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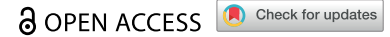


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ORIGINAL RESEARCH



The indirect costs of human papillomavirus-related cancer in Central and Eastern Europe: years of life lost and productivity costs

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ABSTRACT

Background: Human papilloma virus (HPV) is a common cause of several types of cancer, including head and neck (oral cavity, pharynx, oropharynx, hypopharynx, nasopharynx, and larynx), cervical, vulval, vaginal, anal, and penile cancers. As HPV vaccines are available, there is potential to prevent HPV-related disease burden and related costs.

Method: A model was developed for nine Central Eastern European (CEE) countries (Bulgaria, Croatia, Czechia, Hungary, Poland, Romania, Serbia, Slovakia, Slovenia). This model considered cancer patients who died from 11 HPV-related cancers (oropharynx, oral cavity, nasopharynx, hypopharynx, pharynx, anal, larynx, vulval, vaginal, cervical, and penile) in 2019. Due to data limitations, Bulgaria only included four cancer types. The model estimated the number of HPV-related deaths and years of life lost (YLL) based on published HPV-attributable fractions. YLL was adjusted with labor force participation, retirement age and then multiplied by mean annual earnings, discounted at a 3% annual rate to calculate the present value of future lost productivity (PVFLP).

Results: In 2019, there were 6,832 deaths attributable to HPV cancers resulting in 107,846 YLL in the nine CEE countries. PVFLP related to HPV cancers was estimated to be €46 M in Romania, €37 M in Poland, €19 M in Hungary, €15 M in Czechia, €12 M in Croatia, €10 M in Serbia, €9 M in Slovakia, €7 M in Bulgaria and €4 M in Slovenia.

Conclusions: There is a high disease burden of HPV-related cancer-related deaths in the CEE region, with a large economic impact to society due to substantial productivity losses. It is critical to implement and reinforce public health measures with the aim to reduce the incidence of HPV-related diseases, and the subsequent premature cancer deaths. Improving HPV screening and increasing vaccination programs, in both male and female populations, could help reduce this burden.

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Introduction


Cancer is one of the leading causes of death globally, with over 695,000 deaths reported in the Central and Eastern Europe (CEE) in 2020¹. The economic burden of cancer is also significant, costing Europe €199 billion in 2018, including €103 billion in cancer care, €26 billion in informal care, and €70 billion in productivity losses².

There are notable differences in cancer epidemiology among European countries, with significant variations in cancer incidence and mortality³. CEE countries generally experience higher cancer mortality rates compared to other European regions, with CEE countries facing excess mortality when compared to Western European countries, with one study estimating that closing the mortality gap could potentially prevent over 55,000 cancer-related deaths^{3,4}. These

regional disparities may be attributed to various factors, such as differences in the prevalence of underlying risk factors, shortcomings in screening and early diagnosis, variations in the distribution of cancer types, and differences in available treatment options and follow-up care^{5,6}. To address the high cancer burden in Europe, European Union (EU) member states have developed or revised their National Cancer Control Programs in the past decade, with the EU Commission developing a “Beating Cancer Plan”, providing recommendations for cancer treatment strategies, including cancer prevention via increased screening and vaccination plans⁷.

Human papilloma virus (HPV) is a sexually transmitted disease and can cause several types of cancer, including head and neck (oral cavity, pharynx, oropharynx, hypopharynx, nasopharynx, and larynx), cervical, vulval, vaginal, anal, and penile cancers⁸. HPV-related cancers were estimated to

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account for 32,348 new cases annually in Eastern Europe, in 2020, resulting in the death of 15,854 patients each year⁹.

HPV vaccination has been shown to be an effective preventive measure for HPV-related cancer, and the first HPV vaccination programmes were introduced in Europe in 2007 as part of national cancer plans⁹. The introduction of HPV vaccination programmes in line with the WHO's targets of eliminating the burden of cervical cancer globally through near-universal screening and HPV vaccination¹⁰. However, CEE has been slower at incorporating these programmes compared to other parts of Europe, and at the time of publication Bulgaria and Romania had not yet included males in the vaccination programme^{9,11}. CEE countries currently fall short of the 90% vaccination rate target⁷.

This analysis aimed to provide quantitative evidence on the impact of premature mortality due to HPV-related cancer on societal costs and to provide support for shaping cancer control policies. The analysis estimated the societal and economic burden by assessing the productivity loss of premature death due to HPV-related cancer in nine CEE countries (Bulgaria, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia, Slovakia, and Slovenia) over a one-year period (2019). More specifically, the study calculated years of life lost (YLL), years of productive life lost (YPLL), and the present value of future lost productivity (PVFLP).

Materials and methods

Model structure

An economic model was developed to calculate the indirect costs resulting from HPV-related cancer deaths. The human capital approach was used to estimate productivity losses due to premature deaths in 2019 in nine CEE countries from 11 HPV-related vaccine preventable cancers. The methodology used is consistent with previously published studies^{12–15}.

The model used the societal perspective and a lifetime horizon to assess three key outcomes: YLL, YPLL, and PVFLP. Costs incurred during a patient's lifetime, such as healthcare system expenses (e.g. treatment costs) were excluded as patients entered the model at the point of death.

The model included cancer patients who died in 2019 from 11 cancers as identified by the following ICD10 codes: oral cavity (C02-06), oropharynx (C01, 09,10), cervical (C53), vulva (C51), vaginal (C52), anal (C21), penile (C60), nasopharynx (C11), hypopharynx (C12-13), pharynx (C14), and larynx (C32) cancers.

Attributable fractions (AFs) were the proportion of total mortality in a cancer type directly caused by an HPV infection. AFs were applied to the number of deaths for each cancer in a year to calculate the number of cancer deaths attributable to HPV infection. YLL calculations considered deaths across all age categories and both sexes, while YPLL and PVFLP calculations excluded YLL lost after retirement age, as loss of wages (the measure of productivity in this model) were assumed to not occur post-retirement. The model used country- and gender-specific retirement ages. The most recent available data prior to 2020 (2019) were used to avoid confounding from the impact of COVID-19 on these parameters.

Model calculations

For the calculation of YLL, YPLL, and PVFLP, the model estimated the projected remaining years of life, had the person not died from cancer, and anticipated remaining productive years as outlined below:

$$\text{Expected life years remaining}_i = \text{life expectancy} - (\text{midpoint of age category})_i$$

$$\begin{aligned} \text{Expected productive life years remaining}_i \\ = \text{retirement age} - (\text{midpoint of age category})_i \end{aligned}$$

where $i = 1, 2, 3 \dots n$ represent the population age groups used in the model, and n corresponds to the total number of age categories, these results were constrained to a minimum value of zero to prevent negative values.

Years of life lost

YLL calculations considered both the number of deaths, the proportion of those deaths attributable to HPV, and the age at which the deaths occurred, using the following formula:

$$\begin{aligned} \text{YLL} = \sum_{i=1}^n (\text{number of cancer deaths}_i * \text{AF}) \\ * (\text{expected life years remaining})_i \end{aligned}$$

where $i = 1, 2, 3 \dots n$ represent the population age groups used in the model.

Years of productive life lost

YPLL calculated the average number of years an individual would have spent in employment (defined within the model as earning a wage) if they had not experienced a premature death due to cancer, formula outlined below:

$$\begin{aligned} \text{YPLL} = \sum_{i=1}^n (\text{YLL}_i) \\ * \left(\frac{\text{expected productive life years remaining}_i}{\text{expected life years remaining}_i} \right) \\ * \text{labor force participation} \end{aligned}$$

where $i = 1, 2, 3 \dots n$ represent the population age groups used in the model.

Present value of future lost productivity

PVFLP was calculated in two steps:

1. The PVFLP per person was calculated by multiplying the productive life years remaining by country-, age-, and gender-specific annual wages.

$$\begin{aligned} \text{PVFLP per person}_i = (\text{Expected productive life years remaining})_i \\ * (\text{discounted annual earnings})_i \\ * (\text{labor force participation}_i) \end{aligned}$$

where $i = 1, 2, 3 \dots n$ represent the population age groups used in the model.

- The PVFLP per person was then multiplied by the age-specific mortality data to calculate the PVFLP for each of the nine CEE countries.

$$PVFLP = \sum_{i=1}^n (PVFLP \text{ per person})_i * (\text{number of deaths})_i$$

where $i = 1, 2, 3 \dots n$ represent the population age groups used in the model.

PVFLP was adjusted to account for country specific labor force participation as a measure of unemployment in the base case, to reflect the actual labor force characteristics. Annual earnings were discounted at a rate of 3% annually to obtain the present value of future earnings¹⁶.

The model calculated outcomes independently as disaggregated results for each country to allow for the use of country specific inputs. To obtain the regional estimate for CEE, each outcome (YLL, YPLL, and PVFLP) was summed across countries to provide an overall estimate. The sum of PVFLP was divided by the total number of deaths to calculate PVFLP per death respectively.

Model inputs

Epidemiological inputs

Epidemiological inputs included mortality data, retirement ages, and life expectancy and were specific to each country included in the model. Mortality data stratified by cancer type and by age were sourced from country specific

Table 1. Attributable fractions applied for HPV-related cancers.

Cancer	Attributable fraction	95% CI (lower bound)	95% CI (upper bound)
Oral cavity	3.7%	2.4%	5.6%
Oropharynx	19.9%	17.2%	22.8%
Cervical	100.0%	90.0%*	100.0%
Vulva	15.9%	13.5%	18.4%
Vaginal	70.2%	62.2%	77.4%
Anal	87.1%	81.0%	91.8%
Penile	29.0%	24.7%	33.7%
Nasopharynx	10.8%	3.0%	25.4%
Hypopharynx	2.4%	0.3%	8.4%
Pharynx (unspecified)	25.0%	10.7%	44.9%
Larynx	2.4%	1.2%	4.1%

Source: Hartwig et al.⁸

The 95% CIs were used as the lower and upper bound in the deterministic sensitivity analysis.

Abbreviations. AF, attributable fraction; HPV, human papillomavirus; CI, confidence interval.

*Lower bound for cervical cancer was assumed to be 90%.

Table 2. Parameter assumptions made in the model.

Model settings	Assumption details
Age groups	<ul style="list-style-type: none"> Individuals within each age group are assumed to be homogenous and will have the same outcomes. Individuals in the 0–14 years age group are assumed to have no income.^a
Retirement ages	<ul style="list-style-type: none"> Individuals in an age group above the average retirement have no YPLL.
Income	<ul style="list-style-type: none"> Average wage is assumed to be equal within each age groups.
Labor force participation	<ul style="list-style-type: none"> Labor force participation is assumed to be equal across age groups.
Attributable fractions	<ul style="list-style-type: none"> AFs were assumed to be homogenous across age groups and countries. Infection is not assumed to impact the prognosis of cancer. AFs were based on the proportion of cancer cases attributable to HPV, which may not be proportional to the number of cancer deaths attributable to infection.

Abbreviation. AF, attributable fraction.

^aThe youngest age group in the dataset was 0–14 years, with the next group being 15–39 years. In order to avoid additional assumptions to delineate the number of individuals aged 15 and 16 within the 15–39 years group, only those in the 0–14 years-year group were assumed to be in full time education.

databases (Supplement 1). Bulgaria, due to data limitations, only included mortality data for cervical, anal, pharynx, and larynx cancers. For Bulgaria, data for anal and pharynx cancers were provided in aggregated cancer groups, which included some non-HPV-related cancers. Pharynx cancer mortality data was included with lip and oral cavity cancer, therefore 2.20% of mortality in the group was assumed to be attributable to pharynx cancer in CEE, based on incidence data from Shield et al.¹⁷ Anal cancer was separated from the colon and rectal cancer grouping, assigning 1.08% of mortality for the group to anal cancer using mortality data from Globocan¹⁸. Gender specific retirement ages and life expectancies were sourced from the World Bank (Supplement 2 and 3)^{19–21}.

Fractions attributable to all HPV types were sourced from Hartwig et al. as it reported AFs for all HPV-related cancers included in this analysis and provided European data including the selected countries⁸. These were applied to calculate the number of cancer deaths attributable to HPV infection and were assumed equal across countries (Table 1)⁸.

Economic inputs

In the base case, average annual earnings were used as the measure of income. The average annual earnings were sourced from the Eurostat database²², with a weighted average used in instances where the age groups in the Eurostat database did not align with those used in the model. Labor force participation rate were sourced from the World Bank²³.

Assumptions

The model used real-world data to inform the epidemiological and economic inputs wherever possible, however several assumptions were made to account for the granularity of data available (Table 2). Assumptions around age groups followed existing model approaches^{12,15}.

Sensitivity analysis

The model included a deterministic sensitivity analysis (DSA) to investigate the sensitivity of results to variation in input parameters. AFs were varied using their 95% confidence intervals (Table 1). CIs for cervical cancer were not reported by Hartwig et al. hence an assumption of 90% as a lower

bound was considered for a conservative estimate. Mortality, life expectancy, measures of income (average wage), labor force participation rate, and retirement age were varied by a relative +/- 10% of the base case value to understand the impact on model outcomes and identify key drivers of results.

A scenario analysis was conducted using GDP per capita in place of annual earnings, assuming GDP per capita was equal across age groups and genders²⁴. As with using the annual earnings, the GDP per capita was only applied to ages below the retirement age.

A secondary scenario analysis was carried out to account for differing discount rates across the included countries. Discount rates differ across the included countries ranging from 3 to 5%¹⁶. Therefore, this scenario included a lower and upper bound of 0% and 5% to cover all plausible ranges.

Results

Base case results

There were a total of 6,832 deaths, 107,846 YLL, 28,330 YPLL, and a PVFLP of approximately €151 million in 2019 from HPV-related cancers in the nine CEE countries of interest (Table 3).

Poland had the greatest number of deaths, at 2,227 deaths (Table 3), as it has the largest population (38 million). However, the overall mortality rate of Poland (0.0059%) is below the average of the nine countries (0.0061%) (Table 4). The second largest country by population, Romania (19 million) had the second highest number of deaths at 1,957 but also had the highest crude mortality rate (0.0101%). These two countries accounted for 56% of total deaths (Table 3). Slovenia had a much lower mortality rate than the other countries (0.0036%), with only 75 deaths.

Following the same trend as the number of deaths, Poland and Romania had the first (34,478) and second (31,617) greatest number of YLL, due to the high absolute mortality in the two countries (Table 3). Slovenia also had the lowest YLL at 1,396.

Romania had the greatest YPLL (8,718) despite the higher mortality in Poland (Table 3). This was partially due to a later retirement age for females (61.9 years versus 60 years),

increasing the years of productive life lost per death (assuming an equal age at death). Additionally, Romania had a higher average year of life lost (AYLL) (16 years vs. Poland's 15 years), indicating a younger age distribution of deaths and thus more productive years lost. Slovenia and Croatia had the lowest YPLL at 402 and 702 respectively, as expected from the countries with the lowest mortality and smallest populations.

Romania had the greatest PVFLP (€44.5 million), followed by Poland (€37.8 million) (Table 3). Slovenia had the lowest PVFLP (€4 million) as it had the smallest population size and the lowest number of deaths. However, Slovenia had the highest PVFLP per death (€57,821), higher than the average PVFLP per death of €22,086 across the nine CEE countries (Table 3).

Cervical cancer had the largest mortality burden in the nine countries, accounting for 72% of deaths, followed by anal cancer at 9% (Table 5). Hypopharynx cancer had the lowest proportion of deaths (0.48%) followed by nasopharynx (0.61%) due to the low rate attributable to HPV. Cervical cancer had the largest PVFLP, at €114 million accounting for 76% of the total PVFLP.

Scenario analysis

When using the lower bound AFs there was a 13.6% decrease in PVFLP (€130,232,680 versus €150,894,499) compared to a 26.2% increase when using the upper bound of the AFs (€164,365,362 versus €150,894,499).

Using GDP as the income measure showed an overall increase in PVFLP per death (€24,135 versus €22,086) as the

Table 4. Population size and crude mortality rates by country in 2019.

Country	Population size	Crude Mortality rate
Bulgaria ^a	6,975,761	0.0051%
Croatia	4,065,253	0.0044%
Czech Republic	10,671,870	0.0049%
Hungary	9,771,141	0.0064%
Poland	37,965,475	0.0059%
Romania	19,371,648	0.0101%
Serbia	6,945,235	0.0080%
Slovakia	5,454,147	0.0062%
Slovenia	2,088,385	0.0036%
All countries	103,308,915	0.0061%

Source: The World Bank²⁵.

^aBulgarian outcomes are only reflective of cervical, anus, larynx, and pharynx cancers due to limitations in mortality data.

Table 3. Total number of deaths, YLL, YPLL, PVFLP and PVFLP/deaths by country in 2019.

Country	Number of deaths	YLL	YPLL	PVFLP (€)	PVFLP (€/death)
Bulgaria ^a	354	5,849	2,147	6,919,951	19,537
Croatia	177	2,780	702	4,284,035	24,219
Czech Republic	526	8,093	1,993	14,938,701	28,419
Hungary	626	9,667	3,456	18,824,584	30,085
Poland	2,227	34,478	6,643	37,889,429	17,017
Romania	1,957	31,617	8,718	44,529,949	22,757
Serbia	555	8,852	2,939	10,300,517	18,549
Slovakia	336	5,113	1,330	8,874,867	26,409
Slovenia	75	1,396	402	4,332,465	57,821
All countries	6,832^y	107,846^b	28,330	150,894,499^b	22,086

Abbreviations. PVFLP, Present value of future lost productivity; YLL, Years of years of potential life lost; YPLL, Years of potential productive life lost.

^aBulgarian outcomes are only reflective of cervical, anus, larynx, and pharynx cancers due to limitations in mortality data.

^bThe reported values have been rounded to the nearest integer; therefore the reported total may not match due to rounding.

GDP per capita for each country is greater than the respective average annual wage (when averaged across sexes) (Table 6). However, four countries which had higher proportional mortality burdens in the male populations, where the average annual wage is greater than the GDP, (i.e. Croatia, Romania, Serbia, and Slovenia) showed a reduction in the PVFLP when using GDP as a measure of income.

Varying the discount rate resulted in a PVFLP of €192,028,923 at a 0% discount rate and €132,026,047 at a 5% discount rate (Supplement 4).

Deterministic sensitivity analyses

The DSA showed the results to be most sensitive to the retirement ages used in the model, with the upper and lower bound PVFLP per death ranging from €12,502 and €38,869

Table 5. PVFLP results stratified by cancer.

Cancer	Estimated proportion of total mortality (%)	PVFLP (€)	PVFLP (€/death)
Oral cavity	1.56%	2,963,529	27,811
Oropharynx	7.70%	14,280,909	27,163
Cervical	71.59%	114,065,236	23,322
Vulva	2.14%	428,077	2,933
Vaginal	1.94%	598,457	4,511
Anal	8.73%	8,312,991	13,943
Penile	1.25%	1,525,592	17,833
Nasopharynx	0.61%	1,402,146	33,634
Hypopharynx	0.48%	866,182	26,635
Pharynx (Unspecified)	2.55%	4,707,844	27,066
Larynx	1.47%	1,743,536	17,383
Total	100.00%^a	150,894,499	22,086

Abbreviation. PVFLP, Present value of future lost productivity.

^aThe reported values have been rounded to the nearest integer; therefore, the reported total may not match due to rounding.

respectively (Figure 1). This is due to the large impact retirement age has on productivity as measured in this model, increasing the number of years a person would remain productive for. Mortality was predicted to not impact PVFLP per death as the variation of mortality did not impact the retirement age and therefore did not affect the YPLL.

Discussion

There were a total of 6,832 deaths from HPV-related cancers in 2019 in the nine CEE countries, with a PVFLP of €151 million, and a PVFLP per death of €22,086. A prior investigation by Bencina et al. revealed that although breast cancer accounted for 19,726 deaths in 2019 in the nine CEE countries, a lower PVFLP per death of €13,152 was reported in comparison to the HPV-related cancers included in this analysis¹². Another study evaluating the economic burden in

Table 6. PVFLP (€) results using GDP as the measure of income.

Country	Base case PVFLP (€/Death)	Scenario analysis PVFLP (€/Death)	Percent change from base case
Bulgaria ^a	19,537	24,027	22.98%
Croatia	24,219	23,448	-3.19%
Czech Republic	28,419	39,217	38.00%
Hungary	30,085	36,494	21.30%
Poland	17,017	18,410	8.18%
Romania	22,757	22,319	-1.92%
Serbia	18,549	15,786	-14.89%
Slovakia	26,409	33,476	26.76%
Slovenia	57,821	54,757	-5.30%
All countries	22,086	24,135	9.28%

Abbreviation. PVFLP, Present value of future lost productivity.

^aBulgarian outcomes are only reflective of cervical, anus, larynx, and pharynx cancers due to limitations in mortality data.

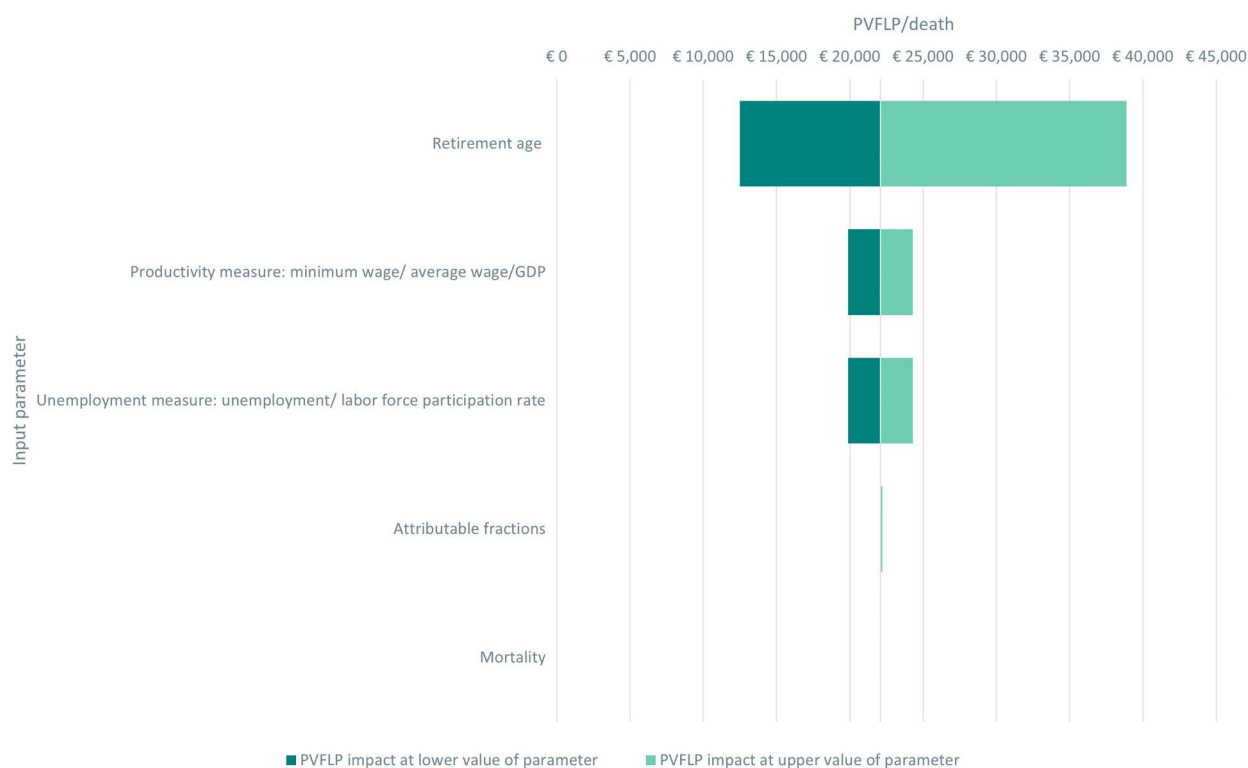


Figure 1. Tornado diagram for PVFLP/death in 2019.

Sweden noted that the indirect costs due to premature mortality in HPV-related cancers amounted to €36 million in 2017, which is similar to the countries with the highest PVFLP in this analysis (Poland, €37.8 million; Romania, €44.5 million)²⁶. While the estimates in this analysis may look low considering the higher population numbers in Poland and Romania and as this analysis included more cancer types, this is offset by the Swedish analysis also including pre-cancers. Similar to this analysis, the Swedish analysis found that cervical cancer represented the majority of the economic burden.

Poland and Romania had a similar absolute number of deaths at 2,227 and 1,957 respectively. This is despite Poland's population being almost double that of Romania (38 million versus 19 million), which means that Romania showed a higher crude mortality (0.0101% versus 0.0059%). Slovenia had the lowest mortality at 76 deaths. This could be in part due to the successful implementation of the NP ZORA National Cervical Cancer Screening Program in 2003, as Slovenia has experienced a large decline in the incidence of cervical cancer since its introduction²⁷. Slovenia now has the 8th lowest age-standardized rate of cervical cancer in Europe and the lowest age-standardized rate for HPV-related cervical cancer burden in the CEE countries⁹. However, Slovenia had the greatest PVFLP per death (€147,466), due to Slovenia having a higher average income than other countries in the region and the joint highest retirement ages, therefore increasing the lost productivity per death (Supplement 5 and 6).

In this analysis, cervical cancer had the greatest mortality burden of all the HPV-related cancers in the region, accounting for 72% of all mortality (Table 5). This aligned with cervical cancer having a large burden in CEE (11th highest cancer prevalence and 14th highest mortality), with more than 95% of cervical cancer cases being attributable to HPV infection^{1,28}. Although cervical cancer had the highest PVFLP at €114 million, the PVFLP per death was lower than the other cancers due to cervical cancer impacting the female population which, on average, had lower average incomes and lower retirement ages than those values for males, leading to a lower economic impact on lost productivity. Nasopharynx, while having a relatively low PVFLP at €1.4 million due to the low HPV AF (10.8%), had the largest PVFLP per death (€33,634) partially due to the large proportion of deaths in the male population (76%).

There are various existing strategies for HPV prevention, with the primary focus on screening and vaccination plans against HPV infection⁷. To achieve global cervical cancer elimination within the next century, the WHO strategy rests on three key pillars and countries reaching the corresponding coverage targets by 2030: "Vaccination: 90% of girls fully vaccinated with the HPV vaccine by the age of 15; screening: 70% of women screened using a high-performance test by the age of 35, and again by the age of 45; treatment: 90% of women with pre-cancer treated and 90% of women with invasive cancer managed"¹⁰. Currently in CEE, eight countries have screening rates greater than 70%, although Romania had a 40% screening rate in 2019²⁹. In terms of HPV vaccination rates among the included countries in this analysis,

Hungary achieved the highest coverage, with over 80% of females vaccinated in 2023¹¹. Czechia and Slovenia had the next highest coverage rate in females at between 50–80%, followed by Slovakia, estimated at 30–49% coverage. Bulgaria and Poland had less than 30% HPV vaccination coverage, with insufficient data available in Croatia, Romania, and Serbia to estimate coverage rates for the countries. HPV vaccination rates in males were significantly lower, with only Hungary having a vaccination coverage rate above 71% in boys aged 12 and above³⁰. The other eight countries had coverage rates below 30%, or insufficient data to estimate coverage rates. Therefore, HPV vaccination rates fall significantly short of the EU and WHO recommendations, with increased uptake of HPV vaccination within the CEE region required to meet targets and decrease the overall clinical and economic burden caused by HPV-related cancers.

While the model results show a significant burden on the female demographic, primarily in cervical cancer, there remains a high mortality burden in non-female specific HPV-related cancers. Recently, both Europe's Beating Cancer Plan and WHO European roadmap to accelerate the elimination of cervical cancer have noted the added benefits of increasing vaccination rates among males^{7,31}. While the WHO roadmap does not explicitly give priority to vaccinating males, it notes that vaccinating males routinely can indirectly safeguard females by helping minimize the transmission of infection and preventing other HPV-related cancers. Furthermore, vaccinating boys and preventing other HPV-related cancers are highlighted in the European Commission's proposal for a council recommendation on vaccine-preventable cancers³². Therefore, introducing vaccination in males could be important to ensure the additional benefit of HPV vaccination coverage. However, a country-level cost-effectiveness analysis should be conducted to inform the decision making.

The key strengths and limitations of the modeling approach have been previously discussed^{12–15}. This model offers quantitative evidence of the indirect economic burden associated with HPV-related cancers. It relies on publicly available datasets from reputable sources, which ensures the generation of robust results. The incorporation of country specific inputs, such as retirement age, life expectancy, and average wage, ensures that the findings accurately reflect the local context. Additionally, considering that some HPV-linked cancers are gender specific, the use of sex-specific inputs where available guarantees a more precise assessment of productivity losses, limiting over- or underestimation of the result. The scenario analysis testing the use of GDP per capita as a measure of income, showing a range of possible values, with the base case and scenario results estimating a similar burden of PVFLP per death (Table 6).

The model limitations pertain to the assumptions necessitated by the complexity of real-world data. For example, the model assumes uniform mortality rates within age brackets and employs average wages to represent the portion of the population currently employed, which simplifies the actual circumstances. In cases where a higher number of fatalities transpire within lower-income segments, this simplification could lead to an overestimation of lost productivity value.

There were also limitations related to the use of AFs. The dataset did not provide information regarding the proportion of deaths that involved individuals who had already received vaccination, and, consequently, these deaths may not accurately reflect HPV-related fatalities. Additionally, because of constraints in the available published data, it was necessary to assume that AFs were uniform across different countries, age groups, and genders. Instead, to maintain comparability across countries and to validate findings from this analysis, a consistent data source employing the same methodology was utilized for AFs, given no breakdown of AFs for all cancer types across all countries were available.

Data availability for Bulgaria also posed limitations on the model. Mortality data for most cancer types were limited, with data only found for cervical, anus, pharynx, and larynx cancers. Moreover, some of the cancers were reported as aggregated and the use of assumptions around the split in the aggregated cancers could potentially have biased the overall understanding of the impact of HPV on specific cancers. However, Bulgaria-specific data were used where possible to reduce this bias. Therefore, the impact of HPV-related cancers in Bulgaria is underestimated in this analysis.

Overall, the analysis will significantly underestimate the total burden of HPV-related cancers, with the direct costs to the healthcare system (such as medication or hospital costs) not considered as an outcome in the model. Hofmarcher et al. (2018) estimated that direct costs accounted for 31% of cancer costs in Europe². Furthermore, simplifying assumptions were employed to ensure robustness in the results and as such will not have captured some of the additional costs that exist, for example productivity loss post-retirement. This analysis may not account for post-retirement costs, particularly considering the increasing trends in late retirement and the significant non-wage contributions to the economy³³. However, due to the paucity of data and complexities in accurately quantifying post-retirement work and non-wage contributions, effectively capturing these aspects remains challenging without sufficient validation. Hence, a more conservative approach was taken. The analysis also does not capture cost attributable to presenteeism and absenteeism, therefore missing a significant portion of indirect costs while the patient is still alive. Studies have demonstrated the considerable impact of reduced health on productivity and indirect costs even when individuals are still alive^{26,34}.

However, the model captured cancer mortality which is frequently employed to guide the prioritization of disease areas in policy development, while also expanding on these reported outcomes. For instance, employing YLL as a metric for mortality considers the age at which individuals pass away, providing a broader perspective on the mortality burden. It is imperative that cancer policies are concentrated in areas where the burden is most substantial, considering both the number of deaths and the age at which these deaths occur. In this regard, it is crucial that the metrics used in shaping these policies capture these intricacies. By additionally incorporating YPLL and the associated costs, the model enhances the depth of these metrics, offering a quantifiable societal standpoint.

Conclusion

There is a high disease burden of HPV-related cancer-related deaths in the CEE region, with a large economic impact to society due to substantial productivity losses. It is critical to implement and reinforce public health measures with the aim to reduce the incidence of HPV-related diseases, and the subsequent premature cancer deaths. Increasing the coverage of HPV screening and vaccination programs, in both males and female populations, could help reduce this burden.

Transparency

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Declaration of financial/other interests

US is an employee of MSD Lithuania, who may own stock and/or hold stock options in Merck & Co., Inc., Rahway, NJ, USA. EK is an employee of MSD Greece, who may own stock and/or hold stock options in Merck & Co., Inc., Rahway, NJ, USA. GB is an employee of MSD Spain, who may own stock and/or hold stock options in Merck & Co., Inc., Rahway, NJ, USA.

DH, AM, GW, and RH are employees of Adelphi Values (PROVE), which was hired by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Author contributions

US, GB and GW conceptualized and designed the study. US and EK collected data inputs. AM and GW supervised the study. DH conducted the data analysis. All authors participated in visualizing and interpreting the data. All authors contributed to the interpretation of the results and commented on the manuscript. All authors read and approved the final version of the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article and its [supplementary materials](#).

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Previous presentations

The results of this analysis have not been previously presented.

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