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Quality of life valuations of HPV-associated cancer health states by the general population

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ABSTRACT

Objectives To obtain health-related quality of life valuations (ie, utilities) for human papillomavirus (HPV)-related cancer health states of vulval, vaginal, penile, anal and oropharyngeal cancers for use in modelling cost-effectiveness of prophylactic HPV vaccination.

Methods Written case descriptions of each HPV-associated cancer describing the 'average' patient surviving after the initial cancer diagnosis and treatment were developed in consultation with oncology clinicians. A general overview, standard gamble questionnaire for each health state and a quiz was conducted in 120 participants recruited from the general population.

Results In the included population sample (n=99), the average age was 43 years (range = 18–70 years) with 54% men, 44% never married/43% married, 76% education beyond year 12 and 39% employed full-time. The utility values for the five health states were 0.57 (95% CI 0.52 to 0.62) for anal cancer, 0.58 (0.53 to 0.63) for oropharyngeal cancer, 0.59 (0.54 to 0.64) for vaginal cancer, 0.65 (0.60 to 0.70) for vulval cancer and 0.79 (0.74 to 0.84) for penile cancer. Participants demonstrated a very good understanding of the symptoms, diagnosis and treatment of these cancers with a mean score of 9 (SD=1.1) on a 10-item quiz.

Conclusions This study provides utility estimates for the specific HPV-related cancers of vulval, vaginal, penile, anal and oropharyngeal cancers valued by a general population sample using standard gamble. The results demonstrate considerable quality of life impact associated with surviving these cancers that will be important to incorporate into modelling cost-effectiveness of prophylactic HPV vaccination in different populations.

INTRODUCTION

Human papillomavirus (HPV) is one of the most common sexually transmitted infections, with more than 50% sexually active persons becoming infected with one or more types.[1] In most cases, infection clears without sequelae but high-risk types are now accepted as a necessary cause of all cervical cancers (predominantly HPV types 16, 18) and low-risk types cause genital warts (predominantly HPV 6, 11) in both genders. With the registration of the quadrivalent (HPV types 16, 18, 6, 11) and bivalent (HPV types 16, 18) vaccines in 2006, many countries have introduced population-level vaccination programmes of young pre-sexually active women with the aim of preventing cervical precancerous lesions/cancer and genital warts. In many countries, including the USA, Europe, Australia and New Zealand, this decision making incorporated an assessment of cost-utility, comparing the incremental costs and benefits in survival and health-related quality of life in vaccinated and unvaccinated populations, with the benefits expressed as quality-adjusted life years.[2]

There is now substantial evidence that the HPV also causes a significant proportion of cancers of the vulva, vagina, penis, anus and oral cavity and oropharynx and that prophylactic vaccination prevents high-grade HPV 16, 18 precancerous anogenital lesions in women and men.[3] Modelling of the cost-utility of introducing or extending HPV vaccination programmes to these populations requires examination of the incremental costs and quality-adjusted life years of vaccination programmes on the full extent of HPV disease. Although health state valuations appropriate for modelled economic evaluations have been undertaken for cervical HPV disease including cancer and precancerous lesions,[4 5] and for genital warts,[6] there is a paucity of information on health state valuations for the other HPV cancer states.[7] Studies that have assigned utility values to non-cervical HPV-related cancers use a generic 'female genital cancer' as a proxy for all the cancer health states.[7] In this study, we obtain health-related quality of life valuations for five health states representative of the average patient surviving with anal, oropharyngeal, penile, vulval and vaginal cancers.

METHODS

Health states

We sought to identify health states related to each cancer that were of significant duration and frequency to be useful for modelling prevention strategies for HPV-associated cancers. We focused on the longer term health state that would apply to the majority of patients for the period starting after the initial treatment effects had resolved out to 5 years after diagnosis. After an initial literature review and discussion with clinical experts, we concluded that the morbidity of the longer term health state is related mainly to the treatment modality, which is itself usually determined by the location and stage of the cancer at diagnosis. The process for developing the health states therefore involved the following steps (1) the most common stage(s) of each of the HPV-associated cancers on diagnosis were identified from the literature, (2) the recommended treatment for the relevant stages(s) of each cancer was identified and confirmed from

published studies and (3) the more common long-term consequences (applying to ≥50% patients) in patients surviving the initial treatment phase were described based on the literature and subsequent refinement by clinical experts involved in managing each cancer. For each of the HPV-associated cancers, we were able to identify a single health state to describe the 'typical' patient surviving after the initial cancer diagnosis and treatment.

As the initial treatment leads to the long-term health state, a brief description of the treatment was included as background but specified as not for valuation.

A presentation on HPV and its role in the development of cancer, the risk factors for HPV-associated cancers and an overview of each cancer including initial symptoms, staging, treatment and long-term survival was developed to introduce the topic in the health state valuation sessions.

Study population

Subjects from the general population were recruited through an external market research company and paid an honorarium of $70. The enrolment criteria included age 18 years or older and fluency in English sufficient to complete a reasonably complicated questionnaire. Participants were also to comprise a mix of currently employed and unemployed. Exclusion criteria included participation in a valuation study in the previous 6 months, employment in a health-related occupation or pharmaceutical company and current participation in a clinical trial.

Health state valuation

Participants attended an hour long session in groups of 30. The presentation was undertaken by a trained presenter, and the study questionnaire was completed by the participants in small groups. Each group had a trained group leader who was available to answer questions throughout. The questionnaire comprised five sections including demographics, experience of HPV-related cancers, understanding of HPV-related cancers in a quiz format, a practice scenario and utility valuation of the five health states using a direct standard gamble methodology.

The presentation and questionnaire were initially trialled in 30 participants. As participants handled the complexity of the questionnaire well and demonstrated good understanding of the background information, no changes were made. Participants also reported that the background treatment information (not for valuation) was important for valuing the long-term health state; this information was included in all subsequent testing. The study was completed by a further 90 participants. The combined results are presented.

For each health state, participants were told to imagine they had been diagnosed and treated for anal, oropharyngeal, vaginal, vulvar and penile cancers. They were asked to consider how being in that health state would impact on their ability to participate in their usual activities such as work, social activities and caring roles; their independence; whether they would still be able to do things without the help of others; their social interactions and how they would feel about these changes. For the standard gamble valuation, participants were asked to choose between living in the health state for the rest of their life or taking a gamble. Probabilities for the gamble were presented in a ping pong fashion starting at 100% chance of perfect health followed by 100% chance of death, then 90% chance of perfect health/10% chance of death followed by 10% chance of perfect health/90% chance of death (see online technical appendix for full questionnaire). The utility score was the gamble probability at the point where the participant was indifferent to taking the gamble or living in the health state. Each participant was presented with the five health states in a random order to prevent cognitive overload at the same stage of the questionnaire and to prevent the possibility of an order effect.

Statistical analysis

The demographic data, experience with the health states data and quiz scores are analysed using descriptive statistics. The standard gamble results for each health state are reported as the utility score (mean, 95% CI; median, IQR). Responses from irrational traders (where answers to two or more scenarios were inconsistent—eg, chose a 40% risk of death but later would not accept a 10% risk of death—or illogical—eg, chose to live in the disease state rather than 100% chance of perfect health) and non-traders (identical responses across all health states) were excluded.

The impact of demographic characteristics on the utility values were assessed using the Kruskal–Wallis test for categorical variables and the Mann–Whitney U test for dichotomous variables.

RESULTS

Cancer health states

For each HPV-associated cancer, a single health state was developed that applied to the majority of patients diagnosed as having the relevant cancer (table 1). Long-term health consequences were related to the most common treatments for the relevant stages. Less common debilitating and disfiguring side effects of treatment were omitted. The full health state descriptions are presented in the online technical appendix.

Utility valuation

Completed questionnaires were received from 118 participants. Of these, five were excluded because of irrational trading and 14 were excluded because of non-trading. Demographic information for participants included in the analysis is summarised in table 2. The average age was 43 years (range 18–70 years; SD 16). They represented a broad cross section of age, education level, employment status and income and were evenly matched by gender. No participants had been diagnosed as having any of the HPV-associated cancers but several had experience with a family member (2%) or a friend or acquaintance (16%) diagnosed as having one of the cancers.

Results from the 10-question true/false style quiz demonstrated that participants had a very good understanding of the symptoms, diagnosis and treatment of these cancers following the information presented at the beginning of the session with a mean score of 9.14 (SD=1.06; median 9; range 5–10). Participants had no appreciable difficulties with the standard gamble questionnaire and all finished the task ahead of the scheduled time.

The utility values for the five health states are presented in table 3. The estimates were very similar for the oropharyngeal, anal, vulval and vaginal cancer health states. The utility value for the penile cancer health state was significantly higher than for the other cancer health states.

None of the demographic variables, including gender, had any influence on the health state utility score (data not shown).

DISCUSSION

This study is the first to provide estimates of health state preferences for the specific HPV-related cancers of the vulval,

Table 1 Cancer stages at diagnosis, primary treatment modalities and corresponding long-term health state descriptions*

Cancer	Stage at diagnosis and primary treatment	Health state descriptions: Cancer stage and treatment	Health state descriptions: Long-term health state in ≥50% patients and patient follow-up for 5 years from primary treatment	Not included
Anal	90% Cases stages I—III.[8] Chemoradiation is the only primary treatment for anal cancer.[9]	Anal cancer stages I—III. Treated with chemoradiation.	Diarrhoea, tiredness and nausea; impact on usual activities; decreased sexual functioning and enjoyment. Review 2—3 times per year (digital rectal examination and anoscopy).	Stage IV. Patients with abdominoperitoneal resection and stoma. Patients treated with surgical excision.
Oropharyngeal	90% Cancers present as stage II/III.[10] Most patients have surgery followed by radiotherapy.[11] †	Oropharyngeal cancer stages II—III. Treated with neck dissection and chemotherapy and/or radiotherapy and/or surgery.	Occasional pain; difficulty chewing and swallowing affecting diet/eating; dry throat affecting speech; reduced neck mobility; tiredness; impact on usual activities. Review 2—3 times per year.	Stage I and stage IV. Disfiguring effects of surgery. Patients who require feeding tubes.
Penile	62% Cases local[12]; 70% penile-preserving treatment is laser therapy.[13]	Penile cancer stage I. Treated with laser therapy only—no disfigurement.	Recovered well and satisfied with surgery; no impairment of sexual functioning/satisfaction. Frequent self-inspection and review 2—4 times per year.	Stages II—IV. Patients requiring partial or complete penectomy.
Vulval	~66% Vulval cancers are localised—predominantly stages I—II.[14] Treatment is radical wide excision where possible + lymph node dissection.[14]	Vulval cancer stage I. Treated with radical wide excision and lymph node dissection.	Vigilance because of risk of lymphoedema; clitoris intact and can still reach orgasm but reduced sexual satisfaction because of disfigurement. Review 2—3 times per year.	Stages II—IV. Patients with radical vulvectomy and/or compromised bowel or urinary function.
Vaginal	~50% cases localised—predominantly stage 1.[15] Radiotherapy + lymph node dissection is standard treatment.[16]	Vaginal cancer stage I. Treated with chemoradiation and lymph node dissection.	Vigilance because of risk of lymphoedema; menopause; sexual problems related to vaginal dryness and scar tissue; bowel and bladder irritation. Review 2—3 times per year (vaginal exam).	Stages II—IV.

*Full details in online technical appendix.
†Data on 548 patients with stage I—IV oropharyngeal squamous cell carcinoma from 10 Australian centres: 55.8% surgery followed by postoperative radiotherapy, 18.9% chemoradiation, 10.8% surgery alone and 14% radiotherapy alone (A Hong, personal communication).

vaginal, penile, anal and oropharyngeal. The study focused on valuing the long-term health state of the average patient surviving through to 5 years after diagnosis and treatment which is the most appropriate state for modelling cost-effectiveness of prophylactic vaccination. Because of the long interval between vaccination and disease, modelling will not be sensitive to short-term health states.

The health states reflect current treatment practices of each of the HPV-related cancers taking into account the usual stage of diagnosis for the particular cancer and recommended and actual treatment practices. The health states were derived from the literature and reviewed and refined by clinical experts involved in managing each cancer.

The utility valuations for the anogenital cancers other than penile cancer were similar, varying from 0.57 for anal cancer, 0.59 for vaginal cancer and 0.64 for vulval cancer with overlapping CIs. Symptoms varied for each health state but included one or more of compromised sexual functioning, bowel and bladder irritation, loss of fertility and reduced general health.

Anal cancer is now primarily treated with radiotherapy and the number of patients undergoing abdominoperitoneal resection is very low.[9] Nonetheless, radiotherapy results in long-term impacts on bowel and bladder function, sexual function and physical and social functioning.[17] Although not directly comparable, the utility estimate for anal cancer in this study is within the range of estimates for colorectal cancer without ostomy using a similar methodology.[18]

Table 2 Summarised demographic information for included participants

Demographic variable	Number of participants	Percentage of participants*
Gender		
Male	53	54
Female	46	46
Marital status		
Never married	44	44
Widowed/divorced/separated	12	12
Married/de facto	43	43
Highest level of education attained		
Tertiary education	76	77
Secondary education	21	21
Primary education	2	2
Employment		
Full time	39	39
Part time (<35 h/week)	28	28
Student	13	13
Retired	9	9
Other	10	11
Income		
$1600 or more per week	28	28
$800—1599	28	28
$1—799	40	40
Nil income	3	3

*Due to rounding, percentages may not total 100%.

Table 3 Utility scores for the five health states

Scenario	N	Mean (95% CI)	Median (IQR)
Anal cancer	95	0.57 (0.52 to 0.62)	0.65 (0.45—0.75)
Oropharyngeal cancer	99	0.58 (0.53 to 0.63)	0.65 (0.45—0.75)
Vaginal cancer	98	0.59 (0.54 to 0.64)	0.65 (0.45—0.75)
Vulvar cancer	98	0.65 (0.60 to 0.70)	0.65 (0.45—0.85)
Penile cancer	97	0.79 (0.74 to 0.84)	0.85 (0.65—1.0)

The treatment of vaginal cancer is very similar to that of cervical cancer involving radiotherapy and chemotherapy. Although there has been very little published on the quality of life impacts of vaginal cancer, the long-term side effects are similar to those of cervical cancer and include early menopause, a narrower, drier and less stretchy vagina, risk of lymphoedema and impact on bladder and bowel function. The utility estimate for vaginal cancer from this study are within the range of estimates reported for cervical cancer. Howard *et al*[4] reported a standard gamble-derived utility of 0.46 for cervical cancer in an Australian population. Myers *et al*[5] reported time trade-off-derived utility of 0.76 and 0.67 for stages I and II–IV cervical cancer, respectively.

Vulval cancer is relatively rare, and there are few studies exploring the impact on quality of life. It differs from the other female gynaecological cancers because the primary treatment modality (surgical excision) directly affects body image and sexuality. Treatment of vulval cancer has been reported to have a major negative impact on sexual functioning and body image and on emotional, physical and social functioning.[19 20]

The health state valuation for penile cancer (0.75) was higher than the other cancers. This corresponds with this health state being the mildest, describing stage I penile cancer treated with laser therapy and with no long-term consequences on general health, sexual functioning or sexuality. This reflects that approximately 60% penile cancer patients receive penile-preserving treatments.[13] It does not capture the health state of patients undergoing partial or complete penectomy. These more mutilating interventions have been reported to have a major impact on sexual function and sexual satisfaction.[21]

The health state valuation for oropharyngeal cancer was similar to that of anal and vaginal cancers. Head and neck cancer has been described as more emotionally traumatic than any other form of cancer.[22] The treatments are debilitating and disfiguring, and patients often go on to live with chronic functional impairment in a range of areas including speech and swallowing as well as effects on oral health and nutrition.[22–25] These changes are reflected in health-related quality of life where there is an immediate decrease on treatment that lasts for months.[22] There is also evidence of long-term decrements in health-related quality of life[25] although these studies are complicated by survivorship effects and a lack of sensitivity of the instruments.[22] In this study, the general population assessment of the utility of the oropharyngeal cancer survivor is similar to that of the female genital cancers.

A strength of this study is that it used the preferences of the general population. There is a general consensus in the literature, including a recommendation from the US Panel on Cost-effectiveness in Health and Medicine, that where valuations are for use in decision making around resource allocation, preferences should be based on the general population in their role as taxpayers rather than caregivers or patients.[26] This is also particularly appropriate for prophylactic vaccine programmes where the target population is the well population.

This study also used the standard gamble to value health states. Compared with rating scales or time trade-off, the standard gamble has a solid foundation in the economic theory underlying the use of utility as a measure for quality of life in cost-utility analysis.[27] Although standard gamble can be difficult for participants to understand, the study was well received with participants handling the complexity of the questionnaire well. The quiz scores show a good understanding of the presentation and the information provided. Few participants were removed from the analysis for either unusable answers or for irrational responses.

Key messages

- Estimates of the impact on quality of life (utilities) of HPV-related cancers are needed for economic evaluations comparing HPV vaccination strategies in men and women.
- This study determined utility valuations of life post-treatment for the average patient with cancer of the anus, vulva, vagina, penis and oropharynx.
- All cancers had a significant impact with utility values between 0.57 and 0.79 compared with a perfect health utility of 1.

There are several limitations of this study. The health state scenarios were developed from the literature and from oncology experts in each cancer, not directly from patient interviews. However, both the literature and the expert opinion are derived from studies of patient-reported outcomes and reflect the experience of patients. Also, the approach taken avoids the difficulties that can arise from evaluations of health state preferences of cancer survivors. Dropouts (death or loss to follow-up), adaptation and response shift are known to influence quality of life estimates in cancer survivors.[22 28] These effects may lead to a bias against preventive therapies. Another limitation is the restriction to a single average health state for each cancer. The health state descriptions represented the most common stages and treatment pathways for cancer survivors and as such contribute most to modelling the impact of preventive measures. Although less common side effects of treatment were omitted, either more severe and debilitating or milder side effects, these would probably not affect model conclusions. Similarly, the short duration health states related to acute treatment phases were not included. Finally, respondents in the study were Australians and hence may not be generalisable to populations from other countries. Utility values have been shown to vary across countries.[29 30] Relative to UK respondents, using standard gamble, Australians reported a lower impact of less severe clinical response states in advanced melanoma and a greater impact of the more severe response states, although the differences were relatively small.[29] In modelling studies, this issue could be addressed with sensitivity analyses.

CONCLUSIONS

The results of this study represent a significant addition to the literature of HPV-related cancer utility values. It is the first study to provide estimates of health state preferences for the specific HPV-related cancers of the vulval, vaginal, penile anal and oropharyngeal. The scenarios focused on the long-term health state of the average patient from resolution of the acute effects of treatment out to 5 years after diagnosis and treatment and were valued by the general population. These valuations can be incorporated into modelling cost-effectiveness of prophylactic HPV vaccination in different populations.

Contributors ELC was involved in the study design, the interpretation of data and the writing of the report. JA was involved in the study design, the interpretation of data, the writing of the report and also conducted the survey and the statistical analysis. KCP, WJL, GLR and GW were involved in the development of the health state descriptions and background information for the survey and reviewed the manuscript before submission. All authors were involved in the decision to submit the manuscript for publication. The publication of the study results was not contingent on the approval of the sponsor company. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Competing interests ELC is an employee of CSL Biotherapies and also owns shares in CSL Limited. JA is an employee of Pretium, a consultancy engaged by CSL Biotherapies to undertake the study. GW has been involved in the research studies for Gardasil and has acted as a consultant and received honoraria for speaking from Merck and CSL Biotherapies. He received no financial compensation for this study. WJL has acted as a consultant for CSL Biotherapies. He received no financial compensation for this study.

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