



Title	Health-related quality of life as measured by the EQ-5D in the prevention, screening and management of cervical disease: A systematic review
Authors(s)	Ó Céilleachair, A., O'Mahony, James F., O'Connor, M., et al.
Publication date	2017-06-26
Publication information	Ó Céilleachair, A., James F. O'Mahony, M. O'Connor, and et al. "Health-Related Quality of Life as Measured by the EQ-5D in the Prevention, Screening and Management of Cervical Disease: A Systematic Review." Springer, June 26, 2017. https://doi.org/10.1007/s11136-017-1628-z .
Publisher	Springer
Item record/more information	http://hdl.handle.net/10197/25011
Publisher's version (DOI)	10.1007/s11136-017-1628-z

Downloaded 2026-05-01 23:36:43

The UCD community has made this article openly available. Please share how this access benefits you. Your story matters! (@ucd_oa)



© Some rights reserved. For more information

Health-related quality of life as measured by the EQ-5D in the prevention, screening and management of cervical disease: A systematic review

A. Ó Céilleachair¹  · J. F. O'Mahony² · M. O'Connor¹ · J. O'Leary³ · C. Normand² · C. Martin³ · L. Sharp⁴

Accepted: 15 June 2017
© Springer International Publishing AG 2017

Abstract

Purpose Cost-effectiveness analyses (CEAs) of screening can be highly sensitive to the health-related quality of life (HRQoL) effects of screen tests and subsequent treatment. Accordingly, accurate assessment of HRQoL is essential. We reviewed the literature regarding HRQoL in cervical prevention and management in order to appraise the current evidence regarding this important input to CEA.

Methods We searched the MEDLINE, Scopus and EconLit databases for studies that estimated HRQoL in cervical cancer prevention and management published January 1995–December 2015. The primary inclusion criterion was for studies that assess HRQoL using the EQ-5D. Data were abstracted from eligible studies on setting, elicitation group, sample size, elicitation instruments, health state valuations, study design and follow-up. We assessed the quality and comparability of the studies with a particular focus on the HRQoL reported across states and groups.

Results Fifteen papers met the inclusion criteria. Most used patient elicitation groups ($n = 11$), 2 used the general public and 2 used a mix of both. Eight studies were cross-sectional and seven were longitudinal. Six studies used both the EQ-5D-3L and the EQ-VAS together with other

measures of overall HRQoL or condition-specific instruments. Extensive heterogeneity was observed across study characteristics.

Conclusions Our results reveal the challenges of sourcing reliable estimates of HRQoL for use in CEAs of cervical cancer prevention and treatment. The EQ-5D appears insufficiently sensitive for some health states. A more general problem is the paucity of HRQoL estimates for many health states and their change over time.

Keywords Health-related quality of life · Health economics · Screening · Cervical cancer · Human papillomavirus · Systematic reviews

Introduction

Cervical cancer and its precursor lesions are a major public health issue. In 2012, 528,000 women were diagnosed with cervical cancer worldwide and 266,000 died from the disease [1]. Fortunately, there is a range of effective options for both primary and secondary prevention of cervical disease. Well-organised screening is effective in reducing disease incidence and mortality [2] and cytology-based screening has been widely offered for decades [3]. The discovery of a causal link between high-risk strains of Human Papillomavirus (HPV) and cervical neoplasia has expanded the options available for cervical cancer prevention [4]. Human Papillomavirus testing is increasingly being considered as part of cervical cancer screening protocols and screening is likely to be based on primary HPV testing in the near future [5, 6]. Furthermore, prophylactic HPV vaccination anticipated to prevent roughly 80% of cervical cancers are now available [7, 8]. Many territories have begun HPV vaccination schemes, typically for girls

✉ A. Ó Céilleachair
a.oiceilleachair@ncrri.ie

¹ National Cancer Registry Ireland, Building 6800, Cork Airport Business Park, Cork, Ireland

² Centre for Health Policy and Management, Trinity College, Dublin, Ireland

³ Coombe Women and Infants University Hospital, Dublin, Ireland

⁴ Institute of Health & Society, Newcastle University, Newcastle upon Tyne, UK

aged 11–12 years. In some, such as Australia and Scotland, the first cohorts of vaccinated women are now presenting for screening [9–11]. Cervical screening providers in many healthcare systems will be serving populations containing both vaccinated and unvaccinated women for many years to come.

There is currently considerable interest in evaluating the effectiveness and cost-effectiveness of current and future cervical cancer prevention strategies. Cost-effectiveness analysis (CEA) is used to compare alternative interventions in terms of their total net costs and total net health gains, which are typically measured in quality-adjusted life-years (QALYs). Quality-adjusted life-years estimation requires a weighting of the various levels of morbidity of the various health states experienced by individual. This weighting is achieved by the application of health-related quality of life weights (HRQoL). Cost-effectiveness analysis of cervical screening can be highly sensitive to the HRQoL weights employed, especially for states experienced by large proportions of the screened population, such as those related to the experience of primary screening [12]. Accordingly, an accurate assessment of HRQoL is essential.

Preference-based measures of HRQoL are required to be used by many guidance bodies such as NICE in the UK and HIQA in Ireland [13, 14]. The most commonly used measure of HRQoL in CEA is the EuroQol EQ-5D [15, 16]. It is a preference-based measure of health-related quality of life that is generic in that it can be applied to all health conditions. While the EQ-5D is a well-understood and accepted instrument, it is not without limitations and it has been shown to lack sensitivity in some settings [17]. It is useful to differentiate the specific conception of HRQoL that is central to CEA from a broader concept of quality of life (QoL) in general. While some specific aspects of QoL relating to cervical screening and cervical intraepithelial neoplasia (CIN) have been explored in the literature previously (including anxiety and distress relating to screening, concerns about fertility and sex that persist after treatment for CIN) [18–21], EQ-5D estimates of HRQoL are much less commonly reported. Furthermore, many of the estimates that do exist, and have been used in earlier cost-effectiveness modelling exercises are old or from unpublished sources [21, 22]. This presents a challenge for economic modellers who require a robust set of HRQoL scores for the many health states in cervical management, covering different models of screening, management and follow-up as well as different disease trajectories to reliably estimate cost-effectiveness as many health systems require evidence of cost-effectiveness before approving technologies for use.

To assist those undertaking CEA in cervical cancer prevention, we conducted a systematic review of the literature pertaining to HRQoL as measured by the EQ-

5D in the screening for, and management of, cervical disease.

Methodology

Search strategy

The review was conducted in accordance with the PRISMA guidelines [23]. We searched the MEDLINE, Scopus and EconLit databases to identify all studies reporting original health state valuations pertaining to HPV vaccination, cervical screening, diagnosis, treatment and follow-up of cervical intraepithelial neoplasia (CIN) and the diagnosis, treatment and follow-up of invasive cervical cancer published between 1 January, 1995 and 31 December, 2015. Studies before 1995 were excluded as the numbers of CEAs published before this point was likely very small [24]. In the MEDLINE search disease and treatment MeSH headings used included “Uterine Cervical Dysplasia”, “Atypical Squamous Cells of the Cervix”, “Papanicolaou Test” and “Colposcopy”. HRQoL-related MeSH headings included “Quality of Life” and “Quality-adjusted life years”. Text and keyword searches were also conducted. We combined disease/treatment and HRQoL terms in the final search string. For Scopus and EconLit, the search strategy was adapted to be as close as possible to that used for MEDLINE as neither of these databases allow interrogation by MeSH heading. The final search strings for all three databases included in the review can be found in Appendix in Table 4.

Two reviewers (AÓC and JOM) independently screened article titles and abstracts to identify potentially relevant articles. Of those articles deemed potentially relevant, full texts were acquired and read by the two reviewers independently. The following inclusion criteria were then applied: (i) the paper was in English and published in a peer-reviewed journal; (ii) the study reported an original health state valuation for some or all aspects of the HPV vaccination-cervical cancer care pathway (Fig. 1); (iii) the setting for the study was a country ranked “very high” on the United Nations Human Development Index (HDI) for 2015 [25]. Papers were considered eligible irrespective of the elicitation method such as time trade off (TTO) standard gamble (SG) and visual analogue scales (VAS)¹ and whether the HRQoL responses were elicited from patients, members of the general public (who had not necessarily been screened or had CIN or cervical cancer), clinicians or any combination of these. Papers published only as abstracts (albeit in a peer-reviewed journal), or which cited health state valuation data from other previously published

¹ Most VAS, including the EQ-VAS run from 0 to 100.



Fig. 1 HPV vaccination—cervical cancer treatment pathway

studies (in practice, this included most cost-effectiveness analyses) were excluded. While reports, conference proceedings and other aspects of the grey literature could contain potentially interesting studies, it is difficult to review such studies systematically and often they rely on HRQoL weights that have been reported elsewhere in the published literature. Consequently grey literature was considered ineligible. Any disagreements regarding study eligibility were resolved by discussion between the two reviewers. Finally, the reference lists of the included papers were hand-searched to identify any further papers meriting inclusion. Figure 2 shows the number of studies identified, screened and included.

Data abstraction and appraisal

The two reviewers independently abstracted data from the eligible papers regarding study setting, year of publication, elicitation group, elicitation instruments used, sample size and composition, study design, health states valued and other HRQoL measures employed (in addition to the EQ-5D). The two reviewers also assessed the methodological quality of the included studies. No existing framework could be found for the quality assessment of HRQoL estimates. Consequently, the authors constructed a quality appraisal framework drawing on the work of two studies by Vistad et al. [26] and O’Connor et al. [20]. This framework assessed quality by comparing the studies in terms of the

HRQoL instruments employed (i.e. using both the EQ-5D self-rater *and* the EQ-visual analogue scale (VAS) as recommended by EuroQol), sample size, the use of comparison groups, elicitation group, clarity of analysis, clearly stated research aims, appropriate use of population norms, and discussion of limitations. Studies could score a maximum of 18 points. A good study was defined as one that scored 12 points. The quality appraisal was complemented with a narrative synthesis of the included studies.

Results

The initial search strategy revealed 2068 potentially interesting studies (Fig. 2). After removing duplicates and reviewing abstracts and titles, 167 full texts were retrieved for detailed consideration. A total of fifteen studies were eligible for inclusion in the final review. No additional papers were revealed by hand-searching the references of the included studies. A large proportion of the initial search hits were ultimately rejected during two rounds of review. Table 1 details the reasons for rejection at the first round of screening of titles and abstracts and at the second round of review of full texts. The primary reason for rejection in both cases was an absence of HRQoL evidence within the candidate studies. Similarly, some studies employed metrics other than the EQ-5D. Many studies were excluded at first round as they were not related to cervical cancer prevention, screening or management. A number of studies from countries with lower HDI scores were excluded. The remaining exclusions were for women not at average risk, non-peer-reviewed studies, study protocols and one analysis that was reported in two separate papers.

Fig. 2 Literature search flow chart with search strategy hits and inclusion criteria

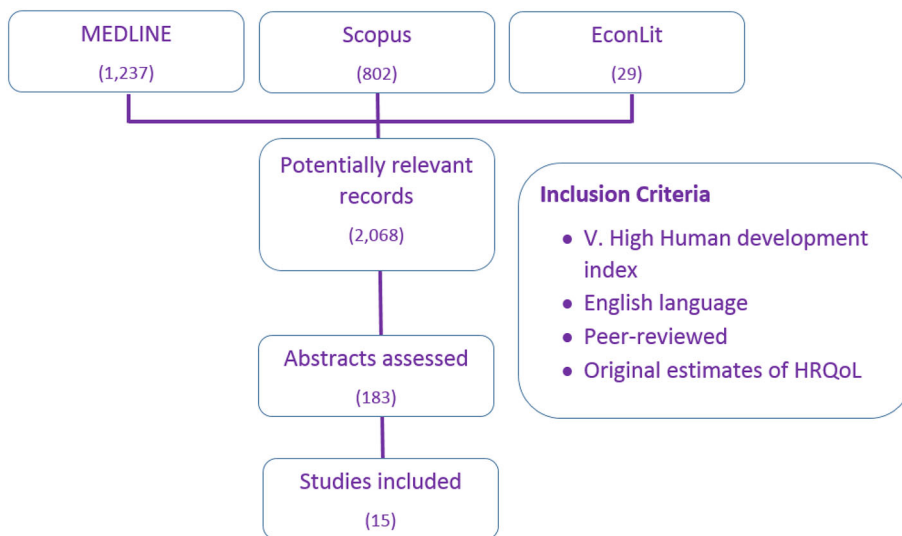


Table 1 Reasons for rejection of candidate studies at first and second round of review

Reason for rejection	First round rejections	Second round rejections
No HRQoL evidence	407	113
Irrelevant disease or intervention	388	2
Lower HDI	158	0
Other HRQoL metric	51	35
Not average risk	13	1
Not peer-reviewed	5	0
Protocol	3	0
Repeated analysis	0	1
Total rejected	1025	152
Total accepted		15

General study characteristics

Table 2 summarizes the included studies. Four studies were from the United Kingdom, three were from the Netherlands, two were from Finland and there were single papers from Taiwan, Australia, Japan, Canada and Italy. The final paper evaluated HRQoL in the UK, Argentina and Chile. Most of the included studies used patient elicitation groups ($n = 11$), two used the general public and two used a mix of both. Eight of the included studies were cross-sectional and seven were longitudinal in design. Study population ranged from large, population-based samples of young women in the general population to small, convenience samples. Two studies examined the HRQoL of HPV vaccinated and unvaccinated women. Four studies addressed cervical screening, seven covered CIN and its management while four covered treatment for invasive cancer. Two of the papers covered more than one part of the pathway from vaccination to treatment for invasive cancer.

HPV vaccination status

Two large cross-sectional studies in Finland based on trials of vaccine effectiveness [27, 28] reported EQ-VAS results for vaccinated women between 5 and 7 years post vaccination with age-matched controls of unvaccinated women. In both studies, health state valuations as measured by the EQ-VAS were slightly above 80 in all age groups and were almost identical for vaccinated and unvaccinated women.

Primary screening studies

Five studies provided health state valuations pertaining to primary cervical screening [29–33]. Maissi and colleagues measured HRQoL at initial receipt of cytology test results (\pm HPV test results) and at six month follow-up in a UK population [29]. At baseline, women with a normal cytology test result reported HRQoL of 0.91. This was 0.81 for

women with an abnormal test result but who were HPV –ve, 0.87 for those who were abnormal and had not had a HPV test and 0.88 for those who both had abnormal cytology and were HPV +ve. At 6 month follow-up, the reported HRQoL was 0.86, 0.90, 0.88 and 0.88, respectively.

In common with Maissi et al. a Canadian study by Drolet et al. took measures of HRQoL from women at primary screening and follow-up (at 12 weeks) using both the EQ-5D self-rater and the EQ-VAS. Those with an abnormal cytology test result reported HRQoL of 0.839 and 78.8 on the self-rater and VAS, respectively. These figures were 0.866 and 81.7 for women with a normal cytology on the self-rater and VAS, respectively. At twelve-week follow-up, the women with abnormal cytology reported their HRQoL as 0.87 and 81.3 on the EQ-VAS. For women with a normal cytology, their scores were 0.887 on the EQ-5D self-rater and 83.2 on the EQ-VAS. [32].

An Australian study reported HRQoL valuations using the EQ-VAS for three screening-related health states [31]. Those with a normal cytology rated their HRQoL as 77.5. For those whose cytology test indicated low-grade squamous intraepithelial lesion (LSIL) this was higher at 78.4 and for those whose cytology indicated high-grade findings (HSIL) it was 76.2.

A Dutch study by Korfage and colleagues looked at HRQoL in women invited for screening both before and after the screening event [34]. Before the women had their smear they reported HRQoL scores of 0.89 and 81 on the EQ-5D self-rater and EQ-VAS, respectively. After the receipt of a normal cytology result, these figures rose to 0.91 and 82, respectively. A reference group of unscreened women reported HRQoL as measured by the EQ-5D self-rater of 0.88 and 81 on the EQ-VAS.

In the United Kingdom, HRQoL findings based on a large trial of women who had undergone screening and who had low-grade results reported average scores of 0.884 on the self-rater and 81.1 on the VAS [30].

Table 2 Characteristics of the studies included in the review

Year	Setting	Author/title	Sample	Elicitation group	Elicitation method	Study design	States valued	Health states
2005	United Kingdom	Maissi et al. [29] The psychological impact of human papillomavirus testing in women with borderline or mildly dyskaryotic cervical smear test results; 6-month follow-up [23]	1376 women undergoing screening, 1011 at 6 month follow-up.	Patients	EQ-5D	Longitudinal	BASELINE Normal 0.91(0.02), Abnormal HPV- 0.89(0.02), Abnormal HPV not tested 0.87 (0.02) Abnormal HPV+ 0.88 (0.02), 6-month follow-Up Normal = 0.86 (0.02), Abnormal HPV- = 0.90 (0.02), Abnormal HPV not tested 0.88 (0.04) Abnormal HPV+ = 0.88 (0.04)	HPV +ve and -ve, abnormal and normal smear results
2008	United Kingdom	Whynes et al. [35] Management of low-grade cervical abnormalities detected at screening; which method do women prefer; Cytopathology [30]	190 women with low-grade cervical abnormalities	Patients	EQ-5D	Cross-sectional	Colposcopy group = 0.90, Surveillance group = 0.88 OVER TIME COLPOSCOPY Recruitment (83.3), Interim (86.4), 12 M (83.5) 18 M (83.3), 24 M (83.3), 30 M (83.8) OVER TIME SURVEILLANCE Recruitment (83.4), Interim (80.8), 12 M (81.8) 18 M (82.5), 24 M (82.8), 30 M (83.0)	Colposcopy group, surveillance group
2008	United Kingdom	Whynes et al. [35] Correspondence between EQ 5D health state classifications and EQ VAS scores; Health & Quality of Life Outcomes [24]	3,132 women with low-grade cytological abnormalities	Patients	EQ-5D and EQ-VAS	Longitudinal	Index = 0.884, EQ-VAS = 81.1	Low-grade cytological abnormalities
2009	The Netherlands	Korfage et al. [34] Anxiety and borderline PAP smear results; European Journal of Cancer [29]	550 women diagnosed with BMD in the previous 6-24 months	Patients	EQ-5D and EQ-VAS	Cross-sectional	Women with BMD - Index = 0.87 (0.21), EQ-VAS = 78.8 (14.7). Screen participants - Index = 0.89 (0.19), EQ-VAS = 81.7 (14.9). OVER TIME Women with BMD - Index = 0.87 (0.21), EQ-VAS = 78.8 (14.7). 6-12 months after BMD	Women with borderline or mild dyskariosis
2009	Australia	Pirotta et al. [31] The psychosocial burden of human papillomavirus related disease and screening interventions; Sexually Transmitted Infections [25]	331 women who had received smear results within the last three months	Patients	EQ-VAS	Cross-sectional	Normal smear - EQ-VAS = 77.5 (16.4), LSIL - EQ-VAS = 78.4 (16.6), HSIL - EQ-VAS = 76.2 (18.9), CIN1 - EQ-VAS = 78.3 (12.5), CIN2/3 - EQ-VAS = 76.8 (16.7)	Normal cytology, LSIL, HSIL, CIN 1,2 or 3, genital warts or normal cytology

Table 2 continued

Year	Setting	Author/title	Sample	Elicitation group	Elicitation method	Study design	States valued	Health states
2011	Finland	Woodhall et al. [27] Impact of HPV vaccination on young women's quality of life a five year follow-up study [21]	905 vaccinated women and 3558 unvaccinated women	Patient and general public	EQ-VAS	Cross-sectional	Vaccinated women: EQ-VAS = 81.6, Unvaccinated women EQ-VAS = 82.7; Placebo-vaccinated women EQ-VAS = 82.8	No specific states
2012	Canada	Drolet et al. [32] The psychosocial impact of an abnormal cervical smear result; Psycho-Oncology [27]	492 women with abnormal cytology and 460 women with normal cytology	Patients	EQ-5D and EQ-VAS	Longitudinal	BASELINE Women with abnormal smear: Index = 83.9 (82.2-85.5), EQ-VAS = 78.8 (77.5-80.3). Women with normal smear: Index = 86.6 (84.8-88.3), EQ-VAS = 81.7(80.2-83.2). TWELVE WEEKS Women with abnormal smear: Index = 87.0 (85.4-88.6), EQ-VAS = 81.3 (80.0-82.7). Women with normal smear: Index = 88.7 (87.0-90.3), EQ-VAS = 83.2 (81.8-84.5).	Normal and Abnormal cytology
2011	Argentina, Chile & the United Kingdom	Galante et al. [36] Estimation and Comparison of EQ-5D Health States' Utility Weights for Pneumococcal and Human Papillomavirus Diseases; Value in Health [31]	39 women and 34 men	General public	EQ-5D and EQ-VAS	Cross-sectional	Results too detailed for table—refer to Supp File "A"	CIN 1,2, and 3, cervical cancer and cured cancer
2012	Taiwan	Lang et al. [41] Quality of life, treatments, and patients' willingness to pay for a complete remission of cervical cancer in Taiwan; Health Economics [36]	530 women diagnosed with BMD in the previous 6-24 months	Patients	EQ-5D and EQ-VAS	Cross-sectional	Table V, By disease stage, Ia1: 0.93, Ia2: 0.83, Ib1 0.87, Ib2-IIIa: 0.88, >IIIa:0.81.	Cervical cancer
2012	The Netherlands	Korfage et al. [33] Having a Pap smear, quality of life before and after cervical screening; a questionnaire study; BJOG [28]	789 women invited for screening with normal test results and 563 age-matched women not due for screening in the next two years	Patients	EQ-5D and EQ-VAS	Longitudinal	Screened women - Index = 0.89 (0.19), EQ-VAS = 81 914). Reference group - Index = 0.88 (0.19), EQ-VAS = 81 (15). Within Screened group: Before Smear - Index = 0.89 (0.19), EQ-VAS = 81 (14); After receipt of favourable smear result - Index = 0.91 (0.17), EQ-VAS = 82 (12)	Normal cytology?

Table 2 continued

Year	Setting	Author/title	Sample	Elicitation group	Elicitation method	Study design	States valued	Health states
2013	United Kingdom	Whyne [37] Impact of alternative management policies on health-related quality of life in women with low-grade abnormal cervical cytology referred for colposcopy [32]	751 women with low-grade abnormal cytology undergoing colposcopy	Patients	EQ-5D and EQ-VAS	Longitudinal	0.906, 0.912, 0.919 Colposcopy, biopsy, LLETZ respectively.	Borderline or mild screening results
2013	Finland	Eriksson et al. [28] Impact of HPV16/18 vaccination on quality of life; a pilot study; European Journal of Contraception & Reproductive Health Care [22]	1143 HPV16/18-vaccinated women, 980 HAV-vaccinated women and 3753 unvaccinated women	Patient and general public	EQ-VAS	Cross-sectional	HPV-vaccinated - 81.91 (0.38), HAV-vaccinated - 82.09 (0.42), Unvaccinated - 81.49 (0.25)	No specific states
2014	The Netherlands	Korfage et al. [38] How distressing is referral to colposcopy in cervical cancer screening; a prospective quality of life study; Gynecologic Oncology [33]	132 women referred for colposcopy and 706 screen participants	Patient	EQ-5D and EQ-VAS	Longitudinal	Colp. Group - Index = 0.90 (0.14), EQ-VAS = 80 (12), Screen Group - Index = 0.90 (0.18), EQ-VAS = 81 (13)	CIN 1, CIN2+
2015	Italian	Marcellusi et al. [40] Health utilities lost and risk factors associated with HPV-induced diseases in men and women; the HPV Italian collaborative study group; Clinical Therapeutics [35]	465 Men and women (126 ASCUS, CIN 1-3, Cervical Cancer) with HPV-induced pathologies cytology and 135 controls	Patient	EQ-5D	Cross-sectional	ASC-US = 0.83 (0.24); CIN1 = 0.88 (0.22), CIN2-3 = 0.81 (0.27), Cerv. Cancer = 0.58 (0.31)	-
2014	Japan	Murasawa [42] Evaluation of Health-related Quality of Life for Hypothesized Medical States Associated with Cervical Cancer; A Pac J Cancer Pre [34]	136 university students	General public	EQ-5D	Cross-sectional	AT DIAGNOSIS: CIN1 0.84 (-0.14), CIN2 0.78 (-0.12), CIN3 0.73 (-0.1), IA1 0.78 (-0.12), IA2 0.72 (-0.12), IB1 0.63 (-0.13), IB2 0.64 (-0.12), IIA 0.68 (-0.08), IIB 0.62 (-0.13), III 0.55 (-0.21), IV 0.18 (-0.24) AFTER INTERVENTION: CIN1 0.84 (-0.12), CIN2 0.81 (-0.12), CIN3 0.84 (-0.12), IA1 0.80 (-0.15), IA2 0.78 (-0.11), IB1 0.64 (-0.15), IB2 0.63 (-0.15), IIA 0.71 (-0.15), IIB 0.50 (-0.17), III 0.52 (-0.17), IV 0.21 (-0.28)	CIN 1, 2 and 3, and multiple cancer states

CIN and its management

Seven of the included studies provided HRQoL valuations for health states related to CIN and its management [31, 35–40]. Two papers by Whyne et al. reported valuations among women who had undergone colposcopy of 0.90 and 0.906 using the EQ-5D self-rater [35, 37] while Korfage et al. [38] and reported a valuation of 0.90. On the EQ-VAS Korfage et al. [38] reported a score of 0.80 for women who had undergone colposcopy. Pirotta et al. Galante et al. and Marcelussi et al. [31, 36, 40], all using the EQ-5D self-rater, reported HRQoL values for CIN1 and a composite of CIN2/3. These ranged from 0.765 to 0.88 for CIN 1 and 0.50 to 0.81 for CIN 2/3. Murasawa et al. was the only study to report a separate health state valuation for CIN2 (0.78 at diagnosis and 0.81 post intervention) and CIN3 (0.73 at diagnosis and 0.84 post intervention) [39].

Cervical cancer

Four studies reported health state valuations pertaining to invasive cervical cancer [36, 40–42]. Two studies only provided a single health state valuation to cover all cancer stages. Marcelussi and colleagues [40] reported a HRQoL weight of 0.58 for invasive cervical cancer in an Italian population, while Galante et al. report estimates of 0.152 and 0.39 for the UK and Chile respectively [36]. The other two studies provided values for each cancer stage. These ranged from 0.80 in those with Stage IA1 from Murasawa et al. in a sample of Japanese nursing students [39] to 0.93 in a Taiwanese study by Lang et al.—also for Stage IA1—[41] in whom values were elicited from women previously diagnosed with borderline or mild dyskariosis (BMD).

Results of quality assessment

Table 3 shows the results of the quality assessment of the included studies. 11 of the 15 included papers scored 12 or more points. No temporal trend in quality score was observed. Several of the methodological factors examined in this assessment were addressed well by the papers. Analyses were clearly explained ($n = 14$) and research aims were clearly stated ($n = 13$). The papers mostly reported on their main limitations and the majority of the included studies ($n = 9$) used a comparator group, which were generally clearly defined ($n = 9$) or could be inferred ($n = 3$). While sample sizes were mostly in excess of 1000 ($n = 8$), this was quite variable. Six studies had a sample size between 100 and 1000 (with many being close to 100), while a single study had less than 100 participants. The studies predominantly used those who had undergone

screening and/or other management to elicit HRQoL estimates ($n = 11$). Two studies asked clinicians, while two studies used convenience samples.

Some other elements were more poorly addressed. Only six studies reported a population norm for comparison with their estimates of HRQoL. Similarly, only six papers employed a longitudinal design. Six studies employed both the EQ-5D self-rater and the EQ-VAS in their analysis, while eight used one or other of the self-rater and VAS together with some other measure of HRQoL and a single study used only the EQ-5D self-rater.

Discussion

In this systematic review of HRQoL pertaining to the HPV vaccination-cervical cancer care pathway, we identified 15 studies published in the last two decades—far fewer than the number of published CEAs in this area. At first glance, the number of studies may seem favourable; however, when we disaggregate by health states the number of studies providing evidence for each state is small. When we consider specific health states such as cancer (which itself is in fact a range of health states) we found only four studies with quite heterogeneous findings. Evidence on HPV vaccination was limited to two studies—albeit large—from the same setting and which assessed HRQoL at a single time point several years after vaccination. This comparative paucity of evidence was compounded by the fact that many of the studies used only one or other of the EQ-5D self-rater or the EQ-VAS rather than both, as recommended by the EuroQol Group [43].

Our original intention in conducting this review was to bring all of the available data which could be used to parameterise cost-effectiveness analyses of cervical cancer prevention, screening and treatment strategies into a single source. We had intended to synthesize the findings by means of meta-analyses so that there would exist a single, useful, robust reference which researchers in this area could rely on to find HRQoL information for various key health states. In fact, the studies themselves and their findings were so heterogeneous that this was impossible. Meta-analyses were precluded because the studies differed too much in terms of elicitation group, disease states, population, design and comparator groups. Moreover, in narrative synthesis, studies that appeared to address similar health states had quite different findings. This seems likely to be due to factors such as heterogeneity in the study populations, elicitation methods employed and when precisely HRQoL was measured.

In addition, quality assessment of the studies showed that, while overall, the quality of the included studies

Table 3 Methodological and quality appraisal of the included studies

Year	Author	QoL measures employed	Controlled estimates	Elicitation group	Sample size (Vistad)	Analysis clearly explained	Research aims clearly stated	Longitudinal design	Comparator group clearly defined	Population norm reported	Main limitations identified	Quality score
2005	Maissi et al. [29].	5D plus another measure, 3. EQ-5D plus VAS and another condition or outcome-	0 No, Yes	(Patients vs. Convenience sample)	1. less than 100. 2. 100–1000. 3. More than 1000	0 No, 1 partly – could be inferred, 2 Yes	0 No, 1 partly – could be inferred, 2 Yes	0 No, Yes 1	0, 1, 2 (Not defined, somewhat clearly defined)	0 No, Yes 1	0 No, Yes 1	16
2008	Whynes et al. [35].		0	1	2	1	1	0	2	0	1	10
2008	Whynes et al. [30]		0	1	3	2	1	1	2	1	0	14
2009	Korfage et al. [34].		1	1	3	2	2	0	2	0	1	15
2009	Pirotta et al. [31].		0	1	2	2	2	0	1	0	1	11
2011	Woodhall et al. [27].		1	2	3	2	2	0	1	0	1	14
2012	Drolet et al. [32].		1	1	2	2	2	1	1	1	0	14
2011	Galante et al. [36].		0	0	1	2	2	0	0	1	0	8
2012	Lang, Chang & Ying [41]		0	1	3	2	2	0	0	0	1	12
2012	Korfage et al. [33]		1	1	3	2	2	1	2	0	1	16
2013	Whynes et al. [37].		1	1	3	2	2	1	2	1	0	15
2013	Eriksson et al. [28].		1	2	3	2	2	0	2	0	1	15

Table 3 continued

Year	Author	QoL measures employed	Controlled estimates	Elicitation group	Sample size (Vistad)	Analysis clearly explained	Research aims clearly stated	Longitudinal design	Comparator group clearly defined	Population norm reference reported	Main limitations identified	Quality score
		5D plus another measure, 3. EQ-5D plus VAS and another condition or outcome-	0 No, Yes 1	(Patients vs. Convenience sample)	1. less than 100. 2. 100–1000. 3. More than 1000	0 No, 1 partly – could be inferred, 2 Yes	0 No, 1 partly – could be inferred, 2 Yes	0 No, Yes 1	0, 1, 2 (Not defined, somewhat clearly defined)	0 No, Yes 1	0 No, Yes 1	
2014	Korfage et al. [38].		1	1	2	2	2	1	2	0	0	14
2015	Marcellusi et al. [40].		1	1	2	2	2	0	2	0	1	12
2014	Murasawa et al. [39].		0	0	2	2	2	0	0	1	1	10

appeared good (11 scored 12 or more points), there were important areas in which the studies scored poorly. These included (non) use of population norms, not employing both the EQ-5D self-rater and the EQ-VAS and design (cross-sectional rather than longitudinal).

Our review highlights three particular issues regarding HRQoL estimation in relation to cervical cancer and its prevention. One is the lack of reported baseline population norms in many studies. Population norms are important because they allow the HRQoL experienced by subjects to be evaluated relative to that experienced by age and gender-matched peers in the general population. While a number of the studies did use age and sex-matched controls/comparator groups, the use of rigorous population norms is preferable and aids with generalisability across studies. Use of both the EQ-5D self-rater and the EQ-VAS is recommended as this allows a greater degree of sensitivity in study findings [44]. Furthermore, estimates based on only one or the other instrument inhibits cross-study comparison and further atomises the available literature.

The second issue of particular note is the limited number of studies employing a longitudinal study design. Longitudinal analysis is important for estimation as it permits the assessment of temporal changes in HRQoL, which may vary significantly over short time periods due to acute phases of worry, uncertainty or discomfort. While some studies did employ this design, the number was small ($n = 6$) and it is possible that this lack of control for short-term variations makes interpretation of different results difficult.

A third particular issue raised in this review is the question of the sensitivity of the EQ-5D instrument. The problem that the EQ-5D may be insufficiently sensitive to changes in health states has long been recognized and is a particular issue in the application of the self-rater questionnaire in which respondents only have three levels of response to choose from over five health domains. Nevertheless, this review found a number of instances in which highly statistically significant differences in specific measures of anxiety between states did not result in statistically significant differences in HRQoL scores. The results are presented in Table 3 of Korfage et al. [38] is a particularly clear illustration of this issue. The adoption of the more recent EQ-5D-5L which features five levels of responses may help address this question of sensitivity. Nevertheless, it remains a concern that certain moments in the prevention and management of cervical cancer which would both intuitively be distressing and demonstrated as such by other evidence do not necessarily result in meaningful differences in HRQoL as measured by the EQ-5D.

The implications of this limited, fragmented, highly variable, evidence-based for researchers and HTA technicians when parametrising their models are serious. The choice of appropriate HRQoL estimates available is far

from satisfactory. Often in this sort of situation, researchers try to mitigate the potentially deleterious effects of such evidence by selecting one study to use in primary analysis and a set of values from another study for sensitivity analysis. This is only an acceptable solution if the two analyses do not produce conflicting cost-effectiveness results. Signs of the effect of this difficult evidence base are apparent in the literature. A recent CEA opted to employ life-years gained (LYGs) as its primary measure of effectiveness rather than quality-adjusted life-years (QALYs) because of insufficient good-quality estimates. While the use of LYGs avoids the problems posed by inadequate HRQoL estimates it does not fundamentally overcome the problem, especially as national HTA agencies typically require CEAs to employ QALYs as the measure of health gain [13, 14].

Consideration of HRQoL in CEA is important in general but especially in the case of cervical screening, CIN and cancer management. Studies of specific quality of life issues indicate that screening for cervical disease as well as management and follow-up of CIN and cancer have an important impact on aspects of HRQoL [45–47]. For example, very high levels of anxiety have been reported in women who have received an abnormal cervical smear test result. Such women also have worries about cancer and fertility. In women who have undergone colposcopy or related procedures, there can be concerns relating to sex and fertility [21, 45, 48]. Similarly, studies in women diagnosed with cervical cancer have shown psychosexual and functional HRQoL impacts. These other findings with regard to specific aspects of HRQoL also illustrate the well-understood limitations of the EQ-5D with respect to sensitivity [44]. An excellent illustration of this is provided in Korfage et al. [38], a study included in this review. Alone of all measures administered by the research team, the EQ-5D did not detect any significant difference in HRQoL between women referred for colposcopy and a reference group of women who had undergone screening.

A further issue of consideration in CEAs is to draw HRQoL estimates from as few sources as possible (preferably from one study) as doing otherwise could introduce uncertainty, particularly when HRQoL weights vary by territory. While developments in HRQoL assessment, such as the introduction and validation of the EQ-5D-5L, present the possibility of better (i.e. more sensitive) estimates becoming available in time, there still exists a serious need for large, comprehensive studies employing common methods that cover health states across as much of the vaccination-cancer pathway as possible.

Limitations

Although we made all practicable efforts to ensure that our search strategy and choice of databases was comprehensive enough to ensure the inclusions of all relevant studies, it is always possible that some were missed in the search or excluded during the initial screen. Additionally, we did not include the grey literature—namely research only reported as conference proceedings or only published as official reports. The nature of these studies makes it difficult to include them in a systematic way, and abstracts usually do not provide sufficient detail to be certain of the detail of the design, methods and findings.

The absence of an existing and accepted quality scoring tool required us devise our own based on existing frameworks. While the outcomes of any such quality scoring tools are contingent upon the items included and their relative weights, our methodology is clearly described and, in as far as possible, based on objective characteristics of the reviewed studies. Given the qualifications regarding scoring tools, readers should interpret the quality appraisal results appropriately.

Conclusion

This systematic review indicates that it is very hard to draw strong conclusions on the effect of primary and secondary prevention of cervical cancer and its treatment on HRQoL (at least as measured by the EQ-5D); the evidence base is simply too fragmented and heterogeneous. Irrespective of this, the shape and nature of cervical cancer prevention is changing and will continue to change for many years. To allow policy decisions in this important area of public health to be underpinned by robust evidence informed by an understanding of QoL, there is an urgent need for more, larger and better studies that capture HRQoL in a consistent way from HPV vaccination through cervical screening and management of CIN to treatment for invasive cancer.

Acknowledgements This study was undertaken as part of the CERVIVA research consortium (www.cerviva.ie). AOC (HRA-HSR/2012/30), JOM (ICE 2015-1037) and MOC (ICE 2015-1037) are supported by grants from the Health Research Board.

Compliance with ethical standards

Conflicts of interest No authors have a potential conflict of interest.

Appendix

See Table 4.

Table 4 Health state values for Galante et al. (2011)

Health state	Argentina		Chile		UK	
	Mean	95% CI	Mean	95% CI	Mean	95% CI
CIN1	0.848	0.808–0.889	0.768	0.728–0.807	0.765	0.715–0.815
CIN2&3	0.688	0.626–0.75	0.515	0.515–0.647	0.575	0.5–0.651
Cervical cancer	0.397	0.344–0.448	0.21	0.142–0.277	0.152	0.086–0.218
Cured cancer	0.782	0.736–0.829	0.69	0.649–0.730	0.691	0.634–0.748

References

- Bray, F., Ren, J.-S., Masuyer, E., & Ferlay, J. (2013). Global estimates of cancer prevalence for 27 sites in the adult population in 2008. *International Journal of Cancer*, *132*(5), 1133–1145. doi:10.1002/ijc.27711.
- International Agency for Research on Cancer. (2005). *IARC Handbooks of Cancer Prevention Vol. 10: Cervix Cancer Screening* (p. 313). Lyons.
- Anttila, A., von Karsa, L., Aasmaa, A., Fender, M., Patnick, J., Rebolj, M., et al. (2009). Cervical cancer screening policies and coverage in Europe. *European Journal of Cancer*, *45*(15), 2649–2658. doi:10.1016/j.ejca.2009.07.020.
- Walboomers, J. M., Jacobs, M. V., Manos, M. M., Bosch, F. X., Kummer, J. A., Shah, K. V., et al. (1999). Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *The Journal of Pathology*, *189*(1), 12–19. doi:10.1002/(SICI)1096-9896(199909)189:1<12:AID-PATH431>3.0.CO;2-F.
- Arbyn, M., De Sanjosé, S., Saraiya, M., Sideri, M., Palefsky, J., Lacey, C., et al. (2012). EUROGIN 2011 roadmap on prevention and treatment of HPV-related disease. *International Journal of Cancer*, *131*(9), 1969–1982.
- Bhatia, R., Kavanagh, K., Cubie, H. A., Serrano, I., Wennington, H., Hopkins, M., et al. (2016). Use of HPV testing for cervical screening in vaccinated women—Insights from the SHEVA (Scottish HPV Prevalence in Vaccinated Women) study: Use of HPV Testing for Cervical Screening. *International Journal of Cancer*, *138*(12), 2922–2931. doi:10.1002/ijc.30030.
- Guan, P., Howell-Jones, R., Li, N., Bruni, L., de Sanjosé, S., Franceschi, S., et al. (2012). Human papillomavirus types in 115,789 HPV-positive women: a meta-analysis from cervical infection to cancer. *International Journal of Cancer*, *131*(10), 2349–2359. doi:10.1002/ijc.27485.
- Lehtinen, M., Paavonen, J., Wheeler, C. M., Jaisamrarn, U., Garland, S. M., Castellsagué, X., ... HPV PATRICIA Study Group. (2012). Overall efficacy of HPV-16/18 AS04-adjuvanted vaccine against grade 3 or greater cervical intraepithelial neoplasia: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. *The Lancet Oncology*, *13*(1), 89–99. doi:10.1016/S1470-2045(11)70286-8.
- Brotherton, J. M., Fridman, M., May, C. L., Chappell, G., Saville, A. M., & Gertig, D. M. (2011). Early effect of the HPV vaccination programme on cervical abnormalities in Victoria, Australia: an ecological study. *The Lancet*, *377*(9783), 2085–2092. doi:10.1016/S0140-6736(11)60551-5.
- Palmer, T. J., McFadden, M., Pollock, K. G. J., Kavanagh, K., Cuschieri, K., Cruickshank, M., et al. (2016). HPV immunisation and cervical screening—confirmation of changed performance of cytology as a screening test in immunised women: a retrospective population-based cohort study. *British Journal of Cancer*, *114*(5), 582–589. doi:10.1038/bjc.2015.474.
- Palmer, T. J., McFadden, M., Pollock, K. G. J., Kavanagh, K., Cuschieri, K., Cruickshank, M., et al. (2016). HPV immunisation and increased uptake of cervical screening in Scottish women: observational study of routinely collected national data. *British Journal of Cancer*, *114*(5), 576–581. doi:10.1038/bjc.2015.473.
- Kim, J. J., Wright, T. C., & Goldie, S. J. (2002). Cost-effectiveness of alternative triage strategies for atypical squamous cells of undetermined significance. *JAMA*, *287*(18), 2382–2390.
- National Institute for Health and Care Excellence. (2013). *Guide to the methods of technology appraisal 2013*. London: National Institute for Health and Care Excellence. Retrieved from <https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781>
- Health Information and Quality Authority. (2014). *Guidelines for the Economic Evaluation of Health Technologies in Ireland* (Guidelines). Dublin, Ireland: Health Information and Quality Authority. Retrieved from https://www.google.ie/url?sa=t&rct=j&q=&esrc=s&source=web&cd=2&ved=0ahUKewiT8uqqqM7QAhWpIMAKHT4aAxoQFggfMAE&url=https%3A%2F%2Fwww.hiqa.ie%2Fsystem%2Ffiles%2FHTA_Economic_Guidelines_2010.pdf&usq=AFQjCNGFcHjU2xjrOfE6hC4Ocqpv_AhxYw&sig2=AmhXqI0IR-pmO_TeHmU4aw
- Rabin, R., & de Charro, F. (2001). EQ-5D: a measure of health status from the EuroQol Group. *Annals of Medicine*, *33*, 337–343.
- Wisløff, T., Hagen, G., Hamidi, V., Movik, E., Klemp, M., & Olsen, J. A. (2014). Estimating QALY gains in applied studies: A review of cost-utility analyses published in 2010. *Pharmacoeconomics*, *32*(4), 367–375. doi:10.1007/s40273-014-0136-z.
- Devlin, N. J., & Krabbe, P. F. M. (2013). The development of new research methods for the valuation of EQ-5D-5L. *The European Journal of Health Economics*, *14*(S1), 1–3. doi:10.1007/s10198-013-0502-3.
- Kavanagh, A. M., & Broom, D. H. (1997). Women's understanding of abnormal cervical smear test results: a qualitative interview study. *BMJ (Clinical research ed.)*, *314*(7091), 1388–1391.
- Gray, N. M., Sharp, L., Cotton, S. C., Masson, L. F., Little, J., Walker, L. G., et al. (2006). Psychological effects of a low-grade abnormal cervical smear test result: anxiety and associated factors. *British Journal of Cancer*, *94*(9), 1253–1262. doi:10.1038/sj.bjc.6603086.
- O'Connor, M., Gallagher, P., Waller, J., Martin, C. M., O'Leary, J. J., Sharp, L., & Irish Cervical Screening Research Consortium (CERVIVA). (2016). Adverse psychological outcomes following colposcopy and related procedures: a systematic review. *BJOG: An International Journal of Obstetrics & Gynaecology*, *123*(1), 24–38. doi:10.1111/1471-0528.13462.
- Gold, M. R., Franks, P., McCoy, K. I., & Fryback, D. G. (1998). Toward consistency in cost-utility analyses: using national measures to create condition-specific values. *Medical Care*, *36*(6), 778–792.
- Myers, E., Green, S., & Lipkus, I. (2004). Patient preferences for health states related to HPV infection: visual analogue scales vs. time trade-off elicitation. In *Proceedings of the 21st International Papillomavirus Conference*. Presented at the 21st International Papillomavirus Conference, Mexico City.

23. Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & PRISMA Group. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Journal of Clinical Epidemiology*, 62(10), 1006–1012. doi:10.1016/j.jclinepi.2009.06.005.
24. Neumann, P. J., Greenberg, D., Olchanski, N. V., Stone, P. W., & Rosen, A. B. (2005). Growth and quality of the cost-utility literature, 1976–2001. *Value in Health: The Journal of the International Society for Pharmacoeconomics and Outcomes Research*, 8(1), 3–9. doi:10.1111/j.1524-4733.2005.04010.x.
25. UNDP. (2015). *Work for human development*. New York, NY: United Nations Development Programme.
26. Vistad, I., Fosså, S. D., & Dahl, A. A. (2006). A critical review of patient-rated quality of life studies of long-term survivors of cervical cancer. *Gynecologic Oncology*, 102(3), 563–572.
27. Woodhall, S., Eriksson, T., Nykanen, A.-M., Huhtala, H., Rissanen, P., Apter, D., et al. (2011). Impact of HPV vaccination on young women's quality of life - a five year follow-up study. *The European journal of contraception & reproductive health care: the official journal of the European Society of Contraception*, 16(1), 3–8.
28. Eriksson, T., Torvinen, S., Woodhall, S. C., Lehtinen, M., Apter, D., Harjula, K., et al. (2013). Impact of HPV16/18 vaccination on quality of life: a pilot study. *The European journal of contraception & reproductive health care: the official journal of the European Society of Contraception*, 18(5), 364–371.
29. Maissi, E., Marteau, T. M., Hankins, M., Moss, S., Legood, R., & Gray, A. (2005). The psychological impact of human papillomavirus testing in women with borderline or mildly dyskaryotic cervical smear test results: 6-month follow-up. *British Journal of Cancer*, 92(6), 990–994.
30. Whynes, D. K., & Group, T. (2008). Correspondence between EQ-5D health state classifications and EQ VAS scores. *Health and quality of life outcomes*, 6, 94. doi:10.1186/1477-7525-6-94.
31. Pirotta, M., Ung, L., Stein, A., Conway, E. L., Mast, T. C., Fairley, C. K., et al. (2009). The psychosocial burden of human papillomavirus related disease and screening interventions. *Sexually transmitted infections*, 85(7), 508–513.
32. Drolet, M., Brisson, M., Maunsel, E., Franco, E. L., Coutlee, F., Ferenczy, A., et al. (2012). The psychosocial impact of an abnormal cervical smear result. *Psycho-oncology*, 21(10), 1071–1081.
33. Korfage, I. J., van Ballegooijen, M., Wauben, B., Looman, C. W. N., Habbema, J. D. F., & Essink-Bot, M.-L. (2012). Having a Pap smear, quality of life before and after cervical screening: a questionnaire study. *BJOG: an international journal of obstetrics and gynaecology*, 119(8), 936–944.
34. Korfage, I. J., van Ballegooijen, M., Huvneers, H., & Essink-Bot, M.L. (2010). Anxiety and borderline PAP smear results. *European Journal of Cancer*, 46(1), 134–141. doi:10.1016/j.ejca.2009.07.003.
35. Whynes, D. K., Woolley, C., Philips, Z., & Trial of Management of Borderline and Other Low-grade Abnormal smears Group. (2008). Management of low-grade cervical abnormalities detected at screening: which method do women prefer? *Cytopathology: official journal of the British Society for Clinical Cytology*, 19(6), 355–362.
36. Galante, J., Augustovski, F., Colantonio, L., Bardach, A., Caporale, J., Marti, S. G., et al. (2011). Estimation and comparison of EQ-5D health states' utility weights for pneumococcal and human papillomavirus diseases in Argentina, Chile, and the United Kingdom. *Value in health: the journal of the International Society for Pharmacoeconomics and Outcomes Research*, 14(5 Suppl 1), S60–S64.
37. Whynes, D. K. (2013). Does the correspondence between EQ-5D health state description and VAS score vary by medical condition? *Health and quality of life outcomes*, 11(101153626), 155.
38. Korfage, I. J., Essink-Bot, M.-L., Westenberg, S. M., Helmerhorst, T., Habbema, J. D. F., & van Ballegooijen, M. (2014). How distressing is referral to colposcopy in cervical cancer screening?: a prospective quality of life study. *Gynecologic Oncology*, 132(1), 142–148.
39. Murasawa, H., Konno, R., Okubo, I., & Arakawa, I. (2014). Evaluation of health-related quality of life for hypothesized medical states associated with cervical cancer. *Asian Pacific Journal of Cancer Prevention*, 15(22), 9679–9685. doi:10.7314/APJCP.2014.15.22.9679.
40. Marcellusi, A., Capone, A., Favato, G., Mennini, F. S., Baio, G., Haessler, K., et al. (2015). Health utilities lost and risk factors associated with HPV-induced diseases in men and women: The HPV Italian collaborative study group. *Clinical Therapeutics*, 37(1), 156–167. doi:10.1016/j.clinthera.2014.11.002.
41. Lang, H.-C. (2012). Quality of life, treatments, and patients' willingness to pay for a complete remission of cervical cancer in Taiwan. *Health Economics*.
42. Murasawa, H., Konno, R., Okubo, I., & Arakawa, I. (2014). Evaluation of health-related quality of life for hypothesized medical states associated with cervical cancer. *Asian Pacific journal of cancer prevention: APJCP*, 15(22), 9679–9685.
43. Parkin, D., Rice, N., & Devlin, N. (2010). Statistical analysis of EQ-5D profiles: does the use of value sets bias inference? *Medical Decision Making*, 30(5), 556–565. doi:10.1177/0272989X09357473.
44. Brooks, R. G. (2013). *The EuroQol Group after 25 years*. Dordrecht; New York: Springer. Retrieved from <http://public.eblib.com/choice/publicfullrecord.aspx?p=1030747>
45. O'Connor, M., O'Leary, E., Waller, J., Gallagher, P., D'arcy, T., Flannelly, G., ... Irish Cervical Screening Research Consortium (CERVIVA). (2015). Trends in, and predictors of, anxiety and specific worries following colposcopy: a 12-month longitudinal study. *Psycho-Oncology*. doi:10.1002/pon.3980.
46. McCaffery, K., Waller, J., Nazroo, J., & Wardle, J. (2006). Social and psychological impact of HPV testing in cervical screening: a qualitative study. *Sexually transmitted infections*, 82, 169–174. doi:10.1136/sti.2005.016436.
47. Heinonen, A., Tapper, A.-M., Leminen, A., Sintonen, H., & Roine, R. P. (2013). Health-related quality of life and perception of anxiety in women with abnormal cervical cytology referred for colposcopy: An observational study. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, 169(2), 387–391. doi:10.1016/j.ejogrb.2013.03.033.
48. Gray, N. M., Sharp, L., Cotton, S. C., Avis, M., Philips, Z., Russell, I., et al. (2005). Developing a questionnaire to measure the psychosocial impact of an abnormal cervical smear result and its subsequent management: The TOMBOLA (Trial of Management of Borderline and Other Low-grade Abnormal smears) trial. *Quality of Life Research*, 14(6), 1553–1562.