Health Utilities Lost and Risk Factors Associated With HPV-induced Diseases in Men and Women: The HPV Italian Collaborative Study Group

Andrea Marcellusi, MSc1,2; Alessandro Capone, MD3; Giampiero Favato, DBA3; Francesco Saverio Mennini, MSc1,3; Gianluca Baio, PhD4; Katrin Haeussler, PhD4; Marco Bononi, MD5; and on behalf of the HPV Italian Collaborative Study Group*

1CEIS - Economic Evaluation and HTA, Faculty of Economics, University of Rome “Tor Vergata”, Rome, Italy; 2Department of Demography, “Sapienza” University of Rome, Rome, Italy; 3Institute for Leadership and Management in Health, Kingston University London, London, United Kingdom; 4Department of Statistical Science, University College London, London, United Kingdom; and 5Department of Surgery Pietro Valdoni, “Sapienza” University of Rome, Rome, Italy

ABSTRACT

Purpose: A complete economic evaluation requires accurate data concerning the resources used, outcomes, and utilities (patient’s preferences) to properly value the cost utility of human papillomavirus (HPV) vaccination strategies. This study was designed to measure the utility loss in health states affected by a broad range of HPV-induced pathologies in both sexes in Italy. As a secondary objective, risk factors influencing the viral transmission and development of HPV infections were also investigated.

Methods: Patients with a diagnosis of several HPV-induced pathologies including atypical squamous cells of undetermined significance (ASC-US), cervical intraepithelial neoplasia (CIN), cervical and anal-colorectal cancer, head and neck squamous cell carcinoma (HNSCC) and anogenital warts (AWs) were evaluated. Utilities, quality of life, and risk factors were elicited using a standardized and computer-guided administration of time trade-off, European Quality of Life 5 Dimensions (EQ-5D), 3 levels, and risk factor questionnaires. Utilities were measured at 6 clinical research centers across Italy. A group of healthy subjects was used as a control. A mean number of 20 research centers across Italy. A group of healthy subjects was used as a control. A mean number of 20

Findings: Overall, 600 respondents were eligible for analysis: 465 patients (mean [SD] age, 44.0 [16.3] years) and 135 controls (mean [SD] age, 44.0 [13.2] years). With the exception of anal and HNSCC cancer, no statistically significant differences were observed between case and control groups, in terms of either age or quality of life at the time of interview. The patients’ perception of their health condition at baseline was equal to an EQ-5D score of 0.87 (0.22). The mean (SD) value of utilities associated with the HPV-induced pathologies corresponded to 0.83 (0.24), 0.78 (0.27), 0.83 (0.22), 0.81 (0.27), 0.58 (0.31), 0.51 (0.26), and 0.69 (0.30) for ASC-US, AWs, CIN 1 (mild), CIN 2–3 (moderate to severe), cervical cancer, anal cancer and HNSCC, respectively. Utility lost due to AWs was significantly higher in females compared with males (0.71 [0.29] vs 0.83 [0.25]; P = 0.018). Having >5 sexual partners increased the risk of acquiring HPV-induced infections as much as 2.52-fold (P = 0.004), whereas for smoking or the age at start of sexual activity younger than 18 years, the risk increased by ~1.62-fold (P = 0.034). High levels of education were associated with a statistically significant protective effect (P < 0.001).

Implications: Risk factors and utilities elicited in this study can be used as part of future economic assessments of other HPV vaccination strategies, including an immunization program for preadolescents of both sexes

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Key Words: anal cancer, anogenital warts, cervical cancer, CIN 1, CIN 2–3, head and neck squamous cell carcinoma, HPV, quality of life, TTO, utilities.

INTRODUCTION

Human papillomavirus (HPV) is likely the most common sexually transmitted viral infection worldwide.1 HPV triggers annually ~600,000 cases of cervical cancer; cancer of the vulva, vagina, anus, and penis, head and neck squamous cell carcinoma (HNSCC), as well as nonmalignant neoplastic diseases such as anogenital warts (AWs) and recurrent respiratory papillomatosis, with a substantial medical and economic burden.2 Italian data derived from an analysis of economic burden, performed from the payer’s perspective, suggest that the annual direct cost associated with incident cases of 9 HPV-related conditions (invasive cervical cancer; cervical dysplasia; cancer of the vulva, vagina, anus, and penis; HNSCC; AWs; and recurrent respiratory papillomatosis) is estimated to be €528.6 million (range, €480–€686 million).3

Two vaccines (HPV bivalent vaccine [Cervarix®] and HPV quadrivalent vaccine [Gardasil®]) are currently available and used, providing protection against HPV genotypes 16 and 18 and 6, 11, 16, and 18, respectively. Because some difference between the vaccines exists, it is necessary to investigate the cost utility of other vaccination strategies, especially those that take into account a suitable multicohort approach in female patients or a vaccination for both sexes (ages 12–18 years).

Although the financing of immunization programs is a governance challenge that public health care providers have to deal with, the valuation of a universal vaccination strategy with a Bayesian model can provide decision makers with more reliable information about both the cost utility of interventions as well as their budgetary implications.4,5 In a recent paper, vaccination of 2 cohorts of girls 12 and 15 years of age showed to be a cost-effective intervention in a pairwise comparison with female-only vaccination and cervical cancer screening, with a discounted cost per quality-adjusted life-year gained corresponding to €12,013 (95% CI: €2,364–€22,481).4 However, in this Bayesian Markov model, clinical benefits of vaccination were focused on the prevention of a limited number of HPV-induced events occurring in females exclusively (ie, abnormal Pap smears, precancerous cervical lesions, cervical cancers, and AWs).

A full economic evaluation requires data about resource use, health outcome of the program under appraisal, and essential data to value consequences with quality-of-life (QoL) weights for cost-utility analyses.6 Variability within different populations with respect to utilities is a critical source of uncertainty in economic evaluations.7

Indeed, after collecting and incorporating specific patients’ health state preferences in probabilistic models, results of a cost-utility analysis can be substantially modified. Several social and cultural factors (ie, age, sex, comorbidities, economic status, lifestyle, education, cognitive capabilities, and even religion) may affect the preferences of patients.8–10

Factors influencing the risk of acquiring HPV infections are other crucial parameters in the economic and clinical evaluation of prevention programs, especially when dynamic interactions in both sexes between susceptible, infected, and immune individuals are considered. The acquisition of HPV infection is associated with many risk factors such as a high number of sexual partners, early age at start of sexual activity, cigarette smoking, number of pregnancies, long-term hormone-based birth control, and previous sexually transmitted diseases (STDs).11–14 Some evidence describing HPV transmission risk can be found15,16; however, these findings are far from definitive, suggesting a great variability within diverse populations, depending on different scenarios (in which some parameters are not directly comparable such as sexual behaviour) and sexual activity.17–19

Moreover, those factors that contribute to an elevated risk of acquiring HPV infection also account for a higher probability of reinfection after clearance.

There are many technical approaches used to directly assess utility scores that determine the value or desirability of a particular health state: rating scales, standard gamble (SG), and time trade-off (TTO) are the most widely used methodologies.20–22 To estimate whether an immunization program targeting 2 cohorts of both sexes (between 12 and 18
years of age) is a cost-utility intervention, utilities and risk factors need to be measured. The primary objective of the current study is to measure in both sexes the utility loss in health states affected by a broad range of HPV-induced pathologies from Italian patients’ perspective. As a secondary objective, risk factors influencing the viral transmission and development of HPV infections, was also investigated.

Methods

Study Design

The study was designed with 2 specific objectives: the measurement of utility loss considering the patients’ perspective and the assessment of risk factors in both patients and healthy individuals. The measurement of utilities was carried out in a multicenter, observational, and retrospective study in male and female patients with HPV-induced diseases. The following conditions were investigated: atypical squamous cells of undetermined significance (ASC-US), cervical intraepithelial neoplasia (CIN), and cervical cancer among females; anal-coloctal cancer, HNSCC, and AWs in both sexes. The European Quality of Life 5 Dimensions (EQ-5D) 3 levels questionnaire (EuroQol Group, Rotterdam, the Netherlands) was used to assess the QoL of each respondent at the time of interview. The elicitation was performed in 6 clinical research centers, each with their own patient records, and located in northern, central, and southern Italian regions: (1) Department of Oncologic Gynecology, National Institute for Cancer Research, Genoa; (2) Department of Obstetrics and Gynecology, Catholic University of the Sacred Heart, Rome; (3) Gynecologic Oncology Unity, Catholic University of the Sacred Heart, Campobasso; (4) Department of Surgery Pietro Valdoni, “Sapienza” University of Rome, Rome; (5) Regional Center for Head and Neck Cancer, University of Padua, Treviso Regional Hospital, Padua; (6) Infectious Dermatology, San Gallicano Dermatological Institute, Rome.

In addition to the assessment of utility loss, the study design was extended to investigate risk factors influencing the viral transmission and potential development of malignant and nonmalignant HPV-induced pathologies. This procedure allowed the collection of quantitative data concerning utilities and risk factors in patients (retrospectively enrolled) and healthy subjects (control group). Subjects included in the control group were enrolled in consecutive order to minimize potential selection bias.

The study was approved both by the local Institutional Review Board in Genoa and the San Gallicano Dermatological Institute Ethics Committee in Rome. Given the retrospective nature of the design and considering that all hospitalized patients necessarily have to sign an informed consent for any implemented procedure, the study did not require the collection of any further informed consent. Nonetheless, in accordance with the current official guidelines enacted by the Italian Medicine Agency for noninterventional observational studies, the ethics committees were notified at most of clinical centers. The Ethics Committee at the San Gallicano Dermatological Institute established the collection of informed consent that was gathered for each patient with AWs.

Patients’ personal data (name, date of birth, personal health code and pathology) were replaced by a unique numerical code to make all clinical records unidentifiable (in full compliance with the Italian privacy law).

Study Population

The study was carried out using a computer-assisted and standardized procedure previously validated for quantifying utilities loss in patients with HPV-induced diseases. All patients with the previously cited pathologies whose clinical data were recorded in the computerized archives of clinical centers within the 16 months preceding the end of the enrollment period (included between October 31, 2008 and July 31, 2012) were eligible as respondents. Two study populations were included. The first group consisted of patients 18 to 75 years of age at the time of diagnosis who consented to complete questionnaires administered during their clinic visit. Patients had to meet the following inclusion criteria: a confirmed (clinically and/or cytologically or microbiologically) diagnosis of ASC-US, CIN (grade 1 and grade 2–3), invasive cervical cancer, anal cancer or anal-coloctal cancer (as a proxy of anal cancer), HNSCC, and AWs; a recorded inpatient or outpatient medical or surgical intervention; and time from intervention to administration of questionnaires no longer than 18 to 20 months (to avoid a potential impairment effect of recollection that might be associated with a stressor event). The study time frame is depicted in Figure 1. The second group (control subjects)
consisted of healthy subjects matched for sex and disease proportion who attended the same clinical centers due to nonpathologic reasons (ie, healthy relatives accompanying patients, follow-up visits in patients cured of different diseases or initial clinical examination in healthy subjects). The control group was considered to capture any difference (irrespective of the statistical significance) between those who suffer from HPV-induced diseases and healthy people. Based on the variability of utility distribution values that was already investigated in the validation study to have an error value of \( \theta = 0.05 \) and a significance level of \( \alpha = 0.05 \) (predetermined value used to calculate the sample size), it was calculated that the sample size would have accounted for 60 patients per each pathology. However, due to the low prevalence of anal cancer, it was calculated to enroll 20 patients with this particular disease on the basis of an error value of \( \theta = 0.09 \) and \( \alpha = 0.05 \). The enrollment procedure was completed in August 2012 when the sample size was large enough to match up the overall level estimated for both cases and control subjects. Patients who did not fully complete all questionnaires used in this study (measuring utilities, QoL, and risk factors) and those with an incomplete clinical record were excluded.

**Elicitation Procedure**

The measurement of utilities was performed using a computerized implementation of the TTO procedure originally developed by Torrance et al and Gafni and Torrance. An algorithm for the computer-assisted administration of a TTO questionnaire was developed for the standardized elicitation of health state preferences in patients with HPV-induced diseases, according to a reference-based guideline to design and produce health-state utility instrumentations. A comprehensive description of derivation, theoretical elements, and validation of this TTO procedure was published; however, full details are provided in the Appendix. TTO-based interviews might be complicated and susceptible to generating errors. Thus, a full comprehension of respondents (using visual aids and written descriptions for each condition) and a homogeneous pattern of administration could be ensured by the computer-assisted method for elicitation. This effectively eliminated both data-entry errors and miscalculations.

The EQ-5D was used to evaluate respondents’ perception of their health conditions at the time of the interview, using 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

Several epidemiological studies identified a number of risk factors that may contribute to the acquisition of HPV infections, their progression to HPV-induced diseases, or their clearance. These risk factors include early age at first intercourse, a high number of sexual partners, smoking habit, long-term (\( \geq 5 \) years) use of oral contraceptives, multiparity and previous occurrence of STDs, such as herpes simplex virus type 2 and chlamydia trachomatis. Among those mentioned, the computer-assisted
administration of the questionnaire on risk factors allowed data to be collected on the following parameters: age at start of sexual activity, number of partners over the years, smoking habit, level of education, and previous STDs.

**Statistical Analysis**

All continuous data are summarized as means and SDs and 95% CIs are provided when appropriate. To limit the impact of assumptions about the distribution of the relevant variables, comparisons between groups were performed using the Mann-Whitney nonparametric test.

Pearson’s correlation coefficient (\( \rho \)) was used to determine whether variables such as age and health conditions (EQ-5D score) collected at the time of the interview correlated with values of elicited utility. A logistic regression model was used to evaluate the association between risk factors and HPV-induced diseases. The crude association of each selected independent variable (risk factors) with the outcome (HPV-induced disease as dependent variable) was estimated using a univariate logistic regression model. Risk factors were dichotomously entered in the model. Univariate predictors with a statistical significance (\( P \leq 0.05 \)) were subsequently entered into a backward stepwise multivariate logistic regression model to control for potential confounders.\(^{28}\)

The variables included as predictors were level of education, occupation, age at first intercourse, number of sexual partners, smoking habit and previous STDs for both sexes; while age at first pap smear, Pap smear frequency (screening intervals), use of oral contraceptives and number of pregnancies for females. Variables that did not reach a statistically significance in the multivariate logistic regression model were dropped one by one until all the remaining were significant. All statistical tests were considered statistically significant at level of \( \alpha \) less than 5%. Analyses were performed with SPSS for Windows, version 17 (SPSS Inc, Chicago, Illinois).

**RESULTS**

Overall, 638 subjects were enrolled and 600 were deemed fully eligible for analyses, providing a response rate of 94.0%. The mean (SD) age of the 465 patients was 44.0 (16.3) years, whereas that of the 135 controls was 44.0 (13.2) years. All characteristics of respondents are summarized in Table I. With the exception of anal and HNSCC, no statistically significant difference was observed between case and control group either in terms of age or quality of life at the moment of interview. The patients’ perception of their health condition at the time of the interview corresponded to a mean (SD) EQ-5D score of 0.87 (0.22). The control group revealed a better health condition, showing a mean (SD) EQ-5D score of 0.94 (0.14) (\( P < 0.0001 \)). All patients who responded (465) were willing to trade off years lived in perfect health rather than live a longer life affected by a disease. The mean (SD) values of utilities associated with the HPV-induced pathologies corresponded to 0.83 (0.24), 0.78 (0.27), 0.83 (0.22), 0.81 (0.27), 0.58 (0.31), 0.51 (0.26) and 0.69 (0.30) for ASC-US, AWs, mild CIN (CIN 1), moderate to severe CIN (CIN 2–3), cervical cancer, and HNSCC, respectively (Figure 2A). Comparing the results of cases with one another, all cancers showed lower levels of utility and the least preferred patient preference was related to anal cancer with a perceived value that was approximately half of that of a fully healthy state. With the exception of cancer diseases, utilities lost due to AWs were always on average higher (\( -0.22 \)) compared with any precancerous cervical lesion (\( -0.17 \) with CIN 1 and \( -0.19 \) with CIN 2–3) as well as ASC-US (\( -0.17 \)). Among pathologies affecting both sexes, a detailed pair comparison in terms of health utilities loss showed divergent mean values (Figure 2B). Differences in utility between sexes were not statistically significant, amounting to 0.64 (0.21) in females and 0.70 (0.32) in males (\( P = 0.353 \)) for HNSCC and 0.54 (0.31) in females and 0.48 (0.24) in males (\( P = 0.572 \)) for anal cancer. In contrast, the value of utility lost due to AWs was more pronounced in the female group (mean utility value of 0.71; 95% CI: 0.64–0.79) compared with males (0.83; 95% CI: 0.77–0.88); in this case, the difference reached statistical significance (\( P = 0.018 \)). However, it is worth noting that the age difference between sexes could have limited this result. Indeed, the mean (SD) age of females corresponded to 29.7 (9.3) years, whereas the mean (SD) age in males was 35.7 (10.2) years (\( P < 0.001 \)).

In Table II, the association of age with health condition at the time of the interview are considered with respect to the patients’ health state preferences. The correlation analysis showed that utilities were basically dependent on the HPV-induced condition, and overall variables such as age and EQ-5D score...
Table I. Mean age, EQ-5D score, and sex of respondents (N = 600) by HPV-related diseases.

<table>
<thead>
<tr>
<th>HPV-Induced Diseases</th>
<th>Variable</th>
<th>N</th>
<th>Mean (SD)</th>
<th>$P^*$ Male vs Female</th>
<th>N</th>
<th>Mean (SD)</th>
<th>$P^*$ Male vs Female</th>
<th>$P^*$ Case vs Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASC-US</td>
<td>Age</td>
<td>44</td>
<td>36.5 (11.4)</td>
<td>—</td>
<td>15</td>
<td>37.8 (8.7)</td>
<td>—</td>
<td>0.531</td>
</tr>
<tr>
<td></td>
<td>EQ-5D</td>
<td>1.0 (0.1)</td>
<td>—</td>
<td></td>
<td>1.0 (0.1)</td>
<td>—</td>
<td></td>
<td>0.965</td>
</tr>
<tr>
<td>CIN 1</td>
<td>Age</td>
<td>61</td>
<td>36.0 (11.1)</td>
<td>—</td>
<td>15</td>
<td>37.3 (9.4)</td>
<td>—</td>
<td>0.445</td>
</tr>
<tr>
<td></td>
<td>EQ-5D</td>
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<td>—</td>
<td></td>
<td>1.0 (0.1)</td>
<td>—</td>
<td></td>
<td>0.321</td>
</tr>
<tr>
<td>CIN 2–3</td>
<td>Age</td>
<td>62</td>
<td>38.1 (9.1)</td>
<td>—</td>
<td>15</td>
<td>38.1 (8.6)</td>
<td>—</td>
<td>0.928</td>
</tr>
<tr>
<td></td>
<td>EQ-5D</td>
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<td>—</td>
<td></td>
<td>1.0 (0.1)</td>
<td>—</td>
<td></td>
<td>0.43</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>Age</td>
<td>61</td>
<td>49.3 (11.0)</td>
<td>—</td>
<td>15</td>
<td>50.5 (11.9)</td>
<td>—</td>
<td>0.754</td>
</tr>
<tr>
<td></td>
<td>EQ-5D</td>
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<td></td>
<td>0.9 (0.1)</td>
<td>—</td>
<td></td>
<td>0.194</td>
</tr>
<tr>
<td>Genital warts overall</td>
<td>Age</td>
<td>132</td>
<td>33.1 (10.2)</td>
<td>—</td>
<td>45</td>
<td>39.8 (11.1)</td>
<td>—</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>EQ-5D</td>
<td>0.9 (0.1)</td>
<td>—</td>
<td></td>
<td>1.0 (0.1)</td>
<td>—</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Females</td>
<td>Age</td>
<td>58</td>
<td>29.7 (9.3)</td>
<td>—</td>
<td>15</td>
<td>38.5 (10.5)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EQ-5D</td>
<td>1.0 (0.1)</td>
<td>—</td>
<td></td>
<td>1.0 (0.1)</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>Age</td>
<td>74</td>
<td>35.7 (10.2)</td>
<td>&lt;0.001</td>
<td>30</td>
<td>40.4 (11.6)</td>
<td>0.621</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>EQ-5D</td>
<td>0.9 (0.1)</td>
<td>&lt;0.001</td>
<td></td>
<td>1.0 (0.1)</td>
<td>—</td>
<td></td>
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<tr>
<td>Anal cancer overall</td>
<td>Age</td>
<td>26</td>
<td>68.3 (7.0)</td>
<td>—</td>
<td>10</td>
<td>60.6 (9.5)</td>
<td>—</td>
<td>0.019</td>
</tr>
<tr>
<td></td>
<td>EQ-5D</td>
<td>0.6 (0.3)</td>
<td>—</td>
<td></td>
<td>0.9 (0.1)</td>
<td>—</td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Females</td>
<td>Age</td>
<td>11</td>
<td>69.5 (5.4)</td>
<td>—</td>
<td>7</td>
<td>59.3 (10.6)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EQ-5D</td>
<td>0.4 (0.3)</td>
<td>—</td>
<td></td>
<td>0.9 (0.1)</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>Age</td>
<td>15</td>
<td>67.5 (8.0)</td>
<td>0.646</td>
<td>3</td>
<td>63.7 (7.1)</td>
<td>0.667</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>EQ-5D</td>
<td>0.7 (0.2)</td>
<td>0.004</td>
<td></td>
<td>0.9 (0.1)</td>
<td>—</td>
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<td>0.833</td>
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<tr>
<td>HNSCC overall</td>
<td>Age</td>
<td>79</td>
<td>65.0 (9.0)</td>
<td>—</td>
<td>20</td>
<td>54.7 (13.3)</td>
<td>—</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>EQ-5D</td>
<td>0.8 (0.2)</td>
<td>—</td>
<td></td>
<td>0.9 (0.3)</td>
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<td>0.094</td>
</tr>
<tr>
<td>Females</td>
<td>Age</td>
<td>17</td>
<td>60.4 (11.3)</td>
<td>—</td>
<td>14</td>
<td>54.3 (10.3)</td>
<td>—</td>
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<tr>
<td></td>
<td>EQ-5D</td>
<td>0.7 (0.2)</td>
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<td></td>
<td>0.8 (0.3)</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>Age</td>
<td>62</td>
<td>66.3 (8.0)</td>
<td>0.046</td>
<td>6</td>
<td>55.7 (20.0)</td>
<td>0.602</td>
<td>—</td>
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<tr>
<td></td>
<td>EQ-5D</td>
<td>0.8 (0.2)</td>
<td>0.203</td>
<td></td>
<td>1.0 (0.1)</td>
<td>—</td>
<td></td>
<td>0.312</td>
</tr>
</tbody>
</table>

ASC-US = atypical squamous cells of undetermined significance; CIN 1 = mild cervical intraepithelial neoplasia; CIN 2–3 = moderate to severe cervical intraepithelial neoplasia; EQ-5D = European Quality of Life 5 Dimensions score; HNSCC = head and neck squamous cell carcinoma; HPV = human papillomavirus. Age is reported in years.

$^*$Mann-Whitney nonparametric test.
Figure 2. A, Mean (SD) and 95% CI of utility values elicited in patients with several human papillomavirus-induced diseases (n = 465) and a control group of healthy individuals (n = 135). Comparison of values collected in patients and control subjects was performed using the Mann-Whitney nonparametric test. B, Mean (SD) and 95% CI of utility values elicited in male and female patients with anogenital warts, anal cancer, and head and neck cancer. Comparison of values collected in males and females was performed using the Mann-Whitney nonparametric test. ASC-US = atypical squamous cells of undetermined significance; CIN 1 = mild cervical intraepithelial neoplasia; CIN 2–3 = moderate to severe cervical intraepithelial neoplasia; HNSCC = head and neck squamous cell carcinoma.
were not narrowly correlated with utilities. The age variable demonstrated a statistically significant effect with a bimodal distribution of values (peaks observed at 34.0 [10.5] and 65.8 [8.5] years on average),
denoting that the highest mean ages were associated with more severe conditions (ie, cancer cases) compared with the lowest ones, which were related to other pathologies such as ASC-US, CIN, and AWs.

On the basis of the backward stepwise multivariate logistic regression method, only those risk factors having statistical significance were evaluated and listed in Table III. The multivariate logistic regression analysis allowed us to distinguish between distinct risk factor profiles: risk factors with significant effects, associated with the number of sexual partners, which increases the risk of acquiring HPV infections in a linear relationship as much as 2.52-fold (95% CI: 1.34–4.74, \( P = 0.004 \), in respondents with >5 partners); risk factors with moderate to low effects, represented by an age younger than 18 years at the start of sexual activity; and smoking habit that increase the risk of infection by 1.62-fold (95% CI: 1.01–2.61, \( P = 0.034 \) and 95% CI: 1.04–2.53, \( P = 0.049 \); for smoking and young age at start of sexual activity, respectively) and factors with a protective effect such as high levels of education, which reduce the odds of being infected by 83.2% (95% CI: 67.3%–91.3%; \( P < 0.001 \)) in respondents with a university education. Although a previous STD was not associated with a statistically significant outcome, a 1.2-fold increased risk of HPV infection was
observed. Finally, the overall rate of individuals at high risk (persons with >5 sexual partners and at least an additional factor included in Table III) corresponded to 26.3% in the respondent population (158 of 600). The proportion of subjects with an “average” risk (respondents with <5 partners and at least an additional factor) amounted to 53.2% (319 of 600).

DISCUSSION
This study took into account utility loss in a wide range of HPV-induced diseases. Despite the complex and sensitive nature of the diseases, technical difficulties related to their management, and especially the heterogeneity of respondents,29 this study provides the most updated and comprehensive estimates of patients’ preferences for health states altered by HPV-induced pathologies in the context of current clinical practice in Italy.

The assessment of risk factors (ie, age at first sexual intercourse, number of partners, and smoking habit), which contribute to biological host-pathogen interactions such as viral transmission, progression of infections, and clearance, is also relevant.

With respect to utility results reported in previous studies carried out either in the United Kingdom or the United States, there are some differences that must be examined. Actually, the utility values that we have presented can fluctuate compared with data measured in the United Kingdom30,31 and the United States,32–34 even though they were elicited with the application of the same TTO procedure. However, this was somehow expected and basically depended on the broad structural differences existing among the considered populations.7 Furthermore, in some circumstances, utilities were exclusively elicited in healthy subjects,35 and this procedure might be associated with a biased estimation of HPV-induced health outcome (more frequently an overestimation than an underestimate of utilities actually lost).36 In our study, with a few exceptions (in AIs and minimally in anal cancer), utilities lost in the control group were always substantially overestimated compared with those collected in patients affected and treated. Additionally, the variability in patients’ health state preferences can also reflect differences between countries in terms of treatment duration and follow-up, rate of cure or recurrence, and disease management setting (home-based rather than clinic-based treatment).

These differences may have a significant effect on compliance and perception of quality and effectiveness of health-care services provided.37 Each risk factor may have an independent effect on the viral transmission and the dynamics of acquiring HPV infections. To some extent, in many individuals, risk factors may coexist. The synergistic combined outcome of risk factors was examined to ascertain whether their cooperation may have amplified the magnitude of the risk of acquiring a HPV infection. Although not achieving a full statistical significance, the analysis of 2 concomitant factors revealed that individuals with an age at the start of sexual activity younger than 18 years of age and number of partners >5 showed a 3.2-fold (P = 0.075) increased risk of acquiring a HPV-induced disease.

This study can be included in a wide and structured research program focused on the assessment of clinical and economic consequences of multicohort HPV vaccination strategies.3,4,10,38 Indeed, this research was conducted to find reliable data that can be used in the future to inform a dynamic evolution of a previous static Bayesian model that we developed to assess the cost utility of HPV vaccination.4,39 In the model, different partner acquisition rates and HPV transmission probabilities will be considered for individuals with a high and an average level of sexual activity.

This study was conducted using a well-known procedure.10,20,40 The 3 most frequently used methods for a direct elicitation of utility are the visual analogue scale (VAS), also referred to as a rating scale, the SG, and the TTO.22,40 A direct measurement performed with an instrument like the TTO is often considered complicated and time-consuming; hence, many researchers tend to use simpler procedures such as the indirect ones (ie, Quality of Well-being Index, Health Utilities Index, or the EQ-5D).41 However, these latter techniques do not measure utilities but rather estimate the relationship between the overall utility weight and health domains throughout a regression analysis.42 Of the 3 direct procedures considered, there is another main divergence: utilities elicited with the SG are typically greater than those collected using the TTO, which are greater than those derived from the VAS.36,43 Although it is a good indicator, in the most rigorous meaning of the term, the VAS is not a utility measure because it does not include trade-offs against
time or risk. Moreover, contrary to the SG or TTO, the VAS does not directly provide cardinal utility values.\textsuperscript{43} Finally, the SG is framed in terms of risk, whereas the TTO is considered to be riskless.\textsuperscript{36} To overcome issues related to TTO administration procedures (ie, complexity and time-consuming), we used a standardized and computer-assisted implementation of the TTO method.\textsuperscript{10}

This study has some limitations that must be mentioned. First, we did not estimate patients’ preferences associated with every single HPV-induced disease. Some diseases such as penis cancer, recurrent respiratory papillomatosis, and vaginal cancer were not considered due to their low annual incidence rates,\textsuperscript{44} and it would have been difficult to find an appropriate number of eligible patients.

With regard to vulvar cancer, the proportion attributable to HPV is relatively modest in Italy, corresponding to 41.1\% (95\% CI: 28.1\%–55.0\%).\textsuperscript{3,44} However, utilities assessed in cervical cancer cases can be used as a proxy of utility lost for both vulvar and vaginal cancer. Second, the sample size of some conditions like anal cancer (and to a lesser degree ASC-US) was limited, and this may have to some extent contributed to overestimation of the utilities lost. Nonetheless, anal cancer has a very low incidence rate compared with other HPV-induced pathologies, and the number of respondent patients was weighted to reflect the relative distribution of patients per each condition according to the incidence curves derived from data collected by the World Health Organization in Italy.\textsuperscript{44} Although a higher number of patients with anal cancer could be found, the time required to achieve this figure would have exceeded the study timeframe and biased utility elicitation due to an impairment effect of recollection (patients may have partially forgot, escaped the memory, or relived the distressing event).\textsuperscript{45}

Third, the group of cases revealed some difference compared with the control subject. Indeed, patients with anal cancer and HNSCC had a lower EQ-5D score at the time of the interview. Nonetheless, only in the anal cancer group was the difference statistically significant compared with the mean (SD) assessed, reporting values corresponding to 0.6 (0.3) ($P = 0.001$) and 0.8 (0.2) ($P = 0.095$) in anal cancer and HNSCC, respectively. The overall lower value of EQ-5D in patients with anal cancer was also a result of negative scores reported in 4 of them (mean [SD] negative score of $-0.13 \pm 0.16$). Moreover, the mean (SD) age of patients with the same oncological diseases (anal cancer and HNSCC) was significantly older than that of subjects in the control group (68.6 [7.0] years vs 60.6 [9.5] years, $P = 0.019$ and 65.0 [9.0] vs 54.7 [13.3] years, $P = 0.001$ for anal cancer and HNSCC, respectively). Although differences observed between patients and control subjects, utility relied on the HPV-induced disease essentially. Age played a partial role, whereas the EQ-5D index score did not affect the value of utility elicited as also shown by the correlation analysis reported in a previously published study.\textsuperscript{10} Finally, it has to be mentioned that enrollment of control subjects was not based on a specific randomization procedure. However, they were enrolled on the basis of a consecutive order to minimize selection bias; furthermore, because we knew the total sample size a priori (matched for sex and disease proportion), the random allocation rule would have theoretically minimized a possible systematic bias, which could have altered the robustness of results.

**CONCLUSIONS**

The HPV vaccination can be considered the epitome of a perfectly proportioned health intervention, and immunization programs currently implemented in Italy are based on policy decisions informed with cost utility indications previously collected. The risk factors and utilities elicited in this study are valuable evidence that can be used as part of the economic assessment of other HPV vaccination strategies, including an immunization program for preadolescents of both sexes.

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The HPV Italian Collaborative Study group: A. Crocetti, A. De Cesare, M. Miccini, and P. Sapienza, Department of Surgery Pietro Valdoni, University of Rome La Sapienza, Rome, Italy; M. C. Da Mosto, P. Boscolo-Rizzo, M. Stellin, and R. Fuson, Regional Center for Head and Neck Cancer, University of Padua, Treviso Regional Hospital, Treviso, Italy; G. Palamara and M. Giuliani, Infectious Dermatology,
San Gallicano Dermatological Institute (IRCCS), Rome, Italy; M. Picardo, Laboratory of Cutaneous Pathophysiology, San Gallicano Dermatological Institute (IRCCS), Rome, Italy; D. Panatto, T. Sasso, and R. Gasparini, Department of Health Sciences, University of Genoa, Italy; P. Cristoforoni and E. Di Capua, Oncologic Gynecology, National Institute for Cancer Research, Genoa, Italy; R. De Vincenzo, C. Ricci, C. Conte, G. Scambia, Department of Obstetrics and Gynecology, Catholic University of the Sacred Heart Rome, Italy; G. Ferrandina, Department of Obstetrics and Gynecology, Catholic University of the Sacred Heart, Rome, and Gynecologic Oncology Unit, Catholic University of the Sacred Heart, Campobasso, Italy.

CONFLICTS OF INTEREST
The authors have indicated that they have no other conflicts of interest regarding the content of this article.

SUPPLEMENTAL MATERIAL
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Address correspondence to: Andrea Marcellusi, MSc, Centre for Eco- nomic and International Study, Economic Evaluation and HTA, Faculty of Economics, University of Rome “Tor Vergata,” Via Columbia 2, 00133 Rome, Italy. E-mail: andrea.marcellusi@uniroma2.it
OVERVIEW OF THE STUDY

This study was designed to assess utilities with a computer-assisted administration of a standardized time trade-off (TTO) procedure in health states affected by human papillomavirus (HPV)-induced pathologies in both sexes in Italy. On the basis of published guidelines to design and produce health-state utility instrumentations, a specific algorithm committed to the computer-guided administration of a questionnaire for the standardized elicitation of utilities in patients with HPV-induced diseases was developed. The logic underlying the relationship of the algorithm can be formulated as follows:

\[
\text{Utility} = \frac{\text{ex}^i}{\text{ex}^i + \text{yn}^i} \quad \text{for } i = 2 \text{ to } 5
\]

where \( \text{ex} \) is the life expectancy, \( y \) indicates a proportion of the life expectancy, and \( i \) indexes the specific question number.

The TTO method is based on trade-offs, and respondents have to trade off survival time and health states. The utility value is measured by finding the point at which the respondent cannot choose between 2 scenarios. In case of short-term and chronic diseases, the choice is generally between the illness for a period of time and perfect health for a shorter time, both followed by death. In contrast, in short-term illnesses, the choice is between the illness for a period of time and a worse health state for a shorter time, both followed by the same specified outcome.

In the conventional implementation, the first alternative offers a suboptimal steady health state with a given duration. A better health status (commonly, perfect health) of shorter duration is offered as the competing alternative, which is then followed by an outcome (ie, death). The point of indifference is reached by varying the duration spent in perfect health. Therefore, on the basis of TTO procedure, utilities are cardinal figures representing the strength of patients’ preferences for particular outcomes.

Another aim of the study was the evaluation of risk factors influencing the viral transmission and the development of HPV-induced diseases. Cigarette smoking, a low education level, young age at starting to be sexual active, and an increased number of partners are generally observed to contribute to a higher risk of acquiring an HPV infection. On the basis of published data, it was noted that the rate of individuals at high risk of acquiring an HPV infection can largely vary from 20% to 40%, and different values of risk are observed and men and women.
The age at the start of sexual activity and the number of sexual partners (in other words, the level of sexual activity) can provide an estimation of both partner acquisition rates and the risk of HPV transmission per partnership. On the basis of risk factor data collected in a given population, it is possible to calculate the HPV transmission probabilities and the sexual mixing matrices to determine HPV infection probability, which depends on age, sex, and sexual interactions between the sexes.

The computer-assisted administration of all questionnaires (TTO, European Quality of Life, 5 Dimensions [EQ-5D], and risk factor assessment) was preceded by an oral explanation of the nature and scope of the study to avoid any misconception by respondents and potential mistakes. Clinical centers were provided with written guidelines to complete the administration of all questionnaires, ensuring that the utility elicitation of HPV-induced diseases was performed as an entirely standardized procedure. To limit the confounding effect of differing methods of administration of questionnaires among clinical centers, interviewers underwent 2 training sessions.

Pathological conditions of interest were presented using a very simply written description. The description of disease states is given below.

**ATYPICAL SQUAMOUS CELLS OF UNDETERMINED SIGNIFICANCE**

Women aged between 25 and 64 years of age are recommended to undergo screening for cervical cancer (Pap test), which is intended to identify minor changes before any problems develop. An abnormal result is not unusual (~1 in 20 women can have a test result showing some abnormality), and atypical squamous cells of undetermined significance (ASC-US) is the most common abnormal Pap test result. Changes in the cells of the cervix are not cancer, are generally asymptomatic, and in the majority of cases, these changes return to normal by themselves. When an ASC-US is reported, gynecologists usually ask patients to return for a repeat screening test in 6 months. If the repeat test result is normal, patients will then go back to receiving routine screening as before. If the repeat test still shows borderline changes or mild cervical intraepithelial neoplasia (CIN1), patients are referred to a clinic for a further examination called colposcopy (a simple examination that allows the gynecologist to decide whether treatment is needed).

Adverse psychological consequences primarily associated with the anxiety about cancer development and the sexually transmitted nature of the virus can be observed. Patients can also be worried about the effect on their sexual relationship and future fertility.

**CERVICAL INTRAEPITHELIAL NEOPLASIA 1**

CIN, also known as cervical dysplasia, is an asymptomatic condition in which small changes can be found in the cells on the cervix (the neck of the womb). Cervical screening (Pap test) is the test designed to pick up minor changes before any problems develop. These changes in the cells of the cervix are not cancer, and return to normal by themselves in the majority of cases (up to 90%). Therefore, commonly there are no consequences for patients. When CIN1 is diagnosed, gynecologists usually ask patients to return for a repeat screening test in 6 months. If the repeat test result is normal, patients will then go back to routine screening as before. If the repeat test result still shows CIN1, patients are referred to a clinic for a further examination called colposcopy (a simple examination that allows the gynecologist to decide whether treatment is needed).

Adverse psychological consequences primarily associated with the anxiety about cancer development and the sexually transmitted nature of the virus can be observed. Furthermore, patients can be worried about the effect on their sexual relationship, future fertility, and disclosing their result to others.

**CERVICAL INTRAEPITHELIAL NEOPLASIA 2–3**

Moderate to severe CIN (CIN 2–3) is asymptomatic lesions (irregularities or changes) found in the cells of the cervix. They are diagnosed with a Pap test (cervical cancer screening procedure) and can be observed with an instrumental examination, colposcopy (a simple examination that allows the gynecologist to decide whether a treatment is needed). This condition generally tends to worsen, and a spontaneous regression is very rare. Treatment is based on the removal of the affected tissue with a loop diathermy (ordinary surgical procedure).

After the administration of a local anesthetic, the gynecologist removes the portion of cervical tissue involved with a hot wire loop. The procedure is painless; however, a sensation of warmth can be produced. The operation does not affect future fertility. This condition may be associated with the
psychological fear of the development of malignant cancer. In addition, a major concern is the risk of possible infection transmitted to the partner and outcomes of future pregnancies.

CERVICAL CANCER
Invasive cervical cancer is a lesion that commonly bleeds after contact (especially during sexual intercourse) or even spontaneously. When the cancer size is extended, it can cause pain in the lower abdomen and other symptoms involving the bladder and rectum. In advanced stages, the bleeding is persistent and difficult to control; radiating back pain (similar to renal colic) is usual and caused by the tumor mass pushing on nearby organs.

The treatment is primarily surgery, which results in the removal of entire uterus. Depending on the tumor size, the surgical intervention can be performed in 2 ways. In the case of very small tumors, the uterus and ovaries are removed (in young women, one ovary may be spared whenever possible), no functional disorders occur, and the woman can have normal sexual intercourse. With larger tumors, surgery is more radical and involves the removal of lymph nodes and tissues surrounding the cervix, including vessels and nerves of bladder and rectum. The postoperative course is longer with an impairment function of bladder and rectum (difficult urination, urinary retention, difficult defecation). Sexual intercourse is more difficult and/or painful. Depression can occur in these patients and their partners, and family relationships can be affected.

ANAL CANCER
Anal cancer is an uncommon disease in which abnormal (malignant) cells are found in the anus. Females are mainly affected, with a ratio of women to men of 3:1 or 4:1. Anal cancer is generally associated with a long history of symptoms/signs such as pain or pressure in the area around the anus, a change in bowel habits, and bleeding, itching, or discharge from the anus. Many of these symptoms may be caused by other benign conditions that can often coexist with the cancer, delaying the proper diagnosis. It usually presents as an ulcer with typical rolled edges or as an excrescence (proliferation of tissue), more or less pigmented. Patients undergo a medical or surgical procedure depending on the severity of the disease (location, size, extent and spread of the tumor).

Surgical treatment consists of a resection (and whenever possible a reconstruction) of the lower part of the colon (the terminal part of the large intestine). Deterioration of anorectal function can occur, and a colostomy is performed (the surgeons sew the end of the intestine to an opening made in the surface of the abdomen, called a stoma, so the bodily waste can be collected in a disposable bag outside the body).

Typically, medical treatment is by radical radiotherapy, which is associated with necrosis (cell death) of the perianal and perineal tissues (area located between the external genitals and the anus). Alternatively, radiochemotherapy is given, depending on the type and stage of the cancer being treated. Anal cancer is frequently associated with significant psychological and social consequences such as embarrassment, anxiety, loss of confidence, and trust in the partner and family members.

HEAD AND NECK CANCER
This cancer is not a single entity, but rather a group including many different types of disease, most of which are moderately common and some are rare. Indeed, cancer affecting the head and neck is relatively frequent in Italy (accounting for ~10,000 to 12,000 cases per year). Males are preferentially affected with a ratio of men to women of 4:1. The majority of these cancers arise from the surface layers of the upper aerodigestive tract: oral cavity (the mouth, lip, and tongue), pharynx (the upper part of the throat and respiratory system), nasopharynx, and larynx (the voice box).

The most common symptom of oral cavity cancer is a persistent sore or lump on the lip or in the mouth, but there may also be pain and/or a lump in the neck. Other symptoms are a white or red patch on the gums, tongue, or lining of the mouth; and pain or numbness and sometimes unusual bleeding (from mouth or nose). Other symptoms may include pain or problems with swallowing (dysphagia), persistent sore throat or a persistent cough, and otalgia (earache). Some patients have difficulty speaking, nasal obstruction, deafness, and postnasal discharge. Only a minority of patients with symptoms have cancer, however. Generally head and neck cancers are triggered by alcohol and tobacco, and high alcohol consumption and smoking have synergistic (ie, multiplicative) effects on the risk of head and neck cancer.
Most head and neck cancers are treated with surgery or radiotherapy or a combination of both. Chemotherapy alone is rarely appropriate for these forms of cancer, but chemotherapeutic agents are sometimes used to enhance the effects of radiotherapy. Plastic or reconstructive surgery and specialized dentistry are often needed. Patients need considerable help and support with nutrition and communication, both during and after primary treatment. The disease and the psychological burden of head and neck cancer are significant. Patients require intensive multimodality treatments and prolonged rehabilitation with long-term support to achieve an adequate recovery. The disease significantly affects eating, drinking, voice, swallowing, smelling, breathing, appearance, social interaction, and work capabilities. Depression is relatively common in these patients, and family or social relationships can be affected.

ANOGENITAL WARTS
Anogenital warts are lesions caused by a virus (HPV) transmitted mainly through sexual intercourse. The warts can appear in any part of the anogenital area. They appear as small pinkish and fleshy lesions. They are normally asymptomatic, but can sometimes cause itching.

Genital warts located on the skin of the genital area and perineum (area located between the external genitals and the anus) can be treated by applying some creams or solutions; in some cases, this may cause a burning sensation and redness. If local drugs are not effective, anogenital warts can be surgically removed with the patient under a local or general anesthesia (if they are very numerous). Warts located on mucosae (ie, vagina or vulva) cannot be treated with creams or solutions; patients undergo surgical removal. After treatment, the anogenital warts may recur. In these cases, surgical removal is needed. Anogenital warts are generally associated with anxiety, with a dirty feeling, and possible rejection by sexual partner.

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