RESEARCH ARTICLE

A Systematic Review of Economic Aspects of Cervical Cancer Screening Strategies Worldwide: Discrepancy between Economic Analysis and Policymaking

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Abstract

Background: Organized cervical screening has decreased the incidence of cervical cancer. However, screening strategies vary in different countries. Objectives: We performed a systematic review to evaluate the economic aspects of different screening methods. Materials and Methods: We searched databases and then data were abstracted from each study. We evaluated articles based on different types of screening tests as well as screening age and intervals, and using incremental cost effectiveness ratio via calculating quality adjusted life years (QALY), or life years gained (LYG) per cost. We compared the incremental cost-effectiveness ratio (ICER) of each study using GDP per capita. Furthermore, we compared national guidelines with recommendations of cost-effectiveness studies in different countries. Results: A total of 21 articles met our criteria, of which 19 studies showed that HPV DNA testing, 13 suggested an age of 30 years or more, and 10 papers concluded that at least a 5-year or longer interval were the most cost-effective strategies. In some countries, the national guidelines did not match the recommendations of the cost-effectiveness studies. Conclusions: HPV testing, starting at age 30 years or older and repeated at 5-year or longer intervals, is the most cost-effective strategy in any setting. Closer collaboration with health economists is required during guideline development.

Keywords: Cervical cancer screening - economic evaluation - cost effectiveness - systematic review

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Introduction

Cervical cancer is the fourth most common cancer found in women worldwide (Ferlay et al., 2013). According to Globocan 2012, the incidence and mortality rates of cervical cancer were 14 and 6.8 per 100000 worldwide (Ferlay et al., 2013). Cervical cancer screening is one of the best methods to find premalignant lesions on the cervix (Wright, 2006), and implementation of cervical screening programs has decreased the incidence and mortality of cervical cancer in high income countries (Ferlay et al., 2007). Notwithstanding the fact that cervical screening has been implemented in many Western countries, the mortality rate of this cancer is still high, indicating that there is still a lack of effective screening programs in these countries. Before the introduction of the Pap smear in 1974, the incidence rate of cervical cancer was 44 per 100,000 in the United States and this has reduced to 5.7 per 100,000 in 2010 through Pap smear screening and cervical cancer prevention programs (Ries, 1999). Different screening tests including; conventional cytology (Pap smear), liquid based cytology (LBC) and human papillomavirus (HPV) DNA testing, Direct Visual Inspection (DVI) are used for cervical screening. However, a combination of these methods with different screening intervals and starting age creates a variety of strategies in a screening program. Regular screening with Pap smears has been the only screening strategy for many years worldwide (Anderson et al., 2008).

In spite of high specificity, cervical cytology has many limitations including; low sensitivity, difficulty in the sampling process and inadequate sampling (Denton et al., 2010; Salit et al., 2010). LBC is the method for sampling and preparing a thin layer of cervical cells used for the detection of abnormal cells. Since HPV infection is the most important risk factor for cervical cancer, new technologies have been developed to find HPV in cervical cancer smears (Wang et al., 2013). No differences between

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LBC and conventional cytology have been found in terms of their sensitivity and specificity, however, LBC improves the sampling technique (Whitlock et al., 2011; Chen et al., 2012). Recent studies have shown that HPV DNA testing is more sensitive than Pap smear testing (Schiffman et al., 2011). Another screening method is DVI which needs simple structure and low equipment, but DVI has low specificity and low positive predictive value. This method is suitable for low resource settings (Sankaranarayanan et al., 2012; Nessa et al., 2013; Parashari and Singh, 2013).

In addition to the effectiveness of screening methods, there are other arguments related to frequency and age range, to show screening effectiveness (Anderson et al., 2008).

The cost-effectiveness studies can provide policy makers with an analytical tool to compare health benefit and cost(Garber and Sox, 2010). A cost-effectiveness analysis (CEA) compares two or more alternative interventions based on the differences in their costs and effectiveness and some CEA studies can simulate final outcomes from current data (Galarraga et al., 2009). Cost in economic evaluation represents a measure of resources used in each strategy, and effectiveness is the health effect of strategies which can be measured both in clinical terms like sensitivity, and specificity of methods, or economic terms such as QALY (Hernandez et al., 2008). The results of a CEA are presented by an incremental cost effectiveness ratio (ICER). An ICER computes the differences between the cost and effectiveness of different strategies and determines the most cost-effective strategy within an acceptable threshold, thereby assisting policy makers to better allocate their resources. ICERs and the acceptable threshold of cost-effective strategy can be presented in a cost-effectiveness plane. In this plane, the acceptability threshold is presented by a gradient line above which the ICERs are high and corresponding interventions are not acceptable (Eichler et al., 2004, Bambha and Kim, 2004).

We performed a systematic review of articles published on the cost-effectiveness of different cervical cancer screening strategies, which included starting age, screening intervals and screening test(s). The main objective of this study was to critically appraise and summarise current evidence on the cost-effectiveness of cervical cancer screening strategies. In specific, we aimed to; *i*) compare cost-effective strategies in low and high income countries, *ii*) compare national guidelines in cervical screening with strategies suggested in the cost-effectiveness analysis.

Materials and Methods

We systematically sought peer reviewed literature databases from 31 May until 7 June 2012. Our search was limited to papers that were published in English including; Medline through Pub Med, Web of Science, Embase and HTA via Ovid. There was no limitation in the year of study in order to avoid publication bias.

The search strategy contained three different parts: *i*) cervical cancer, *ii*) prevention, and *iii*) economic evaluation. Mesh terms such as; vaginal smears, cervix dysplasia, CIN, screening, QALY, cost effectiveness, diagnostic error, sensitivity and specificity, and text words such as Pap smear, conventional cytology, LBC, HPV DNA testing, modeling and Markov model, were used in different combinations in the data bases. Our search strategy is available on request. We followed the PRISMA guidelines in this study (Moher et al., 2009).

Inclusion and exclusion criteria

We only included studies that compared both cost and effectiveness. In addition, we included studies that compared two or three of these interventions (LBC, HPV DNA testing and conventional cytology) as primary screening tests.

The exclusion criteria were; original papers which compared screening strategies using DVI which is more suitable for use in low resource settings(Nahar et al., 2011), HPV vaccination, and studies that evaluated cost-effectiveness of screening strategies in special populations such as HIV infected women or hepatitis. Review articles, editorials and protocols were also excluded from our analyses. At least two methods were evaluated. We excluded studies if just one screening method was assessed, for example the cost effectiveness of Pap smear strategies only. Because cervical cancer is a chronic disease and the screening process performed over the life time of a woman, multistate models based on Markov process are well defined methods to evaluate the transitional rate of disease stage (Jackson et al., 2003). Therefore, we excluded papers where the author(s) did not use a Markov model in their analyses.

PICOD

Our PICOD included; population (P) (women of screening age), interventions (I) and comparison (liquid based cytology, conventional method (C), (HPV–DNA testing), outcomes (O) (cost-effectiveness including, incremental cost-effectiveness ratios (ICERs)) and design (D) (full economic evaluation).

Sifting process

Sifting was conducted systematically through four different steps, and carried out by two different assessors. After screening of the papers' titles, the abstracts were obtained and screened during the second sift. Subsequently we studied and critically appraised the full text of the papers using a checklist, and we included papers that met our criteria in our final analyses.

Data extraction

We extracted some variables from each paper including; author's name, published year, country, discounting rate, cost, quality of life adjusted life years gained (QALY), age range (based on the most cost-effective strategy), interval of screening (based on the most cost-effective strategy), and incremental cost effectiveness ratio (ICER). Full economic evaluation studies were selected for this study. Therefore, we assumed ICER as an outcome instead of other base case assumptions, such as test performance and costs. Data were extracted by two reviewers, independently. Because currencies differ

between different countries, the ICERs were estimated based on purchasing power parities (PPP) in international dollars for 2011 to integrate the ICERs(Sharifah et al., 2009). For articles performed in The United States we used the inflation rate to integrate the ICERs(Stat). Then we compared the converted ICERs with GDP per capita for each country. We divided starting age of screening into two subgroups by age (i.e., less and more than 30 years) and four subgroups by screening intervals (i.e., 2, 3, 5 and 10 year intervals). In addition, we categorized countries into three groups based on their income (i.e., high, middle and low income countries). Finally, we compared the cost-effective strategy suggested in the articles with latest screening guidelines in corresponding countries to see how scientific evidence is applied in public health practice.

Critical appraisal

We used Drummond's check list (Drummond MF, 2005) for critical appraisal of the selected papers. The check list contains 10 questions in the context of consequences and costs including; opportunity cost or resources, measurement of cost effectiveness, e.g., QALY, life years gained, type of sensitivity analysis (one or two ways), and generalizability. Critical assessment was performed by two reviewers independently and the reviewers were not blinded to the name of authors. The differences were discussed and resolved by consensus. We set up a meeting with a third reviewer to reach a consensus.

Statistical analysis

Although it is possible to perform a meta-analysis of economic evaluation studies in theory, it is not usually applicable to reach summary estimates because of the heterogeneity found in the methodology and insufficient data about the details(Reviews et al., 2009) . As a result, we could not perform any meta-analysis and the results were evaluated qualitatively.

Results

Result of the sifting process

The systematic review search retrieved 2911 potentially relevant titles. We read 1235 abstract then in third step 90 full text reviewed, finally in the four step of sifting process, 21 full texts were included in the review, and based on our evaluation 20 articles were of high quality and one article remained in the low quality category (Figure1).

Comparison of starting age of screening

Only three studies suggested that screening is cost-effective if started at an age less than 30 years. Mandelblatt et al. (2002) in the USA, showed that a combination of cytology and HPV DNA testing (co-screening) every two years in 20-year-old women was cost-effective (Mandelblatt et al., 2002b). Kulasingam et al. performed a study in Canada and found that a strategy with initial HPV DNA testing in women at 25 years was cost-effective (Kulasingam et al., 2009). Vijayaraghavan (2010) in the USA, expressed that implementing a program with HPV triage every three years after 30 years was the most cost-effective strategy (Vijayaraghavan et al., 2010a).

Thirteen articles suggested that screening with a starting age of more than 30 years was a cost-effective method. Goldie et al. (2001) in South Africa, suggested HPV DNA testing every three years from age 35 as the most cost-effective strategy. Although PICOD, did not include direct visual inspection (DVI), it was suggested by Goldie as another cost-effective strategy (Goldie et al., 2001). In another study conducted by Goldie et al. in the USA in 2004, liquid based cytology with HPV DNA testing only for atypical squamous cells of undetermined significance (ASCUS) management with a starting age of 30 years was the most cost-effective strategy (Goldie et al., 2004). According to Andres-Gamboa et al. (2008), the most cost-effective strategy in Colombia was HPV DNA testing every five years starting in 30 year old women (Andres-Gamboa et al., 2008). In another project conducted in five less developed countries including; Kenya, Peru, South Africa and Thailand in 2005, Goldie suggested that applying HPV DNA testing just two times per lifetime i.e., at age 35 and 45 years was the most cost-effective, moreover, this strategy was dominated in India (Goldie et al., 2005). In Sweden, Bisoleti et al. showed that combined HPV DNA testing and cervical cytology three times per life time starting at age 32 was the most cost effective method (Bistoletti et al., 2008). Levin suggested rapid HPV DNA testing three times in a lifetime and starting at age 35 was the most cost-effective strategy at the national, township and county level in China (Levin et al., 2010).

Mandelblatt et al. in Thailand modeled three strategies including; VIA, HPV DNA testing, and Pap smears and concluded that VIA with immediate treatment for women aged 35-55 years was the most cost-effective strategy (Mandelblatt et al., 2002a). Sroczynski et al. conducted a study in Germany and reported that HPV DNA testing alone every two years starting at age 30 was the most cost-effective strategy. In addition he mentioned that for women aged 25-29 cytology was cost effective(Sroczynski et al.,

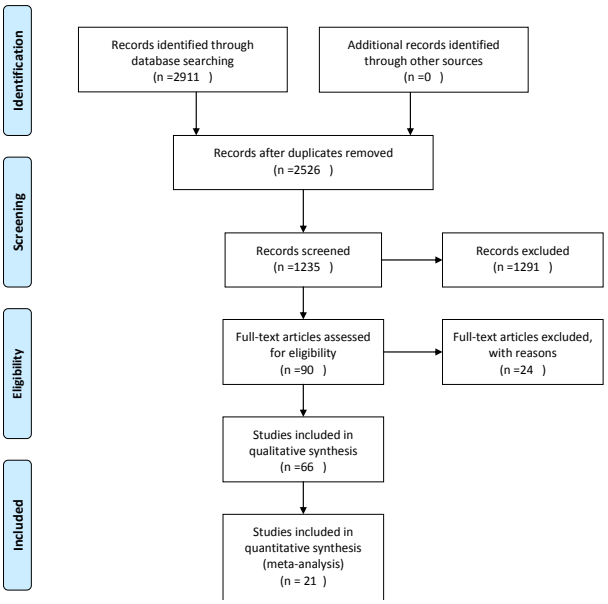

Figure 1. Sifting Process of Systematic Review of Studies Published about Cost Effectiveness of Cervical Sceening Strategies

2011). Chuck et al. remarked that Pap smear screening every three years for all Canadian women and HPV triage for women older than 30 years with ASCUS were the most cost-effective strategies (Chuck, 2010). Chow et al. from Taiwan, suggested that HPV triage every five years for women older than 30 years was the most cost-effective strategy in 2010 (Chow et al., 2010). De Kok designed and performed a cost-effectiveness study in European countries and concluded that HPV DNA testing after the age of 30 years was the dominant strategy (de Kok et al., 2012). Burger et al. indicated that cytology for younger women and HPV DNA testing every four years after the age of 34 years was the most cost-effective in Norway (Burger et al., 2012). Kim et al. compared four European countries including; France, the Netherlands, Italy and the United Kingdom, they concluded that HPV DNA testing, both in combination with cytology or triage, for ages higher than 30 years was cost effective (Kim et al., 2005). Bidus et al. and Maxwell et al. did not clearly suggest any specific age to start screening. However, Bidus mentioned that screening after the age of 30 years was not cost-effective (Maxwell et al., 2002; Bidus et al., 2006). Berkhof et al. (2010) in the Netherlands, indicated that starting screening with HPV triage with 5 years interval was the most cost effective strategies (Berkhof et al., 2010).Vijayaraghavan in South Africa reported that co-screening with HPV testing was less costly and the most effective strategy (Vijayaraghavan et al., 2009).

Based on income we just found 5 articles in high income countries suggested starting age of screening below age 30 (Mandelblatt et al., 2002b; Kulasingam et al., 2009; Chuck, 2010; Vijayaraghavan et al., 2010a; Sroczynski et al., 2011)(Table1).

Four articles in four high income countries (Goldie et al., 2001; 2004; Mandelblatt et al., 2002a; Goldie et al., ; Bistoletti et al., 2008; Burger et al., 2012; de Kok et al., 2012), nine middle income countries from seven articles (Goldie et al., 2005; Andres-Gamboa et al., 2008; Vijayaraghavan et al., 2009; Chow et al., 2010; Levin et al., 2010) and 1 article in low income countries suggested starting age after age 30 (Goldie et al., 2005)(Table 1).

Comparison of strategies by screening interval

Considering the intervals of screening with the various strategies, we categorized four groups of 2, 3, 5, and 10 year intervals. We excluded some articles that did not include the interval in their analyses because they chose different intervals from our selected categories. Three studies suggested two year intervals of screening combined with a co-screening strategy (Mandelblatt et al., 2002b; Bidus et al., 2006; Sroczynski et al., 2011). Five articles recommended three-year intervals (Brown and Garber, 1999; Goldie et al., 2001, Maxwell et al., 2002; Chuck, 2010; Vijayaraghavan et al., 2010a), and three selected co-screening every three years (Maxwell et al., 2002; Sherlaw-Johnson and Philips, 2004; Chuck, 2010). One article remarked that HPV DNA triage should occur every three years (Vijayaraghavan et al., 2010a), another declared that HPV DNA testing or VIA every three years was most effective (Goldie et al., 2001), and one suggested Pap smears with 10% re-screening every three years with PAPNET, which is a type of LBC method (Brown and Garber, 1999). Goldie in the USA, declared that a two- to three-year interval for screening with a co-screening strategy was best (Goldie et al., 2004). Burger in Norway, suggested screening with cytology for younger women and HPV DNA testing strategy every four years after the age of 34 years (Burger et al., 2012). Seven papers suggested a five-year interval with various strategies such as HPV DNA testing (Andres-Gamboa et al., 2008; Kulasingam et al., 2009; Levin et al., 2010), HPV DNA triage (Berkhof et al., 2010; Chow et al., 2010), and primary HPV DNA in both types of co-screening or triage (de Kok et al., 2012). Mandelblatt suggested VIA with immediate treatment every five years as the most cost-effective method in Thailand (Mandelblatt et al., 2002b). One article modeled screening strategies and concluded that HPV DNA triage with three- and five-year intervals and co-screening every three years were the most cost-effective strategies in Italy, the United Kingdom, France and the Netherlands (Kim et al., 2005). Bistoletti studied the cost-effectiveness of screening methods in Sweden and concluded that co-screening strategy at nine-year intervals was the most effective strategy (Bistoletti et al., 2008). Two articles indicated that 10-year intervals with HPV DNA testing was the most cost-effective strategy for five less developed countries and a co-screening strategy for South Africa (Vijayaraghavan et al., 2009).

From the point of view of economic aspect of articles in high income countries, four articles suggested 2 years interval of screening (Mandelblatt et al., 2002b; Goldie et al., 2004; Bidus et al., 2006; Sroczynski et al., 2011). Six articles proposed 3-5 years interval (Brown and Garber, 1999; Maxwell et al., 2002; Kim et al., 2005; Chuck, 2010; Vijayaraghavan et al., 2010b; Burger et al., 2012) and three articles showed that 5 years interval between screenings was cost effective (Kulasingam et al., 2009; Berkhof et al., 2010; de Kok et al., 2012). We just found one article in Sweden indicating that 9 years interval was cost effective (Bistoletti et al., 2008)(Table1).

In middle (High and Low) income countries one article suggested 3 years interval of screening (Goldie et al., 2001). In four articles 5 years interval was recommended (Mandelblatt et al., 2002a; Andres-Gamboa et al., 2008; Chow et al., 2010; Levin et al., 2010)and six countries in 2 articles indicated that 10 years interval was cost effective (Goldie et al., 2005; Vijayaraghavan et al., 2009)(Table1).

In one low income country, Goldie et al. were suggested 10 years interval of screening (Goldie et al., 2005) (Table1).

Reviewing the most cost effective strategies

The reviewed articles comprised the most cost-effective strategies (Table 2). The table clearly shows that the various strategies were found to be the most cost-effective based on Markov modeling in each setting. The most recommended strategy by authors was HPV DNA testing (Goldie et al., 2001; 2005; Andres-Gamboa et al., 2008; Kulasingam et al., 2009; Levin et al., 2010; Sroczynski et al., 2011; Burger et al., 2012; de Kok et al., 2012). However, the most cost-effective strategy in three articles was not related to our PICOD (Goldie et al.,

Table 1. Comparison of National Guidelines with Recommendations of Cost-Effectiveness Analyses in the Corresponding Countries about Cervical Screening Tests, Starting Age and Screenig Intervals Stratified by the Economic Situaiotn of the Countires

Authors(Year)/Country	Country	Screening Interval		Screening Interval		Screening test	
		Suggestion	National guideline	Suggestion	National guideline	Suggestion	National guideline[2]
High income country							
Berkhof(2010)/	Netherlands	5	5*	-	30*	HPV-T	PLC, PC*
Bistoletti(2008)	Sweden	9	3**	>30	25**	Co screening	PC, HPV-T**
Burger(2012)	Norway	4	3*	34	20*	Cytology for younger & HPV DNA after 34	PC, PLC*
Kim(2005)	UK	3-5	3(25-49)-5(50-64) *	-	25 and 50*	HPV-T	PLC*
Kim(2005)	Netherlands	3-5	5*	-	30*	HPV-T	PLC, PC*
Kim(2005)	France	3-5	1 and 3*	-	25 and 27*	HPV-T	PC, HPV-P*
Kim(2005)	Italy	3-5	3*	-	25*	HPV-T or co screening	PLC, PC, HPV-P*
Sroczynski(2011)	Germany	2	1**	25-29/30	20**	PC/ HPV-P	PC**
De Kok(2012)	Europe	5	-	>30	-	-	-
Vijayaraghavan(2010)	USA	3	3*	<30	21*	HPV-T	PLC, PC*
Mandelblatt(2002)	USA	2	3*	20	21*	Co screening	PLC, PC*
Goldie(2004)	USA	2-3	3*	>30	21*	Co screening	PLC, PC*
Bidus(2006)	USA	2	3	-	21	PLC, reflex HPV	PLC, PC*
Brown(1999)	USA	3	3	-	21	PC, 10% PLC	PLC, PC*
Maxwell(2002)	USA	3	3*	-	21*	Co Screening	PLC, PC*
Chuck(2010)	Canada	3	Varies by Prov. *	>30	21*	PC, HPV-P,PC	PLC, PC*
Kulasimgam (2009)	Canada	5	Varies by Prov. *	25	21*	HPV-P	PLC, PC*
Middle income country							
Chow(2010)	Taiwan	5	1[35]**	30	30-69[35]**	HPV-T	PC[35]**
Andres-Gamboa(2008)	Colombia	5	1-1-3[28]***	30	21[28]***	HPV-P	PC[28]**
Levin(2010)	China)	5(3 times)	-	35	35*	HPV-P	PC, PLC, VILI/VIA*
Vijayaraghavan(2008)	South Africa	10(3 times)	10[42]**	-	>30[42]**	Co screening	PC[42]**
Mandelblatt(2002)	Thailand	5	3	35	VIA with immediate treatment		-
Goldie(2001)	South Africa	3	10[42]**	35	>30[42]**	HPV-P or DVI	PC[42]**
Goldie(2005)	India	10	-	35	-	HPV-P or DVI	-
Goldie(2005)	Thailand	10		35		HPV-P or DVI	-
Goldie(2005)	Kenya	10	-	35	-	HPV-P or DVI	-
Goldie(2005)	South Africa	10	10[42]**	35	>30[42]**	HPV-P or DVI	PC[42]**
Low income country							
Goldie(2005)	Peru	10	2	35	25	HPV-P or DVI	-

*From International Cancer Screening Network67; **From articles; ***PLC=Liquid-based cytology; PC=Pap test; HPV-T=HPV test triage; HPV-P=HPV test primary screening; DVI=Direct visual inspection

Table 2. The Most Cost Effective Cervical Screening Strategies Suggested by Different Research Groups Worldwide between 1999and 2012

Cost effective Strategies	High income countries	Middle Income Countries	Low income countries
HPV DNA triage	Kim(2005),Vijayaraghavan(2010), Berkhof(2010),Bidus(2006)	Chow(2010)	-
Cytology with HPV combination (co-screening)	Kim(2005),Mandelblatt(2002), Goldie(2004), Bistoletti(2008), Maxwell(2002)	vijayaraghavan(2008)	-
HPV DNA testing	De Kok(2012), Burger(2012), Kulasingam(2009), Sroczynski(2011)*	Goldie(2001), Andrés-Gamboa(2008), Levin(2010), Goldie(2005)	Goldie(2005)
3 year Pap+ HPV+ Pap age(Pap screening every 3 years for all women and HPV triage for women older than 30 with ASCUS)	Chuck(2010)	-	-
VIA with the immediate treatment	-	Mandelblatt (2002)	-
Pap smear with 10% rescreening with Pap net	Brown(1999)	-	-

*For age 25-29 cytology was cost effective

2001; Mandelblatt et al., 2002a; Goldie et al., 2005). In addition, Goldie et al. in 2001 and 2005, recommended HPV DNA testing in low resource settings, they also remarked that DVI once or twice per lifetime can play another cost-effective role in low resource settings (Goldie et al., 2005; 2001).

Results by outcomes

We extracted the ICER of countries in each article. Methods for calculating the ICER in six articles were; cost/ QALY (Mandelblatt et al., 2002b, Berkhof et al., 2010; Chuck, 2010; Chow et al., 2010; Vijayaraghavan et al., 2009; 2010a), in 13 studies the ICER were estimated by cost/LYG (Brown and Garber, 1999; Maxwell et al., 2002; Mandelblatt et al., 2002a; Goldie et al., 2001; 2004; 2005; Kim et al., 2005; Bidus et al., 2006; Andres-Gamboa et al., 2008; Kulasingam et al., 2009; Levin et al., 2010; Sroczynski et al., 2011; Burger et al., 2012). Two studies did not report their ICER (Bistoletti et al., 2008; de Kok et al., 2012). The converted ICER of each country was compared with GDP per capita; in the USA, the ratio of ICER based on GDP per capita was approximately five fold (Goldie et al., 2004), and in other countries it was up to three times higher. We could not estimate ICER for one study in European countries due to a lack of data such as a separate ICER for each country (de Kok et al., 2012), and one article did not report the index year (Chow et al., 2010) .

Comparison of studies based on income

According to World Bank (Moore et al., 2007), we classified studies into high, middle and low income countries. Fourteen studies were categorized as a high income countries (Brown and Garber, 1999; Mandelblatt

et al., 2002b; Maxwell et al., 2002; Goldie et al., 2004; Kim et al., 2005; Bidus et al., 2006; Bistoletti et al., 2008; Kulasingam et al., 2009; Berkhof et al., 2010; Chuck, 2010; Vijayaraghavan et al., 2010a; Sroczynski et al., 2011; Burger et al., 2012; de Kok et al., 2012). Six studies were designed in middle income countries (Goldie et al., 2001; Maxwell et al., 2002; Andres-Gamboa et al., 2008; Vijayaraghavan et al., 2009; Chow et al., 2010; Levin et al., 2010). One study by Goldie et al. (2005) compared screening strategies in two income setting (middle and low income countries) (Goldie et al., 2005)(Table 1).

Comparison of suggested strategy and national screening guidelines

We found discrepancies between the national guidelines and the most cost-effective strategy suggested by researchers in the studied countries. In high income countries six article out of 14 articles suggested interval (Brown and Garber, 1999; Maxwell et al., 2002; Goldie et al., 2004; Kim et al., 2005; Berkhof et al., 2010; Vijayaraghavan et al., 2010a), in one article the suggested starting age (Vijayaraghavan et al., 2010a), and in four articles the suggested screening test (Brown and Garber, 1999; Bidus et al., 2006; Chuck, 2010; Sroczynski et al., 2011) were the same as national guideline. In middle income countries, from seven article the suggested interval in two article (Goldie et al., 2005; Vijayaraghavan et al., 2010a) and in three article the starting age was similar to the national guideline (Goldie et al., 2001; 2005; Levin et al., 2010) (Table 1).

Discussion

We conducted a systematic review to show the importance of using new technologies in different strategies of screening for women in any setting in terms of economic evaluation.

Following the development of new technologies in cervical screening, several mathematical models have been published in the past few years to determine which intervention has achieved the greatest effectiveness within the constraints of limited resources. Decision analytical models are quantitative models which represent real life conditions (Cantor et al., 2003). We found that current screening strategies in various countries were different from the cost-effective strategies suggested in the scientific articles. Choosing the most cost-effective strategy may not only save money but would also be more effective, alternatives include; starting cervical screening over the age of 30 years, screening intervals of five years or more and using HPV DNA testing.

Based on our knowledge, this is the first systematic review of articles which has reviewed the economic aspects of cervical cancer screening using mathematical models in both high and low settings. A systematic review conducted by Muhlberger et al. for the Germany Federal Ministry of Health showed that human papillomavirus-based cervical cancer screening was the most cost-effective in developed countries. However, they did not discuss the starting age of screening(MUhlhlberger et al., 2008).

This study had some limitations including the different currencies for each country. While many articles used international dollars (Maxwell et al., 2002; Mandelblatt et al., 2002a; 2002b; Goldie et al., 2001; 2004; 2005; Kim et al., 2005; Bidus et al., 2006; Andres-Gamboa et al., 2008; Vijayaraghavan et al., 2009; 2010a; Levin et al., 2010; Burger et al., 2012,), several authors used their own currency in their countries (Kulasingam et al., 2009; Berkhof et al., 2010; Chow et al., 2010; Chuck, 2010; Sroczynski et al., 2011). Another limitation was that each article only presented cost- effectiveness results based on their own strategies. It would appear that if all of the respective articles had compared the same strategies, their results would be different in each setting. We could not find the full text of 24 articles, one of the included articles did not provide a clear conclusion, so we decided to exclude it, as well (Sherlaw-Johnson and Philips, 2004). We included only peer reviewed literature in English. There may be a risk of publication bias which means a risk of negative findings that might not have been published in English (Higgins et al., 2008).

One of the most important objectives of this study was compatibility of screening starting age. According to the natural history of cervical cancer, women at ages lower than 30 years have more HPV infections than older women, although the virus in this age group tends to regress and it is often self-limited. Moreover, older women may experience the progression of this virus 116 times more frequently than younger women (Malloy et al., 2000; Hank et al., 2013). Therefore, HPV DNA testing after the age of 30 years seems to be more effective than before the age of 30. A higher age for starting the screening would also reduce the frequency of screening per lifetime and, thus, decrease the costs associated with screening. As we showed in this review, there were a number of articles which suggested that starting screening in women after 30 years-of-age is the most cost-effective strategy. The comparability of strategies based on a country's income showed that using new technologies and changing strategies to include an older age at screening commencement, would be the most cost-effective approach specially in middle income countries (Table 1).

The incidence and mortality of cervical cancer has decreased due to cytology screening in many countries (Arbyn et al., 2011; Dickinson et al., 2012). To prevent only one death from cervical cancer many screening program recommend cytology screening every year for 10 years, this is the area that many researchers want to show the importance of finding optimal intervals for screening (Kobayashi et al., 2012). In this review, many articles suggested that choosing a longer interval is one of the best strategies, not only in terms of screening effectiveness, but also to reduce the cost of the program (Table 1). Note that the ability to increase the length of the screening interval is dependent to a great extent on the testing modality and its sensitivity.

Many studies demonstrated that adding HPV DNA testing to cytological smears in screening programs enhances the detection of grade 2 or 3 cervical intraepithelial neoplasia (Naucler et al., 2007). From an economic point of view, we found two studies that did not suggest implementation of any type of HPV DNA testing in screening programs in Thailand and the USA (Brown

and Garber, 1999; Mandelblatt et al., 2002a). In addition to Mandelblatt who recommended visual inspection with acetic acid(VIA) with immediate treatment as the most cost-effective strategy in Thailand (Mandelblatt et al., 2002a), another study by Goldie (2005) suggested that HPV DNA testing or direct visual inspection(DVI) once or twice per lifetime was the most cost-effective strategy in Thailand and four other countries including; India, Peru, South Africa and Kenya (Goldie et al., 2005). We did not include VIA or DVI in our study because these methods are only appropriate for low resource settings (Nahar et al., 2011). Future systematic reviews utilizing these modalities in these settings are recommended. However, based on our results, many studies have suggested strategies that contain HPV DNA testing in low resource settings (Table 1).

The ICERs in each study were calculated based on their base case assumptions such as test costs, test performances, prevalence of HPV, and survival data. Comparing this variety of parameters was not possible in our study.

To allocate resources, decision makers need a tool to decide which technology is preferred for their setting. ICER as the outcome of CEA can help them to find their priorities (Hyewon and Levine, 2012).To estimate ICER, many authors did not choose similar effectiveness. Referring to the methodology of cost-effectiveness analysis, and to improve the comparability of outcomes, it would be rational to choose uniform effectiveness (Nienhaus et al., 2011). In health care systems, decision makers could authorize technologies with higher ICERs until the termination of their budget (Simoens, 2010b). The ICER will compare with ICER thresholds which represent the maximum cost per unit of outcomes that health care payers are willing to pay for (Simoens, 2010a). Using a fixed threshold for ICER is not appropriate, and for decision making a weighted threshold may need to be used depending on the type of treatment or disease and the decision making context (Simoens, 2010b). Despite the lack of a standard threshold for the ICER (Goldie et al., 2007), many countries such as; Australia, Canada, New Zealand, England and Wales, the Netherlands, Scotland and Japan(Shiroiwa et al., 2010; Simoens, 2010b), have chosen a threshold for the ICER by themselves, and the World Health Organization(WHO) has suggested GDP per capita in each region as a threshold for the ICER (Sachs, 2002). According to Williams, a common sense value for the ICER threshold is GDP per capita (Williams, 2004). Regardless of clinical outcome (QALY or LYG) used, ICERs were compared to the describe threshold. Except for two articles that did not report the ICER for their suggested strategies (Chow et al., 2010; de Kok et al., 2012). In the articles selected, most ICERs of HPV DNA testing in the screening programs were below one–fold of GDP per capita, while one article reported the ICER as five-fold the GDP per capita (Goldie et al., 2004). Although we showed that most studies reported; HVP DNA testing, starting cervical screening at age 30 years or older, and five years or more interval of screening, as the most cost-effective strategies for testing, national screening practice guidelines in most countries are more conservative and resistant to change if they are based solely on scientific evidence. The use of thresholds in a decision making process is determined by their flexibility. If policy makers only consider the results of the ICERs, they are using a hard threshold. On the other hand, in the soft threshold approach other factors are taken into consideration such as different perspectives between policy makers and researchers, timeliness and accessibility, reliability of studies, burden of diseases, equity and budget impact (Drummond and Weatherly, 2000; Devlin and Parkin, 2004; Eichler et al., 2004). Furthermore, it is noteworthy that CEA results and country guidelines may be endogenous. Investigators often conducting CEA based on the screening data provided through the clinical practice and implemented guidelines. Guideline committees and policy makers should revise often consider CEA results only to varying degrees. It is also important to note that moving from cytology screening to HPV DNA testing requires a major intervention in a health care system and the need to overcome different barriers including the screening providers and system barriers (Jhala and Eltoum, 2007). Governments are hesitant to remove old machinery used for conventional screening, invest in new technology, and plan for training of the providers. Furthermore, because of the reliability and effectiveness of Pap smear test screening, Farnsworth concluded that he was against changing from Pap smear testing to HPV testing in Australia (Farnsworth, 2011).

Therefore, it may take several more years to adapt the new technology and use HPV DNA testing for cervical screening.

In conclusion, despite the variety of different screening strategies available for cervical cancer prevention, implementing HPV DNA testing seems to be the most appealing and cost-effective strategy for almost all populations and should be included in the screening program. In addition, we suggest starting the cervical screening at the age of 30 years or older and repeating the screening in the 5-year or longer intervals. Closer collaboration with health economists is required during the development of guidelines in order to achieve the most cost-effective program for cervical cancer prevention.

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