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The Estimated Lifetime Medical Cost of Diseases Attributable to Human Papillomavirus Infections Acquired in 2018

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Abstract

Introduction: We estimated the lifetime medical costs of diagnosed cases of diseases attributable to human papillomavirus (HPV) infections acquired in 2018.

Methods: We adapted an existing mathematical model of HPV transmission and associated diseases to estimate the lifetime number of diagnosed cases of disease (genital warts; cervical intraepithelial neoplasia; and cervical, vaginal, vulvar, penile, anal, and oropharyngeal cancers) attributable to HPV infections that were acquired in 2018. For each of these outcomes, we multiplied the estimated number of cases by the estimated lifetime medical cost per case obtained from previous studies. We estimated the costs of recurrent respiratory papillomatosis in a separate calculation. Future costs were discounted at 3% annually.

Results: The estimated discounted lifetime medical cost of diseases attributable to HPV infections acquired in 2018 among people aged 15–59 years was $774 million (in 2019 U.S. dollars), of which about half was accounted for by infections in those aged 15–24 years. HPV infections in women accounted for about 90% of the lifetime number of diagnosed cases of disease and 70% of the lifetime cost attributable to HPV infections acquired in 2018 among ages 15–59 years.

Conclusions: We estimated the lifetime medical costs of diseases attributable to HPV infections acquired in 2018 to be $774 million. This estimate is lower than previous estimates and likely

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represents the impact of HPV vaccination. The lifetime cost of disease attributable to incident HPV infections is expected to decrease further over time as HPV vaccination coverage increases.

Summary:

The estimated discounted lifetime medical cost of diseases attributable to HPV infections acquired in 2018 among people aged 15–59 years was $774 million.

Background

Human papillomavirus (HPV) imposes a considerable health and economic burden in the United States.[1–3] An estimated 34,800 cancers were caused by HPV annually in the United States from 2012 through 2016, including 13,500 oropharyngeal cancers among men and women, 10,900 cervical cancers among women, 6,200 anal cancers among men and women, 3,400 vaginal and vulvar cancers among women, and 800 penile cancers among men.[4] The lifetime direct medical costs of diseases caused by HPV infections acquired in 2008 was estimated at $1.9 billion (updated to 2019 US dollars).[2]

The purpose of this study was to update the estimated cost of incident HPV infections in the United States. Specifically, we estimated the lifetime medical costs of diseases caused by HPV infections acquired in 2018. This updated cost estimate is warranted for three main reasons. First, the most current available estimate[2] was calculated for HPV infections acquired in 2008, and thus is over a decade old. Second, numerous cost studies published over the past four years[5–11] have suggested that the average medical treatment cost per HPV-associated cancer is substantially greater than estimated by older studies. Third, by reducing HPV incidence, HPV vaccination can substantially reduce the lifetime medical costs attributable to incident HPV infections. In fact, the HPV vaccination program in the United States launched in 2006 has already shown promising results in reducing the health burden of HPV.[12] For example, notable reductions in HPV prevalence,[13–16] genital warts,[17–19] and cervical cancer precursors[20–23] have been documented. Over time, more pronounced effects of HPV vaccination are expected, including reductions in HPV-associated cancers.[24,25] This study provides an updated estimate of the lifetime medical costs attributable to HPV infections acquired in a given year in the context of the ongoing HPV vaccination program in the United States.

Our estimation of the lifetime medical costs of treating diseases attributable to HPV infections acquired in 2018 is part of a larger project to update the available estimates of the incidence, prevalence, and cost of major STIs in the United States in 2018.[26,27] In 2013, estimates of the prevalence and incidence[28] of STIs in the United States and of the corresponding lifetime medical costs[2] were provided for 2008. These 2008 estimates have been cited in governmental budget justifications,[29] in published HPV vaccination recommendations of the Advisory Committee on Immunization Practices,[30] and in STI treatment guidelines,[31s] illustrating the usefulness of these data for policymakers.

Methods

We estimated the lifetime medical costs attributable to HPV infections acquired in 2018 among persons aged 15–59 years in the United States. We focused on HPV infections acquired by those aged 15–59 years to be consistent with the estimates of HPV incidence and prevalence presented by Lewis and colleagues in this Special Issue,[32s] in which an upper age of 59 years was necessitated by the availability of prevalence data from the National Health and Nutrition Examination Survey (NHANES). We examined costs from the health care sector perspective, thereby including direct medical costs regardless of payer (e.g., insurer, government, patient co-pay). Costs were estimated in 2019 U.S. dollars.

Our analysis of the lifetime medical costs attributable to HPV infections acquired in 2018 consisted of three main steps. In the first step, we used a model to estimate the lifetime number of diagnosed cases of disease attributable to HPV infections that were acquired in 2018. The health outcomes assessed by the model were: genital warts; cervical intraepithelial neoplasia (CIN) grade 1 (CIN1) and grade 2/3 (CIN2/3); and cervical, vaginal, vulvar, penile, anal, and oropharyngeal cancers. We included CIN outcomes because the HPV advise model included cervical cancer screening. However, the model did not include screening for other cancers (such as anal cancer) and thus we did not include precancerous lesions for non-cervical cancers. In the second step, for each of these outcomes, we multiplied the estimated number of cases by the estimated lifetime medical cost per case to estimate the lifetime medical costs attributable to HPV infections acquired in 2018. In the third step, we expanded this estimate of the lifetime medical costs to include two additional health outcomes: juvenile-onset recurrent respiratory papillomatosis (JORRP) and adult-onset recurrent respiratory papillomatosis (AORRP). We estimated the costs of JORRP and AORRP separately as these two outcomes were not included in the HPV model we applied in this study. These three steps are described in more detail below.

Step one: Model-based estimates of health outcomes attributable to *HPV infections acquired in 2018*

We used HPV-ADVISE, a dynamic, individual-based model of HPV infection and disease that has been calibrated to U.S. data and applied in cost-effectiveness analyses of a range of HPV vaccination strategies in the United States.[24,33s–35s] The model was calibrated to pre-vaccination data and its predictions have been validated against updated surveillance data.[36s] Complete details of the model, including model structure, cervical cancer screening assumptions, data sources, calibration, and validation are available online at https://marc-brisson.net/HPVadvise-US.pdf.

Our model approximated the HPV vaccination program in the United States. Specifically, we modeled the introduction of 4-valent vaccination of girls in 2007 and of gender-neutral vaccination in 2011, and the introduction of 9-valent vaccination in 2015. HPV vaccination coverage in the model was based on historical HPV vaccination coverage data in the United States, in order to reflect the ongoing HPV vaccination program.[33s,37s–40s] We assumed age-specific vaccine uptake rates to be constant at 2016 values from 2017 onwards. This simplifying assumption was based on data availability at the time the model simulations were run. However, even when keeping uptake rates constant at 2016 values, vaccination

coverage in the population continued to increase over time in the model due to cohort effects. We assumed 0% vaccine efficacy until the 2nd dose, and that full efficacy (95%) is achieved with the 2nd dose. The Appendix provides more details about historical HPV vaccination coverage in the model.

We used the model to estimate the cumulative number of detected cases of disease over a time horizon of 90 years that could be attributed to HPV infections acquired in 2018. Long time horizons of 90–100 years are commonly applied in health economic models of HPV to ensure inclusion of all relevant future outcomes, such as HPV cancers that can occur decades after HPV infection.[33s,41s–43s] We defined a disease case attributable to HPV acquisition in 2018 as one that resulted from progression of an infection that was acquired in 2018. The model included 18 HPV types: 6/11/16/18/31/33/35/39/45/51/52/56/58/59/66/68/73/82.

When assessing the number of CIN1 cases, false positive CIN1 results (CIN1 results for which the underlying true state is not CIN1) were excluded. We also excluded results when the true state was CIN1, but the diagnosis was normal or CIN2/3. Similarly, when assessing the number of CIN2/3 cases, CIN2 and CIN3 diagnoses differing from the underlying true state (such as false positives) were excluded. The number of CIN2/3 diagnoses reflects the sum of CIN2 and CIN3 diagnoses. In the model, some women diagnosed with CIN2 may, for reasons such as treatment failure or loss to follow-up, have a subsequent colposcopy with a CIN3 result. In such cases, both the CIN2 and the CIN3 outcomes were counted.

The HPV-ADVISE model applied the 50 parameter sets that provided the best fit to over 700 data target points for sexual behavior, HPV epidemiology, and cervical cancer screening in the United States.[24] For each parameter set, the model ran 20 simulations. For our base case results, we applied the average number of disease cases caused by infections acquired in 2018 across all model simulations. In the sensitivity analyses, we incorporated data from the 10th and 90th percentiles of results across the 50 parameter sets.

Step two: Multiplying by the discounted, lifetime medical cost per case

The lifetime medical cost estimates we used (Table 1) were based primarily on a recent study of the cost-effectiveness of HPV vaccination in the United States,[44s] which compiled cost data from a range of sources.[1,5–11,43,45–53] For this analysis, the cost estimate we used for penile cancer incorporated data from a 2019 study[11] following the same general methods used to compile cancer cost estimates in the recent cost-effectiveness study.[44s] These compilation methods ensured that the resulting base case cost estimate for each cancer site was not based on a single study (e.g., the anal cancer cost was a combination of estimates from a study of Medicare data and a study of national health care claims data). All costs have been updated to 2019 U.S. dollars using the Personal Consumption Expenditures Price Index for health care (https://www.bea.gov/).

For each health outcome, the total lifetime cost was calculated by multiplying the estimated number of diagnosed cases of the outcome attributable to HPV infections acquired in 2018 by the discounted cost per case of the outcome. For example, for anal cancer in women, we multiplied the estimated number of diagnosed cases of anal cancer in women attributable to HPV infections acquired in 2018 according to the HPV-ADVISE model by the estimated

discounted cost per case of anal cancer listed in Table 1 ($30,000). The discounted cost per case estimates were calculated using the estimated cost per diagnosed health outcome, discounted to the year 2018 at a rate of 3% annually (Table 1). To simplify the model calculations, we discounted the cost of each health outcome for the number of years listed in Table 1. These values reflect assumptions regarding the median duration from HPV acquisition to diagnosis of the health outcome, based on modeling estimates,[2,33s,54s] studies of placebo arms of HPV vaccine trails,[55s,56s] and the median age of cancer diagnosis[57s] as described in the Appendix. For example, for all cases of anal cancer in women attributable to HPV infections acquired in 2018 in the HPV-ADVISE model, we discounted the treatment cost for 39 years (Table 1), although these anal cancer cases could have occurred at any time in the 90-year time horizon we examined.

Step three: Estimating the burden of recurrent respiratory papillomatosis (RRP)

As noted previously, the HPV-ADVISE model that we applied did not include the health outcomes of JORRP and AORRP. The HPV-ADVISE model was calibrated to highly-stratified sexual behavior and HPV epidemiology data from the United States. A main reason why HPV-ADVISE does not include RRP is that the necessary data (e.g., age-specific incidence estimates for JORRP and AORRP) are limited and subject to considerable uncertainty. In order to include RRP in this analysis, we simply assumed that the burden of RRP could be estimated as a function of the burden of genital warts. We used the genital warts cost burden to approximate the RRP cost burden because HPV types 6 and 11 account for 90% to 100% of RRP and genital warts.[1,3] In Australia, declines in incidence of 80% or more have been reported for genital warts among young adults and for JORRP since the onset of their national HPV vaccination program in 2007.[58s–60s] These comparable declines suggest that after a decade or so of HPV vaccination, relative declines in genital warts can be a reasonable proxy measure for relative declines in RRP.

We assumed that the combined medical cost burden of JORRP and AORRP would be equal to 60% that of genital warts. This assumption was based on the relative cost burden of these health outcomes in a 2012 study, in which the estimated annual cost (updated to 2019 dollars) was $328 million for genital warts, $140 million for JORRP, and $55 million for AORRP.[1] The 60% adjustment was calculated as ($140+$55)/$328.

Sensitivity analyses

We first examined how our estimates of the discounted lifetime cost of diseases attributable to HPV infections acquired in 2018 would change when we varied assumptions about either the cost per case of each health outcome or the lifetime number of health outcomes attributable to HPV incidence in 2018. When varying the cost per case assumptions, we simultaneously set all cost per case assumptions to either their lower or upper bound values (Table 1). When varying the number of health outcomes attributable to HPV infections acquired in 2018, we simultaneously applied either the 10^{th} percentile or 90^{th} percentile of results from the HPV-ADVISE model. We also conducted probabilistic sensitivity analyses in which the discounted lifetime cost of diseases attributable to HPV infections acquired in 2018 was estimated 10,000 times, each time drawing a random value for the lifetime number of cases of each outcome, the discounted cost per case of each outcome, and for the ratio of

RRP costs to genital warts costs. To illustrate the distribution of these 10,000 simulations, we calculated the 2.5th, 10th, 25th, 75th, 90th, and 97.5th percentiles.

The distributions we used for drawing these random values are summarized here and described in more detail in the Appendix. For each health outcome in the model, we applied a custom distribution designed to match the 10th, 25th, 75th, and 90th percentiles of the model results. Because of correlation across simulations of the HPV-ADVISE model in the predicted numbers of health outcomes (e.g., model simulations in which HPV incidence in 2018 is higher than the average across all simulations are likely to yield predictions that are higher than average for the lifetime number of cervical cancers and penile cancers attributable to infections acquired in 2018), we assumed a 50% correlation across the health outcomes in the 10,000 estimations in our probabilistic sensitivity analysis. We assumed the lifetime cost per case estimates followed a lognormal distribution. For the cost estimate for each health outcome, we chose distribution parameters consistent with the mean and range listed in Table 1 as described in the Appendix. Because of similarities in methodology and data sources for the cost per case estimates for cancer (e.g., the use of medical claims data from Texas informed our cost estimates for cervical cancer and oropharyngeal cancer),[5,9] we assumed a 50% correlation across the cancer cost estimates in the 10,000 estimations in our probabilistic sensitivity analysis. To account for uncertainty in our estimate of the costs of RRP, the ratio of RRP costs to genital warts cost (assumed to be 60% in the base case) was varied from 20% to 100% using a uniform distribution.

Results

The mean estimated number of diagnosed cases of HPV-associated health outcomes attributable to HPV infections acquired in 2018 among ages 15–59 years ranged from 454 for penile cancer to 162,974 for CIN1 (Table 2). For HPV infections acquired in 2018 among ages 15–24 years, these estimates ranged from 265 for penile cancer to 103,660 for CIN1.

The estimated discounted lifetime medical costs of diseases attributable to HPV infections acquired in 2018 was $774 million among people aged 15–59 years and $407 million for infections acquired among people aged 15–24 years (Table 3). The health outcome CIN1 accounted for the largest proportion of cost of any of the health outcomes (29% for ages 15–59 years and 35% for ages 15–24 years). HPV infections in women accounted for about 90% of the lifetime number of diagnosed cases of disease and 70% of the lifetime cost attributable to HPV infections acquired in 2018 among ages 15–59 years, and the burden on women was even more disproportionate for ages 15-24 years.

The cost of diseases attributable to HPV infections acquired in 2018 among ages 15-59 years ranged from $431 million when applying the lower cost per case for all health outcomes to about $1,143 million when applying the upper bound cost per case estimate for all health outcomes (Table 4). This cost estimate ranged from $362 million to $1,398 million when applying the 10th and 90th percentiles of the HPV-ADVISE model predictions regarding the number of lifetime cases of each health outcome attributable to HPV infections acquired in 2018. In the probabilistic sensitivity analyses, the 10th and 90th percentiles of the 10,000

calculations of the total cost of diseases attributable to HPV infections acquired in 2018 ranged from $413 million to $1,280 million for ages 15-59 years and from $206 million to $721 million for ages 15–24 years.

Discussion

We estimated that the lifetime medical costs of diseases attributable to incident HPV infections in 2018 was about $774 million in the base case, and within a range of about $362 million to $1,398 million in most of the sensitivity analyses. Increased adherence to recommendations for routine vaccination at age 11 or 12 years and for catch-up vaccination through age 26 years could decrease burden of disease and costs due to HPV infection.[61s]

Our findings will contribute to updated estimates of the overall medical cost burden of STIs in the United States. Previous estimates of the medical burden of STIs[2,62s] have been cited not only in policy-related documents such as government budget justifications[29] and HPV vaccination recommendations[63] but also in cost-effectiveness studies that can inform policy.[64s–66s]

The current $774 million estimate is consistent with, but lower than, a previous estimate of $1.9 billion (updated to 2019 dollars) for incident HPV infections in 2008.[2] Obtaining a lower estimate for the costs of diseases attributable to incident HPV infections in 2018 compared to 2008 was expected, given the impact of the HPV vaccination program initiated in mid-2006 in the United States.[12] Moreover, the difference between our estimate for 2018 and the previous estimate for 2008 would have been even more pronounced if our analysis had not incorporated recent cost estimates for the treatment of HPV-associated cancers,[5–11,51s] as these recent cancer cost estimates are substantially higher than those applied in the previous study.[2]

Our estimate of $774 million for the lifetime medical costs of diseases attributable to incident HPV infections in 2018 is substantially lower than a previously reported $9.1 billion (updated to 2019 US dollars) estimated annual cost of the prevention and treatment of prevalent disease associated with HPV in the United States in the pre-vaccine era.[1] However, these estimates are not directly comparable, for two main reasons. First, of the $9.1 billion estimate, about $6.1 billion was attributable to routine cervical cancer screening, which was not included in our study. Second, our $774 million estimate reflects costs associated with diseases attributable to incident HPV infections, whereas the $9.1 billion estimate includes costs of treating prevalent HPV diseases, regardless of the year in which the causal HPV was acquired and without discounting to the time of infection. Our study has provided an updated estimate of the cost of diseases attributable to incident HPV infections; updated estimates of the cost of prevalent diseases attributable to HPV are needed in order to provide a more complete picture of the medical cost burden of disease attributable to HPV.

Our estimates of the lifetime number of diagnosed cases of disease attributable to HPV infections acquired in 2018 are subject to considerable uncertainty. The variation in results across the many simulations performed by the HPV-ADVISE model reflects uncertainty in all the factors that can affect the burden of HPV, such as sexual behavior, the probability

of HPV transmission, the natural history of HPV, and cervical cancer screening. By using 50 different parameter sets that produced results that closely matched available data, the HPV-ADVISE model was able to capture and quantify this uncertainty.

Our analysis did not consider potential changes in screening for HPV-associated cancers, such as modifications to existing cervical cancer screening activities. Changes in screening could affect the probability that an HPV infection acquired in 2018 would eventually lead to diagnosed cases of cancer or precancerous lesions. Our analysis did not include the costs associated with HPV infections acquired in 2018 among those younger than 15 years and older than 59 years. However, the degree of bias resulting from this limitation is likely limited, given that the percentage of all incident infections that occur outside of the 15- to 59-year age group is small and that HPV infections acquired after age 59 years might be relatively less likely to incur long-term cancer costs due to higher competing mortality risks.

The HPV-ADVISE model includes 18 HPV types, not all HPV types. However, because only a small percentage of HPV-associated health outcomes are attributable to HPV types other than the 18 HPV types in the model, the effect of excluding these other HPV types on our estimates of the number and cost of HPV-associated health outcomes attributable to HPV acquisition in 2018 is likely trivial.

The HPV-ADVISE model did not include RRP; therefore, we performed a simple approximation of the costs of JORRP and AORRP. Because the estimated costs of JORRP and AORRP represent a small fraction (<4%) of the total estimated cost of diseases attributable to HPV infections acquired in a given year, it is unlikely that the approximation for estimating the costs of RRP had a substantial effect on our total cost estimate.

Our analysis focused on the direct medical costs of diseases attributable to HPV infections acquired in 2018 in the context of current cervical cancer screening uptake in the United States. We did not include costs associated with prevention of HPV and HPV-associated health outcomes, such as the costs of HPV vaccination and the cost of routine cervical cancer screening. The cost burden of HPV would be greater if these prevention activities were included. Further, in the absence of these prevention efforts, HPV incidence in 2018 and the lifetime costs of diseases associated with this incidence would likely be substantially higher than we estimated. However, assessments of the health economics of HPV vaccination and cervical cancer screening were beyond the scope of this analysis. Instead, we note that detailed projections of the number of cancer cases averted, medical costs averted, and number of quality-adjusted life-years saved over the first 70 to 100 years of HPV vaccination in the United States have been published elsewhere, based on the HPV-ADVISE model[24,34s] and other models.[41s,42s,44s] Similarly, estimates of the cost-effectiveness and health impacts of cervical cancer screening[67s–69s] and interventions to increase HPV vaccination coverage are also available.[70s,71s]

Our study has four main strengths. First, the HPV-ADVISE model we applied has been vetted through peer review in numerous previous applications.[24,33s–35s] Importantly, model predictions of the early effects of HPV vaccination in the United States have closely matched available data regarding reductions in HPV prevalence and genital warts.[36s]

Second, the model was able to estimate the number of HPV incident infections in 2018 and to track these infections for up to 90 years to assess the number of adverse health outcomes attributable to these infections. In contrast, previous estimates of the cost of diseases attributable to incident HPV infections[2,62s] were approximated by performing back-calculations to existing estimates of the cost of prevalent diseases attributable to HPV. Third, our analysis incorporates recent data on the medical treatment cost per case of HPV-associated health outcomes,[10,44s] although the treatment cost estimates we applied are nonetheless limited in that they are not age-specific and they do not fully reflect nationally-representative averages. Fourth, we performed a probabilistic sensitivity analyses to account for uncertainty in our analysis, not only in the number of adverse health outcomes attributable to HPV infections acquired in 2018 but also in the direct medical cost per case of each of these outcomes.

In summary, to our knowledge this is the first study of the lifetime costs of diseases attributable to incident HPV infections to include modeling of HPV natural history from infection to disease and to account for uncertainty in the lifetime incidence and cost of HPV-associated health outcomes. We estimated the cost of diseases attributable to HPV infections acquired in 2018 to be $774 million. This cost is lower than the $1.9 billion estimate for 2008 HPV incidence and likely represents the impact of HPV vaccination to some degree, although the two estimates are not suitable for comparison due to differences in methods. The annual cost of incident HPV (i.e., the lifetime medical cost burden of diseases attributable to HPV infections acquired in the given year) is expected to decrease further over time as HPV vaccination coverage increases in the population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1.

Estimated direct medical cost per case of HPV-associated health outcomes (undiscounted and discounted), and number of years of discounting of costs

Health outcome	Undiscounted cost per health outcome*			Number of years of discounting**	Discounted cost per health outcome†		
	Base case	Lower bound	Upper bound		Base case	Lower bound	Upper bound
Genital warts, females	$870	$440	$2,830	0.5	$860	$430	$2,790
Genital warts, males	$870	$440	$2,830	0.5	$860	$430	$2,790
CIN grade 1	$1,410	$970	$1,840	1	$1,370	$940	$1,790
CIN grade 2 or 3	$2,600	$1,090	$4,210	3	$2,380	$1,000	$3,850
Penile cancer	$66,600	$22,500	$81,300	46	$17,100	$5,800	$20,900
Cervical cancer	$73,900	$44,200	$83,800	26	$34,300	$20,500	$38,900
Vulvar & vaginal cancer	$85,300	$28,800	$104,100	44	$23,200	$7,800	$28,400
Anal cancer, females	$95,100	$53,800	$136,200	39	$30,000	$17,000	$43,000
Anal cancer, males	$95,100	$53,800	$136,200	36	$32,800	$18,600	$47,000
Oropharyngeal cancer, females	$128,500	$66,400	$149,200	40	$39,400	$20,400	$45,700
Oropharyngeal cancer, males	$128,500	$66,400	$149,200	38	$41,800	$21,600	$48,500

CIN: cervical intraepithelial neoplasia.

All cost estimates have been updated to 2019 U.S. dollars using the personal consumption expenditures price index for health care (https://www.bea.gov/). Cost estimates were rounded to the nearest $10 for genital warts, CIN1, and CIN2/3, and to the nearest $100 for cancers.

*The cost per health outcome shows the estimated average lifetime cost per diagnosed case of the given outcome, discounted to time of diagnosis. These cost estimates were obtained from a recent cost-effectiveness study[44s] which compiled data from a range of cost studies of CIN,[45s,46s] genital warts,[47s,48s] cervical cancer,[5,49s,50s], anal cancer,[6,7,52s] vaginal and vulvar cancer,[8,50s,52s] oropharyngeal cancer,[9,51s,52s] and penile cancer.[52s] The combined cost estimate for vaginal and vulvar cancer reflects the average of the vaginal cancer cost estimate and the vulvar cancer cost estimate. We updated the penile cancer cost estimates by incorporating a 2019 study[11] following the same general methods used to compile cancer cost estimates in the recent cost-effectiveness study.[44s]

**Future costs for each outcome were discounted at an annual rate of 3% for the number of years shown. The number of years of discounting reflects assumptions regarding the median duration from HPV acquisition to diagnosis of the health outcome, based on modeling estimates,[2,33s,54s] studies of placebo arms of HPV vaccine trails,[55s,56s] and the median age of cancer diagnosis[57s] as described in the Appendix.

†The discounted base case cost of infection shows the base case cost estimate discounted from the time of diagnosis to the time of HPV infection (year 2018) at an annual rate of 3%. For example, the value $34,300 for cervical cancer was calculated as the base case cost of cervical cancer at the time of diagnosis ($73,900) multiplied by β^x, where β is (1/1.03) and the exponent *x* was set to 26 (the number of years that cervical cancer costs were discounted).

Table 2:

Estimated lifetime number of diagnosed cases of disease attributable to HPV infections acquired in 2018

Health outcome	Mean (10^{th}–90^{th} percentiles) result from HPV-ADVISE model	
	Ages 15–59 years	Ages 15–24 years
Genital warts		
Females	25,442 (15,621–35,484)	6,310 (4,632–8,531)
Males	24,967 (16,721–33,128)	2,325 (3,217–1,555)
Total	50,409 (32,343–68,612)	8,635 (7,849–10,087)
CIN grade 1	162,974 (11,572–393,451)	103,660 (6,953–275,583)
CIN grade 2 or 3	52,074 (33,752–66,540)	29,707 (18,751–40,031)
Penile cancer	454 (279–838)	265 (169–474)
Cervical cancer	3,153 (1,912–4,674)	1,978 (1,307–2,782)
Vulvar & vaginal cancer	849 (559–1,300)	550 (381–751)
Anal cancer		
Females	780 (524–1,218)	441 (320–593)
Males	675 (402–1,271)	268 (174–491)
Total	1,456 (925–2,489)	708 (494–1,084)
Oropharyngeal cancer		
Females	587 (388–904)	370 (260–505)
Males	3,665 (2,233–6,868)	1,462 (964–2,655)
Total	4,252 (2,621–7,772)	1,832 (1,225–3,160)

Case numbers were calculated for females and males using rates of health outcomes per 100,000 from the HPV-ADVISE model multiplied by 2018 population estimates from the 2018 American Community Survey 1-Year Estimates, Table S0201,using American FactFinder; http://factfinder.census.gov. Total case numbers were calculated as the sum of case numbers in females and males. The age groupings refer to age at the time of the causal HPV infection (2018), not the age at which the health outcome was diagnosed.

Table 3:

Estimated lifetime number of diagnosed cases of health outcomes attributable to HPV infections acquired in 2018, discounted cost per case, and total discounted lifetime costs attributable to HPV infections acquired in 2018

Health outcome	Lifetime number of diagnosed cases attributable to HPV infections acquired in 2018		Average discounted cost per health outcome	Total discounted lifetime cost of health outcomes attributable to HPV infections acquired in 2018	
	Ages 15–59 years	Ages 15–24 years		Ages 15–59 years	Ages 15–24 years
Genital warts, females	25,442	6,310	$860	$21,880,000	$5,427,000
Genital warts, males	24,967	2,325	$860	$21,472,000	$2,000,000
CIN grade 1	162,974	103,660	$1,370	$223,274,000	$142,014,000
CIN grade 2 or 3	52,074	29,707	$2,380	$123,936,000	$70,703,000
Penile cancer	454	265	$17,100	$7,763,000	$4,532,000
Cervical cancer	3,153	1,978	$34,300	$108,148,000	$67,845,000
Vulvar & vaginal cancer	849	550	$23,200	$19,697,000	$12,760,000
Anal cancer, females	780	441	$30,000	$23,400,000	$13,230,000
Anal cancer, males	675	268	$32,800	$22,140,000	$8,790,000
Oropharyngeal cancer, females	587	370	$39,400	$23,128,000	$14,578,000
Oropharyngeal cancer, males	3,665	1,462	$41,800	$153,197,000	$61,112,000
RRP	NA *	NA *	NA	$26,011,000	$4,456,000
All outcomes, females	245,859	143,016	NA	$543,463,000	$326,557,000
All outcomes, males	29,761	4,320	NA	$204,572,000	$76,434,000
All outcomes, total	275,620	147,336	NA	$774,046,000	$407,447,000

CIN: cervical intraepithelial neoplasia. RRP: recurrent respiratory papillomatosis. NA: not applicable.

The age groupings refer to age at the time of the causal HPV infection (2018), not the age at which the health outcome was diagnosed.

Costs are in 2019 U.S. dollars. Future costs for each outcome were discounted at an annual rate of 3%. Total costs were rounded to the nearest $1,000.

* RRP was not included in the HPV-ADVISE model. Costs for RRP included juvenile-onset RRP and adult-onset RRP and were estimated as a fraction (60%) of the costs of genital warts as described in the text.

Table 4.

Results of sensitivity analyses: Estimated total discounted lifetime cost attributable to HPV infections acquired in 2018 when varying key assumptions (2019 US dollars)

Description of analysis	Ages 15–59 years	Ages 15–24 years
Base case analysis *	$774,046,000	$407,447,000
One-way sensitivity analyses		
Lower cost per case for all health outcomes **	$430,798,000	$231,073,000
Higher cost per case for all health outcomes **	$1,143,331,000	$555,948,000
Lower number of cases (10th percentile) of health outcomes attributable to HPV †	$361,540,000	$185,072,000
Higher number of cases (90th percentile) of health outcomes attributable to HPV †	$1,397,540,000	$774,711,000
Probabilistic sensitivity analyses ‡		
2.5th percentile	$313,701,000	$162,728,000
10th percentile	$413,288,000	$205,947,000
25th percentile	$552,264,000	$272,602,000
Median	$769,221,000	$393,671,000
75th percentile	$1,012,965,000	$538,292,000
90th percentile	$1,279,783,000	$720,805,000
97.5th percentile	$1,570,867,000	$899,222,000

Costs occurring after 2018 were discounted to 2018 at an annual rate of 3%. Results have been rounded to the nearest $1,000.

The age groupings refer to age at the time of the causal HPV infection (2018), not the age at which the health outcome was diagnosed.

* The base case results are the same as listed in Table 3 and are included here for ease of comparison.

** These results were obtained when setting all the cost per case estimates (Table 1) to their lower bound values, or when setting all to their upper bound values.

† These results were obtained when setting the numbers of diagnosed cases predicted by the HPV-ADVISE model (Table 1) to the lower bound values (10th percentile of model projections) for all health outcomes, or when setting all to their upper bound values (90th percentile of model projections).

‡ These results were obtained from the probabilistic sensitivity analyses in which the total estimated lifetime cost of diseases attributable to HPV infections acquired in 2018 was calculated 10,000 times, each time obtaining a random value for all cost values listed in Table 1, all case numbers listed in Table 2, and the ratio of recurrent respiratory papillomatosis (RRP) costs to genital warts costs as described in the methods section.