The Indirect Costs Related to HPV-Attributable Cancer Mortality in European Countries: Years of Life Lost and Productivity Costs

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Background and objectives

- Human papillomavirus (HPV) is a leading cause of various cancer types, including cervical, vulvar, vaginal, anal, penile, and head and neck cancers[1]
- HPV-related cancers were estimated to account for 67,500 new cases annually across the 27 European Union (EU) countries in 2022[2]
- HPV vaccination has proven to be an effective preventive measure against HPV-related cancers, with the first vaccination programs introduced in Europe in 2007[3]
- The results of this analysis aim to support European policymakers in quantifying the burden of HPV-related cancers that are vaccine-preventable and to help prioritize vaccination and increase vaccine uptake

Methods

Model structure

Inputs and assumptions

- A model was developed to reflect the economic burden to society by calculating productivity loss due to premature deaths from 11 HPV-related cancers in 5 European countries – Belgium, Denmark, Lithuania, Portugal, and Switzerland – using the human capital approach
- The primary outcomes of the model were years of life lost (YLL), years of productive life lost (YPLL), and the present value of future lost productivity (PVFLP). Individuals entered the model at time of death using a single year of mortality, and outcomes were projected over the average lifetime

- The model included individuals with cancer who died from up to 11 cancers potentially preventable by HPV vaccination in 2019. The following ICD-10 codes were used to identify these cancers: 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)[1]
- Based on availability of country-specific mortality data, 7 cancer types were included in Belgium, 10 types in Denmark, 11 types in Lithuania, 11 types in Portugal, and 11 types in Switzerland
- Attributable fractions (AF) – the proportion of cancer-related deaths related to a specific infection – were applied to the number of deaths for each cancer type to estimate the number of cancer cases related to HPV
- Epidemiological inputs, such as mortality data, retirement age, and life expectancy, were specific to each country in the model. Mortality data, categorized by cancer type and age, were obtained from country-specific national registries, whereas life expectancy, retirement age, annual wage, and labor force participation were sourced from international sources[4-13]

Estimating the humanistic burden

- YLL were estimated from the number of deaths, life expectancy, and the attributable fractions for each cancer type. AF for HPV-related cancers, stratified by cancer type, was sourced from Hartwig, et al[1] (**Table 1**)

YLL=number of deaths x expected life years remaining x AF

- YPLL estimated the average number of years a person would have been engaged in productive employment (defined in the model as earning a wage) had they not died prematurely from cancer. It was assumed that the population would retain full economic activity until retirement age (unemployment accounted for by labor force participation rates). At retirement age, all economic activity ceases

YPLL=YLL x (expected productive life years remaining/expected life years remaining) x labor force participation

Estimating the economic burden

- PVFLP was estimated by first calculating the PVFLP per person, multiplying YPLL by annual wages specific to each country, age group, and sex. This value was then multiplied by age-specific mortality data to determine the overall PVFLP for each country
- PVFLP incorporated country-specific labor force participation rates to accurately represent labor force characteristics. In addition, annual earnings were discounted at a rate of 3% per year to calculate their present value.[14] PVFLP represents 2022 cost level

Table 1. Attributable fractions applied for HPV-related cancers

HPV-related cancer type	Attributable fraction
Oral cavity	3.7%
Oropharynx	19.9%
Cervical	100.0%
Vulva	15.9%
Vaginal	70.2%
Anal	87.1%
Penile	29.0%
Nasopharynx	10.8%
Hypopharynx	2.4%
Pharynx (unspecified)	25.0%
Larynx	2.4%

Source: Hartwig, et al.[1]
Abbreviations: HPV, human papillomavirus.

Results

- In 2019, there were 1,184 HPV-related cancer deaths and 19,888 YLL across the 5 European countries considered in this analysis (**Table 2**). The estimated economic impact of premature mortality due to HPV-related cancer deaths was €103,747,969. Cervical cancer had the highest mortality burden (60% of total HPV-related cancers deaths), followed by anal cancer (13% of total HPV-related cancers deaths) (**Table 3**)
- Cervical cancers accounted for the higher proportion of economic burden (72%), followed by oropharynx cancer (13%), compared to other cancers (**Figure 1**)

Figure 1. Proportion of economic burden (measured in PVFLP) imposed by each cancer type
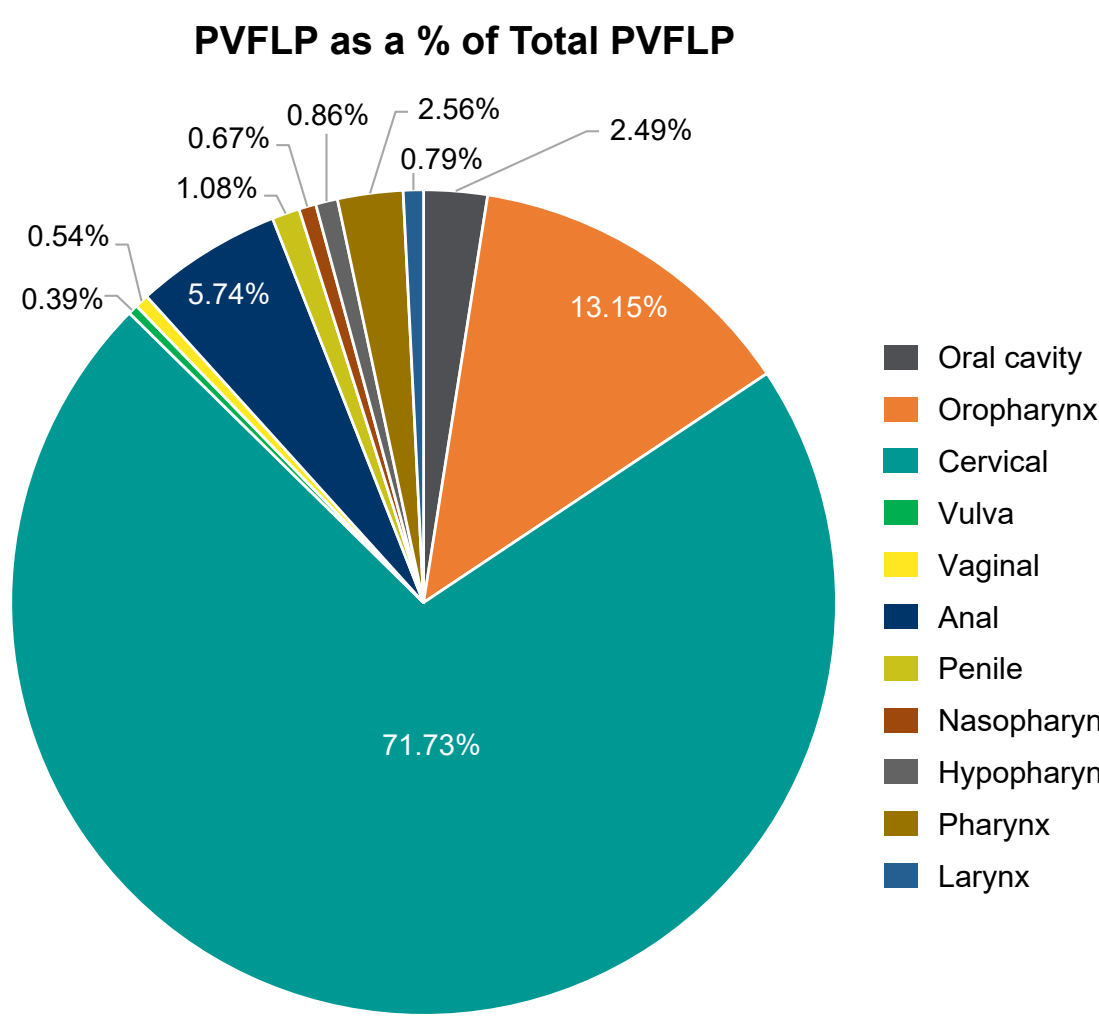

PVFLP as a % of Total PVFLP

- Oral cavity 0.39%
- Oropharynx 13.15%
- Cervical 71.73%
- Vulva 0.54%
- Vaginal 1.08%
- Anal 5.74%
- Penile 0.67%
- Nasopharynx 0.86%
- Hypopharynx 0.79%
- Pharynx 2.56%
- Larynx 2.49%

Table 2. Humanistic and economic burden of HPV-related cancers in 5 European countries

Region	Deaths	Deaths (% male/ female)	YLL	YPLL	PVFLP (€)	PVFLP/ death (€)
Belgium	193	19%/81%	3,532	1,088	€24,315,988	€125,974
Denmark	178	27%/73%	2,382	653	€20,716,310	€116,412
Lithuania	251	14%/86%	3,818	1,526	€10,380,857	€41,318
Portugal	378	23%/77%	7,088	2,325	€22,012,989	€58,304
Switzerland	184	28%/72%	3,068	867	€26,321,825	€143,153
Total	1,184	22%/78%	19,888	6,460	**€103,747,969**	**€87,651**

Abbreviations: PVFLP, present value of future lost productivity; YLL, years of life lost; YPLL, years of productive life lost.

Table 3. Humanistic and economic burden of HPV-related cancers stratified by cancer type and country

	Number of deaths in 2019					YLL[e]					PVFLP[e]				
	Belgium[a,c]	Denmark[b]	Lithuania	Portugal[c]	Switzerland[d]	Belgium	Denmark	Lithuania	Portugal	Switzerland	Belgium	Denmark	Lithuania	Portugal	Switzerland
Oral cavity	7	4	5	10	5	101	48	53	169	65	€613,224	€435,015	€213,682	€732,017	€586,893
Oropharynx	31	27	15	26	29	424	347	142	466	495	€2,567,161	€3,337,955	€640,654	€2,022,911	€5,073,765
Cervical	143	85	190	221	75	2,862	1,296	3,217	4,775	1,816	€20,336,196	€11,642,408	€8,379,724	€13,971,127	€20,092,355
Vulva	NR	5	5	16	6	NR	46	35	158	54	NR	€253,296	€36,811	€113,953	NR
Vaginal	NR	4	6	15	8	NR	58	37	153	78	NR	€536,283	€21,693	NR	NR
Anal	NR	43	18	45	45	NR	471	223	680	403	NR	€3,375,073	€565,648	€2,014,205	NR
Penile	NR	5	4	10	3	NR	53	32	109	22	NR	€606,337	€183,671	€334,667	NR
Nasopharynx	2	1	2	6	1	24	20	33	41	11	€146,408	€238,735	€149,849	€59,148	€101,419
Hypopharynx	2	2	2	3	1	24	22	17	51	25	€147,982	€154,196	€73,211	€208,804	€305,921
Pharynx	4	NR	1	18	9	51	NR	12	406	79	€306,109	NR	€44,410	€2,305,461	NR
Larynx	4	2	3	7	1	45	20	18	81	19	€198,909	€137,011	€71,504	€250,696	€161,473

Assumptions: [a]Anal, vulvar, vaginal, and penile cancers were excluded for Belgium due to limited mortality data. [b]Danish pharynx cases have been included in the reported oropharynx cases due to data limitations (as ICD-10 code C14 is included in the ICD-10 codes for oropharynx: C01, C05.1-C05.2, C09, C10.0, C10.2-C10.9, C14.0, and C14.2-C14.8 in the Nordcan Database). [c]Mortality data for Belgium and Portugal were transformed and normalized using Shield et al., 2016,[15] as the mortality data was aggregated into ICD C00-C14 (Belgium) and C00-C10 (Portugal). [d]Mortality data for Switzerland was assumed to be uniformly distributed within each age group. [e]Incurred over lifetime.
Abbreviations: PVFLP, present value of future lost productivity; YLL, years of life lost; NR, not reported.

Limitations

- Direct costs such as treatment were not captured. Only productivity costs accrued after death were considered in this analysis
- Due to limited mortality data for certain HPV-related cancers (eg, anal, vulvar, vaginal, penile, or pharynx), these cancer types were not included in this analysis, resulting in potentially underestimated economic burden in these countries. Yet, these estimates could be considered a lower bound of the economic burden, as the model focused on indirect costs
- The model relies on the AFs to estimate the number of deaths related to HPV. Due to data limitations, case-related AFs were used (instead of mortality); this introduces the assumption that case-related and mortality-related AFs are equivalent
- While this study seeks to provide a snapshot of the cost accumulated by HPV-related cancers in 2019, the constantly changing landscape of vaccinated individuals and the pool of at-risk individuals prevents the model from capturing the true burden of disease

Conclusions

- The results of this analysis demonstrate the high mortality and economic burden associated with HPV-related cancers in all five European countries
- The outcomes of the analysis underscore the need for continued investment in HPV vaccination programs and vaccine uptake

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