chapter 7

Systematic review and evidence synthesis of non-cervical human papillomavirus-related disease health systems costs and quality of life estimates

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ABSTRACT

Background

Many economic evaluations of human papillomavirus (HPV) vaccination consider multiple disease outcomes in addition to cervical cancer, including anogenital warts, recurrent respiratory papillomatosis, and anal, oropharyngeal, penile, vulvar and vaginal cancers. However, these evaluations mostly derive cost and utility parameters for these outcomes from single studies or informal rapid literature reviews.

Methods

We conducted a systematic review of articles up to June 2016 to identify costs and utility estimates admissible for an economic evaluation from a single-payer health care provider’s perspective. Meta-analysis was performed for studies that used same utility elicitation tools for similar diseases. Costs were adjusted to 2016/17 US dollars.

Results

Sixty one papers (35 costs; 24 utilities; 2 costs and utilities) were selected from 10,742 initial records. Cost per case ranges were US$124–US$883 (anogenital warts), US$6,912–US$52,579 (head and neck cancers), US$12,936–US$51,571 (anal cancer), US$17,524–34,258 (vaginal cancer), US$14,686–28,502 (vulvar cancer), and US$9,975–27,629 (penile cancer). Total cost for 14 adult RRP patients was US$137,601 (1 paper).

Utility per warts episode ranged from 0.651–1 (12 papers, various utility elicitation methods), with pooled mean EQ-SD and EQ-VAS of 0.86 (95% CI 0.85–0.87) and 0.74 (95% CI 0.74–0.75), respectively. Fifteen papers reported utilities in head and neck cancers, with range across studies of 0.29 to 0.94. Mean utility reported ranged from 0.5 to 0.65 (anal cancer; range across studies), 0.59 (0.54–0.64) (vaginal cancer), 0.65 (0.60–0.70) (vulvar cancer), and 0.79 (0.74–0.84) (penile cancer).

Conclusions

Differences in values reported from each paper reflect variations in cancer site, disease stages, study population, treatment modality/setting, and utility elicitation methods used. As patient management changes over time, corresponding effects on both costs and utility need to be considered to ensure health economic assumptions are up-to-date and closely reflect the case-mix of patients.
KEY MESSAGES

1. This systematic review identified 61 papers (35 costs; 24 utilities; 2 costs and utilities) reporting economic parameters for HPV-related non-cervical diseases.

2. Differences in cost and utility estimates arise from study population, disease stage, cancer type, treatment strategies and country perspective taken.

3. Authors of economic evaluations need to consider economic parameter assumptions to ensure they accurately reflect the timing and perspective of the population considered.

INTRODUCTION

Almost a hundred economic evaluations of human papillomavirus (HPV) vaccination had been published by June 2016[1–3]. Initially most of these analyses focused on the health and economic benefits of HPV vaccination in preventing cervical cancer and its precursors, since these were the only cancer outcomes listed in the initial licensure indication for the first two licensed HPV vaccines (the bivalent vaccine Cervarix and the quadrivalent vaccine Gardasil) [4,5]. More recently, evidence has emerged of other diseases that are potentially HPV vaccine-preventable, including recurrent respiratory papillomatoses (RRP) and non-cervical cancers such as vulvar, vaginal, anal, penile, and head and neck cancers[6,7]. Although attributable risk of HPV in each of these non-cervical cancers varies[7], these outcomes are important to incorporate into cost of illness studies of HPV-related diseases and economic evaluation of HPV vaccination for two reasons: (i) they give a comprehensive picture of the (direct and indirect) benefits of introducing HPV vaccination, and (ii) they are the key drivers of comparative evaluations of different strategies for vaccination, such as gender-neutral compared with female-only vaccination and the choice between nonavalent, quadrivalent and bivalent vaccination.

Economic evaluations require input parameters in terms of the costs and disutilities (measured in units such as quality adjusted life years or QALYs) for different disease outcomes. To our knowledge, most published economic evaluations to date have relied on data from the authors’ own knowledge or from informal rapid reviews of the literature. Additionally, there exist a number of systematic reviews (without quantitative evidence synthesis) conducted before 2013 covering quality of life for specific diseases such as anogenital warts[8] and head and neck cancers[8–11] but none known of in more recent years covering a wider range of non-cervical HPV-related diseases on both costs and utilities. This gap in the literature may have led to bias in published economic evaluations because they may have failed to consider the entirety of the literature in their parameter estimates.

To address this shortcoming, we have conducted a systematic review to compile and summarise costs and quality of life (utility) estimates relevant to HPV-related diseases apart from cervical cancer. We have selected studies that would be admissible for an economic evaluation from the perspective of a single-payer health care provider such as...
the reference case used by the National Institute for Health and Care Excellence (NICE) in the United Kingdom[12].

**METHODS**

**Search Methods**

A search of the databases Ovid Medline, Embase, Cinahl, Scopus and NHS Economic Evaluations Database was performed in June 2016. The search strategy combined terms for HPV-related diseases with health economics terms. HPV-related disease terms included both free text and, where available, subject headings for the following (ICD-10 codes in parentheses): anogenital warts – AGW (A63.0), recurrent respiratory papillomatosis – RRP (D14), cervical cancer (C53), vulvar cancer (C51), vaginal cancer (C52), anal cancer (C21), penile cancer (C60), oropharyngeal cancer (C09 and C10), oral cavity cancer (C01 to C05) – including cancer of the tonsil, laryngeal cancer (C32), and head and neck cancer as a general term included for completeness, recognising that not all head and neck cancers are HPV-attributed. Health economics terms included terms for health utilities/disutilities, costs, quality of life, quality of life instruments (e.g. EQ-5D) and measurement methods such as time-trade off (TTO) and standard gamble (SG). Results were limited to peer-reviewed full research articles in the English language only. Inclusion criteria covered all papers on HPV-related diseases costs and/or disutilities from high-income countries as defined by the Organisation for Economic Cooperation and Development, stated in Appendix 1[13].

Details of the full search strategies used are provided in Appendix 1.

**Result Screening**

Screening was undertaken from September to December 2016. The initial 10,742 articles identified were independently single screened based on titles and abstracts to identify potentially relevant papers (KJO, MC, CP). Allocation decisions at this stage were done leniently, with titles that were uncertain marked for a further round of screening. The 2,785 references selected were entered into another round of single screening (KJO, MC, CP), whereby the results were reconsidered and categorised by type (cost or disutility) and disease area.

Although the objective of this systematic review focused on non-cervical diseases, for completeness, the search strategy and first two stages of single screening included cervical precancer/cancer. Selected titles for cervical precancer/cancer can be made available to interested researchers.

**Selection criteria**

Once titles from the second single screen had been identified, full-text papers were proportionately distributed to each reviewer (KJO, MC, CP) for the final round of paper selection and data extraction. For HPV-related disease management costs we included only papers that took the perspective of a health care provider from a country with universal
healthcare system (either Bismarck-type or Beveridge-type). For utility estimates, any paper that reported on quality of life loss that was reported on a scale from 0 to 1 and measured using either an indirect generic utility elicitation tool such as the EuroQol EQ-5D, or one of the primary/direct methods such as time-trade off or standard gamble were included. These criteria ensured that selected studies would be admissible for economic evaluations in most single-payer health care jurisdictions (eg. the NICE reference case[12]).

Data extraction
A standard form to collect the data was created. Relevant data extracted from the papers are described in Appendix 2.

Data extraction was done by one reviewer and checked by a second reviewer, with discrepancies resolved through discussion.

Data synthesis
A descriptive comparison of data extracted from different papers was made. Costs were adjusted to 2016/17 US dollars using the hospital and community health services inflation indices, with foreign currencies converted to US dollars using historical Bank of England average exchange rates for a reported year[14,15]. Quality of life values were presented separately for utility score and duration of disutility, if reported in a paper.

Meta-analyses using random effect models were conducted for AGW utility estimates for papers whereby utility estimates were generated using standard utility elicitation instruments, such that outcomes measured were comparable. Meta-analyses were not conducted for utility weights of non-AGW outcomes nor were they conducted for any cost estimates, given higher heterogeneity in how costs were measured and the specific disease type and stages considered.

Software
References were collected in EndNote and transferred to Eppi-Reviewer 4 software (Thomas J, Brunton J, Graziosi S, 2010) for screening. Final papers were captured in Mendeley Version 1.15.3. Data extraction was collated in Microsoft Excel 2010. Meta-analysis was conducted in STATA13.

RESULTS
The initial search strategy identified 10,742 records after deduplication. Screening based on titles and abstracts reduced these to 729 full-text papers that were reviewed. Of these, 61 papers were selected. A PRISMA flow diagram is presented in Figure 1.

Costs
A total of 37 papers reported non-cervical HPV-related disease management costs[16–52], about half of which reported costs for AGWs[16–35]. Four papers reported costs for more
than one disease[26,30,36,37]. Management costs from studies differed by country, disease stages or management settings used, and data collection method.

Figure 2 (Panel A) presents a summary of the various cost per case estimates, where presented, for AGWs. Estimated cost per case of AGW ranged from US$124 per case in a patient seen for care in Canada[25] to US$883 per case in Spain[34]. AGW management costs were derived from information collected from case note reviews (13 papers)[18–22,25,26,28,29,31–34], expert opinion (3 papers)[16,24,35], surveillance data (3 papers) [17,23,27] or the literature (1 paper) [30].
Figure 2. Disease management costs reported in selected papers. Panel A outlines costs reported for anogenital warts (AGWs). Panel B contains an extraction of non-cervical cancer management costs; Panel A: Cost per case of AGWs management as reported in the relevant papers; Note that overall cost per patient is presented where this information is available, otherwise, cost per patient broken down by e.g. gender or new/recurrences presented and these are specified; Herse et al., 2011 not included as they presented minimum and maximum total cost of all patients, not per patient; Cost per patient for resistant cases reported in Hillemanns et al., 2008 not presented on this figure; Panel B: Cost per case of cancer management; Figure only presents cost per patient for their cancer management, excluding where only annual costs were reported or where total cost to the healthcare system was reported but not per patient cost; Note: H&N=Head and neck; Preuss, 2007, minimum and maximum costs reported for oropharyngeal carcinomas treatment with surgery and postoperative radio(chemo)therapy.
### Panel A

<table>
<thead>
<tr>
<th>Author, year</th>
<th>ES (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marcellusi, 2015</td>
<td>0.90 (0.88, 0.92)</td>
<td>14.91</td>
</tr>
<tr>
<td>Dominik-Felden, 2013</td>
<td>0.90 (0.88, 0.92)</td>
<td>14.96</td>
</tr>
<tr>
<td>Drolet, 2011 (combined)</td>
<td>0.83 (0.79, 0.87)</td>
<td>13.53</td>
</tr>
<tr>
<td>Senecal, 2011</td>
<td>0.79 (0.76, 0.81)</td>
<td>14.42</td>
</tr>
<tr>
<td>Woodhall, 2011</td>
<td>0.87 (0.85, 0.89)</td>
<td>14.77</td>
</tr>
<tr>
<td>Marra, 2009</td>
<td>0.76 (0.72, 0.80)</td>
<td>13.36</td>
</tr>
<tr>
<td>Woodhall, 2009</td>
<td>0.96 (0.93, 1.00)</td>
<td>14.04</td>
</tr>
<tr>
<td>Overall (I-squared = 95.2%, p = 0.000)</td>
<td>0.86 (0.82, 0.90)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

**NOTE:** Weights are from random effects analysis.

### Panel B

<table>
<thead>
<tr>
<th>Author, year</th>
<th>ES (95% CI)</th>
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<tbody>
<tr>
<td>Vriend, 2014 (combined)</td>
<td>0.80 (0.75, 0.86)</td>
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<tr>
<td>Dominik-Felden, 2013</td>
<td>0.78 (0.76, 0.80)</td>
<td>15.61</td>
</tr>
<tr>
<td>Drolet, 2011 (combined)</td>
<td>0.79 (0.77, 0.81)</td>
<td>15.47</td>
</tr>
<tr>
<td>Senecal, 2011</td>
<td>0.77 (0.75, 0.79)</td>
<td>15.39</td>
</tr>
<tr>
<td>Woodhall, 2011</td>
<td>0.77 (0.76, 0.79)</td>
<td>16.01</td>
</tr>
<tr>
<td>Marra, 2009</td>
<td>0.65 (0.60, 0.70)</td>
<td>10.09</td>
</tr>
<tr>
<td>Pirotta-2009</td>
<td>0.71 (0.63, 0.80)</td>
<td>6.03</td>
</tr>
<tr>
<td>Woodhall, 2008</td>
<td>0.86 (0.82, 0.90)</td>
<td>12.09</td>
</tr>
<tr>
<td>Overall (I-squared = 85.8%, p = 0.000)</td>
<td>0.77 (0.75, 0.80)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

**NOTE:** Weights are from random effects analysis.
Cost per case reported for the various cancers is presented in Figure 2 (Panel B). Six papers reported management cost for anal cancers\cite{30,36–40}, but half of these were annual treatment costs\cite{37,39,40} not cost per case. Cost per anal cancer case ranged from US$12,936 (Italy\cite{30}) to US$51,571 (Denmark\cite{36}). Twelve reported head and neck cancer treatment costs and differed depending on cancer site and stage\cite{30,37,41–50}, with costs ranging from US$6,912 (Laryngeal cancer, T1 carcinoma, the Netherlands\cite{48}) to US$52,579 (weighted average costs for cancers of the oral cavity, larynx or oropharynx, the Netherlands\cite{45}). There were four papers each that reported cost for vaginal\cite{26,30,36,37}, vulvar\cite{26,30,36,37}, and penile\cite{30,36,37,51} cancers, with cost ranges of US$17,524–34,258, US$14,686–28,502, and US$9,975–27,629, respectively. Six papers only presented total spend and/or annual spend for the non-cervical cancers\cite{37,39,40,42,44,52}, detailed findings are reported in Appendix 2.

One paper reported on total treatment cost covering 14 adult patients seen for RRP care at a clinic in Glasgow, Scotland, between January 2013 to April 2014 was reported at US$137,601\cite{52}.

Utilities
A total of 25 papers on health-related quality of life were identified (full reference list in Appendix 2)\cite{19,20,53–60;W1-W15}. Two of these covered multiple diseases\cite{53,W15}. Fifteen papers covered head and neck cancers, including oral and laryngeal cancers\cite{53,W2–W15}, whilst another 12 papers reported on quality of life for AGWs\cite{19,20,53–60,W1,W16}.

Utility per case of AGW ranged from 0.651–1, depending on the method of utility elicitation used. Utility values were generally higher when measured using EQ-5D, compared with Visual Analog Scale (VAS), TTO, or SG methods used within a single study. Full details of study background and findings are presented in Appendix 2. Meta-analyses of EQ-5D and EQ-VAS, from nine papers each, found high heterogeneity (I-squared >90%) in the utility values reported (Figure 3). Pooled mean EQ-5D and EQ-VAS were 0.86 (95% CI 0.85-0.87) and 0.74 (95% CI 0.74-0.75), respectively.

Methods used to elicit utility for HPV-related cancers included EQ-5D, EQ-VAS, HUI3 (Health Utility Index Mark 3), TTO, SG, SF-36 (Short-Form 36), SF-6D (Short-Form Six-Dimension), and 15D. Utility estimates for head and neck cancers differed depending on the utility elicitation method used to generate utility scores, cancer site, patient age, the disease stage at point of completion of the quality of life questionnaire, and treatment modality. For example, patients who had early stage oral cancers completed utility questionnaires at a later point in time in Govers et al. [W3], whilst another study by Loimu et al. [W7] was a prospective.
<table>
<thead>
<tr>
<th>Number</th>
<th>Author (year)</th>
<th>Cancer type; notes</th>
<th>Country</th>
<th>n</th>
<th>Utility elicitation instrument used; mean (unless otherwise specified) values and/or ranges reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Aro et al (2016) [W2]</td>
<td>Head and neck</td>
<td>Finland</td>
<td>214</td>
<td>15D; 0.872</td>
</tr>
<tr>
<td>2</td>
<td>Govers et al (2016) [W3]</td>
<td>Oral; mean years after treatment range 1.9 (SD 1.4, range 0.4–4.1) to 5.2 (SD 3.2, range 0.4–11.0)</td>
<td>The Netherlands</td>
<td>174</td>
<td>EQ-5D; range 0.794 (SE 0.04) to 0.863 (SE 0.05) EQ-VAS; range 69.7 (SE 3.7) to 79.6 (SE 4.8)</td>
</tr>
<tr>
<td>3</td>
<td>Pickard et al (2016) [W4]</td>
<td>Head and neck</td>
<td>USA</td>
<td>50</td>
<td>EQ-5D; 0.828 EQ-VAS; 60.8</td>
</tr>
<tr>
<td>4</td>
<td>Rettig et al (2016) [W5]</td>
<td>Head and neck; sites include larynx, oral cavity, oropharynx, hypopharynx, nasopharynx and nasal cavity/paranasal sinuses</td>
<td>USA</td>
<td>1653</td>
<td>SF-6D; range 83.7 (95% CI 82.0 to 85.4) to 88.0 (95% CI 86.2 to 89.7)</td>
</tr>
<tr>
<td>5</td>
<td>Kent et al (2015) [W6]</td>
<td>Oral cavity and pharynx</td>
<td>USA</td>
<td>64</td>
<td>SF-6D; 0.69 (95% CI 0.68 to 0.70)</td>
</tr>
<tr>
<td>6</td>
<td>Loimu et al (2015) [W7]</td>
<td>Head and neck</td>
<td>Finland</td>
<td>64</td>
<td>15D; range 0.829 (0.12) to 0.886 (0.10)</td>
</tr>
<tr>
<td>7</td>
<td>Noel et al (2015) [W8]</td>
<td>Head and neck</td>
<td>Canada</td>
<td>119</td>
<td>EQ-5D; range 0.82 (SD 0.18, range −0.07 to 1.0) EQ-VAS; 0.76 (SD 0.19, range 0.2–1.0) SG; 0.91 (SD 0.17, range 0.2–1.0) TTO; 0.94 (SD 0.14, range 0.3–1.0) HUI3; 0.75 (SD 0.25, range −0.06 to 1.0)</td>
</tr>
<tr>
<td>8</td>
<td>Pottel et al (2015) [W9]</td>
<td>Head and neck</td>
<td>Belgium</td>
<td>81</td>
<td>EQ-5D; median (Q1, Q3) range 0.29 (0.0, 0.76) to 0.66 (0.55, 0.76)</td>
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<tr>
<td>9</td>
<td>Lango et al (2014) [W10]</td>
<td>Head and neck</td>
<td>USA</td>
<td>159</td>
<td>EQ-5D; median 85 (IQR: 70–90)</td>
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<tr>
<td>11</td>
<td>Rogers et al (2006) [W12]</td>
<td>Head and neck</td>
<td>UK</td>
<td>119</td>
<td>EQ-5D; range 0.75 (SE 0.02; range −0.18 to 1.0) EQ-VAS; 74 (SE 1)</td>
</tr>
<tr>
<td>12</td>
<td>Ringash et al (2000) [W13]</td>
<td>Laryngeal</td>
<td>Canada</td>
<td>84</td>
<td>TTO; 0.878 (SD 0.174; range 0.25–1)</td>
</tr>
<tr>
<td>13</td>
<td>Downer et al (1997) [W14]</td>
<td>Oral</td>
<td>UK</td>
<td>100</td>
<td>SG; range 0.68 (SD 0.33) to 0.88 (SD 0.20)</td>
</tr>
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<td>14</td>
<td>Marcellusi et al (2015) [53]</td>
<td>Anal</td>
<td>Italy</td>
<td>26</td>
<td>EQ-5D; 0.6 (SD 0.3) TTO; range 0.5 (SD 0.26; 95% CI 0.4 to 0.61) to 0.52 (SD 0.25; 95% CI 0.36 to 0.67)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Head and neck; squamous cell carcinoma</td>
<td>Italy</td>
<td>79</td>
<td>EQ-5D; 0.8 (SD 0.2) TTO; range 0.69 (SD 0.3; 95% CI 0.62 to 0.75) to 0.59 (SD 0.3; 95% CI 0.46 to 0.72)</td>
</tr>
<tr>
<td>Number</td>
<td>Author (year)</td>
<td>Cancer type; notes</td>
<td>Country</td>
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<td>Utility elicitation instrument used; mean (unless otherwise specified) values and/or ranges reported</td>
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<td>15</td>
<td>Conway et al (2012) [W15]</td>
<td>Anal</td>
<td>Australia</td>
<td>95</td>
<td>SG; 0.57 (95% CI 0.52 to 0.62); median 0.65 (IQR 0.45–0.75)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oropharyngeal</td>
<td>Australia</td>
<td>99</td>
<td>SG; 0.58 (95% CI 0.53 to 0.63); median 0.65 (IQR 0.45–0.75)</td>
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<td></td>
<td>Vaginal</td>
<td>Australia</td>
<td>98</td>
<td>SG; 0.59 (0.54–0.64); median 0.65 (IQR 0.45–0.75)</td>
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<td></td>
<td></td>
<td>Vulvar</td>
<td>Australia</td>
<td>98</td>
<td>SG; 0.65 (0.60–0.70); median 0.65 (IQR 0.45–0.85)</td>
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<tr>
<td></td>
<td></td>
<td>Penile</td>
<td>Australia</td>
<td>97</td>
<td>SG; 0.79 (0.74–0.84); median 0.85 (IQR 0.65–1.0)</td>
</tr>
</tbody>
</table>

EQ-5D, EuroQol-5 Dimension; EQ-VAS, EuroQol visual analogue scale; HPV, human papillomavirus; HUI3, Health Utility Index Mark 3; SF-6D, Short-Form Six-Dimension; SG, standard gamble; TTO, time-trade-off.
study where patients with laryngeal, pharyngeal or nasal cavity carcinoma had their utility measured at month-0, 3, 6, and 12 after treatment initiation. We present summary study details and key utility output presented in each of these 15 papers on quality of life for HPV-related cancers in Table 1 with further details in Appendix 2.

DISCUSSION

Statement of principal findings

This systematic review provides an updated and comprehensive summary of the cost and utility evidence for non-cervical HPV-related diseases that can be used in economic evaluations conducted from the perspective of a national health care provider. There appeared to be high heterogeneity in the papers identified, in terms of disease stages, population studied, treatment modality and setting, as well as utility elicitation methods used. The EuroQol EQ-5D or EQ-VAS was commonly used in AGWs and in at least half of the non-cervical cancers studies.

Whilst the evidence in terms of both costs and utility values appear to be abundant for AGWs, it is less so for other cancers. This may reflect the fact that protection against AGWs is one of the main differentiating factors between the two competing HPV vaccines (quadrivalent and bivalent) on the market until licensure of the nonavalent vaccine in 2015, with several published economic evaluations focusing on the difference in cost-effectiveness between the two vaccines[W17].

Strengths and weaknesses of the study

Many papers did not report a single overall cost or utility estimate for a disease episode. Instead, they reported cost or utility values at different stages of the disease, which means that to obtain a single overall figure over entire disease episode, further details about patient case mix and changes in utility over time are needed. This includes a combination of treatment received at different stages of disease. For example, Kim et al., 2011, reported post-operative management cost for a selective group of head and neck cancer patients who had received surgical resection[43].

In addition, treatment modalities are likely to change over time, with corresponding effects on both treatment costs and quality of life (due to changes in recovery time and patient experience). This means that applying the same methodology to the same group of patients but managed differently will likely return different costs and utility estimates.

The NICE-recommended utility elicitation method is EQ-5D completed by patients and scored using population norms. This type of evidence is not always available. When alternative utility elicitation methods are used, such as direct utility elicitation methods, their score can be quite different, as demonstrated by Noel et al., 2015[68]. In their study, patients with upper aerodigestive tract cancer completed five direct/indirect utility measures (EQ-5D, VAS, HUI3, standard gamble, and time trade-off). The authors found that direct utility elicitation methods (SG and TTO) returned higher utility scores, possibly due to
patients being more risk-averse. When the SG method was used in another study (Conway et al., 2012[W15]) completed by general population, the utility score for oropharyngeal cancers was lower than head and neck cancers scored using SG in Noel et al., 2015[68], although this could be due to the scenario descriptions used.

Meaning of the study: possible mechanisms and implications for clinicians or policymakers
This systematic review highlights the importance of understanding the data source used in economic evaluation, ensuring that health economic assumptions are up-to-date and closely reflect the case-mix of patients considered in the analysis.

Unanswered questions and future research
During the paper screening and evaluation of eligibility stage, many papers on head and neck cancers were identified but they often used SF-36 generic utility measures and reported two summary scores covering physical and mental domains separately. Only four studies[56,59,W5,W6] reported a single summary score and were included. To be most applicable to economic evaluations, mapping exercises are needed to convert SF-36 values to single SF-6D scores specific to a country’s population. Future analyses could consider extracting findings from relevant papers and converting to SF-6D scores, especially for diseases with insufficient utility estimates evidence.

Future research can also focus on identifying the duration of disutility to be applied to a disease, since quality of life changes over time, and is an important component of the QALY calculations.

AUTHORS’ CONTRIBUTIONS
KJO, MJP, and MJ conceived and planned the systematic review. LB conducted the systematic literature searches. KJO, MC, and CP, carried out sifting and data extraction of the systematic literature search results. KJO conducted the meta-analysis and took the lead in writing the manuscript, with guidance from MJP and MJ. All authors provided critical feedback on the manuscript.

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