Original Research

Cervical cancer mortality in young adult European women

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Abstract *Background:* The process of social, political and economic transformation, which took place in Central and Eastern Europe in the early 90's, has affected many spheres of Europeans' lives, including health-associated issues. These changes also had an impact on mortality rates due to cervical cancer (CC). Therefore, the aim of this study was to analyse CC mortality trends in Europe after 1990.
Methods: Data on death due to CC, uterine cancers and unspecified uterine cancers, in women aged 20—44, were taken from the WHO Mortality Database. Trends in European countries between 1990 and 2017 were assessed using the Joinpoint Regression Program.
Results: Most of the countries experienced a decrease in CC mortality. Although the lowest rates were observed in EU15 Member States, the highest decreases were observed in Central and Eastern Europe. However, there are still differences in mortality in these countries. There are also a few countries like Belarus, Latvia and Ukraine, which experienced an increase in mortality. The range of mortality across Europe in 2017 was between 0.6 and 5.2/100,000 women.
Conclusions: It is essential to introduce well-organised screening programmes for early detection of CC with coverage of a correspondingly high percentage of the population, particularly in East-Central Europe, as well as to introduce high-coverage HPV vaccination in all European countries.
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1. Introduction

Every year in Europe, more than 60,000 new cervical cancer (CC) cases are diagnosed and over 25,000 women die from the disease [1]. This makes it the second most common cancer in women aged 15−44 years [1]. Standardised incidence rate of CC in Europe averages at 11.2/100,000 women and standardised mortality rate at 3.8/100,000 women.

After the Second World War, East-Central Europe was incorporated into the so-called Eastern Bloc and the Soviet Union sphere of influence. Its countries had planned and centralised economy, and many aspects of the social life were controlled by the state. Health care was free and was provided to all citizens. The Soviet Union collapse began in 1989. Political, economic and social changes took place in Europe, which influenced health policy of particularly the so-called transitional countries [2]. These are countries of the former communist states in Europe after collapse of the "Iron Curtain" in 1989−1990 (Estonia, Latvia, Lithuania, Czech Republic, Slovakia, Poland, Hungary, Slovenia, Romania, Bulgaria, Croatia, Albania, Bosnia and Herzegovina, Macedonia, Montenegro, Serbia, Belarus, Moldova and Ukraine), which experienced major political, economic, social and epidemiological changes [3−5]. Later, these countries formed independent governments and began to lead their own, independent policies, also regarding health care systems. However, they were struggling with insufficient financial resources and, therefore, in many cases, health care was no longer free and was not provided to all citizens. After 1990, most of these countries began to introduce organised programmes for prevention of CC. Implementing such programmes on a national level is the only way to eliminate CC, and from the standpoint of public health, elimination of CC means mortality below 1/100,000 women in a given population [6,7].

Levi et al. [8] analysed CC mortality in women aged 20−44 in Europe over the period between 1960 and 1998. The reason for the choice of this age group was a difference in the classification of uterine tumours between individual countries. It was difficult to present a reliable analysis concerning the analysed years, because it was impossible to distinguish between cervical and corpus uteri cancers based on death certifications. Several deaths were attributed to unspecified uterine cancer and its percentage differed significantly comparing particular countries and particular years of observation in a given country [8]. To avoid classification bias, authors decided to present mortality rates from CC, cancer of corpus uteri and unspecified uterine cancer as a single group, only among women under 45. The reason was that the majority of death causes due to uterine cancers, among women in this age group, is caused by CC [8,9]. Mentioned differences in the classification of reproductive organ tumours between individual countries are still present.

The aim of the study was to continue the observation of Levi et al. and analyse CC mortality rates and trends in 20−44 years old women in European countries and to examine changes that have occurred in the epidemiology of the disease after 1990.

2. Materials and methods

We carried out an analysis of trends in CC mortality among women aged 20−44 between 1990 (or in the first year after 1990 for which data were available) and 2017 (or in the last year before 2017 for which data were available) in selected European countries. In addition to the European Union (EU) Member States, the situation was also analysed in the European transitional countries, because this group was expected to show the biggest changes in trends, due to political transformations, which took place after 1990. We excluded Bosnia and Herzegovina, Montenegro, Cyprus, Malta and Luxembourg from this analysis because of small numbers of deaths.

Data on death due to CC together with uterine cancers and unspecified uterine cancers were taken from the World Health Organization (WHO) Mortality Database. This database provides information concerning the number of deaths by causes defined in the International Classification of Diseases (ICD), according to gender, age and calendar year. The analysis included deaths as specified in the ICD-9 by number 180, 179 and 182 and in ICD-10 by code C53, C54 and C55. Standardised mortality rates expressed per 100,000 women were calculated using world standard population [10]. No extrapolation was made for the missing data.

In the majority of the selected countries, data were available for the period 1990−2014, −2015, −2016 or −2017 (Table 2), with the exception of Serbia, for which data were available since 1998. There was lack of some data for Belarus, Poland, Portugal, Slovakia, Ukraine and United Kingdom. Probably this type of data has not been provided by relevant national organizations.

The analysis of CC mortality trends in European countries was performed using Joinpoint Regression Analysis (Joinpoint Trends Analysis Software, version 4.5.0.1 [11]). This software allowed for the testing of whether time trend changes within the studied time interval were significant ($p < 0.05$). The maximum number of joinpoints was set at three in each analysis. The best-fit model was chosen with the statistically significant Annual Percentage Changes (APC). APC between two joinpoints are shown in the diagrams of individual countries. In addition, we calculated the average APC between 1990 and 2017.

The following terms: EU15 Member States (member countries in the European Union before 2004) and

Baltic States (Latvia, Lithuania and Estonia) were used for the purpose of this analysis.

3. Results

Table 1 presents the absolute number of deaths due to CC, uterine cancer and unspecified uterine cancer among women aged 20−44 in selected European countries at the beginning and at the end of the observation. Initially, the percentage of uterine cancers located outside the cervix ranged between 2.1% in the Netherlands and 77.8% in Albania. In the last year of

the observation, this percentage ranged from 0% in Estonia, Latvia, Slovakia and Slovenia and 66.7% in Albania. In addition, in particular countries the percentage changed over the analysed years, as in the case of Greece, where it was almost 62% in 1990 and 29% in 2016.

Table 2 presents standardised mortality rates of women due to CC and APC between the beginning and the end of the observation. In 1990, higher CC mortality rates were observed in Eastern European countries and in Baltic States than in EU15 Member States. The observed rates were in most of these cases above 3.5/

Table 1
Number of deaths due to CC, uterine cancer and unspecified uterine cancer and percent of other than cervical parts of uterus on all uterine cancers among women aged 20−44 in selected European countries at the beginning and at the end of the observation, 1990[a] and 2017[b].

Country	Number of deaths in 1990[a]		Number of deaths in 2017[b]	
	Cervical cancer	Corpus and unspecified uterine cancer (%)	Cervical cancer	Corpus and unspecified uterine cancer (%)
Albania (Alb)	2	7 (77.8)	1	2 (66.7)
Austria (Aus)	18	21 (53.8)	7	2 (22.2)
Belarus (Bela)	39	13 (25.0)	78	12 (13.3)
Belgium (Bel)	24	9 (27.3)	16	8 (33.3)
Bulgaria (Bul)	67	39 (36.8)	53	18 (25.4)
Croatia (Cro)	19	7 (26.9)	9	1 (10.0)
Czech Republic (Cze)	87	21 (19.4)	37	7 (15.9)
Denmark (Den)	20	1 (4.8)	15	1 (6.3)
Estonia (Est)	13	7 (35)	6	0 (0.0)
Finland (Fin)	3	1 (25)	8	4 (33.3)
France (Fra)	133	82 (38.1)	78	38 (32.8)
Germany (Ger)	365	55 (13.1)	141	30 (17.5)
Greece (Gre)	13	21 (61.8)	17	7 (29.2)
Hungary (Hun)	110	14 (11.3)	48	10 (17.2)
Ireland (Ire)	16	1 (5.9)	25	1 (3.8)
Italy (Ita)	63	124 (66.3)	68	54 (44.3)
Latvia (Lat)	8	3 (27.3)	14	0 (0.0)
Lithuania (Lit)	31	4 (11.4)	15	3 (16.7)
Macedonia (Mac)	2	3 (60.0)	5	5 (50.0%
Moldova (Mol)	24	12 (33.3)	33	3 (8.3)
Netherlands (Net)	46	1 (2.1)	30	5 (14.3)
Poland (Pol)	388	56 (12.6)	90	18 (16.7)
Portugal (Por)	25	30 (54.5)	21	4 (16.0)
Romania (Rom)	338	63 (15.7)	154	27 (14.9)
Serbia (Ser)	73	24 (24.7)	56	5 (8.2)
Slovakia (Slo)	43	9 (17.3)	37	0 (0.0)
Slovenia (Sla)	12	4 (25.0)	5	0 (0.0)
Spain (Spa)	75	39 (34.2)	70	18 (20.5)
Sweden (Swe)	29	4 (12.1)	18	2 (10.0)
Ukraine (Ukr)	287	84 (22.6)	392	69 (15.0)
United Kingdom (UK)	400	20 (4.8)	177	26 (12.8)
Total	2773	779 (21.9)	1724	380 (18.1)

[a] 1990 or first available year after 1990.
[b] 2017 or last available year before 2017.

Table 2
Cervical cancer mortality rates, Annual Percentage Change and data availability, in the age group of 20−44 years.

Country	Data availability (years)	Cervical cancer mortality rates (per 100,000 women)		
		1990[a]	2017[b]	Annual Percentage Change between 1990[a] and 2017[b] with 95% CI (%)
Northern Europe				
Latvia (Lat)	1990−2015	2.08	3.81	2.4 (0.8; 4.0)
Lithuania (Lit)	1990−2017	4.97	3.57	−0.7 (−1.8; 0.4)
Ireland (Ire)	1990−2015	2.62	2.75	−1.4 (−2.5; −0.3)
Estonia (Est)	1990−2016	6.25	2.51	−4.1 (−5.6; −2.6)
United Kingdom (UK)	1990−2016	3.78	1.75	−3.0 (−3.7; −2.3)
Denmark (Den)	1990−2015	1.99	1.58	−3.3 (−4.4; −2.2)
Finland (Fin)	1990−2016	0.4	1.31	2.1 (0.4; 3.9)
Sweden (Swe)	1990−2016	1.98	1.17	−0.7 (−1.9; 0.5)
Western Europe				
Germany (Ger)	1990−2016	2.84	1.24	−4.1 (−4.6; −3.6)
Netherlands (Net)	1990−2016	1.47	1.22	−1.3 (−2.0; −0.6)
Belgium (Bel)	1990−2016	1.67	1.18	−1.9 (−2.8; −0.9)
France (Fra)	1990−2015	1.79	1.0	−2.1 (−2.6; −1.6)
Austria (Aus)	1990−2017	2.68	0.55	−5.0 (−6.2; −3.8)
Eastern Europe				
Ukraine (Ukr)	1990−2017	3.7	5.22	1.2 (0.6; 1.8)
Bulgaria (Bul)	1990−2015	6.0	5.05	−0.5 (−1.2; 0.1)
Belarus (Bela)	1990−2014	2.63	4.75	1.3 (0.7; 2.0)
Moldova (Mol)	1990−2017	4.33	4.7	−0.3 (−1.4; 0.8)
Romania (Rom)	1990−2017	9.37	4.53	−3.3 (−4.0; −2.6)
Slovakia (Slo)	1992−2014	4.59	3.19	−3.2 (−4.3; −2.0)
Hungary (Hun)	1990−2017	5.75	2.67	−3.5 (−4.2; −2.8)
Czech Republic (Cze)	1990−2017	4.99	1.94	−3.3 (−3.9; −2.7)
Poland (Pol)	1990−2016	5.47	1.38	−5.0 (−5.4; −4.6)
Southern Europe				
Serbia (Ser)	1998−2016	6.2	4.52	−2.2 (−3.4; −1.0)
Macedonia (Mac)	1991−2013	1.37	2.44	−2.9 (−5.1; −0.6)
Croatia (Cro)	1990−2016	2.79	1.33	−2.5 (−3.7; −1.3)
Portugal (Por)	1990−2016	2.91	1.25	−3.8 (−4.7; −2.9)
Slovenia (Sla)	1990−2015	3.86	1.23	−4.5 (−6.3; −2.7)
Greece (Gre)	1990−2016	1.8	1.13	−2.3 (−3.3; −1.2)
Italy (Ita)	1990−2015	1.67	1.02	−2.3 (−2.9; −1.8)
Spain (Spa)	1990−2016	1.6	0.87	−2.4 (−2.9; −1.9)
Albania (Alb)	1992−2010	1.67	0.56	−2.5 (−6.1; 1.2)

[a] 1990 or first available year after 1990.
[b] 2017 or last available year before 2017.

100,000 women. The observed mortality rates in this region of Europe were in the range of 1.4−9.4/100,000 women. At that time, in most EU15 Member States, the mortality rate did not exceed 2.7/100,000. The observed rates were even lower in most of these countries at the end of the observation, when the average mortality rate was around 1/100,000. The situation also improved in most of Baltic States as well as in Southern and Eastern European countries, where the highest decreases in the mortality rate were observed. However, this is a group of countries, where we still observe differences in mortality from CC, but the variety of rates is smaller than in 1990 (0.6−5.2/100,000 women). In this part of Europe, there are countries which experienced a decrease in CC mortality and achieved mortality rates around 2/100,000 in 2017, but there are also countries where the rate remained around 4.5/100,000 (Romania Serbia, Bulgaria and Moldova). There are also countries that experienced increase in mortality rates, including Belarus, Latvia, Ukraine and Finland. However, in Finland, we recorded the mortality rate in 2017 to be around 1/100,000 women. Fig. 1 compares the APC in CC mortality among young adult women between 1990 (or first available) and 2017 (or last available) with the mortality rate in 2017. With a few exceptions, the falls tended to be greater in countries with originally higher rates.

Five different patterns of CC mortality trends were observed (Fig. 2). The first one, observed in Austria, Belgium, Croatia, Czech Republic, Denmark, Estonia, France, Germany, Greece, Ireland, Netherlands, Poland, Serbia, Slovakia, Slovenia and Spain, shows a decrease throughout the observation period (A). The second pattern (B), observed in Bulgaria, Hungary, Lithuania, Macedonia, Moldova, Portugal, Romania and Ukraine, was characterised by an increase in the

first phase and a decrease in the second phase of the observation. The third pattern (C) was first characterised by a decrease and then by an increase and concerned Italy and the UK. The fourth pattern (D) was recorded in Albania and Sweden and was characterised with no changes in the mortality trend during the observation. The last and unfavourable trend (E) was characterised by a steady increase and concerned Belarus and Latvia. Finland is one of the countries with the lowest mortality due to CC. Additionally, there were no joinpoints identified over the analysed period. Therefore, Finland should be included in the group of countries with constant mortality due to CC.

4. Discussion

Just like two decades ago, current classification of deaths due to CC in particular countries in Europe is problematic. After 1990, uterine cancer and unspecified uterine cancer diagnoses among young adult women still constitute a high percentage of all tumours of the uterus, and their number often exceeds registered death cases due to CC. To minimize classification bias, we analysed deaths due to uterine cancers regardless of their location.

Levi *et al.* noted a significant difference in CC mortality between Western European countries, where the mortality in the studied period decreased, and Eastern European countries, where it grew. A significant increase in the mortality in Eastern European countries resulted from ineffective screening. In fact, the problem was more complex, resulting from the changes in the health care systems that occurred in late '80s in the countries belonging to the former Eastern Bloc [12]. Remnants of these changes as well as the perception of
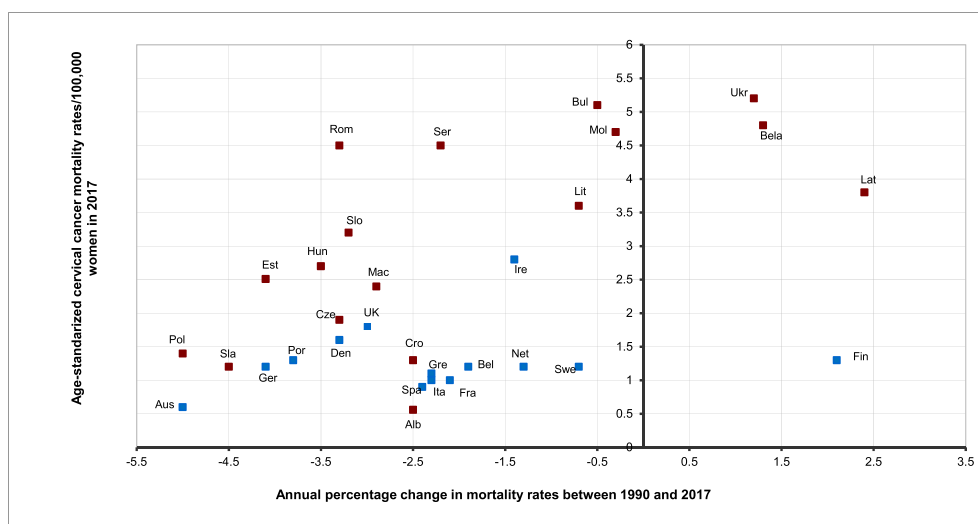
* or first available year after 1990
** or last available year before 2017

Fig. 1. Annual Percentage Change in cervical cancer mortality, in 20−44 years old women, between 1990* and 2017** and the mortality rate in 2017**.
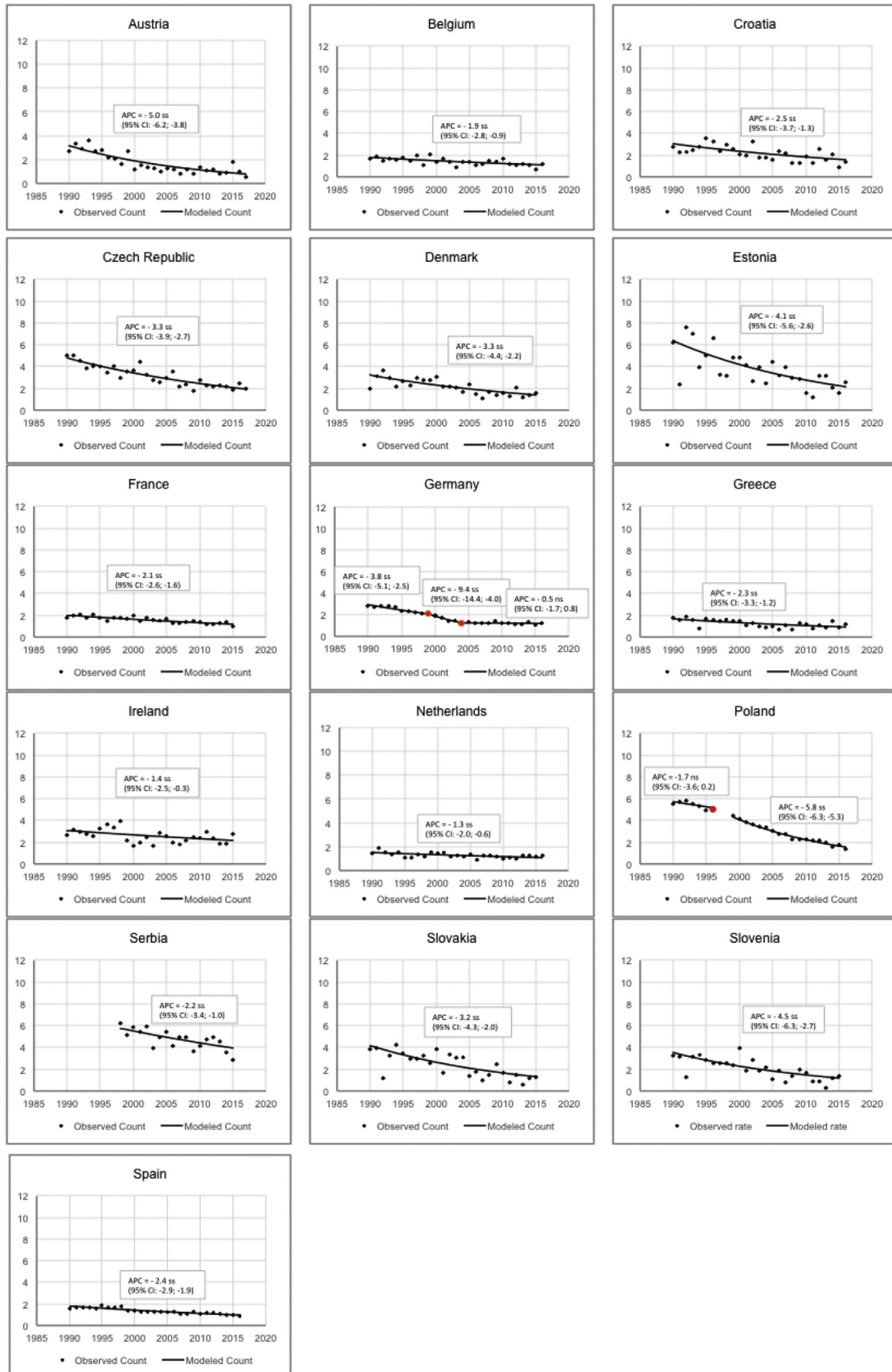
A. First pattern

Fig. 2. Cervical cancer mortality trends in 20−44 years old women in the European countries, 1990−2017.
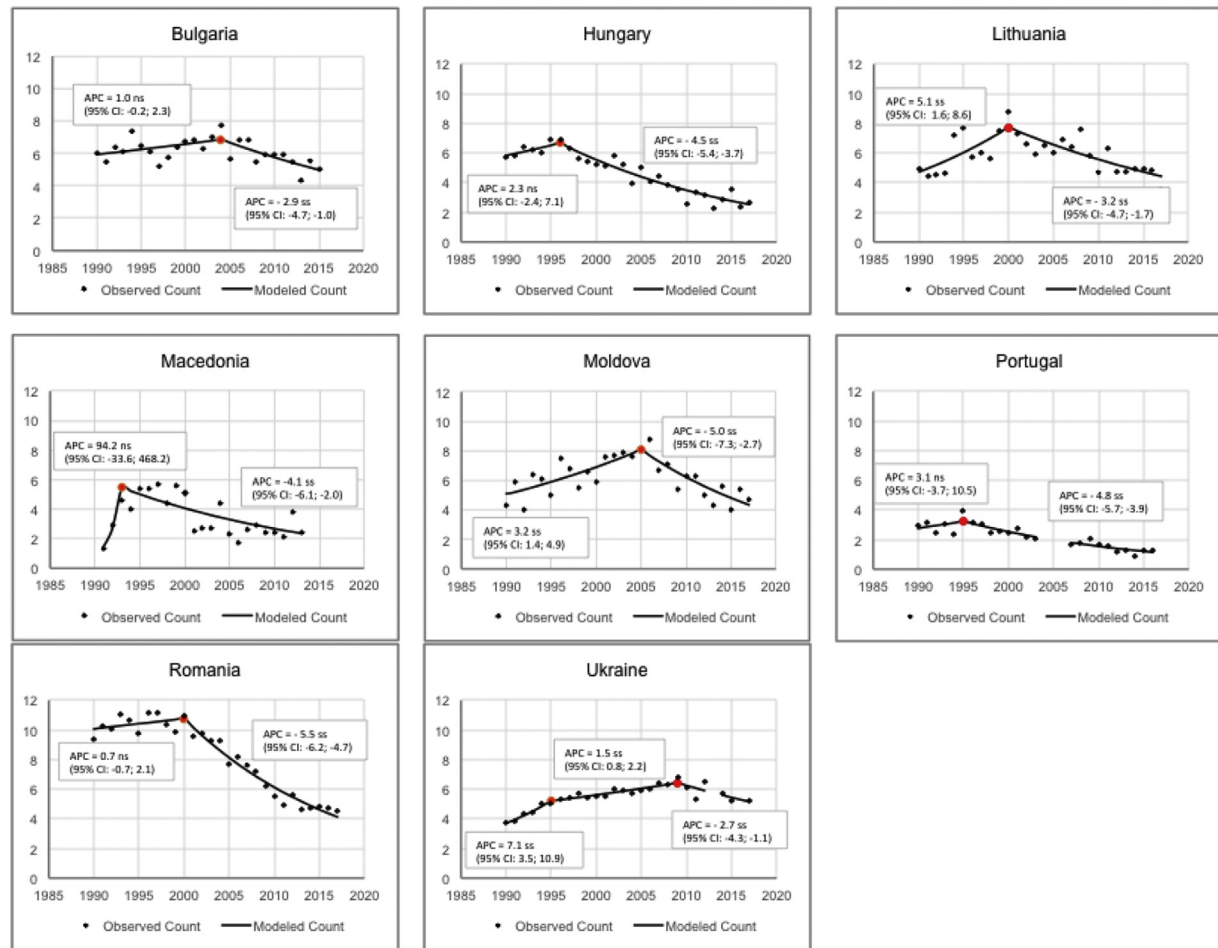
B. Second pattern

Fig. 2. (*continued*).

public health, which emphasised the importance of clinical medicine, survived in many Central and Eastern European countries after the collapse of the Eastern Bloc [2,13,14].
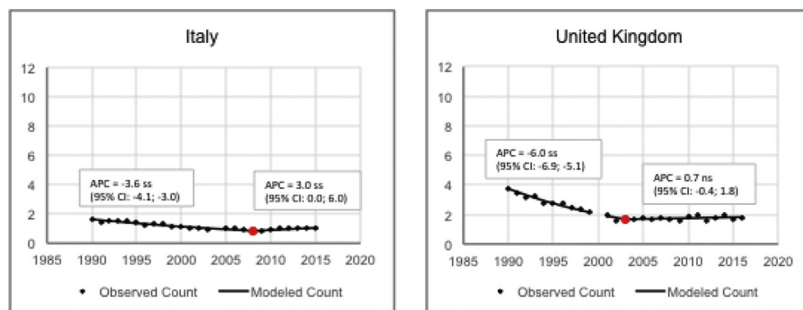
Epidemiological transition in this case refers to the change in the pattern of CC mortality trend in women, observed over a period of dozen years [15]. While analysing CC mortality trends of young adult women in Europe over recent decades, the countries can be divided into three groups, depending on the character of the epidemiological transition of the disease. The first group comprises countries where the epidemiological transition of CC is completed—their CC mortality rate is around 1/100,000 women [6,7]. This situation concerns EU15 Member States, and Finland serves as a model example. In 1960, its CC mortality rate was 5/100,000 women [12]. At that time, Finland introduced an organised screening programme for CC, which led to a steep decrease in the rate by 1973, when it was below 1/100,000 and has remained at that level since then [12]. In these countries, introduction of vaccination against

HPV is the only way to further decrease the mortality level in the future, provided that the vaccines are prevalent and the appropriate percentage of a given population is vaccinated [6]. The rate of change in mortality is less relevant at the levels around and less than 1/100,000, because minor fluctuations, insignificantly or not reflected in the trend change, are present.
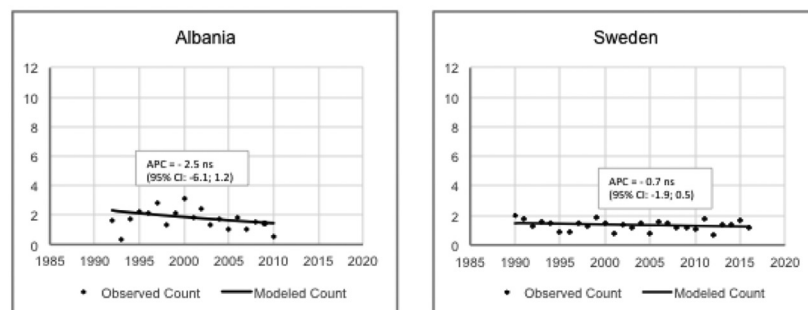
The second group comprises those countries in which CC mortality is decreasing, but the epidemiological transition has not been completed yet. It includes East-Central European countries, where a gradual decrease of the CC mortality trend has been observed since the '90s. Moreover, if the rate of decline continues in Poland and Slovenia, their CC mortality will be brought under control. The third group comprises countries with an adverse pattern of the epidemiological transition, which concerns Belarus and Latvia. In their cases, an increase in CC mortality is observed.

The aforementioned patterns of epidemiological transition have various reasons. In EU15 Member States, where screening programmes for CC have been
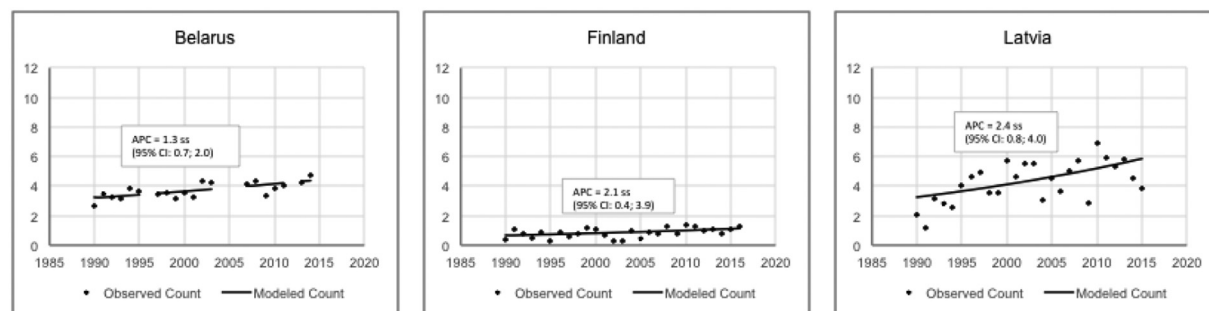
C. Third pattern

Italy

APC = -3.6 ss
(95% CI: -4.1; -3.0)

APC = 3.0 ss
(95% CI: 0.0; 6.0)

• Observed Count —— Modeled Count

United Kingdom

APC = -6.0 ss
(95% CI: -6.9; -5.1)

APC = 0.7 ns
(95% CI: -0.4; 1.8)

• Observed Count —— Modeled Count

D. Fourth pattern

Albania

APC = - 2.5 ns
(95% CI: -6.1; 1.2)

• Observed Count —— Modeled Count

Sweden

APC = - 0.7 ns
(95% CI: -1.9; 0.5)

• Observed Count —— Modeled Count

E. Fifth pattern

Belarus

APC = 1.3 ss
(95% CI: 0.7; 2.0)

• Observed Count —— Modeled Count

Finland

APC = 2.1 ss
(95% CI: 0.4; 3.9)

• Observed Count —— Modeled Count

Latvia

APC = 2.4 ss
(95% CI: 0.8; 4.0)

• Observed Count —— Modeled Count

Red dot -   joinpoint
ss   -   statistically significant
ns   -   statistically insignificant

Fig. 2. (*continued*).

functioning for many years, the mortality is low and the change in the trend or intensification of the downward trend was usually preceded by implementing such programmes. Moreover, stable political situation, which has been observed over recent decades, has turned these programmes into an integral part of health care systems in these countries. The transformation that underwent in East-Central European countries after 1990 marked the beginning of health-related changes. In the Soviet Union, the health care system was based on the Siemaszko's model. This centralised health care system meant a widespread and state-funded access to medical care and its priority was to create an effective model of

care for mother and child. Access to gynaecological healthcare became widespread and annual preventive visits became compulsory for all women. Because of the fact that pap smear tests constituted an integral part of the examination [13,16], CC mortality rate in former Soviet Union countries was low and amounted to, for example, 2.08/100,000 in Latvia or 2.63/100,000 in Belarus. Thus, the epidemiological situation in these countries was close to controlled in 1990. Higher mortality rates were observed in the countries not belonging to the Soviet Union (Poland, Hungary, Romania, Bulgaria, Czech Republic, Slovakia and Slovenia). These countries pursued a partly independent health

policy. After 1990, the situation changed in all East-Central European countries. In some of them, for example in Poland, although no organised early detection screening programmes for CC were organised, opportunistic screening with well-functioning laboratory base and access to professionals was present. As a result, CC mortality rates began to fall in these countries and implementation of such programmes accelerated the rate of decline. In other countries, for example in Latvia and Belarus, abandoning obligatory preventive gynaecological visits has led to losing control over the epidemiological situation and an increase in CC mortality among women. The situation in these countries has not been brought under control since then.

An aim of screening is not only to prevent mortality due to CC, but also to minimize morbidity. The analysis of incidence rates over recent years reveals that the situation in Europe has not changed significantly. According to the GLOBOCAN report of 2002, CC incidence rate in Europe was 11.05/100,000 women at that time [17], whereas in 2018, it was 11.2/100,000 women [1]. Considerable differences are, however, observed between particular European regions. Higher rates are observed in Eastern European countries (16.0/100,000 women) and lower ones in Western Europe (6.8/100,000 women) [1]. Lower incidence rates are observed in the EU countries compared to other countries in Europe. However, differences between old and new EU members are visible [17]. Currently, downward trends in CC morbidity are observed in almost all East-Central European countries, with the exception of Latvia, Belarus and Ukraine [18].

5. Conclusions

A decline in CC mortality has been observed in most European countries over the last decades. However, there are huge disproportions with regard to the mortality and its trends between individual countries. Those differences are particularly pronounced between EU15 Member States and other European countries. Significant differences are also observed within the group of Eastern-Central and Southern European countries. Some of them have reached the level of control over CC. Others, however, still have CC mortality rates of 4.5/100,000. It is essential to introduce well-organised screening programmes for early detection of CC with coverage of a correspondingly high percentage of the population, particularly in East-Central Europe, as well as to introduce high-coverage HPV vaccination in all European countries.

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Conflict of Interest statement

None declared.

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