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## Estimates of the annual direct medical costs of the prevention and treatment of disease associated with human papillomavirus in the United States

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### Abstract

Estimates of the direct medical costs attributable to human papillomavirus (HPV) can help to quantify the economic burden of HPV and to illustrate the potential benefits of HPV vaccination. The purpose of this report was to update the estimated annual direct medical costs of the prevention and treatment of HPV-associated disease in the United States, for all HPV types. We included the costs of cervical cancer screening and follow-up and the treatment costs of the following HPV-associated health outcomes: cervical cancer, other anogenital cancers (anal, vaginal, vulvar and penile), oropharyngeal cancer, genital warts, and recurrent respiratory papillomatosis (RRP). We obtained updated incidence and cost estimates from the literature. The overall annual direct medical cost burden of preventing and treating HPV-associated disease was estimated to be \$8.0 billion (2010 U.S. dollars). Of this total cost, about \$6.6 billion (82.3%) was for routine cervical cancer screening and follow-up, \$1.0 billion (12.0%) was for cancer (including \$0.4 billion for cervical cancer and \$0.3 billion for oropharyngeal cancer), \$0.3 billion (3.6%) was for genital warts, and \$0.2 billion (2.1%) was for RRP.

### Keywords

Human papillomavirus; cost; intraepithelial neoplasia; vulvar; vaginal; anal; oral cavity; oropharyngeal cancer; genital warts; health economics

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## 1. Introduction

Infection by human papillomaviruses (HPV) induces a spectrum of benign and malignant diseases whose incidence can potentially be reduced by HPV vaccination [1]. A subset of HPVs are the main cause of virtually all cervical cancers. These HPV types are also responsible for a variable proportion of other anogenital malignancies, including most anal cancers, approximately one-half of vulvar and vaginal cancers, and one-third of penile cancers, as well as a substantial proportion of oropharyngeal cancers [2]. In addition, HPV causes genital warts, non-genital warts, and recurrent respiratory papillomatosis (RRP). Two preventive HPV vaccines have been approved by the U.S. Food and Drug Administration, HPV2 (Cervarix, GlaxoSmithKline) and HPV4 (Gardasil, Merck & Co, Inc.) [3]. Both vaccines could potentially reduce the incidence of all of these HPV-associated cancers, and one of the vaccines (HPV4) could, in addition, prevent the majority of genital warts and RRP.

Estimates of the direct medical costs of preventing and treating disease associated with HPV can help to quantify the economic burden of HPV and to illustrate the potential benefits of HPV vaccination. The purpose of this study was to update the estimated annual direct medical costs of the prevention and treatment of HPV-associated disease in the U.S., for all HPV types implicated in anogenital and upper respiratory tract infection.

## 2. Methods and Materials

The prevention costs we included were limited to cervical cancer screening costs (i.e., we did not include costs associated with HPV vaccination or any other HPV prevention activity). The treatment costs we included were for the following HPV-associated health outcomes: cervical cancer, other anogenital cancers (anal, vaginal, vulvar and penile), oropharyngeal cancer, genital warts, and recurrent respiratory papillomatosis (RRP).

This update incorporates recent estimates of the annual number of Pap tests performed and the cost per test; the number of HPV-associated cancers in the U.S. and the cost per case of cancer; and estimates of the annual incidence and costs of genital warts and RRP. Our cost calculations reflect the lifetime costs of new cases that occur annually, based on recent incidence estimates. In addition, all cost estimates were updated to 2010 U.S. dollars using the medical care component of the consumer price index, available at <http://www.bls.gov>.

### 2.1 Costs of cervical cancer screening

The baseline estimate of the annual cost of routine cervical cancer screening was calculated as the estimated annual number of women screened multiplied by the approximate cost per screening. We assumed 52 million Pap tests are performed in the U.S. annually, with a range of 36 [4] to 65 million [5, 6]. The base case estimate (52 million) was calculated from the 65 million estimate based on National Health Interview Survey data [5, 6] multiplied by 0.80 to account for overestimation of self-reported Pap testing [5, 7], and is consistent with the National Cancer Institute's estimate of 55 million Pap tests per year [8]. We applied \$103 as the cost per screening, which reflects the average of two cost estimates: \$75 for women in

the National Breast and Cervical Cancer Early Detection Program [9] and \$131 for women in a large U.S. health plan [10].

The annual cost of follow-up for abnormal screening results (\$1.2 billion) was obtained from a previous study of administrative and laboratory records of the Kaiser Permanente Northwest health plan [11], extrapolated to the U.S. general population. The \$1.2 billion estimate is the sum of the \$0.4 billion cost of follow-up of false-positive Pap tests and the \$0.8 billion cost of treatment of cervical intraepithelial neoplasia (CIN). The annual \$0.8 billion cost of CIN is consistent with an estimate of \$0.7 billion obtained from a more recent analysis of medical claims data from a larger, more geographically diverse population [12]. Because we applied a total cost of \$1.2 billion for costs associated with false-positive Pap tests and CIN, we did not calculate the number of women for whom follow-up was required or the average cost per follow-up. A range for the follow-up screening costs was calculated by assuming the same relative distribution as for the routine screening costs (e.g., the ratio of the upper bound value to the base-case value for follow-up screening was the same as the ratio for routine screening). We assumed all cervical screening costs (routine and follow-up) are attributable to HPV.

## 2.2 Costs of HPV-associated cancers

The annual burden of each of the HPV-associated cancers was calculated as the estimated annual number of cases of each cancer in the U.S. [13] multiplied by the estimated percentage of these cases in which HPV is present [2] multiplied by the cost-per-case estimates [14–16]. The range of estimates for the number of HPV-associated cancer cases was calculated using the lower and upper bound values of the percent of each cancer attributable to HPV (Table 1).

## 2.3 Costs of genital warts and RRP

An estimated 340,000 new cases of genital warts occurred in 2004, based on episodes of care for genital warts in a study of medical claims data [17]. We increased this estimate by 5% to account for population growth since 2004 [18] and thereby assumed 355,000 new cases of genital warts each year, with a range of 250,000 to 1,000,000 [14]. The cost per case of genital warts was set at \$810 [17], with a range of \$410 [14] to \$930 [17].

An estimated 80 to 1500 cases of juvenile-onset RRP (JORRP) occurred in 1999 [19]. We increased the upper-bound estimate by 4% to account for population growth among youth since 1999 [18] and thereby assumed 80 to 1560 new cases of JORRP annually, with an average of 820 cases. The cost per case of JORRP was set at \$150,000 [14, 20, 21], with a range of \$72,000 [14] to \$387,000 [20].

To estimate the annual cost burden of adult-onset RRP (AORRP), we assumed that the ratio of annual costs of AORRP to that of JORRP is 0.39 [22]. We assumed that 100% of genital warts and RRP are attributable to HPV, as HPV infection is the necessary cause of both outcomes.[19, 23]

### 3. Results

From 2004–2007, an average of 32,456 cases of cervical, vaginal, vulvar, anal, and oropharyngeal cancers occurred each year. An estimated 25,110 of these cancers were attributable to HPV, and almost three-fourths of these HPV-associated cancers were in women (Table 1).

The overall annual direct medical cost of preventing and treating HPV-associated disease is about \$8.0 billion (Table 2, bottom row). About 82% of this cost is for cervical cancer screening (\$6.6 billion), of which \$5.4 billion is for routine cervical cancer screening and \$1.2 billion is for follow-up costs. About 12% of the total cost is for cancer (\$1 billion), most of which is accounted for by cervical cancer (\$441 million) and oropharyngeal cancer (\$306 million). Genital warts and RRP account about 3.6% (\$288 million) and 2.1% (\$171 million) of the total annual costs, respectively. Excluding cervical cancer screening costs, about two-thirds of the annual costs of HPV-associated disease could be attributed to disease in women (results not shown).

### 4. Discussion

Our estimated burden of \$8.0 billion in the U.S. is higher than, but generally consistent with, the sum of previous estimates of approximately \$5 billion for the prevention and treatment of cervical HPV-related disease [7] and \$0.5 billion for the treatment of noncervical HPV 6-, 11-, 16-, and 18-related disease [14]. Our updated estimate is higher than these previous estimates for three reasons. First, screening costs have increased in recent years, primarily due to the increased use of liquid-based cytology [10] as well as increases in overall health care costs over this period. Second, our estimate of the cost of oropharyngeal cancer attributable to HPV is higher than that of Hu and Goldie (2008) [14] because we applied updated, higher estimates of the percent of oropharyngeal cancers attributable to HPV. Third, we included the cost of cancers attributable to all HPV types whereas Hu and Goldie's (2008) burden estimates included cancers attributable to HPV types 16 and 18 only.

Cervical cancer screening and follow-up together account for about \$6.5 billion of the \$8 billion total, or a little over 80% of the total estimated costs. This observation is consistent with findings from numerous studies that the cost-effectiveness of HPV vaccination could be enhanced greatly if vaccination is combined with reductions in routine cervical cancer screening costs through a delayed age of onset of screening or less frequent screening, or both [16, 24–26]. Further, vaccination can help to reduce the follow-up costs of cervical cancer screening, such as costs associated with cervical intraepithelial neoplasia. Another feature of these estimates is that although RRP is a relatively uncommon non-malignant condition, its estimated cost of \$170 million is greater than the individual cost of each of the HPV-associated cancers except for cervical and oropharyngeal cancer. However, there is a greater range of plausible estimates for the overall burden of RRP owing to uncertainty not only in the number of cases of RRP each year but also in the cost per case of RRP.

Our study is subject to limitations. First, there is considerable range in the estimates of the annual cost of cervical cancer screening. Second, we do not include the costs of HPV

testing, which can be used as part of both screening and management strategies, as these costs were not included in the two source studies we applied for the cost per women screened [9, 10]. Third, estimates of the cost per case of HPV-associated cancers, genital warts, and RRP are subject to uncertainty. Fourth, it is difficult to estimate with precision the HPV-attributable fraction of each of the health outcomes we included in this analysis. Although we applied currently-accepted estimates of the percentage of cases that can be attributed to HPV, these estimates are subject to bias.[2, 27]

Despite these uncertainties and limitations, this study provides a useful update of the annual cost of prevention and treatment of HPV-associated diseases. This updated estimate underscores the substantial economic burden of HPV and highlights the potential for HPV vaccination to reduce this burden.

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**Highlights**

- We estimated the annual direct medical costs attributable to HPV in the USA.
- The overall annual direct medical cost burden was estimated to be \$8.0 billion.
- Most of this cost was for cervical cancer screening and follow-up (\$6.6 billion).

Estimated HPV-associated cancers, by sex, 2004–2007

Table 1.

Anatomic area	Average annual number of cases*	Estimated percent of cases in which HPV is present (%) <sup>+</sup>	Estimated annual number of HPV associated cancers
	Base case	Range	Base case
			Range
Cervix	11,845	95 – 97	11,370
Vulva	3,062	37 – 65	1,560
Anus & Rectum (Female)	2,977	86 – 97	2,770
Oropharynx (Female)**	2,306	50 – 75	1,450
Vagina	714	43 – 82	460
Total (Female)	20,903		17,610
Oropharynx (Male)**	8,936	50 – 75	5,630
Anus & Rectum (Male)	1,618	86 – 97	1,500
Penis	1,000	26 – 47	360
Total (Male)	11,553		7,490
<b>Total</b>	<b>32,456</b>		<b>25,110</b>
			<b>22,530 – 27,420</b>

Source: Saraiya 2011 [13], based on National Program of Cancer Registries and Surveillance, Epidemiology, and End Results Program.

\* Defined by histology and anatomic site; Watson M et al. 2008 [27].

<sup>+</sup> Gillison ML, et al. 2008 [2].

\*\* Oropharynx includes the palatine and lingual tonsils, the posterior one-third (base) of the tongue, the soft palate, and the posterior pharyngeal wall [13]. Totals may not match sums of individual components due to rounding or due to inclusion in totals of case counts that were suppressed in the individual components.



**Table 2.** Estimates of the annual direct medical costs of preventing and treating HPV-associated disease

Cost component	Number of cases		Cost per case (U.S. dollars)		Annual cost (millions, U.S. dollars)		Percent of cost burden
	Baseline	Range	Baseline	Range	Baseline	Range	
Cervical screening: routine	52 million	36 to 65 million	103	75 – 131	5,356	2,700 – 8,515	67.0%
Cervical screening: follow-up	NA	NA	NA	NA	1,224	617 – 1,946	15.3%
Cervical cancer	11,370	11,250 – 11,490	38,800	30,700 – 52,600	441	345 – 604	5.5%
Oropharyngeal cancer*	7,080	5,620 – 8,430	43,200	20,100 – 61,200	306	113 – 516	3.8%
Anal cancer*	4,270	3,950 – 4,460	36,200	17,500 – 70,200	155	69 – 313	1.9%
Vulvar cancer	1,560	1,130 – 1,990	23,600	15,500 – 31,700	37	18 – 63	0.5%
Vaginal cancer	460	310 – 590	27,100	20,300 – 34,100	12	6 – 20	0.2%
Penile cancer	360	260 – 470	19,800	9,800 – 38,800	7	3 – 18	0.1%
Genital warts*	355,000	250,000 – 1,000,000	810	410 – 930	288	103 – 930	3.6%
Juvenile-onset RRP*	820	80 – 1,560	150,000	72,000 – 387,000	123	6 – 604	1.5%
Adult-onset RRP*	NA	NA	NA	NA	48	2 – 236	0.6%
<b>Total burden</b>					<b>8,000</b>	<b>4,000 – 13,800</b>	<b>100.0%</b>

NA: not applicable (see text for details). RRP: recurrent respiratory papillomatosis.

Number of cases and cost per case are not presented for follow-up of cervical cancer screening and for adult-onset RRP because the total costs of follow-up and adult-onset RRP were calculated using previously-published estimates of the total costs of these outcomes. Cost per case estimates and ranges were obtained from Hu and Goldie (2008) for non-cervical cancers and from Insinga and colleagues (2008) and Kim and Goldie (2008) for cervical cancer [14–16]. The source studies on which the cost-per-case estimates for cancer were based used different methodologies. Although these estimates in general reflect the cost of diagnosis and treatment of cancer, the inclusion of other cost categories (e.g., follow-up, recurrence, terminal care) varied across the source studies such that the cancer cost estimates differ in their degree of completeness.[14–16] We did not include screening costs for non-cervical cancers owing to a lack of data on the number of people screened each year and/or the cost per person screened. See manuscript text and Table 1 for a description of other sources and assumptions.

\* Includes outcomes in males and females. Outcomes without asterisk are sex-specific.

Costs are reported in 2010 U.S. dollars.