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Cancer Epidemiology, Biomarkers & Prevention

*Research Article*

# Costs Associated with Management of Cervical Human Papillomavirus-Related Conditions

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## Abstract

**Background:** Oncogenic types of human papillomavirus (HPV) have been linked to 99.7% of cervical cancer cases worldwide.

**Methods:** This retrospective claims-based analysis was conducted to assess patterns of use and costs associated with diagnostic and treatment procedures for disease attributed to HPV performed before the introduction of HPV vaccination (January 1, 2001–May 31, 2006). Percentages of commercially insured health plan enrollees who underwent each procedure of interest were calculated for each year. Annual costs (combined patient and health plan-paid amounts) were calculated from qualifying medical claims. Descriptive statistics were used to assess trends in procedure rates and costs.

**Results:** Data for approximately 14.2 million enrollees were obtained. Hysterectomy was the most commonly administered treatment. With the exception of colposcopy with LEEP, all other treatment procedures experienced a decline in rate of use. The most frequently performed diagnostic procedure was colposcopy with endocervical curettage (ECC). With the exception of ECC, rates of diagnostic procedures reached a peak among 20- to 24-year-olds, and followed a downward trend across older groups. Hysterectomy was the most expensive treatment (median $7,383; mean $8,384) per procedure in 2006.

**Conclusion:** Results reveal high rates of use and high-associated costs of diagnostic procedures and treatments related to disease attributed to HPV.

**Impact:** The data presented may be useful in cost-effectiveness analyses and to guide decision makers evaluating how best to optimize prevention strategies. *Cancer Epidemiol Biomarkers Prev; 21(9); 1469–78. ©2012 AACR.*

## Background

Human papillomavirus (HPV) is the most common sexually transmitted infection (STI) in the United States and a known cause of cervical cancer (1–3). Oncogenic types of HPV have been linked to 99.7% of cervical cancer cases worldwide (3). At any one time, 20 million Americans aged 15 to 49 (approximately 15% of the population) are infected with HPV, and an estimated 6.2 million people contract the virus annually (1). Nearly 3 of 4 Americans between the ages of 15 and 49 have been infected with some form of genital HPV in their lifetime (4). Most HPV infections resolve without treatment (5, 6). However, persistent infection with oncogenic HPV types can progress through a series of cervical abnormalities and may ultimately lead to cervical cancer (5, 7–10).

Cervical cancer has the second highest incidence among cancers in women and is the third most common cause of cancer-related mortality in women (11). In the United States, more than 11,000 women are diagnosed with cervical cancer and almost 4,000 die from the disease annually (12). Deaths from cervical cancer dropped 74% between 1955 and 1992 and have continued to drop approximately 4% each year thereafter (12, 13).

Healthcare costs associated with HPV-related conditions range from $2.3 to $4.6 billion annually (2005 US$), as reported by the authors of a systematic literature review of 9 cost-of-illness studies of HPV-related conditions (14). According to a study conducted in 2000 (15), HPV accounted for a significant portion of the total cost of STIs ($2.9 billion) and was among the most costly in terms of total estimated direct medical costs (second only to HIV). This estimate encompassed costs associated with cervical abnormalities (diagnosis and management of cytologic abnormalities, preinvasive cervical neoplasia, and invasive cervical cancer) as well as costs associated with external anogenital warts. A more recent estimate of the annual direct medical costs associated with the prevention and treatment of anogenital warts and cervical HPV-related disease put this figure at approximately $4

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**Note:** Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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billion (16). Routine cervical screenings account for more than 63% of total HPV-related healthcare costs (17). Reoccurring lesions that require repeat procedures and follow-up also contribute significantly to overall costs (18).

Recently, there have been significant advances in the development of prophylactic HPV vaccines, which can prevent infection of HPV types among individuals uninfected with these types. These vaccines have the potential to significantly reduce the incidence of cervical cancer and precancerous lesions (19–22). Cervarix®, manufactured by GlaxoSmithKline and approved by the US Food and Drug Administration in October 2009, has been shown in clinical trials to be highly effective and well tolerated in girls and young women for prevention of cervical precancers and cervical cancer related to HPV types 16 and 18 (23), which account for 71% of cases (16, 24). In a subgroup of clinical trial participants without oncogenic HPV infection at the time of first vaccination and without evidence of prior exposure to HPV 16 and 18, the vaccine showed an overall 70% efficacy against precancerous lesions, regardless of HPV type (23). The quadrivalent (HPV types 6, 11, 16, and 18) L1 virus-like particle vaccine (Gardasil®, manufactured by Merck and approved by the U.S. Food and Drug Administration in 2006) has also been shown in clinical trials to be highly effective, with the potential to prevent approximately 70% of cervical cancer cases. Among subjects naive to a given HPV type at baseline and throughout the 3-dose vaccination, vaccine efficacy against cervical intraepithelial neoplasia (CIN) grade II-III or adenocarcinoma *in situ* was 99% (95% confidence interval 93%–100%) (25, 26). Results of trials of Cervarix® and Gardasil® have shown efficacy against cervical infection and cervical lesions associated with HPV-16/18 for up to 8.4 years and 5 years, respectively (27). Gardasil® also has shown efficacy against HPV types 6 and 11 (the most important HPV types causing genital warts), although these do not progress to CIN grade 2/3 or cervical cancer. Vaccines, therefore, may help to decrease costs associated with screening and management of cervical abnormalities.

To our knowledge, only one previous study assessed the incidence and economic burden of CIN in a US commercially insured population (28). It is difficult to identify the incidence of CIN in national databases for several reasons. First, administrative database diagnosis codes may not be reliable (i.e., databases may contain unspecified codes, and accurate diagnostic codes are not always required for billing). Using procedural codes to estimate the number of cytology pathologies performed related to HPV and cervical neoplasia/cancer outcomes from health plans may be more reliable (29). The impact of vaccination can be observed in reductions in procedures, but procedure coding may not provide a reliable estimate either, as it is primarily used to ensure reimbursement. Administrative database codes are accessible across a wide range of health plans. Although the results associated with the data in this study must be interpreted with caution, they offer a perspective that can readily serve as a benchmark for future assessments of the impact of vaccines.

The objective of this study was to assess the frequency and costs of HPV-related diagnostic and treatment procedures conducted before introduction of HPV vaccination. Although primary screening represents the highest cost burden, this study focuses on follow-up costs associated with diagnosis and abnormalities. By doing so, benchmarks can be established that enable future evaluations of the impact of HPV vaccination on resource consumption. We studied healthcare costs associated with procedures related to disease most likely attributable to HPV in the United States using a large, geographically diverse health claims database. A wide range of procedures were examined from 2001 to 2006. The rates of use and direct costs associated with these procedures were evaluated. We did not differentiate between oncogenic and nononcogenic HPV types.

## Materials and Methods

### Data source

We used retrospectively collected claims data from OptumInsight's proprietary research database. The database, which has been described in several published studies (28, 30, 31), contains medical, pharmacy, and enrollment information for members with commercial health insurance coverage through a large US health plan. Data pertaining to dates of service, procedures performed, filled prescriptions, paid amounts, dates of enrollment, patient age, and patient gender are captured. All healthcare sites and all healthcare services reimbursed by the plan, including specialty, preventive, and office-based treatments, are included. In 2006, this health plan provided approximately 14 million individuals with both medical and pharmacy coverage and about 8.6 million with medical benefits only. Although enrollees resided in geographically diverse areas across the United States, the greatest representation was in the South and Midwest census regions.

Claims data are de-identified, and each enrollee is assigned a randomly generated unique identifier before being placed in the database. The study was conducted using data determined to be statistically de-identified in accordance with established privacy guidelines under the Health Insurance and Portability and Accountability Act, making a separate Institutional Review Board approval unnecessary.

### Study population

All procedures related to disease most likely due to HPV occurring from January 1, 2001 through May 31, 2006 were identified from medical claims. They included those with a procedure code [International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and Common Procedure Coding System (CPT)]

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for: Pap smear, HPV DNA testing, colposcopy, biopsy, endocervical curettage (ECC), loop excision electrosurgical procedure (LEEP), conizations, cauterization, hysterectomy, or cervical amputation/destruction (Appendix Table A). Analysis was carried out at the unique procedure level to allow for a detailed understanding of utilization and cost associated with each procedure. For hysterectomy, a confirmatory diagnosis code for cervical abnormalities within 30 days of the procedure [ICD-9-CM 180.0–180.9, 233.1×, 622.10-622.12, 795.0× (excluding 795.08), 795.1] was required for study inclusion, because hysterectomy is commonly performed for a variety of conditions unrelated to cervical abnormality (e.g., uterine fibroids).

### Variables

***Rates.*** Rates of the various procedures were analyzed for each calendar year from 2001 through 2005, and were stratified by age categories ranging from the youngest (<10 years) up to the oldest group (60–64). Each procedure was counted only once per day, yet multiple procedure types could be counted on the same day. A partial year was identified in 2006 (January 1 through 31 May), representing the period before introduction of the HPV vaccination in June 2006 in the United States. Percentages of female enrollees who underwent each procedure were calculated for each year. Because length of enrollment varied and procedures may have been carried out more than once on a single individual during the observation period, the rate of each procedure per 1,000 patient-years was calculated.

***Costs.*** Costs were calculated separately for each year of analysis as combined patient and health plan-paid amounts from qualifying medical claims, and were adjusted to 2,006 dollars based on the Consumer Price Index medical component. Outpatient procedure costs were calculated from all claims with the same date of service as the procedure; inpatient procedure costs were calculated from claims for all services on and between admission and discharge dates. This approach allowed for the inclusion of costs specific to the procedure as well as for services related to the procedure, such as physician visits and application of anesthesia. Median costs are presented to minimize the impact of skewing in the distribution of cost data, and mean (SD) costs are presented to reflect the range of costs.

## Results

### Population description

Over the entire analytic period (January 1, 2001 to May 31, 2006), data from approximately 14.2 million commercially insured female enrollees aged 0 to 64 were obtained (Table 1). Women were classified into age groups: 0 to 9 (16.8%), 10 to 14 (7.2%), 15 to -19 (7.1%), 20 to 24 (9.2%), 25 to 29 (9.2%), 30 to 34 (9.7%), 35 to 39 (9.4%), 40 to 44 (9.4%), 45 to 49 (8.2%), 50 to 54 (6.6%), 55 to 59 (4.7%), and 60 to 64 (2.6%). In each year, the number of female enrollees available for analysis ranged from 5.8 million to 6.7 million. Data from an individual enrollee was used in multiple years and for more than 1 procedure, if applicable. Female enrollees contributed approximately 26.3 million person-years of enrollment (~1.5–2.0 years of enrollment per enrollee).

**Table 1.** Numbers and Ages of Enrollees (age as of 2003)

| | Female enrollees |
|---|---|
| Year | |
| 2001 | 6,293,702 |
| 2002 | 6,438,199 |
| 2003 | 6,469,970 |
| 2004 | 6,429,766 |
| 2005 | 6,654,478 |
| 2006 | 5,763,885 |
| Age group (y) | |
| 0–9 | 2,382,356 |
| 10–14 | 1,016,514 |
| 15–19 | 1,011,019 |
| 20–24 | 1,303,779 |
| 25–29 | 1,302,356 |
| 30–34 | 1,381,805 |
| 35–39 | 1,326,272 |
| 40–44 | 1,329,871 |
| 45–49 | 1,164,786 |
| 50–54 | 929,356 |
| 55–59 | 660,022 |
| 60–64 | 367,005 |
| Total | 14,175,141 |

### Procedure utilization

We first determined the percentage of female enrollees who received a Pap smear. In 2001, 21.9% of female enrollees had a Pap smear (1,381,139 of 6,293,702 female enrollees in 2001). Use increased to 24.5% in 2002 (1,578,530 of 6,438,199), and remained steady at 24.7% in 2003, 24.4% in 2004, and 23.5% in 2005. Of 5.8 million female enrollees contributing data from January 2006 through May 2006, only 13.1% sought a Pap smear during the first half of the year ($n$ = 761,124). Adjusting for enrollment and multiple procedures per patient per year, we found the rate at which women receive Pap smears decreased slightly from 2004 (345 Pap smears per 1,000 patient-years) to 2006 (311 per 1,000 patient-years) (Table 2).

The percentage of female enrollees who underwent HPV DNA testing increased over the 6-year period. Just 0.2% (14,808 of 6,293,702) had an HPV DNA test in 2001. Use of HPV DNA testing tripled in 2002, to 0.6%. In 2003, 0.9% of enrollees were tested, in 2004 1.4% were tested, and in 2005 2.1% were tested. For the partial year through May 2006, 1.7% of female enrollees were tested for HPV. Adjusting for variable enrollment and multiple procedures per enrollee per year, we found a substantial and

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**Table 2.** Procedures by year

| | Number of patients with procedure (% of enrollees; procedures per 1,000 patient-years) | | | | | |
|---|---|---|---|---|---|---|
| | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 |
| Pap smear | 1,381,139 (21.9%; 343.40) | 1,578,030 (24.5%; 350.45) | 1,596,914 (24.7%; 345.12) | 1,570,520 (24.4%; 344.62) | 1,564,952 (23.5%; 325.78) | 761,124 (13.2%; 310.52) |
| HPV DNA testing | 14,808 (0.2%; 3.58) | 35,891 (0.6%; 7.78) | 54,792 (0.9%; 11.74) | 88,498 (1.4%; 19.16) | 137,857 (2.1%; 28.37) | 97,679 (1.7%; 39.65) |
| Biopsy | 731 (0.0%; 0.17) | 782 (0.0%; 0.16) | 774 (0.0%; 0.16) | 717 (0.0%; 0.15) | 446 (0.0%; 0.09) | 165 (0.0%; 0.07) |
| Colposcopy | 8,972 (0.1%; 2.26) | 10,452 (0.2%; 2.35) | 10,673 (0.2%; 2.33) | 10,232 (0.2%; 2.29) | 11,028 (0.2%; 2.33) | 6,134 (0.1%; 2.54) |
| Colposcopy & biopsy | 0 (0.0%; 0.00) | 0 (0.0%; 0.00) | 3,698 (0.1%; 0.76) | 5,784 (0.1%; 1.23) | 6,524 (0.1%; 1.32) | 3,733 (0.1%; 1.50) |
| Colposcopy & ECC | 39,273 (0.6%; 9.50) | 46,059 (0.7%; 9.97) | 42,914 (0.7%; 9.07) | 42,234 (0.7%; 9.10) | 45,100 (0.7%; 9.24) | 23,829 (0.4%; 9.64) |
| ECC | 2,854 (0.1%; 0.68) | 3,359 (0.1%; 0.73) | 3,396 (0.1%; 0.71) | 3,402 (0.1%; 0.73) | 3,379 (0.1%; 0.69) | 1,920 (0.0%; 0.78) |
| Cauterization | 10,884 (0.2%; 2.59) | 12,235 (0.2%; 2.60) | 12,030 (0.2%; 2.50) | 10,663 (0.2%; 2.27) | 8,970 (0.1%: 1.82) | 4,210 (0.1%; 1.73) |
| Cervical amputation | 1,645 (0.0%; 0.38) | 1,784 (0.0%; 0.37) | 1,641 (0.0%; 0.33) | 1,549 (0.0%; 0.32) | 859 (0.0%; 0.17) | 334 (0.0%; 0.13) |
| Colposcopy & LEEP or conization | 4,297 (0.1%; 1.01) | 4,723 (0.1%; 0.98) | 4,678 (0.1%; 0.95) | 4,741 (0.1%; 0.99) | 4,963 (0.1%; 0.99) | 2,509 (0.0%; 1.01) |
| Conization | 8,003 (0.1%; 1.88) | 9,227 (0.1%; 1.94) | 8,907 (0.1%; 1.83) | 8,469 (0.1%; 1.78) | 8,334 (0.1%; 1.67) | 4,137 (0.1%; 1.69) |
| Hysterectomy | 21,609 (0.3%; 4.99) | 23,967 (0.4%; 4.92) | 23,123 (0.4%; 4.65) | 22,117 (0.3%; 4.54) | 21,956 (0.3%; 4.30) | 10,781 (0.2%; 4.30) |

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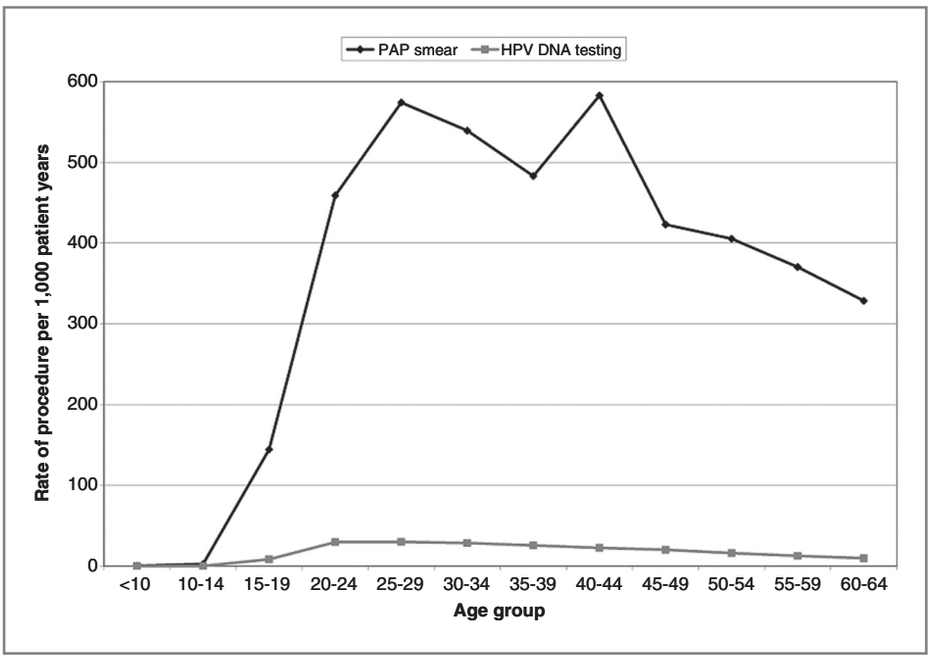


Figure 1. Rate of Pap Smear and HPV DNA Testing by Age Group.

steady increase in HPV DNA testing from 3.58 procedures per 1,000 patient-years in 2001 to 39.65 procedures per 1,000 patient-years in 2006.

Testing rates for both Pap smears and HPV DNA testing per 1,000 patient-years increased steadily with age among enrollees in the 15–19, 20–24, and 25–29 age groups (Fig. 1). Rates of both procedures then declined for subsequent older age categories, with one exception: A noticeable spike in Pap smears occurred among those 40–44 years of age.

Rates of HPV-related diagnostic procedures remained mostly stable (Fig. 2). Colposcopy with endocervical curettage (ECC) was the most common procedure across all years; 0.6% of currently enrolled females (39,273 total) received this procedure in 2001, and 0.7% (45,100 total) received it in 2005. The rate of colposcopy with ECC was 9.50 per 1,000 patient-years in 2001 and remained relatively stable over time, with a rate of 9.64 in 2006. Colposcopy alone was the next most common procedure, with 2.26 per 1,000 patient-years in 2001 and 2.33 per 1,000 patient-years in 2005. In the partial year 2006, the rate of colposcopy was 2.54 per 1,000 patient-years, only slightly higher than the 2001 rate. No colposcopy with biopsy procedures were identified in 2001 or 2002, as the codes used to identify this procedure were introduced in 2003. In 2003, the rate of colposcopy with biopsy was 0.76 per 1,000

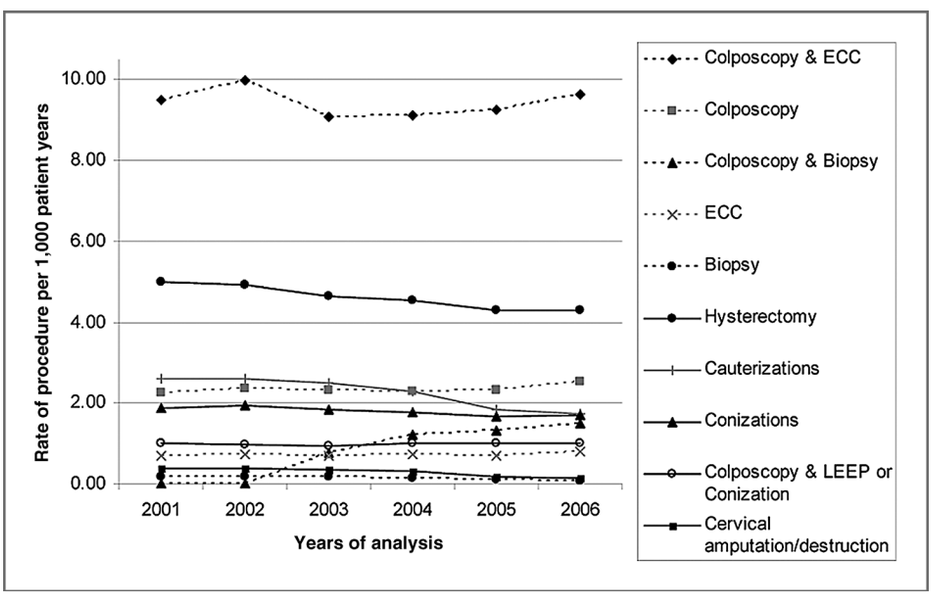


Figure 2. Rates of HPV-related Diagnostic Procedures and Treatments Per 1000 Patient-Years. Note: Diagnostic procedures are those with dotted lines. Treatments are those with solid lines.

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patient-years, and this increased to 1.23 per 1,000 patient-years in 2004, 1.32 per 1,000 patient-years in 2005, and 1.50 per 1,000 patient-years in the partial year 2006. Biopsy alone and ECC alone were relatively uncommon during the analytic period.

Hysterectomy attributable to HPV was the most commonly performed procedure for treating HPV-related disease, but the number of hysterectomies decreased from 4.99 per 1,000 patient-years in 2001 to 4.30 per patient-years in the partial year 2006. Procedures for treating HPV-related disease declined during the analytic period (Fig. 2). With the exception of colposcopy with LEEP, all other procedures also experienced a decline in the rate of use over the 6-year analysis period. Cauterization was performed at a rate of 2.59 per 1000 patient-years in 2001, and this rate remained steady for 3 years before declining to 1.82 and 1.73 per 1,000 patient-years in 2005 and 2006, respectively. With the exception of ECC, the rates of HPV-related diagnostic procedures reached a peak among enrollees aged 20–24, and followed a downward trend across the older age groups (Fig. 3, Appendix Table B). ECC experienced its peak among the 25–29 age group. Diagnostic procedures were used infrequently for those under age 15. Rates of treatment procedures were highest among patients aged 20–29 and followed a pattern of decline in older age groups, similar to what was observed for diagnostic procedures (Appendix Table B). Hysterectomy, an exception, was highest in the 45–49 age group (30,143 women, or 1.8% of those aged 45–49).

Appendix Table C presents rates of procedures in the subset of patients for whom HPV vaccination is licensed. In 2005, 3.8% of 11- to 18-year-old females (52.69 per 1,000 patient-years) and 28.2% of 19- to 26-year-old females (475.02 per 1,000 patient-years) had a Pap smear, and 0.3% of those aged 11–18 (4.44 per 1,000 patient-years) and 2.7% of those aged 19–26 (44.00 per 1,000 patient-years) had an HPV DNA test. The most commonly used treatments were cauterization (6.20 per 1,000 patient-years) and conizations (4.59 per 1,000 patient-years).

## Costs

The median cost for a Pap smear (same day costs) increased from $134 per procedure in 2001 to $163 per procedure in 2006, a 21.7% increase (Table 3, Appendix Fig. A). All procedure-associated costs were captured, including the physical exam portion of the outpatient visit. Mean cost increased from $155 in 2001 to $194 in 2006. By contrast, the cost for HPV DNA testing decreased by 22.9% over the same period, from a median of $266 (mean $296) in 2001 to a median of $205 (mean $237) in 2006. ECC, colposcopy with ECC, and colposcopy with biopsy had costs in the mid-$300 range, and remained steady during the analytic period. Colposcopy alone was the least expensive diagnostic procedure, at just under $200.

Hysterectomy was the most expensive HPV-related treatment procedure. Median hysterectomy cost was $7,383 (mean $8,384) per procedure in 2006, a 7.4% increase over the 2001 cost. Cervical amputation and conizations were the next most expensive treatments, and they both increased substantially in cost over the 6-year analytic period. Cervical amputation costs increased from a median of $2,132 (mean $2,831) per procedure in 2001 to a median of $2,854 (mean $4,239) in 2006 (a 33.9% increase), and conization costs increased from a median of $1,420 (mean $1,822) in 2001 to a median of $1,710 (mean $2,140) in 2006 (a 20.4% increase) (Table 3).

Costs varied significantly by patient age for 3 treatments and 1 diagnostic procedure (Appendix Table D). Among treatments, hysterectomy was associated with the widest variation in costs, ranging from a median of $5,382 (mean $7,324) for females aged 15–19 to a median of $8,388 (mean $9,862) for those aged 60–64.

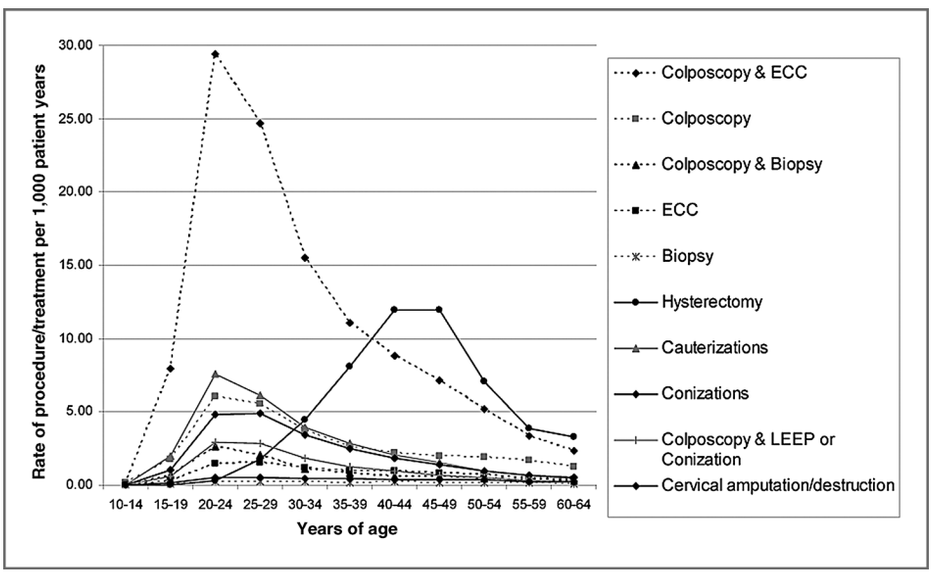


Figure 3. HPV-related Diagnostic Procedures and Treatments by Age Group. Note: Diagnostic procedures are those with dotted lines. Treatments are those with solid lines.

Published OnlineFirst July 10, 2012; DOI: 10.1158/1055-9965.EPI-11-1019



**Table 3.** Median [mean (SD)] procedure costs by year

| | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 |
|---|---|---|---|---|---|---|
| Pap smear | $134 [$155 ($202)] | $144 [$164 ($192)] | $149 [$173 ($231)] | $153 [$179 ($494)] | $160 [$188 ($200)] | $163 [$194 ($193)] |
| HPV DNA testing | $266 [$296 ($300)] | $247 [$275 ($197)] | $235 [$267 ($190)] | $213 [$246 ($232)] | $208 [$238 ($246)] | $205 [$237 ($219)] |
| Biopsy | $1,571 [$2,366 ($3,067)] | $1,423 [$2,523 ($4,810)] | $1,617 [$2,688 ($5,492)] | $1,218 [$2,466 ($3,726)] | $1,035 [$2,332 ($3,491)] | $1,348 [$3,476 ($5,617)] |
| Colposcopy | $164 [$384 ($1,669)] | $176 [$368 ($1,287)] | $190 [$412 ($1,766)] | $200 [$382 ($1,185)] | $193 [$373 ($1,216)] | $194 [$371 ($1,241)] |
| Colposcopy & biopsy[a] | $ — | $ — | $361 [$468 ($578)] | $361 [$442 ($478)] | $346 [$423 ($516)] | $353 [$426 ($501)] |
| Colposcopy & ECC | $309 [$370 ($332)] | $316 [$382 ($376)] | $328 [$395 ($341)] | $341 [$411 ($358)] | $344 [$412 ($334)] | $345 [$417 ($332)] |
| ECC | $316 [$670 ($1,086)] | $341 [$662 ($1,082)] | $352 [$684 ($1,105)] | $369 [$706 ($1,180)] | $366 [$685 ($1,141)] | $367 [$713 ($1,188)] |
| Cauterization | $228 [$954 ($1,518)] | $240 [$1,037 ($1,570)] | $263 [$1,166 ($1,699)] | $254 [$1,129 ($1,733)] | $226 [$930 ($1,607)] | $216 [$862 ($1,516)] |
| Cervical amputation/ destruction | $2,132 [$2831 ($2,493)] | $2,176 [$3,024 ($3,367)] | $2,349 [$3,104 ($2,836)] | $2,589 [$3,372 ($3,208)] | $3,035 [$4,035 ($4,145)] | $2,854 [$4,239 ($5,029)] |
| Colposcopy & LEEP or conization | $698 [$1,208 ($1,287)] | $715 [$1,225 ($1,319)] | $803 [$1,392 ($1,490)] | $810 [$1,372 ($1,442)] | $815 [$1,400 ($1,493)] | $870 [$1,462 ($1,482)] |
| Conization | $1,420 [$1,822 ($1,644)] | $1,391 [$1,871 ($1,803)] | $1,540 [$1,985 ($1,778)] | $1,548 [$2,022 ($1,901)] | $1,620 [$2,084 ($1,914)] | $1,710 [$2,140 ($1,938)] |
| Hysterectomy | $6,874 [$7,546 ($5,924)] | $7,035 [$7,726 ($5,308)] | $7,019 [$7,888 ($5,210)] | $7,099 [$8,082 ($6,037)] | $7,217 [$8,130 ($5,706)] | $7,383 [$8,384 ($6,379)] |

[a]The codes used to identify "Colposcopy & Biopsy" were released in 2003.

Published OnlineFirst July 10, 2012; DOI: 10.1158/1055-9965.EPI-11-1019



Median costs for cervical amputation/destruction ranged from $1,698 for the 15–19 age group to $2,743 for the 40–44 age group (mean $2,305 to $3,663, respectively), and conization was associated with median costs ranging from $1,326 for the 20–24 age group to $1,782 for the 55–59 age group (mean $1,781 to $2,246, respectively). Biopsy costs ranged from a median of $732 for 15- to 19-year-olds to a median of $2,035 for 55- to 59-year-olds (mean $1,704 to $3,241, respectively).

We also examined median and mean costs per procedure among women targeted for HPV vaccination (Appendix Table E). The main cost drivers for both the 11–18 age group and the 19–26 age group were hysterectomy, cervical amputation/destruction, and conizations. For those aged 11–18, median costs were $8,008 for hysterectomy (mean $18,023), $2,854 for cervical amputation/destruction (mean $3,376), and $1,265 for conizations (mean $1,842). For women aged 19–26, median costs were $6,360 for hysterectomy (mean $7,763), $2,101 for cervical amputation/destruction (mean $2,843), and $1,475 for conizations (mean $1,909).

## Discussion

These data indicate the frequency of HPV-related diagnostic and treatment procedures in a US commercially insured population and the costs associated with these procedures within a national health plan population of more than 14.2 million female enrollees, with 5.8 to 6.7 million annually between 2001 and 2006. Hysterectomy was the most commonly administered treatment, and this was driven by older age groups, but hysterectomies decreased in prevalence from 4.99 per 1,000 patient-years in 2001 to 4.30 per 1,000 patient-years in the partial year 2006. With the exception of colposcopy with LEEP, all other treatment procedures also experienced a decline in rate of use over the 6-year analysis period.

Rates of HPV-related diagnostic procedures remained mostly stable. The most frequently performed diagnostic procedure was colposcopy with endocervical curettage, with the highest rates occurring among women aged 20–24. With the exception of ECC, rates of HPV-related diagnostic procedures reached a peak among enrollees aged 20–24, and followed a downward trend across the older age groups.

Biopsy was the most expensive diagnostic procedure, with a median cost ranging from $1,035 (in 2005) to $1,617 (in 2003; mean $2,332 to $2,688, respectively). Hysterectomy was the most expensive treatment, with a median cost of $7,383 (mean $8,384) per procedure in 2006, representing a 7.4% increase over the 2001 cost.

We found a small decline in rates of women receiving a Pap smear from 2001 to 2006, which may have been due to a move toward less frequent screening as recommended in the 2009 ACOG guidelines (32), whereas the rate of HPV DNA testing showed a consistent increase over the same period. However, the absolute number of HPV tests conducted remains very low compared with Pap smears. The lower rates of Pap smear screening observed in our study compared with previous estimates such as those reported by Insinga and colleagues (17) are likely due to differences in study populations and variations in screening practices (HMOs versus fee-for-service plans).

The use of all other HPV-related diagnostic procedures over time was relatively stable (or showed slight increases). On the other hand, treatment procedure rates generally declined or remained stable from 2001 to 2006. This pattern of use may be reflective of more aggressive diagnostic efforts, which in turn reduced the need for invasive treatment.

The sample included in this study was of commercially insured women up to 64 years of age, representative of a large segment of the US commercially insured population. Trends found in this study likely reflect changing patterns of care and disease epidemiology among this population of insured women.

Of interest, we found a substantial increase in use of HPV DNA testing over time. Pap smear services (inclusive of physician services, laboratory costs, etc.) had a median cost of $163 (mean $194) in 2006, and the median cost for HPV DNA testing services for that year was $205 (mean $237). HPV DNA testing is usually carried out as part of a gynecologic exam inclusive of Pap smear, so the costs shown for HPV DNA testing likely include Pap smear and annual exam services costs (33). However, following a negative HPV test, Pap smears are recommended less frequently (34), which could lead to potential savings of $326 per woman over 3 years [cost of Pap smear = $163 plus cost of DNA testing = $205; in the event of negative DNA, no Pap smear is required in Year 2 (savings of $163) or in Year 3 (savings of $163), resulting in a total savings of $326]. Patients in the target age groups for HPV vaccination (11–18 years and 19–26 years) had relatively low rates of Pap screening, and more importantly, very low rates of HPV DNA testing.

Our analysis for this subset was conducted in 2005, the year before the implementation of HPV vaccinations. HPV vaccination is expected to have an effect on the costs of procedures related to disease most likely due to HPV (35). The cost-effectiveness of vaccination depends on the duration of immunity (which cannot be predicted) and whether vaccination affects subsequent screening delay or frequency (36). Modeling studies comparing the cost-effectiveness of vaccination when various screening regimens are used suggest that vaccination is more cost-effective when screening is started later and is conducted less frequently (36, 37). Therefore, use of HPV vaccination may have the potential to lead to substantial cost savings for HPV-related diagnostic and treatment procedures, due to reduced need for screening and improved prevention.

Furthermore, our study population included a substantial number of enrollees younger than 21 years of age, and, according to 2009 ACOG guidelines (32), cervical cancer screening should begin at age 21. New 2012 U.S. Preventive Services Task Force screening guidelines recommend that women aged 21 to 29 should be screened by cytology

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every 3 years, and women aged 30 to 65 should be screened either by cytology every 3 years or, for those who want a longer screening interval, cotesting with cytology and HPV testing every 5 years (38).

Several study limitations are present that impede our ability to make projections relating to overall costs of care and trends in procedure rates. Analyses were performed using claims associated with the procedure alone. This approach may underestimate costs, as it excludes codes submitted by multiple providers for ancillary services associated with the procedure, but not for the procedure itself. Conversely, the cost of Pap smears was very likely considerably overestimated, as it included the cost of the physical exam portion of the visit.

For patients with more than one relevant procedure code on a single day, each code was treated separately, and rates were determined individually for each specific procedure code. Although physicians should use combined codes when appropriate (i.e., billing colposcopy with ECC using the single procedure code rather than separate codes for colposcopy and for ECC), it is possible that variations in billing practices occurred over the 6-year study period and that codes were not always appropriately used. Further, some codes were not available in early years, while others were eliminated during the study period.

Finally, these results pertain to a commercially insured population and cannot necessarily be extrapolated to Medicare-insured or uninsured populations. However, these study patients were younger than 65 and therefore differ substantially from Medicare patients based on age alone.

## Conclusions

This study provides a current perspective on rates of procedures related to disease most likely due to HPV and associated costs, and establishes benchmarks for a commercially insured female population as well as for age-specific cohorts recommended for vaccination. The high costs of HPV-related diagnostic procedures and treatments we observed suggest an opportunity for significant savings following successful implementation of HPV vaccination programs across the US female population.

The data presented here may be useful in cost-effectiveness analyses and to guide decision makers evaluating how best to optimize primary and secondary prevention strategies. Further research is needed to examine factors that may have an impact on cost, such as provider and patient compliance with screening and management guidelines.

## Disclosure of Potential Conflicts of Interest

Denise Kruzikas was employed by GSK at the time this study was conducted. Jennifer Smith has received research grants, consultancies or honorarium over the past five years from GSK, Merck Corporation, and Hologic Inc. Carolyn Harley and Paul Buzinec are employed by OptumInsight, the company hired by GSK to conduct this study.

## Authors' Contributions

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**Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.):** C. Harley
**Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis):** D.T. Kruzikas, J.S. Smith, P. Buzinec, C. Harley
**Writing, review, and/or revision of the manuscript:** D.T. Kruzikas, J.S. Smith, P. Buzinec
**Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases):** P. Buzinec, C. Harley
**Study supervision:** D.T. Kruzikas, J.S. Smith

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