European Journal of Cancer 194 (2023) 113350

Available online at www.sciencedirect.com

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journal homepage: www.ejcancer.com

Original Research

European trends in ovarian cancer mortality, 1990–2020 and predictions to 2025

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Received 8 August 2023; Received in revised form 28 August 2023; Accepted 8 September 2023
Available online 26 September 2023

KEYWORDS
Ovarian cancer;
Epidemiology;
Trends;
Europe

Abstract ***Introduction:*** Over the last decades, ovarian cancer mortality in Europe has been decreasing, but disparities in trends were observed. In this paper, we analysed ovarian cancer mortality trends in Europe over the period 1990–2020 and predicted the number of deaths and rates by 2025.

Methods: We extracted population and death certification data from ovarian cancer in women for 31 European countries, between 1990 and 2020 from the World Health Organization database. We computed age-standardised mortality rates (ASMR) per 100,000 women-years, based on the world standard population. We also obtained predictions for 2025 using a joinpoint regression model and calculated the number of avoided deaths over the period 1994–2025.

Results: Over the observed period, mortality from ovarian cancer showed a favourable pattern in most countries. In the EU-27, rates declined by 5.9% from 2010–2014 to 2015–2019, reaching an ASMR of 4.66/100,000. During the same period, the decline in ovarian cancer mortality was more pronounced in the EU-14 countries (−7.0%) compared to Transitional countries (−2.1%). Declines were also observed in the United Kingdom, to reach an ASMR of 5.29. Decreases in mortality from ovarian cancer are predicted until 2025, to 4.17/100,000 for the EU-27.

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https://doi.org/10.1016/j.ejca.2023.113350
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Conclusions: Favourable trends in ovarian cancer mortality are expected to persist in Europe and can be mainly attributed to the increased use of oral contraceptives in subsequent generations of European women. Decreased use of menopausal Hormone Replacement Therapy and improved diagnosis and management may also have played a role.
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1. Introduction

Ovarian cancer mortality has been increasing in Europe until the late 1980s. Over the past three decades, this trend has reversed, and a decline in ovarian cancer mortality has been observed in most European countries, with however different patterns [1]. While France and Italy followed the average European trends in mortality, Germany experienced a shift in trend in the early 1980s, while Spain and Poland's declines started later [1]. The recent declines in mortality rates in Europe are largely the result of favourable changes in Western European countries. In Eastern Europe, the slope of decline has been noticeably slower [2]. Therefore, it is important to monitor ovarian cancer mortality trends in Europe with geographical comparisons.

Using data provided by the World Health Organization (WHO), this study aims at analysing trends and patterns in ovarian cancer mortality across Europe over the period 1990–2020, as well as predictions of mortality rates for the largest European countries and selected European regions to 2025. We identified a group of so-called Transitional countries [3,4]. These are Central and Eastern European countries that became market economies after the period of transformations in the early 1990s

2. Material and methods

We retrieved official death certification data from ovarian cancer for selected European countries, from 1990 up to 2020 or the most recent available calendar year, provided WHO mortality database [5]. To classify deaths from ovarian cancer, we used three different Revisions of the International Classification of Diseases (ICD) available over the study period, with the following codes: "183″ for the ICD-8 and ICD-9 [6,7] and "C56-C57.4″ for the ICD-10 [8]. From the same WHO database, we extracted estimates of the resident populations, based on official censuses and, when unavailable, we used the Eurostat database [9]. We restricted the analysis to countries with a high mortality coverage (i.e. over 90%), high data quality, and more than 2 million women, identifying a total of 31 European countries.

Using the merged database with certified deaths and resident populations, we computed annual age-specific rates for 5-year age groups (from 0–4 to 85+ years). We then obtained the age-standardised mortality rates (ASMR) per 100,000 person-years, based on the world standard population [10], at all ages and at age groups 20–49, 50–69, 70–79 and 80+. We also derived ASMRs for the European Union defined as 27 Member States (EU-27), for the EU-14 (as 14 EU Member States before 2004), and for a group of countries defined as "Transitional countries" (including Belarus, Bulgaria, Croatia, Czech Republic, Estonia, Hungary, Latvia, Lithuania, North Macedonia, Poland, Republic of Moldova, Romania, Serbia, Slovakia, and Slovenia). We reported the ASMRs during the calendar years 2010–2014 and 2015–2019 with the corresponding change in rates.

For 21 major countries (with more than 3 million resident women), plus the EU-27, EU-14 and Transitional countries, we carried out a joinpoint regression analysis over the 1990–2020 period [11]. We thus identified the time point(s), called 'joinpoints', when a change in the linear slope (on a log scale) of the temporal trend occurred, by testing from zero up to a maximum of four joinpoints. We estimated the annual percent change for each identified linear segment, and the weighted average annual percent change over the entire study period [12,13].

We also predicted age-specific numbers of deaths and 95% prediction intervals (PIs) for 2025, for France, Germany, Italy, Poland, Spain, and the United Kingdom (UK), and for the EU-27, EU-14 and Transitional countries, by applying linear regression to the mortality data from each age group over the most recent trend segment identified by the joinpoint model. We computed predicted age-specific and age-standardised death rates with 95% PIs using predicted age-specific numbers of deaths and predicted populations from the Eurostat [9].

We estimated the number of avoided cancer deaths over 1994–2025 by comparing observed deaths and expected ones on the basis of the 1993 age-specific peak rates.

Statistical analyses were computed using the software SAS (SAS Institute Inc., Cary, NC), R software version 4.1.1 (R Development Core Team 2017) and Joinpoint software version 4.9.0.0.

3. Results

Table 1 gives ASMRs from ovarian cancer at all ages in the 31 selected European countries, the EU-27, EU-14 and Transitional countries, in 2010–2014 (quinquennium) and 2015–2019, the annual average deaths of the

Table 1
Age-standardised (world population) mortality rates per 100,000 women from ovarian cancer at all ages in selected European countries in 2010–2014 and 2015–2019 (or the last available year indicated in parenthesis), annual average deaths of the latest period and the corresponding change in rates (%).

	ASMR 2010–14	ASMR 2015–19	Annual average deaths 2015–19	% Difference 2015–19 versus 2010–14
EU countries				
Austria	4.68	4.49	515	−4.1
Belgium (2018)	4.65	4.01	607	−13.8
Bulgaria	5.60	5.26	424	−6.1
Croatia	6.25	6.15	328	−1.6
Czech Republic	6.23	5.44	672	−12.7
Denmark (2018)	5.89	5.23	368	−11.2
Finland	5.72	5.43	424	−5.1
France (2017)	4.33	3.96	3482	−8.5
Germany	5.05	4.62	5573	−8.5
Greece	3.78	4.00	553	5.8
Hungary	6.20	5.88	711	−5.2
Ireland (2018)	7.26	6.39	280	−12.0
Italy (2017)	4.21	4.02	3342	−4.5
Latvia	7.76	8.16	201	5.2
Lithuania	7.61	7.03	263	−7.6
Netherlands	5.51	4.74	1035	−14.0
Poland	6.87	6.61	2755	−3.8
Portugal (2018)	2.97	2.83	386	−4.7
Romania	5.05	5.12	1076	1.4
Slovakia	5.87	5.46	309	−7.0
Slovenia	5.82	5.92	150	1.7
Spain	3.79	3.60	2002	−5.0
Sweden (2018)	5.30	4.84	585	−8.7
Other European countries				
Belarus (2018)	4.90	4.71	469	−3.9
Norway (2016)	6.09	5.70	307	−6.4
Republic of Moldova (2018)	3.90	3.99	116	2.3
Russian Federation	5.58	5.12	7620	−8.2
Serbia	5.69	5.76	456	1.2
Switzerland	4.41	4.04	443	−8.4
Ukraine	5.71	5.04	2130	−11.7
UK	5.83	5.29	4147	−9.3
EU-27 (2017)	4.95	4.66	25,934	−5.9
EU-14 (2017)	4.54	4.22	19,011	−7.0
Tansitional countries (2018)	6.05	5.92	7634	−2.1

ASMR: Age-standardised mortality rate.

latest period and the corresponding change in rates. Fig. 1 gives the mortality rates observed in 2010–2014 and 2015–2019, ordered from the highest to the lowest 2015–2019 rate. Ovarian cancer mortality rates declined in all analysed countries during the studied period. In the EU-27, mortality decreased from 4.95/100,000 women to 4.66/100,000 women (−5.9%). During the same time frame, the decline in mortality was more pronounced in the EU-14 countries (−7.0%) compared to the Transitional countries (−2.1%). The largest declines were observed in the Netherlands (−14.0%) and Belgium (−13.8%), while the lowest one was observed in Croatia (−1.6%). Increases in mortality rates were observed in Greece (5.8%), Latvia (5.2%), the Republic of Moldova (2.3%), Slovenia (1.7%), Romania (1.4%), and Serbia (1.2%). In 2015–2019 the highest mortality rates were observed in Latvia (8.16/100,000 women) followed by Lithuania (7.03/100,000 women), Poland (6.61/100,000 women) and Ireland (6.39/100,000 women). The lowest mortality rates were observed in Portugal (2.83/100,000), Spain (3.60/100,000), and France (3.96/100,000). In the same period, the ASMR was 5.92/100,000 women in Transitional countries and 4.22/100,000 in the EU-14. The mortality rate for women in the UK was 5.29/100,000.

Table 2 gives ASMRs from ovarian cancer for different age groups in 31 European countries and the EU-27, EU-14 and Transitional countries, in the periods 2010–2014 and 2015–2019, the annual average number of deaths in 2015–2019 and percent changes in rates between 2010 and 2014 and 2015–2019. Among women aged 20–49 years, decreases in mortality were observed in all countries, and were generally larger than at older ages. Declines were similar in the EU-14 countries (−11.3%), the EU-27 (−10.1%) and Transitional countries (−11.2%). Among individual European countries, the largest declines were observed in Lithuania (−27.1%), but decreases greater than 20% were also observed in Croatia, Denmark, Ireland, and Poland. Increases in mortality were noted in Greece, Latvia, Portugal, Slovakia, Slovenia, Norway, the Republic of Moldova, and Serbia. Among women aged 50–69, decreases in mortality were observed in most countries, except in Greece, Latvia, Slovenia, the Republic of Moldova, Romania, Belarus, and Serbia. The change in mortality rate for women in this age group was −7.6% in the EU-27 and −8.8% in the EU-14, while in the Transitional countries, it was −2.7%. The largest differences were observed in the oldest age groups of women. Among women aged 70–79, increases in mortality were observed in Croatia, Norway, Poland, and the Republic of Moldova. Mortality decreased in the rest of the analysed countries and the largest drops were in Eastern European countries (Belarus, the Czech Republic, and Slovakia). In this age group, a stable mortality trend was observed in the EU-27 countries, while in older women, mortality slightly decreased (−1.9%). In the EU-14 countries, mortality decreased in the 70–79 age group (−2.5%) and the older women group (−3.0%). In Transitional countries, mortality increased (5.9% in the 70–79 age group and 6.3% in older women). The largest proportional differences between individual countries were observed in the 80+ age group. Most countries experienced decreases in mortality, excluded Belarus, Croatia, Finland, Lithuania, and Poland.

Joinpoint analysis results for the EU-27, the EU-14, the Transitional countries and major European countries

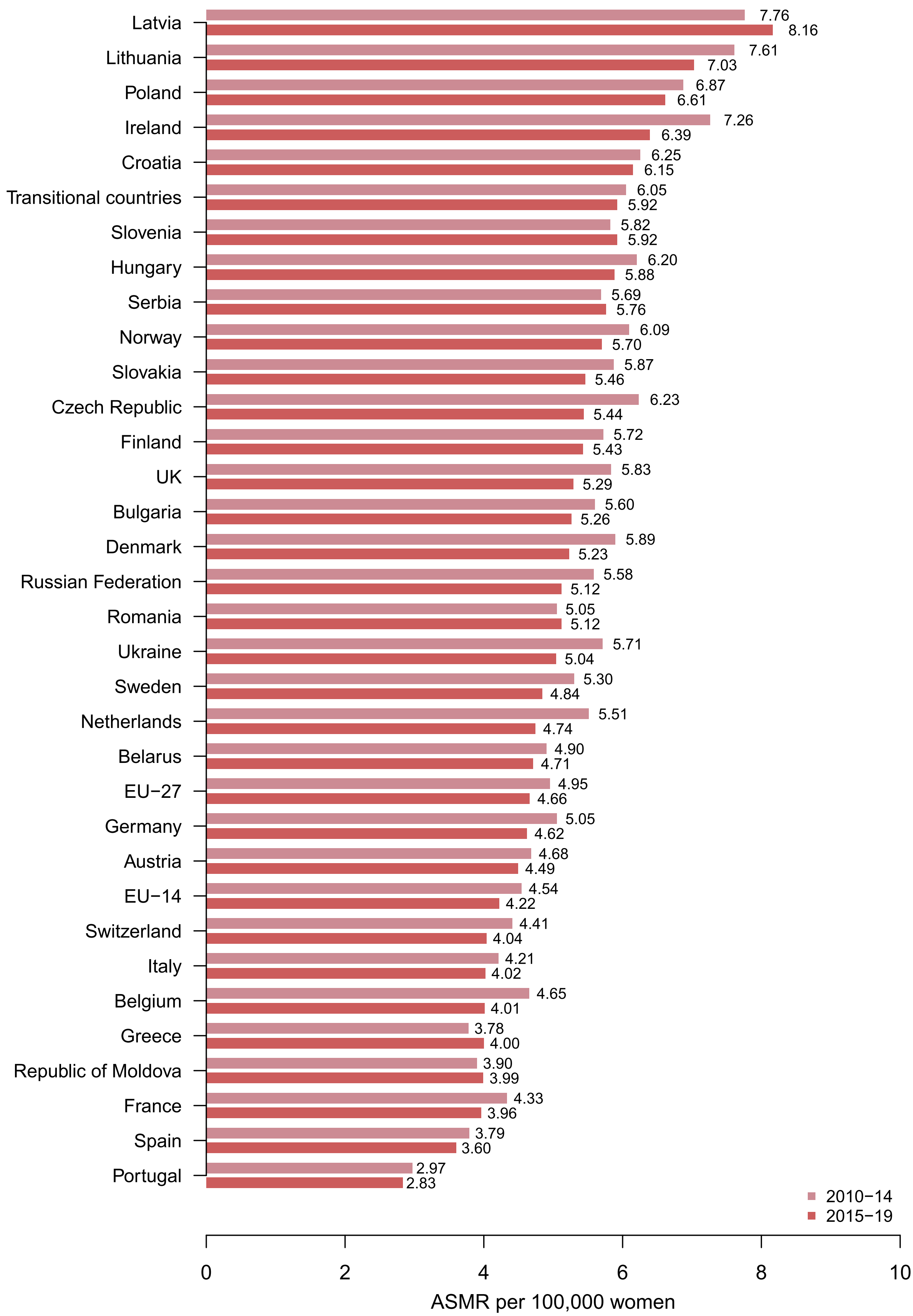

Fig. 1. Bar plots of age-standardised (world population) mortality rates per 100,000 from ovarian cancer for the periods 2010–14 and 2015–19 in selected European countries, the EU-27, the EU-14, and the transitional countries.

Table 2
Age-standardised (world population) mortality rates per 100,000 women from ovarian cancer for different classes of age in selected European countries during 2010–2014 and 2015–2019 (or the last available year as indicated in parenthesis), average annual deaths over the latest period and the corresponding change in rates (%).

Country	Group of age	ASMR 2010–2014	ASMR 2015–2019	Annual average deaths 2015–2019	% Difference 2015–19 versus 2010–2014
EU countries					
Austria	20–49	1.19	1.14	24	−4.2
	50–69	15.55	14.71	174	−5.4
	70–79	37.31	37.40	163	0.2
	80+	60.06	54.85	155	−8.7
Belgium (2018)	20–49	1.17	0.99	25	−15.4
	50–69	15.15	12.06	182	−20.4
	70–79	38.32	37.91	186	−1.1
	80+	61.01	53.61	215	−12.1
Bulgaria	20–49	3.15	2.67	44	−15.2
	50–69	19.87	19.05	201	−4.1
	70–79	28.35	28.77	116	1.5
	80+	29.84	28.46	63	−4.6
Croatia	20–49	2.58	2.06	19	−20.2
	50–69	22.42	21.40	134	−4.5
	70–79	39.41	44.35	96	12.5
	80+	43.81	57.42	80	31.1
Czech Republic	20–49	1.85	1.60	40	−13.5
	50–69	22.86	19.96	301	−12.7
	70–79	44.63	38.39	202	−14.0
	80+	49.01	45.17	129	−7.8
Denmark (2018)	20–49	1.48	1.09	13	−26.4
	50–69	20.03	17.34	132	−13.4
	70–79	47.25	46.32	128	−2.0
	80+	67.73	61.64	95	−9.0
Finland	20–49	1.30	1.21	13	−6.9
	50–69	19.05	16.89	140	−11.3
	70–79	51.08	51.54	144	0.9
	80+	62.27	66.68	127	7.1
France (2017)	20–49	1.07	0.95	136	−11.2
	50–69	14.54	12.70	1161	−12.7
	70–79	35.53	34.96	943	−1.6
	80+	50.51	49.03	1241	−2.9
Germany	20–49	1.39	1.20	215	−13.7
	50–69	16.48	15.13	1797	−8.2
	70–79	42.73	38.62	1777	−9.6
	80+	57.00	55.60	1783	−2.5
Greece	20–49	1.45	1.58	41	9.0
	50–69	13.02	13.68	202	5.1
	70–79	24.17	26.48	146	9.6
	80+	37.74	38.01	164	0.7
Hungary	20–49	2.46	2.24	54	−8.9
	50–69	21.53	19.87	288	−7.7
	70–79	43.12	43.65	223	1.2
	80+	47.62	48.14	146	1.1
Ireland (2018)	20–49	1.63	1.21	14	−25.8
	50–69	25.13	21.11	110	−16.0
	70–79	59.09	59.88	89	1.3
	80+	80.55	73.46	67	−8.8
Italy (2017)	20–49	1.47	1.38	212	−6.1
	50–69	14.56	13.66	1178	−6.2
	70–79	29.66	29.56	956	−0.3
	80+	38.96	38.05	994	−2.3
Latvia	20–49	3.59	3.72	17	3.6
	50–69	26.56	29.30	86	10.3
	70–79	47.73	48.81	58	2.3
	80+	56.87	51.81	40	−8.9

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Table 2 (*continued*)

Country	Group of age	ASMR 2010–2014	ASMR 2015–2019	Annual average deaths 2015–2019	% Difference 2015–19 versus 2010–2014
Lithuania	20–49	3.51	2.56	17	−27.1
	50–69	27.18	25.29	110	−7.0
	70–79	44.06	47.90	77	8.7
	80+	51.56	52.39	60	1.6
Netherlands	20–49	1.38	1.14	43	−17.4
	50–69	18.22	14.45	347	−20.7
	70–79	47.54	45.63	348	−4.0
	80+	61.44	59.73	297	−2.8
Poland	20–49	2.75	2.18	185	−20.7
	50–69	25.69	24.37	1359	−5.1
	70–79	41.29	46.21	713	11.9
	80+	41.70	44.30	498	6.2
Portugal (2018)	20–49	0.95	1.06	27	11.6
	50–69	10.30	9.57	144	−7.1
	70–79	21.80	20.94	113	−3.9
	80+	27.12	25.11	102	−7.4
Romania	20–49	2.17	2.07	102	−4.6
	50–69	18.77	18.83	513	0.3
	70–79	30.38	32.02	290	5.4
	80+	25.49	29.72	170	16.6
Slovakia	20–49	2.06	2.14	28	3.9
	50–69	20.45	19.14	146	−6.4
	70–79	41.92	36.87	81	−12.0
	80+	43.93	43.73	54	−0.5
Slovenia	20–49	2.01	2.05	10	2.0
	50–69	19.67	20.82	62	5.8
	70–79	39.49	40.97	39	3.7
	80+	65.07	54.22	39	−16.7
Spain	20–49	1.47	1.21	146	−17.7
	50–69	13.20	12.68	770	−3.9
	70–79	24.84	25.01	512	0.7
	80+	33.25	32.21	573	−3.1
Sweden (2018)	20–49	1.10	1.02	21	−7.3
	50–69	18.75	16.22	204	−13.5
	70–79	44.32	44.26	206	−0.1
	80+	52.46	49.41	153	−5.8
Other European countries					
Belarus (2018)	20–49	2.44	2.05	46	−16.0
	50–69	18.94	19.10	279	0.8
	70–79	24.19	19.80	77	−18.1
	80+	14.51	24.03	67	65.6
Norway (2016)	20–49	1.18	1.22	14	3.4
	50–69	22.87	20.27	129	−11.4
	70–79	42.84	48.31	92	12.8
	80+	65.60	52.18	72	−20.5
Republic of Moldova (2018)	20–49	2.01	2.05	17	2.0
	50–69	14.95	15.26	73	2.1
	70–79	17.86	20.26	21	13.4
	80+	12.37	7.37	4	−40.4
Russian Federation	20–49	2.87	2.49	838	−13.2
	50–69	20.50	19.04	4225	−7.1
	70–79	29.93	27.79	1662	−7.2
	80+	23.14	22.92	887	−1.0
Serbia	20–49	2.50	2.57	40	2.8
	50–69	20.51	20.66	230	0.7
	70–79	35.89	36.53	123	1.8
	80+	32.21	31.99	63	−0.7
Switzerland	20–49	1.01	0.83	17	−17.8
	50–69	14.09	12.38	136	−12.1
	70–79	39.11	40.39	150	3.3
	80+	57.16	52.06	141	−8.9

(*continued on next page*)

Table 2 (*continued*)

Country	Group of age	ASMR 2010–2014	ASMR 2015–2019	Annual average deaths 2015–2019	% Difference 2015–19 versus 2010–2014
Ukraine	20–49	3.42	2.87	290	−16.1
	50–69	21.34	18.95	1222	−11.2
	70–79	25.70	24.01	477	−6.6
	80+	12.29	10.94	139	−11.0
UK	20–49	1.45	1.33	192	−8.3
	50–69	19.63	17.12	1427	−12.8
	70–79	48.99	46.44	1328	−5.2
	80+	62.77	61.86	1198	−1.4
EU-27 (2017)	20–49	1.59	1.43	1466	−10.1
	50–69	17.16	15.85	9702	−7.6
	70–79	36.45	36.12	7575	−0.9
	80+	46.77	45.87	7181	−1.9
EU-14 (2017)	20–49	1.33	1.18	927	−11.3
	50–69	15.31	13.96	6470	−8.8
	70–79	35.77	34.86	5710	−2.5
	80+	47.97	46.53	5897	−3.0
Tansitional countries (2018)	20–49	2.49	2.21	593	−11.2
	50–69	22.11	21.52	3617	−2.7
	70–79	37.08	39.25	2054	5.9
	80+	38.46	40.87	1368	6.3

ASMR: Age-standardised mortality rate.

are presented in Fig. 2 and Supplementary Table 1. Recent trends were downward in most European countries, except for Croatia, Greece, Hungary and Romania showing stable rates over the most recent period. However, most Western and Northern European countries have shown favourable trends since the beginning of the 1990s, as well as some Eastern European countries, i.e. Belarus, the Czech Republic and Hungary. In the remaining Eastern European countries, despite an initial increase in mortality rates, a change in trend was generally observed in the second half of the 1990s, except in Poland, the Russian Federation and Serbia where a trend reversal only occurred during the first two decades of the 21st century. Transitional countries showed less favourable recent mortality trends than EU-27 and EU-14. In contrast, over the whole studied period, Bulgaria, Greece and Romania showed increasing mortality trends, starting however from lower ovarian cancer mortality rates at the beginning of the 1990s than the rest of Europe. In the EU-27 and EU-14, ovarian cancer mortality trend has been decreasing since the beginning of 1990s, while it remained stable in Transitional countries.

Fig. 3 shows join point analysis results for different age groups, for the EU-27, the EU-14 and the transitional countries. In the EU-27 and EU-14, a decrease in mortality was observed across all age groups of women, while the largest differences were observed in Transitional countries. Among women aged 20–49, the trend was similar to the other two analysed country groups. Among women aged 50–69, mortality rates remained stable throughout the entire analysed period. Among women aged 70–79 and the oldest age group, mortality rates increased over the observed period.

Table 3 presents ovarian cancer mortality predictions for 2025 for the seven major European countries and the three groups of countries considered. Compared to 2015–2019 rates, the largest decrease was predicted for Germany (about −20.6%), reaching a predicted mortality rate of 3.67/100,000 women. A substantial decrease was also predicted for the Russian Federation (−18.3%), followed by France (−14.6) and the UK (−11.8%). The highest mortality rate in 2025 is predicted for Poland, with an ASMR of 5.98/100,000 women, while the lowest ones are in Spain and France, with ASMRs around 3.4/100,000. Italy is the only major country where no decrease in ovarian cancer mortality is predicted. In all analysed groups of countries, ovarian cancer mortality is expected to decrease. The largest decrease in mortality is predicted to be in Transitional countries (−14.4%), followed by EU-14 (−14.2%), and EU-27 (−10.6%).

Fig. 4 shows the estimated number of avoided ovarian cancer deaths in the six major European countries and three groups of European countries, between 1994 and 2025, assuming constant age-specific rates in 1993 (light grey area). Over the 33-year period considered, we estimated about 24,600 avoided ovarian cancer deaths in France, 12,700 in Italy, 59,500 in Germany and 20,100 in the UK. The corresponding figure in the EU-27 is 130,700 deaths, while around 7000 averted ovarian cancer deaths were estimated for the Transitional countries. No appreciable number of

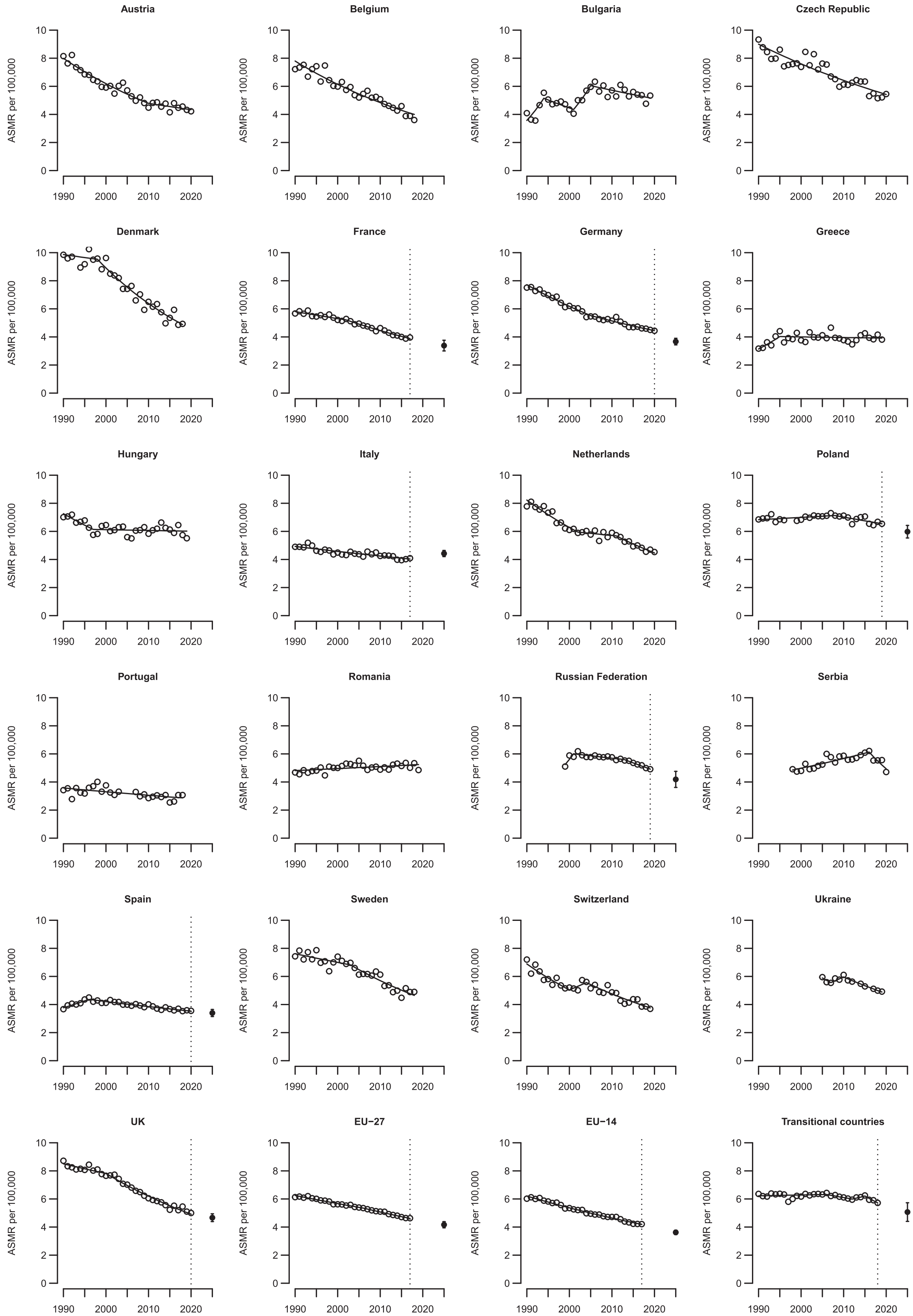

Fig. 2. Annual age-standardised (world standard population) mortality rates per 100,000 females at all ages from ovarian cancer in major European countries (> 3 million resident women) and the EU-27, EU-14, and transitional countries, the resulting joinpoint regression models and predicted rates (only for countries with > 20 million women and the three European areas) for the year 2025 with 95% prediction intervals.

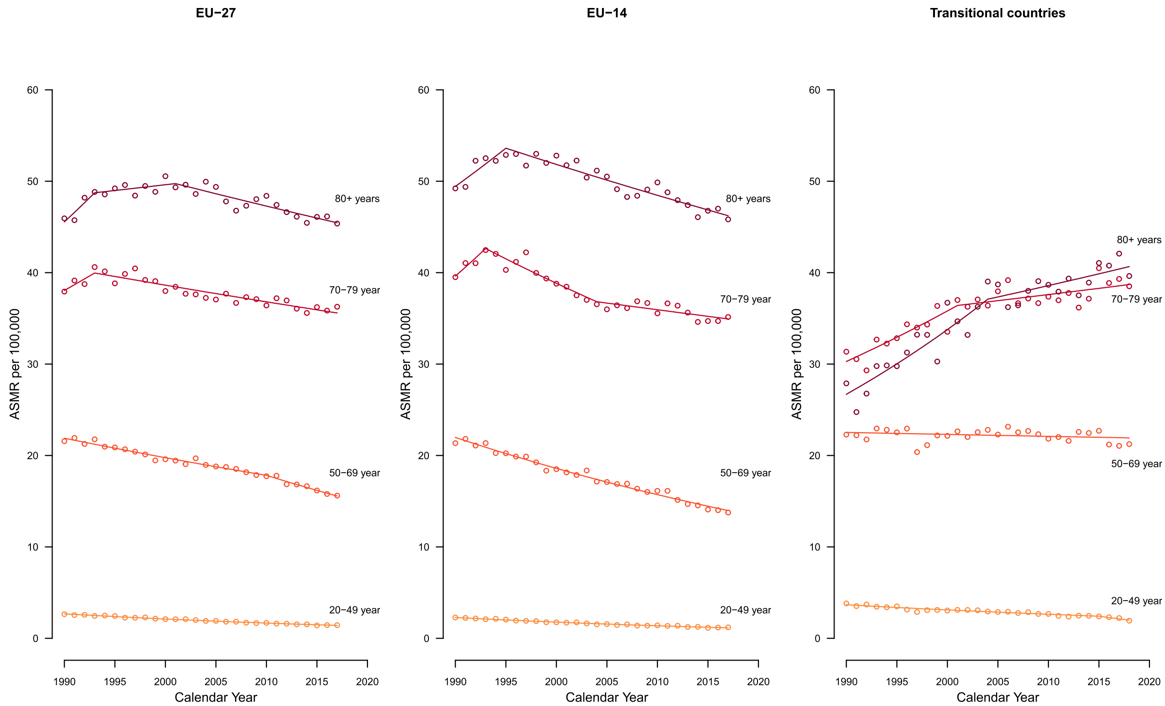

Fig. 3. Annual age-standardised (world standard population) mortality rates from ovarian cancer per 100,000 women at age 20–49, 50–69, 70–79, and over 80 years in the EU-27, EU-14, and transitional countries.

avoided deaths from ovarian cancer was estimated in Poland and Spain.

4. Discussion

Our study shows a decrease in ovarian cancer mortality rates in the last decades in most European countries, with only a few exceptions. In most EU-14 countries, the favourable mortality trend has been observed since the beginning of the 1990s, while in most Transitional countries it occurred later. We predicted a further decline in mortality rates from ovarian cancer in the near future.

Ovarian cancer has the highest mortality rates among all gynaecological neoplasms [14]. The overall 5-year survival rate is below 40%, and only moderate improvements have been recorded since the 90s in Europe overall [15]. It is the eighth most commonly diagnosed cancer in women in Europe [16]. According to Global Cancer Observatory database (GLOBOCAN 2020), the highest incidence rates were observed in Central, Eastern-Europe with age-standardised incidence rates exceeding 10.0/100,000 women, while lower incidence rates in the other European areas (around 7.1–8.8/100,000) [16].

Differences in the geographical mortality patterns can be partly related to changes in the prevalence of risk factors. Among these, there are mainly changes in the use of oral contraceptives (OCs), a well-known protective factor for ovarian cancer [17]. The widespread use of OCs plays a key role in the favourable trends in ovarian

Table 3
Number of predicted deaths and mortality rates from ovarian cancer, for all ages, for the year 2025 and comparison figures for 2015–2019, for the most populous European countries, plus the EU-27, EU-14 and transitional countries group, with 95% prediction intervals (PIs).

Country	Annual average deaths 2015–2019	Predicted number of deaths 2025 (95% PI)	Observed ASMR 2015–2019	Predicted ASMR 2025 (95% PI)
France	3482	3650 (3310–3990)	3.96	3.38 (3.00–3.76)
Germany	5573	4900 (4580–5170)	4.62	3.67 (3.43–3.90)
Italy	3342	3900 (3790–4110)	4.02	4.42 (4.20–4.64)
Poland	2755	2900 (2740–3080)	6.61	5.98 (5.53–6.42)
Russian Federation	7620	7100 (6320–7910)	5.12	4.19 (3.61–4.76)
Spain	2002	2100 (1940–2210)	3.60	3.40 (3.15–3.65)
UK	4147	4150 (3960–4340)	5.29	4.67 (4.39–4.94)
EU-27	25,934	26,900 (25,640– 28,260)	4.66	4.17 (3.95–4.38)
EU-14	19,011	18,700 (18,080– 19,350)	4.22	3.62 (3.47–3.77)
Transitional countries	7634	10,100 (9050– 11,130)	5.92	5.07 (4.40–5.73)

ASMR, age-standardised mortality rates (using the world standard population).

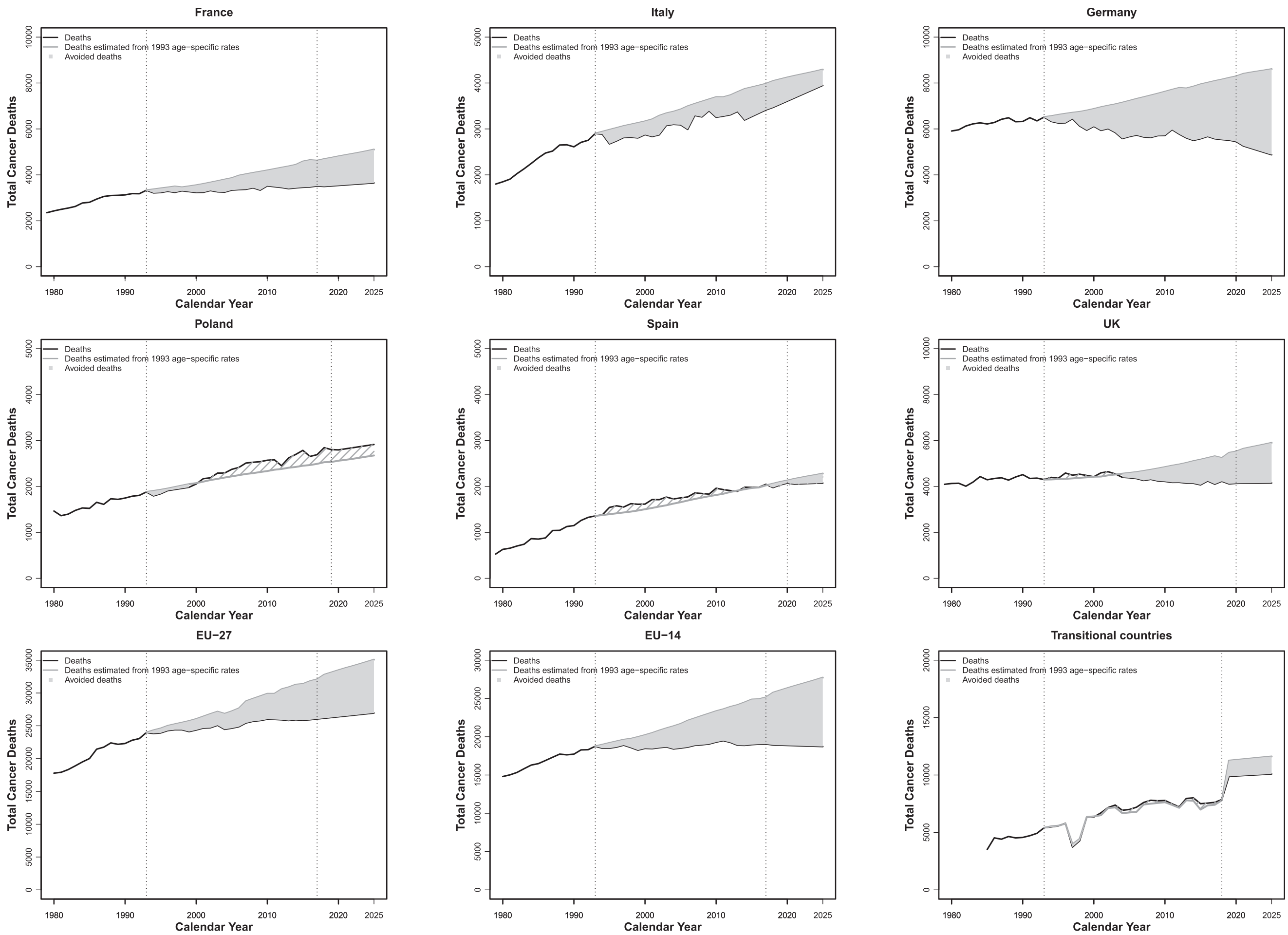

Fig. 4. Estimated numbers of avoided ovarian cancer deaths between the top rate in 1993 and 2025 (light grey area); observed and predicted numbers of ovarian cancer deaths from 1994 to 2025 (black line); estimated numbers of ovarian cancer deaths by applying 1993 age-specific peak mortality rates (grey line).

cancer mortality in Europe and can explain some of the differences across countries [1,17,18]. The strength of the protective effect of OCs depends on the duration of its use and persists for up to 30 years after discontinuation. For women who never used OCs, it was estimated that 1.2 out of 100 are diagnosed with ovarian cancer by age 80 years, and 0.7 die from it. After 10 years of OC use the cumulative incidence declined to 0.8 and 0.5 per 100 women respectively. OC use in the period 1960–1989 was associated with similar proportional risk reductions, independently for the type of OCs [19]. Since the 1960s, OCs have been widely available in Northern Europe and were adopted earlier in Western and Northern European countries compared to Southern Europe. Before 1990, OCs were available in most countries of Central and Eastern Europe, but their accessibility was limited and high cost was an additional barrier to their use [20]. The prevalence of OC use increased in the 1990s in this part of Europe, which is reflected in the shifted patterns of ovarian cancer mortality.

Besides the major favourable impact of increasing OC use in subsequent generations, increases over time in oophorectomy and salpingectomy following surgery for uterine myomas and other benign conditions may also have played a favourable role, though adequate data for various countries are not available.

The reduction in the use of menopause hormone replacement therapy (HRT) may also have contributed to the decline in mortality in some Western European countries. The results of the Women's Health Initiative (WHI) randomised controlled trial and the Million Women Study had a significant impact on the use of HRT in Europe [21,22]. Before 2002, countries of Central and Northern Europe had the highest prevalence of HRT utilisation. However, following the results of the WHI, there was a sharp decrease in HRT use [23], which may have contributed to the more marked decline in ovarian cancer mortality rates in those countries.

Other risk factors for ovarian cancer, such as early age at menarche, and late age at menopause are unlikely to have had an appreciable impact on ovarian cancer mortality [18] The fertility rate steadily declined from the mid-1960s in Europe. For nearly three decades, there has been an observed trend of approximately stable fertility rates in most European countries [24]. Changes in fertility rates, however, did not reflect ovarian cancer mortality. The low mortality rates observed in Mediterranean countries can be at least in part explained by the favourable impact of diet in reducing the risk of ovarian cancer [25,26]. Parity, a recognised protective factor for ovarian cancer, was higher in Mediterranean countries than in Central and Northern Europe, but it had already decreased (to about 2.5 births per woman) in women diagnosed with ovarian cancer in the period considered, largely born between the 1920s and the 1950s. A transgenerational epigenetic effect can therefore be considered, at least as a hypothesis [27]. Other modifiable risk factors, such as overweight and obesity, as well as lack of physical activity, are weakly linked to ovarian cancer occurrence [28]. However, those potential risk factors likely had no noticeable impact on mortality rates, as their prevalence is stable or slightly increasing in Europe [29,30].

The decline in ovarian cancer mortality can also be partly attributed to advancements in surgery and novel chemotherapeutic regimens, as well as the ability to offer these treatments to older women [1]. The gold standard treatment for ovarian cancer is surgical cytoreduction followed by chemotherapy, and an important prognostic factor influencing the survival of women with ovarian cancer is the extent of residual disease after cytoreduction [15,31]. Platinum-based chemotherapy schemes were implemented almost 40 years ago, and taxanes use started 10 years later. These drugs remain to date the first-line treatment of ovarian cancer. More recently, the use of gemcitabine, bevacizumab, and Poly(adenosine diphosphate-ribose) polymerase inhibitors as well as intraperitoneal chemotherapy have been proposed [1,15,32,33]. Progresses in the proposed forms of therapy continue, such as the development of SIK2 inhibitors [34]. Despite an initial response to primary therapy, approximately half of the women experience disease recurrence within the first few years after completing treatment, and in some cases, they also develop platinum or primary chemotherapy resistance.

The pandemic of Covid-19 may have some impact on ovarian cancer diagnosis, incidence, and mortality. However, at least in 2020, the impact of the pandemic was major on respiratory, vascular and metabolic diseases, but negligible on cancer [35]. Still, some future impact due to delayed diagnosis/treatment at the peaks of the epidemic in 2020 and 2021 is possible but probably minor. The Russian aggression in Ukraine has caused major damage to health infrastructure and a substantial impact on the Ukrainian population, influencing to an undefined degree any estimation for 2025 [36]. For this reason, we were unable to make a valid prediction for Ukraine.

We retrieved death certification data provided by the WHO mortality database, which may entail some limitations, like national coverage or inaccuracy in death certificates. To minimise these limitations, we included only countries with death certification coverage over 90%. The use of the 3-digit code in ICD-9 classification (183) was due to deficiencies in codification in the form of 4-digit codes for most European countries, including Transitional countries and other less populous Eastern countries and Russia. Some of the cancers certified as ovarian may have arisen from fallopian tubes, but these present similar pathological and clinical characteristics as well as similar classification, diagnosis, management and treatments.

5. Conclusions

Over the study period, ovarian cancer mortality has been declining in most of Europe, and favourable trends are also expected in the near future. Ovarian cancer, especially in the early stages, poses significant diagnostic challenges. This is due to its early asymptomatic nature, discreet tumour development, and lack of an effective screening programme [37–39]. Furthermore, frequent relapses contribute to the persistently high mortality rate, which is expected to increase globally in the coming decades [40], despite the favourable short-term projections in European countries. Emphasis should be on primary prevention, reducing the strongest well-known risk factors, such as HRT use. Moreover, increasing the availability and access to high-quality ovarian cancer care and treatment could improve the prognosis.

Funding

This work was supported by the Italian Association for Cancer Research Foundation (AIRC Foundation, project N. 22987) and by EU funding within the NextGeneration EU-MUR PNRR Extended Partnership initiative on Emerging Infectious Diseases (Project no. PE00000007, INF-ACT). The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and the decision to submit the manuscript for publication.

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Anna Odone: Methodology, Writing – original draft, Supervision. **Michał Ciebiera:** Investigation, Writing – original draft. **Eva Negri:** Methodology, Writing – original draft, Supervision, Funding acquisition. **Andrzej Wojtyła:** Investigation, Writing – original draft, Supervision, Project administration, Funding acquisition. **Carlo La Vecchia:** Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2023.113350.

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