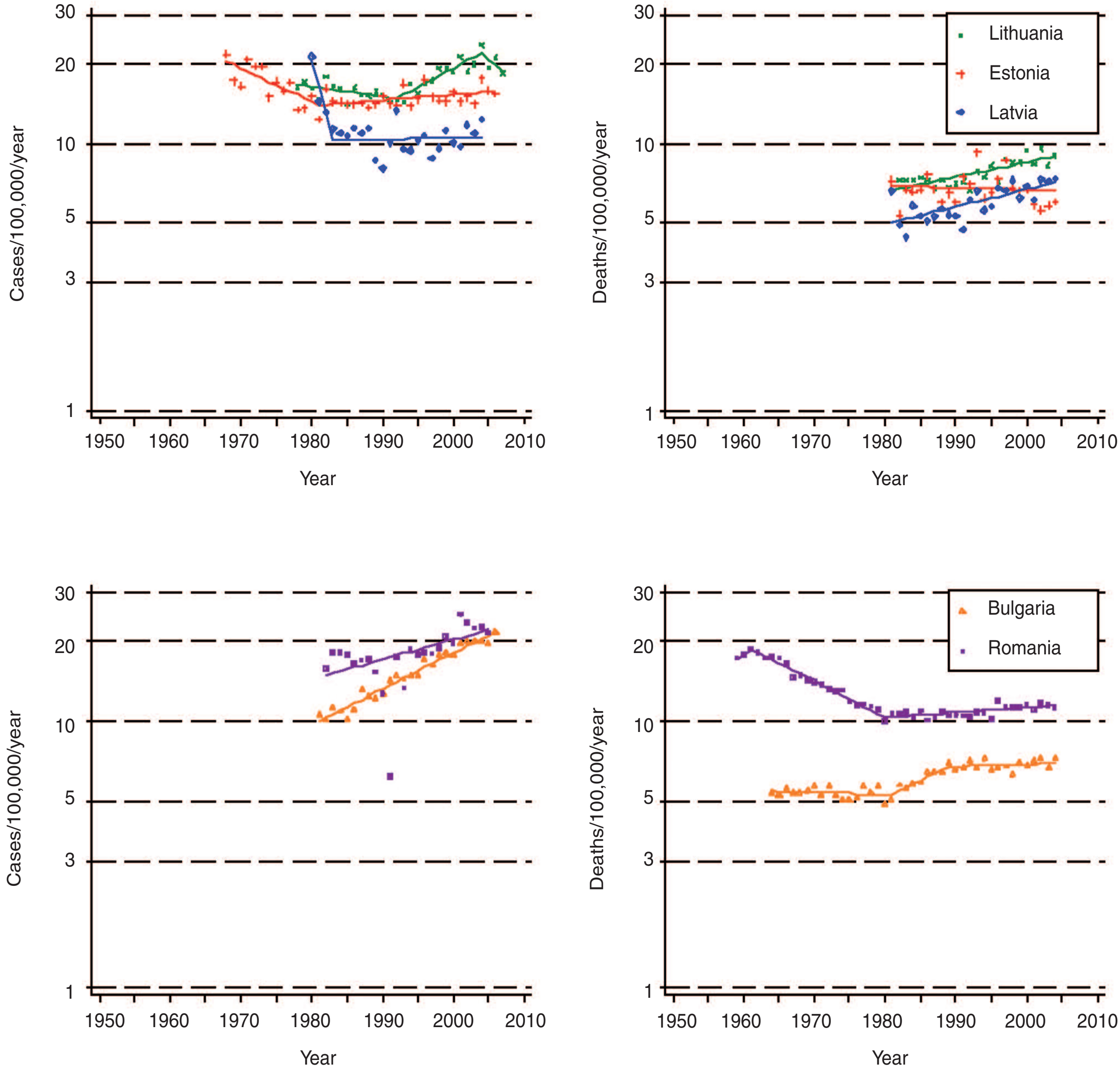

Figure 1 - Age standardized rate (world standard) of cervical cancer incidence (at left) and mortality (at right) in Estonia, Latvia and Lithuania (on top) and in Bulgaria and Romania (bottom). Dots represent observed rates, lines those fitted using joinpoint regression.

Latvia (2004), 15.4 in Estonia (2006), 18.4 in Lithuania (2007), 21.3 in Romania (2004) and 21.4 in Bulgaria (2006).

The standardized corrected mortality rates increased at a constant rate in Latvia (APC = 0.7, 95% CI: 0.2-1.2) and Lithuania (APC = 1.0, 95% CI: 0.6-1.4) (Figure 1). Trends that were statistically significantly rising over a limited time period were observed in Bulgaria (APC = 3.5, 95% CI: 1.2-5.7, between 1981 and 1988) and in Romania (APC = 0.4, 95% CI: 0.2-0.6, since 1980). The corrected mortality rates, observed in 2004, were respectively: 6.1 in Estonia, 7.2 in Bulgaria, 7.4 in Latvia, 9.0 in Lithuania and 11.1 in Romania.

Age-specific trends by birth cohort

Age-specific incidence and mortality trends are plotted against birth cohort in Figure 2. Age groups starting with 5 (25-29, 35-39, ...75-79) were omitted for reasons of graphical clarity.

In the Estonia, Latvia and Lithuania, women aged 50 or older and born before 1940 displayed a decreasing or horizontal incidence trend, whereas incidence rates among younger women, born after 1940, were rising. Mortality rates in women older than 50 were stable or slightly declining. The cohorts born 1940-1965, exhibited rising mortality rates, in particular in the age groups 40-49 in Estonia, age groups 30-49 in Latvia and age

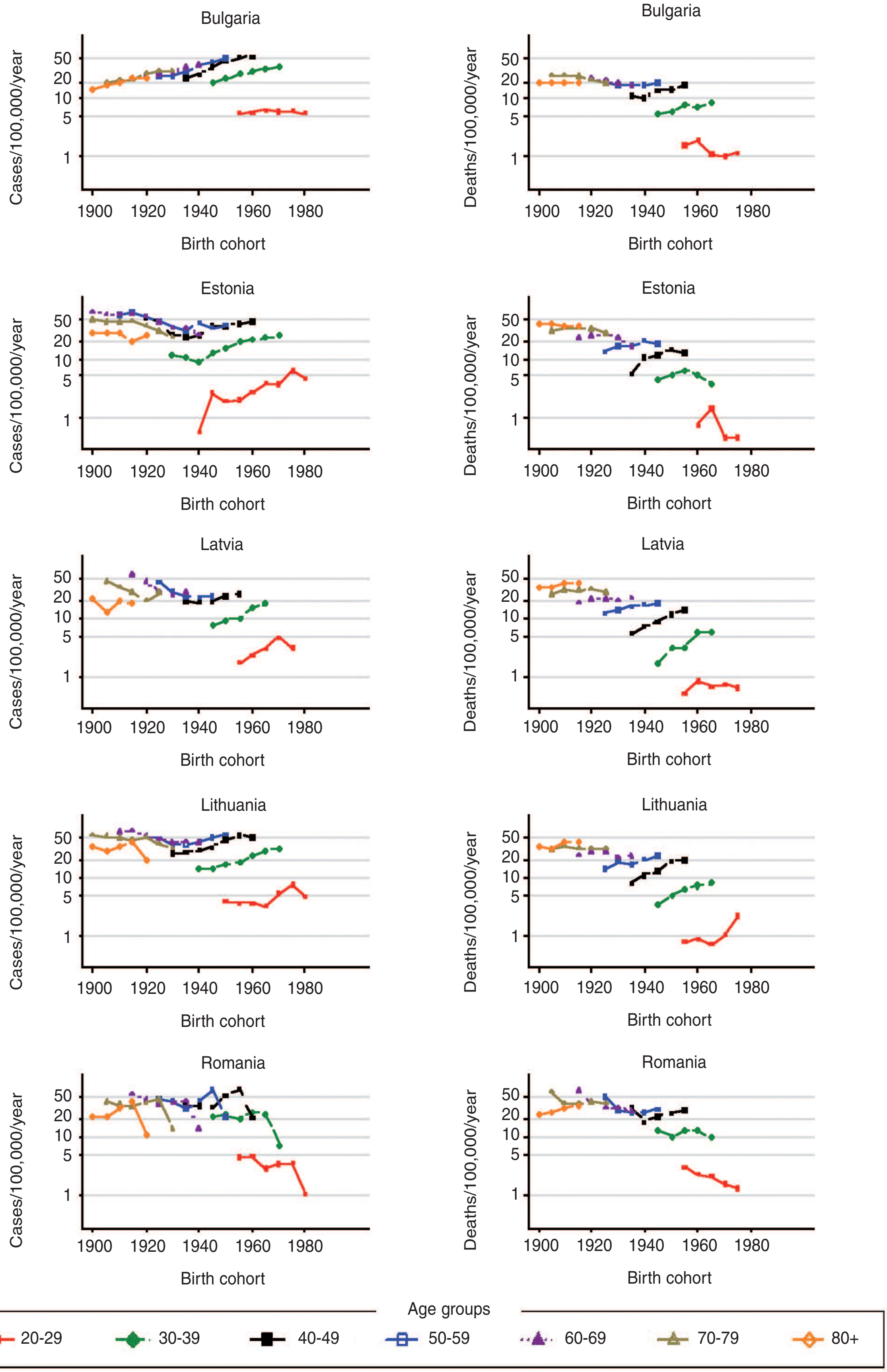

Figure 2 - Age-specific rates of cervical cancer incidence (left) and mortality (right) by birth cohort.

groups 25-49 in Lithuania. The slopes of the mortality rates among younger age groups were stable or decreasing.

In Bulgaria and Romania, incidence rates generally raised in all age groups with a more steep increase after 1940. However, the youngest cohorts, born since 1960 did not show any further increase anymore. For both countries, mortality data were available over longer periods (since 1959 for Romania and 1964 for Bulgaria). The mortality rates in these two countries, decreased slightly for women aged 55 or older, born before 1940. For the age groups 25-54, mortality increased over the range of cohorts 1940-1960, but the trend was interrupted for the youngest cohorts born later.

Cohort effects

Statistically significant V-shaped cohort effects (with decreasing and increasing or stable risks for women born before and after the 1935-1940 cohorts, respectively) were observed for incidence in all the five countries and for mortality in Bulgaria, Lithuania and Romania. The evolution of the cohort effect in the incidence and mortality is illustrated for Lithuania in Figure 3.

Discussion

The main etiologic factor for cervical cancer is persistent infection with sexually transmittable high-risk human papillomaviruses[18]. By well-organized screening and treatment of screen-detected high-grade cervical intraepithelial neoplasia (CIN) invasive cancer can be avoided[19]. 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[20,21]. We will subsequently discuss the elements that may have driven the trends in the five studied countries.

Data quality

An important question is whether the applied correction for inaccuracies in the certification of death causes allows the study of the true rates of cervical cancer mortality. For Lithuania, the proportion of uterus NOS deaths was small (<25%) and therefore corrected rates can be considered as reliable. Even if the assumption of random allocation was incorrect, the error would be limited. The assumption that the Lithuanian proportions are applicable to those of Estonia and Latvia looks plausible given the common background risk and history of preventive health care[9]. However, the application of proportions from Hungary to adjust data from Bulgaria and Romania could be considered as problematic. 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[22-24].

Incidence data received from the five national cancer registries suffered less from certification problems since the proportion of NOS cases among all uterine cancers was small. However other biases may have intervened. In Latvia for instance, the abrupt drop in incidence between 1980 and 1983, in the period before the CI5 quality control (Figure 1) looks spurious. Exclusion of carcinoma *in situ* cases, abrupt in the first years and more gradual thereafter could have hidden a rise in incidence of invasive cervical cancer. An alternative explanation is the under-declaration of cases by the Latvian cancer registry after 1983. Arguments for this latter statement are: the higher and increasing mortality/incidence ratios in Latvia (0.48 in the 1980s and 0.64 after 2000) indicating worsening survival. In the two other Baltic

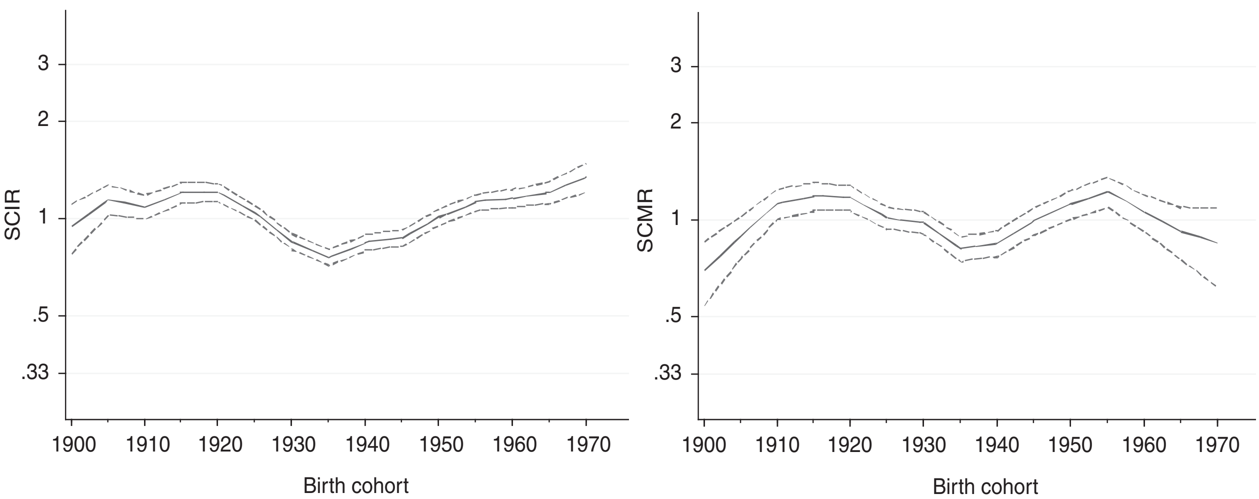

Figure 3 - Standardized cohort incidence ratio (SCIR, left), standardized cohort mortality ratio (SCMR, right), with 95% confidence intervals, for cervical cancer in Lithuania.

countries the incidence/mortality ratios were lower and rather stable over time: 0.46 and 0.47 in respectively Estonia and Lithuania in the 1980s and, 0.44 in both countries after 2000. In Lithuania, since 2006, personalized information from death certificates is unavailable for the cancer registry and *Death Certificated Only* (DCO) cases are not added to the incident cases anymore. This change in registration practice could be responsible for the observed incidence decrease in years 2006 and 2007.

Cohort effects

In general, the risk of developing cervical cancer or dying from it decreased for women born between the two world wars, whereas cohorts born after 1940 expressed increasing risks. These cohort effects were also observed in many other industrialized countries[9]. The decreasing risk before 1940 may be due to poorly understood etiological (co-) factors, linked to improved social conditions and access to health care[25]. The greater SCIR and SCMR in the cohorts born between the 1940s and 1960s are most plausibly explained by changes in sexual behavior resulting in higher rates of HPV infection which may be enhanced by increased frequency of smoking and oral contraception[26-29]. It is also possible that some other factors such as early diagnosis of invasive cancer among younger women due to increased access to gynecological care may be responsible for cohort effects observed in the deaths rates.

Screening effects

In most West-European countries with either well-organized screening programs or widespread opportunistic screening, it was shown that the rising cohort effect (also observed for women born after 1940) was counterbalanced by a protective period effect. This period effect was strongly correlated with screening coverage[20,30-34].

The increasing trends of cervical cancer incidence and/or mortality observed in all the five countries is most plausibly explained by the absence of screening programs or by the poor quality and coverage of opportunistic screening practice since the last decades.

Recently, national cytology-based screening programs were initiated in the three Baltic countries and a regional program was set up in the province of Cluj (Romania), whereas, in Bulgaria, plans for organized screening are not started yet[19,35,36]. All these programs suffer of understaffing, insufficient resources and management capacity and reach less than 20% of the target population. Obviously, more time, continued efforts and comprehensive EU support will be needed to bend cervical cancer trends downwards.

Survival

Among the five countries studied, only Estonia and Lithuania are included in international survival comparisons[37-39]. The average European 5-year age-standardized relative survival among cervical cancer patients diagnosed from 1990 to 1994 was 63%, whereas 53% for Estonia[37]. The trend of the 5-year survival revealed a slow but steady increase of about 2% per year among cancer patients diagnosed in the period 1983-94 in Europe[39]. No improvement was noted in the areas where survival was lowest (Central/Eastern Europe and UK). A more recent period-based analysis, over the years 2000-04, showed lowest survival rates for Lithuania (52%) and Poland (53%) without significant improvement[38]. Low 5-year survival was also reported for patients with cervical cancer in Bulgaria for the period 1993-2002[40].

Conclusion

There is an elevated burden of cervical cancer in the three Baltic countries, Bulgaria and Romania. Moreover, incidence and mortality rates tend to increase or remain stable. Public health authorities should set-up well-organized cervical cancer prevention programs without delay as recommended by the European Council[41,42] according to the European Guidelines for Quality Assurance in Cervical Cancer Screening[5]. It is particularly challenging for public health experts to define, in the future, how prophylactic HPV vaccination besides screening will contribute in tackling this preventable disease.

References

1. Arbyn M, Raifu AO, Autier P, Ferlay J: Burden of cervical cancer in Europe: estimates for 2004. Ann Oncol, 18: 1708-1715, 2007.
2. Arbyn M, Autier P, Ferlay J: Burden of cervical cancer in the 27 member states of the European Union: estimates for 2004. Ann Oncol, 18: 1425-1427, 2007.
3. Ferlay J, Bray F, Pisani P, Parkin DM: GLOBOCAN 2002: Cancer Incidence, Mortality and Prevalence Worldwide. IARC CancerBase No. 5, version 2.0. IARCPress, Lyon, 2004.
4. EUROCHIP: European Cancer Health Indicator Project. Available at http://www.tumori.net/eurochip/ (accessed 21 March 2010).
5. European Commission: European Guidelines for Quality Assurance in Cervical Cancer Screening. 2nd ed. Office for Official Publications of the European Communities, Luxembourg, 2008.
6. Arbyn M, Anttila A, Jordan J, Ronco G, Schenck U, Segnan N, Wiener H, Herbert A, von Karsa L: European Guidelines for Quality Assurance in Cervical Cancer Screening. Second Edition - Summary Document. Ann Oncol, 21: 448-458, 2010.
7. Arbyn M, Raifu AO, Antoine J: Trends of cervical cancer mortality in Europe. IPH/EPI-REPORTS 2009-07: 1-54, 2009.
8. Arbyn M, Antoine J, Mägi M, Smailyte G, Stengrevics A, Suteu O, Valerianova Z, Bray F, Weiderpass E: Trends in cervical cancer incidence and mortality in the Baltic countries, Bulgaria and Romania. Int J Cancer 2010 (epub ahead of print).

9. Arbyn M, Raifu AO, Bray F, Weiderpass E, Anttila A: Trends of cervical cancer mortality in the member states of the European Union. Eur J Cancer, 45: 2640-2648, 2009.
10. Waterhouse JAH, Muir CS, Shanmugaratnam K: Cancer Incidence in Five Continents. 4 ed. International Agency for Research on Cancer, Lyon, 1976.
11. National Cancer Institute: Join Point Regression Programme. Version 3.2. (Software produced by the Statistical Research and Application Branch), 2008.
12. Lerman PM: Fitting segmented regression models by grid search. Appl Stat, 29: 77-84, 1980.
13. Kim H-J, Fay MP, Feuer EJ, Midthune DN: Permutation tests for joinpoint regression with applications to cancer rates. Stat Med, 19: 335-351, 2000.
14. Devesa SS, Donaldson J, Fears T: Graphical presentation of trends in rates. Am J Epidemiol, 141: 300-304, 1995.
15. 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, 60: 73-100, 2002.
16. Beral V: Cancer of the cervix: a sexually transmitted infection? Lancet, 25: 1037-1040, 1974.
17. Osmond C, Gardner MJ: Age, Period and Cohort Models Applied to Cancer Mortality Rates. Stat Med, 1: 245-259, 1982.
18. IARC Monograph Working Group: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol 90: Human Papillomaviruses. IARCPress, Lyon, 2007.
19. IARC: Cervix Cancer Screening. IARC Handbooks of Cancer Prevention. Vol. 10. IARCPress, Lyon, 2005.
20. Laara E, Day NE, Hakama M: Trends in mortality from cervical cancer in the Nordic countries: association with organised screening programmes. Lancet, 1: 1247-1249, 1987.
21. Bray F, Loos AH, McCarron P, Weiderpass E, Arbyn M, Moller H, Hakama M, Parkin DM: Trends in cervical squamous cell carcinoma incidence in 13 European countries: changing risk and the effects of screening. Cancer Epidemiol Biomarkers Prev, 14: 677-686, 2005.
22. 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, 35: 243-247, 2002.
23. Suzan F, Séblain C, Boussac-Rarebska M, Poillot ML, Arveux P, Laurent F, Carré N: 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 Epidemiol Hebdom, 9: 79-81, 2007.
24. Capocaccia R, Martina L, Inghelmann R, Crocetti E, De L, V, Falcini F, Guzzinati S, Rosso S, Tagliabue G, Tumino R, Vercelli M, Zanetti R, De Angelis R: A method to estimate mortality trends when death certificates are imprecisely coded: an application to cervical cancer in Italy. Int J Cancer, 124: 1200-1205, 2009.
25. Parkin DM, Bray FI, Devesa SS: Cancer burden in the year 2000. The global picture. Eur J Cancer, 37: 4-66, 2001.
26. Laukkanen P, Koskela P, Pukkala E, Dillner J, Laara E, Knekt P, Lehtinen M: Time trends in incidence and prevalence of human papillomavirus type 6, 11 and 16 infections in Finland. J Gen Virol, 84: 2105-2109, 2003.
27. Lehtinen M, Kaasila M, Pasanen K, Patama T, Palmroth J, Laukkanen P, Pukkala E, Koskela P: Seroprevalence atlas of infections with oncogenic and non-oncogenic human papillomaviruses in Finland in the 1980s and 1990s. Int J Cancer, 119: 2612-2619, 2006.
28. International Collaboration of Epidemiological studies of cervical cancer: Carcinoma of the cervix and tobacco smoking: Collaborative reanalysis of individual data on 13,541 women with carcinoma of the cervix and 23,017 women without carcinoma of the cervix from 23 epidemiological studies. Int J Cancer, 118: 1481-1495, 2006.
29. Smith JS, Green J, Berrington de Gonzalez A, Appleby P, Peto J, Plummer M, Franceschi S, Beral V: Cervical cancer and use of hormonal contraceptives: a systematic review. Lancet, 361: 1159-1167, 2003.
30. Quinn M, Babb P, Jones J: Effect of Screening on Incidence an Mortality from Cancer of the Cervix in England: Evaluation Based on Routinely Collected Statistics. BMJ, 318: 904-908, 1999.
31. Nygard JF, Skare GB, Thoresen SO: The cervical cancer screening programme in Norway, 1992-2000: changes in Pap smear coverage and incidence of cervical cancer. J Med Screen, 9: 86-91, 2002.
32. Rebolj M, van Ballegooijen M, Berkers LM, Habbema JDF: Monitoring a national cancer prevention programme: Successful changes in cervical cancer screening in the Netherlands. Int J Cancer, 120: 806-812, 2007.
33. Anttila A, Nieminen P: Cervical cancer screening programme in Finland with an example on implementing alternative screening methods. Coll Antropol, 31 (Suppl 2): 17-22, 2007.
34. 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, 102: 649-654, 2002.
35. Nicula F, Anttila A, Neamtiu L, Zakelj-Primic M, Tachezy R, Chil A, Grce M, Kesic V: Challenges in starting organised screening programmes for cervical cancer in the new member states of the European Union. Eur J Cancer, 45: 2679-2684, 2009.
36. Suteu O, Lazar L, Irimie A, Nicula F, Coza D, Duma M, Pais R, Neamtiu L: Organization and implementation of cervical screening pilot program in County of Cluj, Transilvania. In: Fifth Proceedings of the International Multidisciplinary Congress EUROGIN 2003, Paris, 2003.
37. Sant M, Aareleid T, Berrino F, Bielska LM, Carli PM, Faivre J, Grosclaude P, Hedelin G, Matsuda T, Moller H, Moller T, Verdecchia A, Capocaccia R, Gatta G, Micheli A, Santaquilani M, Roazzi P, Lisi D: EUROCARE-3: survival of cancer patients diagnosed 1990-94-results and commentary. Ann Oncol, 14: 61-118, 2003.
38. Gondos A, Bray F, Brewster DH, Coebergh JW, Hakulinen T, Janssen-Heijnen ML, Kurtinaitis J, Brenner H: Recent trends in cancer survival across Europe between 2000 and 2004: A model-based period analysis from 12 cancer registries. Eur J Cancer, 44(10): 1463-1475, 2008.
39. 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, 105: 609-619, 2007.
40. Kostova P, Zlatkov V, Danon S: Five-year overall survival and prognostic factors in patients with cervical cancer in Bulgaria. J BUON, 13: 363-368, 2008.
41. Council of the European Union: Council Recommendation of 2 December 2003 on Cancer Screening. Off J Eur Union, 878: 34-38, 2003.
42. Arbyn M, Primic Zakelj M, Raifu AO, Grce M, Paraskevaidis E, Diakomanolis E, Kesic V, Nicula F, Suteu O, von Karsa L: The burden of cervical cancer in South-East Europe at the beginning of the 21st century. Coll Antropol, 31: 7-10, 2007.