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THE ECONOMIC BURDEN OF NONCERVICAL HUMAN PAPILLOMAVIRUS DISEASE IN THE UNITED STATES

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Abstract

Objective—The purpose of this study was: (1) to estimate the direct medical costs of 7 major noncervical human papillomavirus (HPV)-related conditions, including genital cancers, mouth and oropharyngeal cancers, anogenital warts, and juvenile-onset recurrent respiratory papillomatosis; and (2) to approximate the economic burden of noncervical HPV disease.

Study Design—For each condition, we synthesized the best available secondary data to produce lifetime cost per case estimates, expressed in present value. Using an incidence-based approach, we then applied these costs to develop an aggregate measure of economic burden.

Results—The economic burden associated with noncervical HPV 6,11,16, and 18-related conditions occurring in Americans in the year 2003 approximates \$418 million (range, \$160 million–\$1.6 billion).

Conclusion—The economic burden of noncervical HPV disease is substantial. Analyses that assess the value of investments in HPV prevention and control programs, should take into account the costs, morbidity, and mortality associated with these conditions.

Keywords

cost analysis; economic burden; human papillomavirus

Introduction

Genital human papillomavirus (HPV) infection is the most common sexually-transmitted disease in the United States [1]. While the majority of infections are asymptomatic or self-limited, acquisition of specific types of HPV can result in clinically significant disease. Most notable among the oncogenic types (i.e., high-risk types) of HPV are types 16 and 18, responsible for approximately 70% of all cervical cancer [2,3] as well as a lower proportion of cancer of the vagina, vulva, penis, anus, mouth and oropharynx [3]; and HPV 6 and 11, responsible for up to 90% of anogenital warts and virtually all cases of recurrent respiratory

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Condensation Using incidence-based methods, we present estimates of the lifetime cost per case and economic burden of 7 major noncervical human papillomavirus-related diseases in the U.S.

papillomatosis (JORRP) [2,4]. Collectively, HPV 6, 11, 16, and 18 impose a substantial disease burden and affect both quantity and quality of life.

This past year, the U.S. Food and Drug Administration (FDA) approved Gardasil, a quadrivalent HPV vaccine that protects against HPV types 6, 11, 16 and 18 and has been highly effective in the prevention of anogenital warts and precancerous lesions of the cervix, vagina, and vulva in women not previously infected with these types [5]. With the emergence of new technologies for prevention and treatment of HPV-related disease (e.g., HPV vaccines and HPV diagnostic tests) information about the clinical and economic burden associated with HPV-related disease can inform cost-effectiveness analyses and budget impact analyses.

Economic studies to date of HPV-related conditions have focused primarily on cervical cancer and its precursor lesions [6–8]. There are substantially fewer costing studies of noncervical HPV-associated sequelae [9–12]. In fact, a recent literature review concluded there are no studies examining the direct medical costs attributable to noncervical HPV-related cancers or assessing the economic burden of noncervical HPV disease [7].

The main objective of this study is (1) to estimate the direct medical costs associated with 7 major noncervical HPV-related diseases, including genital cancers, mouth and oropharyngeal cancers, anogenital warts, and JORRP; and (2) to provide an aggregated measure of the economic burden of noncervical HPV-related disease.

Material and Methods

We focused on seven HPV-related conditions: HPV type 6 and 11-associated anogenital warts, HPV 6 and 11-associated JORRP, HPV 16 and 18-associated noncervical genital cancers (including anus, penis, vagina, vulva) and cancers of the mouth and oropharynx.

Lifetime Cost Per Case of Noncervical HPV-Related Conditions

For each of the seven conditions, we used the best available secondary data to estimate the lifetime cost per case. Because these costs are intended for use in economic evaluations, we sought to develop cost per case estimates that represent the stream of direct medical costs, expressed in present value, from the time of diagnosis to cure or death (henceforth referred to as *discounted lifetime cost per case*). Cost data used to inform estimates were identified from a literature review (see Appendix). Whenever possible, we sought published discounted lifetime cost per case estimates (anogenital warts, JORRP, anal cancer) [9,10,13]. However, because of the paucity of available studies, especially regarding noncervical HPV-related cancers, we approximated the discounted lifetime cost per case by using the best available data and simple modeling exercises to reflect the lifetime cost stream (mouth/oropharyngeal cancer, penile cancer, vaginal cancer, and vulvar cancer) [14–20]. Further details of the estimation approach are provided in the disease-specific sections in the Results.

To the extent possible, data sources from the U.S. were used [9,10,14–20] although we supplemented these data with studies from Canada and Europe [13,21,22]. Costs were adjusted for inflation, and expressed in 2003 US\$ [23]. Future costs associated with individual cases of HPV-related conditions were discounted 3% annually to reflect their present value.

Economic Burden of Noncervical HPV Disease

To develop an aggregate measure of the economic burden of noncervical HPV-related conditions, we adopted an incidence-based approach whereby the discounted lifetime cost per case associated with each condition was applied to the total number of HPV 6, 11, 16, and 18-attributable incident cases occurring among men and women over a representative one-year

period (2003) [1–4,6,24–34]. The resulting estimates were then added for the seven conditions to approximate the total economic burden of noncervical HPV-related disease.

Results

Juvenile-Onset Recurrent Respiratory Papillomatosis (JORRP)

Cost estimates for juvenile-onset recurrent respiratory papillomatosis were obtained from a published study [9]. In this study, the discounted lifetime cost per case was estimated at \$131,910 with a wide plausible range of \$54,800–\$276,170. Base case assumptions included: an average duration of illness of 4.2 years during which each patient underwent 4.4 surgical procedures per year; a ratio of follow-up office visits to surgery of 3 to 1; and a tracheotomy rate of 11% [9]. Costs considered focused on those related to the primary treatment of JORRP which consisted of surgery (i.e. physician fees and hospitalization) and follow-up visits (i.e. physician fees), and to tracheotomy (i.e., physician fees, hospitalization, and maintenance). In the absence of published data, the authors assumed the yearly cost of tracheotomy maintenance to be \$94,980 (range, \$75,980–\$113,980). However, this figure has considerable uncertainty because the majority of JORRP patients with tracheotomy do not require mechanical ventilation which comprises the bulk of tracheotomy-associated costs. As a result, we elected to use this study's lower bound estimate of \$54,800 as our base case value for the average lifetime cost per case of JORRP.

Estimates of the annual incidence of JORRP vary widely, from 80 to 1,500 and 1,448 to 3,260 new cases [26,27]. Assuming a midpoint yearly incidence of 1,500 and all cases of JORRP are attributable to HPV 6 or 11, the estimated total lifetime direct medical cost associated with new cases of JORRP over a representative one-year period is \$82.2 million. When upper- and lower- bound values for JORRP incidence and lifetime cost per case are used, this cost ranges from \$4.4 million to \$900 million.

Anogenital Warts

Because a single episode of anogenital warts is often associated with the use of a combination of different therapies and there is wide variation in cost among the different treatment options, we sought published estimates of the cost per episode of newly diagnosed genital warts. We used the average cost per case of \$505 from two available estimates from the CDC (\$510) and a published study (\$500, range \$420–\$580) [6,10]. In the latter study, cost per episode estimates were derived from the Marketscan database by summing up all payments on the basis of diagnosis code for a single episode of anogenital warts (defined as a 12-month interval free of anogenital wart care preceding and following the current episode) [10]. Costs reflect health plan payments to physicians for office visits related to diagnosis, treatment, and/or follow-up and to pharmacies for self-applied medications or analgesics [10]. To estimate the discounted lifetime cost per case of anogenital warts, we sought estimates for the average cost per episode of care and applied this cost to 75% of all new wart cases, assuming a spontaneous cure rate of 25% [6] and an average duration per episode of care of 3 months [10]. These assumptions yielded a lifetime direct medical cost per case of anogenital warts of \$379. Estimates of the annual incidence of anogenital warts are imprecise and range from 250,000 to 1,000,000 [6]. Using the midpoint estimate of 500,000 new cases per year and assuming 90% of all anogenital warts are caused by HPV 6 or 11 [7], we estimated the total lifetime cost associated with all new cases of anogenital warts occurring within a given year to be \$171 million. This estimate closely approximates the figure of \$190 million reported by Chesson *et al* [6]. The range for our estimate is \$71 to 392 million, using the upper- and lower-bound estimates of incidence and lifetime cost per case.

Anal Cancer

Because published U.S. cost estimates for anal cancer were unavailable, the discounted lifetime cost per case of anal cancer was approximated from a Canadian costing study of rectal cancer [13]. Cost estimates included diagnostic assessment, staging work-up, initial treatment, surveillance, treatment of recurrent disease, management of metastatic disease, and terminal care. The estimated discounted lifetime cost per case of \$27,660 was consistent with the estimate of \$26,850 (range, \$13,420–\$53,700) reported by Goldie *et al* [35], who used data from a U.S. study of colorectal cancer to approximate anal cancer costs.

In 2003, the American Cancer Society projected there were 4,000 new cases of anal cancer in the U.S. [25] Assuming 82.8% of all anal cancer is attributable to HPV types 16 and 18 [3, 32,33], we estimated the total lifetime cost of all HPV-attributable incident cases of anal cancer occurring in 2003 to be \$92 million with a range of \$44 to \$178 million.

Penile Cancer

We identified three publications with cost estimates for penile cancer [16,36,37]. Our base case estimate was developed from an Institute of Medicine (IOM) study of the costs and benefits of HPV vaccination [16]. In this study, an expert committee developed a stage-specific clinical scenario for penile cancer in order to characterize resource utilization and estimate health care costs. For example, costs related to local penile cancer included a primary care physician visit, surgery, anesthesia, hospitalization, radiation (in 50% of patients), chemotherapy (in 50% patients), and a single physician visit with a specialist. With advanced penile cancer, the clinical scenario was almost identical with the exception of an additional six specialist physician visits due to the increased morbidity associated with advanced cancer (i.e., urinary and sexual dysfunction). Cost estimates include direct medical costs related to initial treatment (i.e., physician fees, hospitalization, surgery, radiation and/or chemotherapy), and short-term follow-up (i.e., one year) but not those associated with diagnostic assessment, long-term surveillance, treatment of recurrent disease, management of metastatic disease, or terminal care. Assuming two-thirds of all penile cancers are local at the time of diagnosis and the remaining one-third are advanced [16], we determined the discounted lifetime cost per case was \$15,120. This estimate falls roughly midway between the two published estimates of \$7,500 and \$29,640, which we used as a plausible range [36,37].

Using data from the American Cancer Society and National Cancer Institute, we estimated 1,145 new cases of penile cancer occurred in the U.S. in 2003 [24,25]. Assuming 25.2% of all penile cancers are attributable to HPV 16 and 18 [3,28], the total lifetime cost of all HPV 16- and 18-associated penile cancers occurring in 2003 was estimated at \$4.4 million dollars (range, \$2.2 to \$8.6 million).

Vaginal Cancer

Estimates for the discounted lifetime cost per case of vaginal cancer were developed using data from a published cost-effectiveness study of Pap smear screening for vaginal cancer after total hysterectomy [17]. Available vaginal cancer-related cost data included the cost of diagnosis (i.e., biopsy and colposcopy) and initial treatment (i.e., surgery or radiation), which were drawn from actual reimbursement rates by third-party payers (base case) with Medicare reimbursement rates representing the lower bound of cost estimates. In accordance with the National Cancer Institute [38], we assumed standard therapy for stage I was radiation or surgery (with treatment equally divided between radiation and surgery), and radiation for stages II, III, and IV. In 2003 US\$, this translated to a lifetime cost for stage I vaginal cancer of \$ 22,726 (range, \$17,044–\$28,568) and for stages II, III and IV of \$ 20,003 (range, \$15,003–\$25,263). Assuming a distribution by stage at diagnosis of 26% stage I, 37.2% stage II, 24.1% stage III,

and 12.7% stage IV [39], we estimated the present value of the lifetime cost of a new case of vaginal cancer at \$20,710 (range, \$15,530–\$26,120).

The American Cancer Society estimates 2,000 new cases of vaginal and other female genital tract cancers occurred in the year 2003 [25]. Vaginal cancer represents approximately 53.8% or 1,077 of all cancers in this category [24]. When we assumed 32% of all vaginal cancer is related to HPV types 16 and 18 [3,31], the total lifetime cost of all HPV 16- and 18-associated vaginal cancers occurring in 2003 was estimated at \$7.1 million (range, \$5.4 to \$9.0 million).

Vulvar Cancer

Because published cost estimates for vulvar cancer were unavailable, we constructed a simple mathematical model to estimate the discounted lifetime cost per case of vulvar cancer. We developed stage-specific estimates which included the cost of diagnosis, initial treatment, and short-term surveillance. (For details, see Appendix). Incorporating cost and clinical data from national databases and the published literature [18–20,40], we estimated the discounted lifetime cost per case of vulvar case to be \$18,050 with a range from \$11,860 to \$24,250.

Assuming 4,000 new cases of vulvar cancer occurred in the U.S. in 2003 and 32% of all vulvar cancer is attributable to HPV 16 and 18 [3,25,29,30], the total lifetime cost of all HPV-attributable cases of vulvar cancer newly occurring in 2003 is \$23.1 million (range, \$15.2 to \$31.0 million).

Oropharyngeal and Mouth Cancer

The discounted lifetime cost per case of oropharyngeal and mouth cancer was estimated from an existing study in which patients with newly diagnosed head and neck cancer from the Surveillance, Epidemiology, and End Results (SEER) registry were matched by age and gender to controls, and direct medical care costs over a 5-year period were compared between the two groups on the basis of Medicare payments [15]. To estimate the lifetime cost per case, we assumed the cost difference between head and neck cancer patients and controls was attributable to cancer care and discounted the cost difference in years 2 through 5 using a rate of 3%. This approach yielded an average cost per case of head and neck cancer of \$33,020.

To construct a plausible range for our estimate, we relied on cost data from two European studies. For the lower bound estimate, we utilized cost data from a British study of the cost-effectiveness of screening for oral cancer [21]. This study reported annual direct medical costs by stage for a three-year period after the initial diagnosis. Using the stage distribution observed in patients in this same study, we estimated the average discounted lifetime costs to be \$15,340. For the upper bound estimate, we used cost data from a retrospective Netherlands study that estimated the cost of treatment, potential recurrence, and follow-up over a 10-year period for oral cavity, laryngeal, and oropharyngeal cancers treated in two university hospitals [22]. Using a 4% discount rate, the study estimated an average lifetime cost per case of \$46,800.

In 2003, the American Cancer Society projected there were 9,200 new cases of mouth cancer and 8,300 new cases of oropharyngeal cancer in the U.S [25]. Assuming 2.9% of all mouth cancer and 10.7% of all oropharyngeal cancer are caused by HPV 16 and 18 [3,34], we estimated the total lifetime costs for all new cases of mouth and oropharyngeal cancer occurring in 2003 to be \$38.1 million (range, \$17.7 to \$54.1 million).

Economic Burden of Noncervical HPV 6, 11, 16, and 18-related Disease

For the seven HPV 6, 11, 16, 18-related conditions considered, the total economic burden (expressed in 2003 dollars) associated with the new cases that occurred in 2003 was \$418 million with a plausible range of \$160 million to \$1.6 billion (See Table 1). Under base case

assumptions, HPV 6 and 11-related conditions accounted for more than 60% of the total burden. This was due to the high incidence and large HPV-attributable fraction of JORRP and anogenital warts as well as the considerable discounted lifetime cost per case associated with JORRP. Three conditions – JORRP, anogenital warts, and anal cancer – were responsible for more than 80% of the costs attributable to noncervical HPV-related conditions.

Comment

Despite formidable data gaps, our review of secondary data and estimation of the direct medical costs associated with 7 HPV-related conditions demonstrate a substantial economic burden imposed by HPV-attributable noncervical disease in the United States. Using an incidence-based approach, the economic burden associated with noncervical HPV-related conditions occurring in Americans in the year 2003 approximates \$418 million. This figure has a considerably wide plausible range of \$160 million to \$1.6 billion, which is driven predominantly by the substantial uncertainty in the cost of JORRP and the incidence of JORRP and anogenital warts.

Two vaccines against HPV-16 and -18 have been found to be highly efficacious against same type incidence and precancerous lesions of the cervix, vagina, and vulva among females without indication of prior infection with these types; and the quadrivalent vaccine currently licensed in the U.S. also prevents infection with HPV-6 and -11, responsible for the majority of genital warts and JORRP. [5] Given these options for primary prevention of HPV-related disease, along with enhanced screening approaches for secondary prevention of HPV-related cervical cancer, there is considerable interest in comparative assessments of the health and economic consequences associated with alternative strategies to reduce the burden of HPV-related disease. Accordingly, we provide a comprehensive estimate of the economic burden of noncervical HPV-related disease in the U.S. Although we consider this figure to be an approximate estimate at best, nonetheless, our results highlight the significant cost dimensions of this health problem and the importance of preventing these conditions to reduce both the health and economic burden of HPV infection. The estimated costs associated with each HPV-related condition can be used in future economic evaluations of HPV vaccination, and the lower and upper bound estimates as the plausible range for sensitivity analyses.

Our study has several limitations which merit acknowledgement. First, sources of cost data were limited and the quality of available information was variable. For example, much of the data used to derive lifetime cost per case estimates were not comprehensive. Many estimates included only selected aspects of care such as diagnosis and treatment and omitted costs related to staging, surveillance, or recurrence. In these instances, cost per case figures likely underestimate the actual lifetime cost of disease. In addition, sources of cost information ranged from private health insurance to Medicare claims, each of which is associated with its own inherent flaws and biases [7,41]. Second, we did not consider nonmedical direct or indirect costs such as transportation costs to healthcare facilities or the value of work time lost receiving health care. Studies addressing these types of costs are unavailable for noncervical HPV-related conditions [7]. Incorporation of these costs would make the economic burden of noncervical HPV-attributable disease even higher. Third, other HPV-attributable conditions such as vulvar, vaginal, penile, and anal intraepithelial neoplasia were not included in our burden analysis. However, since there are no screening recommendations for these conditions and the fraction of cases attributable to HPV is unknown, the contribution of these conditions to the total HPV cost burden is also unknown. Fourth, the population attributable fraction of noncervical cancers to HPV is uncertain. Because HPV is highly prevalent in healthy subjects, this method may overestimate the fraction of cancers attributable to HPV infection [3]. Finally, there was considerable uncertainty surrounding the cost of JORRP and the incidence of JORRP and anogenital warts. Since these two conditions may account for more than 60% of the economic

burden of noncervical HPV disease, we feel refinement of these estimates to be of particularly high priority for future research studies.

Directly comparable estimates of the total economic burden of noncervical HPV-related disease associated with incident cases over a one-year period are not available. Prior studies have focused primarily on individual facets of this health problem such as anogenital warts or JORRP [6,7,9,10,26]. We were unable to identify any published estimates of the total lifetime direct medical cost of anal, penile, vaginal, or vaginal cancer. This may be due to the fact that these cancers are relatively uncommon. As a result, economic burden data for HPV have been largely confined to cervical disease [6–8] and likely represent an underestimate of the economic burden posed by HPV infection.

Quantification of the cost dimensions of noncervical HPV-attributable disease is important because it offers insight into not only the overall economic magnitude but also the relative contribution of different HPV-related conditions. For example, while cervical disease is responsible for the majority of the cost burden associated with HPV-related disease, the contribution of noncervical disease is still considerable, with our base case estimate representing nearly 9% of the total economic burden when incidence-based estimates are used [6,8]. Among the noncervical HPV-attributable conditions, anogenital warts contribute to the largest fraction of the total burden, followed by anal cancer and JORRP. In fact, non-cancerous conditions due to HPV 6 and 11 (JORRP and anogenital cancer) are responsible for more than 60% of the total economic burden of noncervical HPV-related disease. Such information may be useful to policymakers and public health researchers to inform decisions about investments in potential HPV prevention programs.

In summary, our results demonstrate the substantial economic burden imposed by HPV-attributable noncervical disease in the U.S. Future research priorities should include refinement of cost estimates for noncervical HPV-related conditions, the incidence of JORRP and anogenital warts, and the population HPV-attributable fraction of noncervical conditions.

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Appendix

A. Literature review of the available costing studies for noncervical HPV-related conditions

Published articles addressing the cost of each of the seven noncervical HPV-related conditions considered in this study (i.e., anogenital warts, JORRP, and cancer of the anus, penis, vagina, vulva, mouth and oropharynx) were identified using a systematic computerized search of MEDLINE and the British National Health Service Economic Evaluation Database (NHS EED), and by manually reviewing the bibliographies of selected articles. The MeSH key world *cost or cost analysis* were combined with the key words *human papillomavirus, anogenital warts, juvenile onset recurrent respiratory papillomatosis, anal cancer, penile cancer, vaginal cancer, vulvar cancer, oropharyngeal cancer, mouth cancer, and head and neck cancer*. Whenever possible, we sought published discounted lifetime cost per case estimates (anogenital warts, JORRP) [6,9,10]. However, because of the paucity of available studies, especially regarding noncervical HPV-related cancers, we approximated the discounted lifetime cost per case by using the best available data and simple modeling exercises to reflect the lifetime cost stream (mouth/oropharyngeal cancer, penile cancer, vaginal cancer, and vulvar cancer) [14–20]. We were unable to identify any published costing studies for anal cancer and

used cost estimates for rectal cancer as a proxy. To the extent possible, data sources from the U.S. were used [9,10,14–20] although we supplemented these data with studies from Canada and Europe [13,21,22].

B. Stage-specific estimation of the cost of vulvar cancer diagnosis and treatment

In developing stage-specific estimates of the average lifetime cost of vulvar cancer, we limited our costs to those related to diagnosis, treatment, and surveillance. Treatment strategies were based on the recommendations of the National Cancer Institute [18] whereby stage I vulvar cancer is treated with surgery alone and stages II–IV are managed using a combination of surgery and radiation. We developed stage-specific clinical scenarios to determine which unit costs should be included in our calculations (Appendix Table 1). For example, diagnosis of all stages consisted of an initial physician office visit, biopsy, examination of the biopsy for pathology, and a follow-up visit to discuss the biopsy results. Treatment costs of stage I vulvar cancer consisted of costs related to vulvectomy, pathological examination of an intraoperative frozen specimen and the entire surgical specimen, and hospitalization. Treatment costs of stages II through IV vulvar cancer included the cost of radiation therapy in addition to the cost of vulvectomy, pathology, and hospitalization. We assumed all patients were seen by a physician on a semiannual basis for surveillance for 5 years' posttreatment. Sources of cost data included the 2004 Medicare Fee Schedule for physician fees related to the various components of care and the Healthcare Cost and Utilization project for hospitalization related costs [19,20]. For physician-related costs, we used non-facility fees as the upper bound estimate and facility fees for the lower bound estimate, averaging the two for the base case estimate. With regard to hospitalization-related costs, we used the mean cost and charge within the category "cancer of other female genital organs" as our plausible range and the average for the base case estimate.

Appendix Table 2 presents the estimated average discounted lifetime costs for vulvar cancer by stage, the distribution of vulvar cancer by stage, and the stage-weighted average lifetime cost per case of vulvar cancer.

Appendix Table 1
Current Procedure Terminology codes and costs used for estimating the total lifetime cost of vulvar cancer*

	CPT Code	Base case (2003 US\$)	Lower Bound Estimate (2003 US\$)	Upper Bound Estimate (2003 US\$)
Diagnosis				
Initial physician visit	99241, 99242, or 99243	108.30	46.22	170.38
Biopsy	56605, 56606, 56820, or 56821	148.41	85.89	210.92
Pathological examination	88305	140.91	140.91	140.91
Follow-up visit	99241, 99242, 99243	108.30	46.22	170.38
Stage I treatment				
Surgical excision or simple vulvectomy	11622, 56620, or 56625	478.35	190.83	765.87
Pathology	88309 +/- 88331	367.82	308.21	427.42
Hospitalization (applied to 50%)		15,828.54	8,680.08	22,977.01
Stage II, III, and IV treatment				
Radical vulvectomy	56630, 56631, or 56632	1,231.77	1,069.64	1,393.91
Pathology	88309 and 88331	367.82	308.21	427.42
Hospitalization		15,828.54	8,680.08	22,977.01
Radiation therapy (applied to 50% of stage II, 100% of stage III/IV)	77263, 77295, 77300, 77336, 77413, and 77427	4,069.96	3,839.43	4,300.49
Surveillance				
Physician office visit	99242	111.73	94.47	128.98

CPT = Current procedure terminology.

Appendix Table 2
Estimated average discounted lifetime cost of vulvar cancer by stage and overall.

Stage	Base case (2003 US\$)	Lower Bound (2003 US\$)	Upper Bound (2003 US\$)	% of all vulvar cancer [40]
I	10,103.03	6,713.05	13,547.11	33.1
II	20,992.38	13,478.27	28,506.49	34.6
III	23,027.36	15,397.98	30,656.74	23.8
IV	23,027.36	15,397.98	30,656.74	8.5
Overall (weighted by stage)	18,045.30	11,859.05	24,249.47	

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Table 1

Number of new cases of disease, percent HPV-attributable fraction, estimated lifetime cost per case, and total direct medical costs of seven major noncervical HPV-attributable conditions, United States, 2003.*

	Incidence (#new cases in 2003)	HPV 6/11 or 16/18 attributable fraction %)[†]	Average discounted lifetime cost per new case 2003 US \$)	Total lifetime cost of new cases occurring in 2003 (2003 US\$) [‡]	References
JORRP	1,500	100	54,800 (54,800– 276,170)	82.2 million	9,14,19,20,26,27
Anogenital warts	500,000	90	379 (315– 435) [§]	171 million	6,7,10
Anal cancer	4,000	82.8	27,660 (13,420– 53,700)	92 million	3,13,25,32,33,35
Penile cancer	1,145	25.2	15,120 (7,500–29,640)	4.4 million	3,16,24,25,28
Vaginal cancer	1,077	32	20,710 (15,530– 26,120)	7.1 million	3,17,24,25,31,38,39
Vulvar cancer	4,000	32	18,050 (11,860– 24,250)	23.1 million	3,18–20,25,29,30,40
Mouth and oropharyngeal cancer	17,500	6.6 ^{//}	33,020 (15,340– 46,800)	38.1 million	3,15,21,22,25,34
All conditions				418 million	

* HPV= human papillomavirus; JORRP= juvenile-onset recurrent respiratory papillomatosis.

[†] Estimated by multiplying the HPV-attributable fraction of disease by the proportion specifically attributed to HPV 6/11 or 16/18.

[‡] Estimated by multiplying the average total lifetime cost per new case, the annual incidence of disease, and the HPV-typespecific attributable fraction.

[§] Assumes 25% of all anogenital warts clear spontaneously without treatment [6].

^{//} Represents a weighted average of the % mouth and oropharyngeal cancer attributable to HPV 16/18 [3,25,34].