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Review Article

Factors associated with human papillomavirus (HPV) test acceptability in primary screening for cervical cancer: A mixed methods research synthesis

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ABSTRACT

Primary screening for cervical cancer is transitioning from the longstanding Pap smear towards implementation of an HPV-DNA test, which is more sensitive than Pap cytology in detecting high-risk lesions and offers greater protection against invasive cervical carcinomas. Based on these results, many countries are recommending and implementing HPV testing-based screening programs. Understanding what factors (e.g., knowledge, attitudes) will impact on HPV test acceptability by women is crucial for ensuring adequate public health practices to optimize cervical screening uptake. We used mixed methods research synthesis to provide a categorization of the relevant factors related to HPV primary screening for cervical cancer and describe their influence on women's acceptability of HPV testing. We searched Medline, Embase, PsycINFO, CINAHL, Global Health and Web of Science for journal articles between January 1, 1980 and October 31, 2017 and retained 22 empirical articles. Our results show that while most factors associated with HPV test acceptability are included in the Health Belief Model and/or Theory of Planned Behavior (e.g., attitudes, knowledge), other important factors are not encompassed by these theoretical frameworks (e.g., health behaviors, negative emotional reactions related to HPV testing). The direction of influence of psychosocial factors on HPV test acceptability was synthesized based on 14 quantitative studies as: facilitators (e.g., high perceived HPV test benefits), barriers (e.g., negative attitudes towards increased screening intervals), contradictory evidence (e.g., sexual history) and no impact (e.g., high perceived severity of HPV infection). Further population-based studies are needed to confirm the impact of these factors on HPV-based screening acceptability.

1. Introduction

Globally, 530,000 cervical cancers cases per year are attributable to the human papillomavirus (HPV) and represent 8% of all cancers occurring worldwide (de Martel et al., 2017). The understanding of the causal connection between persistent infection with high-risk HPV types and cervical cancer (Walboomers et al., 1999; Franco et al., 2009) has led to new primary and secondary prophylaxis measures. Although primary prophylaxis of cervical cancer through HPV vaccination is considered a major achievement, secondary prophylaxis through

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screening will remain extremely important in addressing cervical cancer for decades to come because current HPV vaccines do not offer protection against all high-risk HPV types, HPV vaccine uptake is variable across the globe and the ultimate length of protection provided by vaccination is to be established yet (Paavonen et al., 2009).

Historically, the mainstay of cervical cancer screening was represented by cytology (i.e., Papanicolaou or Pap test) to screen for cervical cellular abnormalities. In recent years, HPV DNA tests (hereafter HPV test or testing) capable of identifying high-risk HPV types have been developed. Multiple studies have shown that HPV testing is more sensitive than cytology in detecting cervical intraepithelial neoplasia in primary cervical cancer screening (hereafter primary screening) (Bulkmans et al., 2007; Naucler et al., 2007; Ronco et al., 2010; Anttila et al., 2010) and has similar specificity compared to Pap testing in women aged 30 and older (Rijkaart et al., 2012). Overwhelming evidence suggests that a negative HPV test provides more reassurance to a woman that she is at low-risk for cervical lesions than a negative Pap test and supports the extension of intervals in primary screening beyond 5 years (Franco et al., 2009; Crosbie et al., 2013; Ronco et al., 2014).

This evidence has led to new recommendations that incorporate HPV testing as a primary screen for cervical cancer in women aged between 30 and 65 years, either as a stand-alone test (von Karsa et al., 2015; Huh et al., 2015; Australian Government Department of Health, 2017) or with cytology (i.e., co-testing) (The American Congress of Obstetricians and Gynecologists, 2017; The American Cancer Society medical and editorial content team, 2017; Moyer, 2012).

Misunderstandings and misconceptions related to HPV testing, fueled by lack of HPV or HPV testing knowledge (e.g., purpose of HPV testing, causal relationship between HPV and cervical cancer, natural history of HPV infection) in Australian women (Foran, 2017), lead to a petition signed by > 70,000 women against the roll out of the new primary cervical cancer screening program (HPV test every 5 years in women aged 25 to 74 years instead of Pap test every 2 years); consequently, the implementation of the program was postponed from May 1 to December 1, 2017 (Australian Government Department of Health, 2017; Williams, 2017).

No synthesis has been carried out to examine what factors' impact (e.g. facilitators, barriers) on HPV test acceptability in *primary* screening. As new guidelines have been developed and are in the process of being implemented worldwide, we aimed to provide a comprehensive description of psychosocial factors related to HPV testing and to assess their influence on HPV testing acceptability in primary screening for cervical cancer with the ultimate goal to guide interventions to promote screening.

2. Methods

We used mixed methods research synthesis (MMRS), which is a form of systematic review (Sandelowski et al., 2006; Sandelowski et al., 2012; Heyvaert et al., 2011), to answer following research questions: "What are the psychosocial factors related to HPV testing in primary screening for cervical cancer?" and "What is the influence of these factors on women's acceptability of HPV testing in primary screening for cervical cancer?". By selecting MMRS, we highlight our opinion that preventive behaviors (e.g., participating in screening) are complex and can be best understood by combining views of constructivism (subjectivity, associated with qualitative research) with views of logical empiricism (objectivity, associated with quantitative research). In integrative MMRS, findings of empirical qualitative, quantitative or mixed methods experimental or observational studies are treated as primary data that are analyzed and synthesized by using mixed methods approaches (Sandelowski et al., 2006; Sandelowski et al., 2012; Heyvaert et al., 2011) (Fig. 1). The PRISMA framework was used to guide the reporting of this review (Moher et al., 2009). The protocol was registered on International Prospective Register of Systematic Reviews (PROSPERO), registration #CRD42017078254.[1]

We searched Medline, Embase, PsycINFO, CINAHL, Global Health and Web of Science for journal articles between January 1, 1980 and October 31, 2017. The search strategy was developed for Medline by our team, validated by an experienced McGill librarian and then adapted for the other databases (Appendix A). The following eligibility criteria were applied: 1) Population: women of all ages for whom primary cervical cancer screening is recommended, 2) Outcome: psychosocial factors related to acceptability of HPV testing in *primary screening* for cervical cancer,[2] 3) Study design: empirical studies, without restrictions of study methodology, 4) Languages: English or French or German. The selection of references was performed by two researchers (OT and AN).

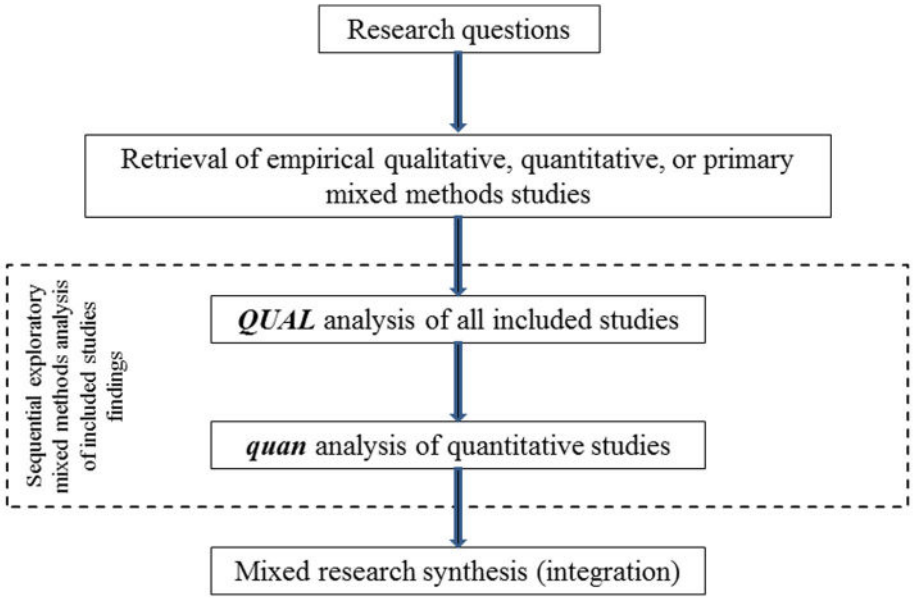
Records were first screened for eligibility based on titles and abstracts (phase one). Then, the full texts of retained records were retrieved and read; the final set of articles was identified based on eligibility criteria (phase 2). Disagreements in phase one and two on whether or not an article should be included were mediated by the senior researcher (ZR). For this review, we did not retain studies related to self-sampling which represents a distinct strategy to increase screening uptake and merits separate consideration. A data extraction sheet was developed in Excel and included author, title, publication date, country, objectives, study design, quantitative data collection and analysis methods, qualitative methodology, qualitative data collection methods and analysis, and number of participants. From qualitative studies, we extracted qualitative raw data without any interpretation or analysis (e.g., quotes). From quantitative studies, we extracted outcomes of acceptability (e.g. proportions, means, odds ratios).

The risk of bias in individual studies was assessed separately by two researchers (OT and ET), with the 16-item Quality Assessment Tool for Studies with Diverse Designs (QATSDD), a valid and reliable instrument developed for appraising studies in the disciplines of psychology, sociology and nursing (Sirriyeh et al., 2012). For overall scores ≤60% and > 60% we report *high* and *low* risk of bias respectively. All articles were included in the analyses, independent of their quality as we aimed to provide a comprehensive synthesis of factors.

We used a sequential exploratory (*QUAL → quan*) mixed methods design to analyze and synthesize findings of retained studies (Heyvaert et al., 2011; Creswell, 2014; Pluye and Hong, 2014). In the first phase, qualitative (*QUAL*), qualitative data from all qualitative and quantitative studies was analyzed; psychosocial factors measured in quantitative studies (e.g., anxiety, embarrassment, number of lifetime sexual partners, history of cervical screening) were treated as qualitative data (Pluye and Hong, 2014). We performed *deductive-inductive* qualitative thematic analysis to identify factors related to HPV testing. *Deductively*, we identified themes based on two frameworks widely used in health behavior research: The Health Belief Model (HBM) (Champion and Skinner, 2008) and the Theory of Planned Behavior (TPB) (Montano and Kasprzyk, 2015). *Inductively*, we developed new themes (i.e., not covered by HBM and TPB) through an iterative process, which consisted of reading the studies (and new themes) multiple times, allowing researchers to assure accurate interpretation of study results. Themes (hereinafter called factors) were further grouped into categories to enable a structured reporting of the results of the qualitative phase. The factors and categories were developed independently by two researchers (OT and ET) and then validated by the research team. The second (*quan*) phase was informed by the first, (*QUAL*) phase; for each

[1] Available at https://www.crd.york.ac.uk/prospero/.

[2] In primary screening for cervical cancer, HPV testing is used in women with no history of cervical cytological abnormalities i.e., abnormal Pap results. Because women will be in various stages of understanding the issue in terms of knowledge, attitudes and actual behavior, for the purposes of this paper we collapsed outcomes of intentions, willingness and uptake into the overarching term 'acceptability'.



Adapted from Sandelowski et al. (2006) and Heyvaert et al. (2013)
Qual indicates qualitative dominant method of analysis; quan indicates non-dominant quantitative method of analysis

Fig. 1. Integrative Mixed Methods Research Synthesis Design.

factor, based on quantitative findings (only where statistical tests for significance were reported), we provide a narrative synthesis of their influence on HPV testing acceptability. As part of the mixed research synthesis, we developed an integration matrix to match each identified factor with the quantitative evidence (for each quantitative study) of its impact on HPV testing acceptability. This approach allowed us to further synthesize the direction of influence of each factor on HPV testing acceptability into four categories: 1) possible barrier (PB, factor identified as a barrier in at least one study), 2) possible facilitator (PF, facilitator in at least one study), 3) contradictory evidence (CE), when two directions of influence (barrier and facilitator) were found for the same factor across studies and 4) no impact (NI), meaning that only evidence for no association was found. The narrative synthesis is organized based on the synthesized direction of influence of each factor on HPV testing acceptability.

3. Results

3.1. Summary of included studies and study quality

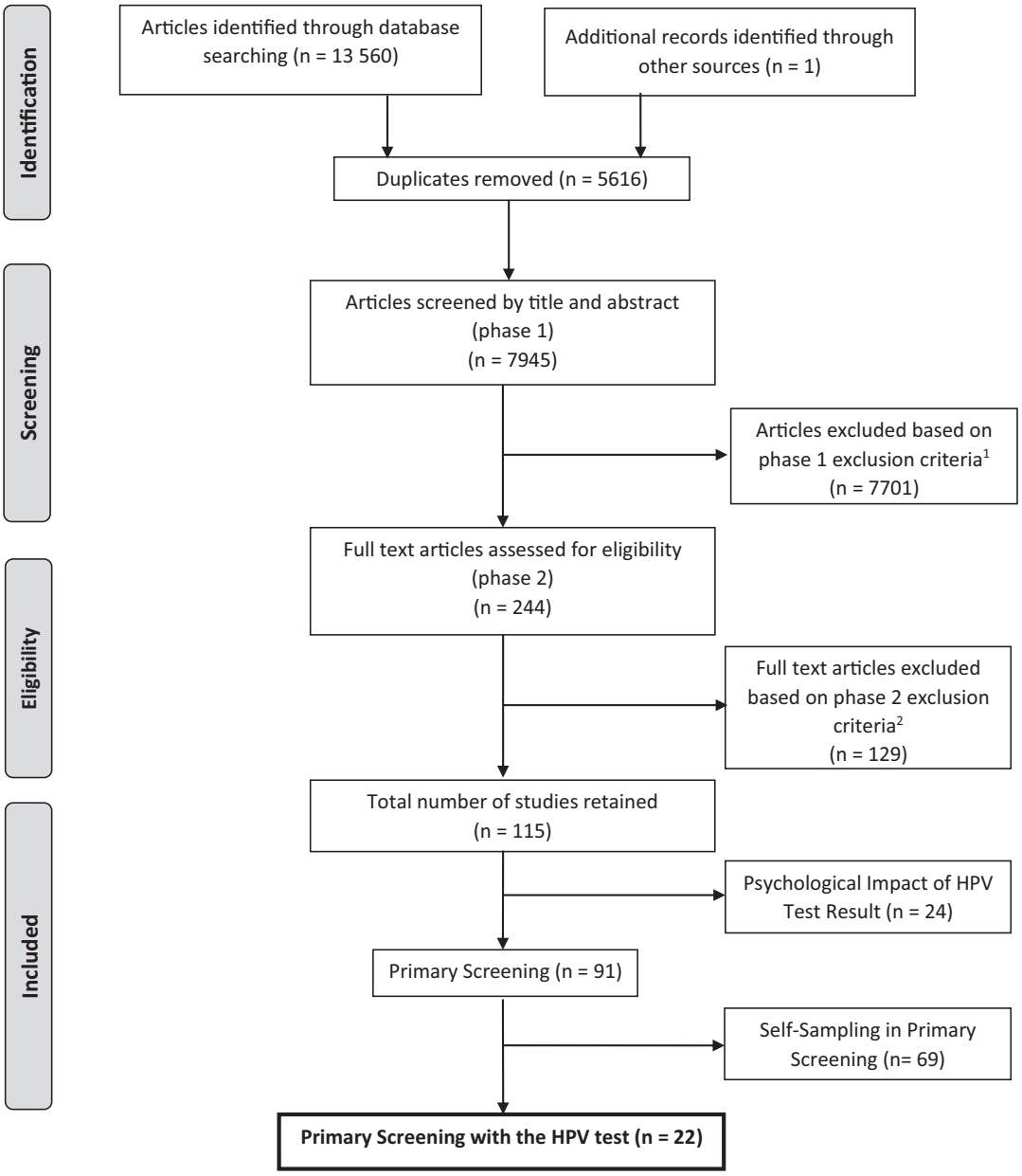
The study selection flow diagram is presented in Fig. 2. We retained 22 primary studies: 5 of qualitative methodology (Filade et al., 2017; Leon-Maldonado et al., 2016; Marlow et al., 2009; Vanslyke et al., 2008; Waller et al., 2005), 15 of quantitative methodology (Acera et al., 2014; Agenor et al., 2017; Alfaro et al., 2015; Burger et al., 2014; Dieng et al., 2013; Huang et al., 2008; Jayasinghe et al., 2016; Kwan et al., 2010; Marlow et al., 2008; Nene, 2007; Ogilvie et al., 2013; Papa et al., 2009; Roland et al., 2016; Schmid et al., 2017; Silver et al., 2015) and 2 in which both methodologies were used (Gerend et al., 2017; Ogilvie et al., 2016). Seventeen studies originate in high income countries (8-USA, 2-Canada, 5-Europe and 2 in Australia) and five in low and middle income countries (1-Mexico, 1-El Salvador, 1-China, 1-India and 1 in Nigeria). In 14 quantitative studies, statistical tests of significance to assess acceptability were reported; these studies were included in the integration phase.

Quality appraisal revealed low risk of bias in 18 studies and high risk of bias in 4 studies (Jayasinghe et al., 2016; Marlow et al., 2008; Papa et al., 2009; Gerend et al., 2017). Among low risk of bias studies, only six were guided by an explicit theoretical framework (Filade et al., 2017; Leon-Maldonado et al., 2016; Marlow et al., 2009; Jayasinghe et al., 2016; Ogilvie et al., 2013; Ogilvie et al., 2016) or provided evidence of pilot testing of the data collection tool (Filade et al., 2017; Vanslyke et al., 2008; Burger et al., 2014; Dieng et al., 2013; Huang et al., 2008; Kwan et al., 2010). In high risk of bias studies, theoretical frameworks were not used, the validity and reliability of the measurement tools was not assessed, no sample size calculations were provided (Jayasinghe et al., 2016; Marlow et al., 2008; Gerend et al., 2017) and few details were provided related to the recruitment procedure and research setting (Papa et al., 2009). Characteristics of included studies and results of quality appraisal are provided in Table 1.

3.2. Qualitative synthesis

3.2.1. Knowledge

Studies examined three types of knowledge: cervical cancer screening, HPV, and HPV testing. *Cervical cancer screening knowledge* includes women's awareness of current cervical cancer screening guidelines (Jayasinghe et al., 2016) and implications of HPV vaccination campaigns on the need for screening (Marlow et al., 2009). Low levels of knowledge may have a particularly negative impact on HPV test acceptability: “But if I don't know anything about cervical cancer, I will hesitate” (Filade et al., 2017). *HPV knowledge* covers information gaps, such as mode of transmission (Marlow et al., 2009; Vanslyke et al., 2008; Waller et al., 2005) “I have a sister who came down with human papillomavirus and it got me thinking and that's why I decided to get tested” (Leon-Maldonado et al., 2016), causal relationship with cervical cancer (Marlow et al., 2009; Burger et al., 2014; Schmid et al., 2017) “I don't think I've ever thought of it (i.e., association between HPV and cervical cancer) in that sense” (Waller et al., 2005). *HPV test knowledge* emerged as a factor since lack of knowledge contributes to women's fear of testing (Filade et al., 2017). Additionally women were unsure about differences between the HPV test and the Pap test (Leon-Maldonado et al., 2016; Marlow et al., 2009; Waller et al., 2005; Schmid et al., 2017), were not familiar with the test procedure (Leon-



[1]Phase 1 exclusion criteria for titles and abstracts: 1) not population of interest (i.e. women), 2) not on primary cervical cancer screening with the HPV DNA test, 3) not outcomes of interest (psychosocial correlates of primary HPV cervical cancer screening), 4) not empirical studies, 5) no abstract
[2] Phase 2 exclusion criteria for full text articles: Phase 1 exclusion criteria AND full text not in English, French or German

Fig. 2. PRISMA Flowchart.

Maldonado et al., 2016; Marlow et al., 2009) or had difficulties interpreting the results (Vanslyke et al., 2008; Burger et al., 2014).

3.2.2. Attitudes, beliefs and subjective norms

Women's attitudes and beliefs are centered around four domains: cervical cancer, cervical cancer screening, HPV infection and HPV testing. *Perceived severity of cervical cancer* e.g., "desire to protect one's family and one's ability to care for their family" (Vanslyke et al., 2008) was viewed as a reason to participate while "fear of receiving a cancer diagnosis and treatment" (Vanslyke et al., 2008) was a reason to refuse HPV testing. Low p*erceived susceptibility of cervical cancer* e.g., "I have never thought that you catch cervical cancer through having too much sex" (Waller et al., 2005) or perceiving low risk of cancer e.g., "not knowing anyone who had cervical cancer" were reasons for refusing HPV testing (Vanslyke et al., 2008; Dieng et al., 2013).

Attitudes towards cervical cancer screening include *delayed start of screening* e.g., "Age 25 is too late. I had a 19-year-old staff member with cervical cancer" (Ogilvie et al., 2016) and/or *increased screening interval* e.g., "I worry that only being tested every 4 years gives plenty of time for issues to arise and go untreated" (Ogilvie et al., 2016), Pap versus HPV test preference (Vanslyke et al., 2008; Silver et al., 2015; Ogilvie et al., 2016) and *general attitudes and beliefs* e.g., presence of early signs and symptoms in cervical cancer (Filade et al., 2017) or physical discomfort "I don't like to get a Pap smear or anything like that, because every time I have one, they have hurt me" (Vanslyke et al., 2008). When both HPV testing and Pap are available, womens' decision depends on the *screening test preference* (Silver et al., 2015; Ogilvie et al., 2016).

The factor *perceived severity of HPV infection* includes the assumption

Table 1
Study characteristics and risk of bias within studies.

First author, country, year	Aim	Data collection method	Cytology screening environment	Intervention (Yes/No)	N	Setting	Participant age	Data analysis method	Risk of bias within studies (%)*
Acera et al., Spain, 2014	To determine the most effective intervention strategy to increase cervical cancer screening coverage in Barcelona	Personal Interview	Opportunistic	Yes	4775	Primary Health Care centers in Cerdanyola, Barcelona	60–70	Chi-square	Low (67%)
Agenor et al., USA, 2017	To examine the associations between sexual behavior and sexual identity, and lifetime HPV testing	Survey administered by interviewer	Opportunistic	No	11,300	National probability sample	15–44	Multivariate logistic regression	Low (67%)
Alfaro et al., El Salvador, 2015	To identify the facilitators and barriers to adherence to cervical cancer screening using HPV DNA testing in El Salvador	Interview	Opportunistic	Yes	409	Salvadorian Ministry of Health led Cervical Cancer Prevention HPV screening program	30–49	Univariate logistic regression, chi square, multivariate logistic regression	Low (69%)
Burger et al., Norway, 2014	To examine whether the contents of a cervical cancer screening invitation letter influence Norwegian women's intent to participate in screening	Web-based survey	Organized	Yes	3540	Representative sample of Norwegian women	25–69	Univariate and multivariate Logistic regression	Low (81%)
Dieng et al., Australia, 2013	To investigate Australian women's cervical cancer screening preferences, information needs and decision-making styles	Semi-structured telephone interview	Organized	No	1279	National survey conducted by the Hunter Valley Research Foundation	18–70	Multivariate logistic regression, descriptive statistics	Low (64%)
Filade et al., Nigeria, 2017	To explore the attitudes of pregnant women to the incorporation of HPV DNA-based testing in routine ANC in Nigeria	Focus groups	Opportunistic	No	82	Hospitals and health facilities in central Nigeria	Mean 28.9 (SD = 4.7)	Qualitative content analysis	Low (90%)
Gerend et al., USA, 2017	To investigate women's acceptance of new cervical cancer screening guidelines	Electronic Survey	Opportunistic	No	376	Online panel maintained by Qualtrics	21–65	Descriptive statistics	High (58%)
Huang et al., USA, 2008	To assess women's interest in obtaining HPV testing as well as their preferences for concomitant Pap testing	Telephone and in-person interviews	Opportunistic	No	Opportunistic 865	Community and university-based practices	50–80	Multivariate logistic regression	Low (64%)
Jayasinghe et al., Australia, 2016	To assess women's attitudes towards guidelines for HPV testing in cervical cancer screening	Electronic Survey	Organized	No	125	Social media	16–28	Fisher's exact test, odds ratios	High (60%)
Kwan et al., China, 2010	To evaluate the effects of educational intervention on Chinese women's intentions to be HPV tested	Questionnaire	Opportunistic	Yes	292	Family Planning Association of Hong Kong's (FPAHK) Wanchai Birth Control Clinic	Mean = 38.3 (SD = 7.41)	Chi Square	Low (88%)
Leon-Maldonado et al., Mexico, 2016	To assess the beliefs and perceptions of HPV and HPV testing among Mexican women who had participated in an early cervical cancer detection program	Semi-structured interviews	Opportunistic	No	24	Two primary care health clinics in Michoacán state, Mexico	30–65	Thematic framework analysis	Low (71%)
Marlow et al., UK, 2008	To examine sociodemographic predictors of self-reported screening attendance, and intention to accept HPV testing.	Home-based, computer assisted interviews	Organized	No	994	National Centre for Social Research Omnibus Survey	25–64	Univariate and multivariate logistic regression	High (52%)
Marlow et al., UK, 2009	To identify British women's HPV and HPV test knowledge requirements	Interviews	Organized	No	21	University College London	18–53	Thematic framework analysis	Low (67%)
Nene et al., India, 2007	To evaluate the sociodemographic variations in the uptake of cervical cancer screening in rural India	Household survey and hospital records	Opportunistic	Yes	79,449	Primary health centers, rural hospitals, and schools in the Osmanabad district in Maharashtra state	30–59	Univariate and multivariate logistic regression	Low (71%)
Ogilvie et al., Canada, 2013	To explore the impact of HPV testing on women's intentions to be screened for cervical cancer	Electronic Survey	Organized in British Columbia	Yes	981	Provincial cervical cancer screening program at the British Columbia Cancer Agency	25–65	Chi square, *t*-test, multivariate logistic regression	Low (83%)

(*continued on next page*)

Table 1 (*continued*)

First author, country, year	Aim	Data collection method	Cytology screening environment	Intervention (Yes/No)	N	Setting	Participant age	Data analysis method	Risk of bias within studies (%)*
Ogilvie et al., Canada, 2016	To describe factors associated with women's intentions to be screened according to new guidelines for primary HPV DNA testing	Electronic Survey	Organized in British Columbia	Yes	981	Provincial cervical cancer screening program at the British Columbia Cancer Agency	25–65	Multivariate logistic regression, Kruskal Wallis, chi-square thematic analysis	Low (81%)
Papa et al., USA, 2009	To assess the impact of educational intervention on women's acceptance of adjunct HR-HPV testing	Questionnaire	Opportunistic	Yes	50	Obstetrics and gynecology faculty practice at the University of Massachusetts Medical School/UMass Memorial Health Care	30–69	Fisher exact test	High (55%)
Roland et al., USA, 2016	To assess the impact of educational intervention on knowledge and beliefs of cervical cancer screening	Survey	Opportunistic	Yes	644	Federally Qualified Health Center clinics in Illinois	30–60	Ordinal and binary logistic regression	Low (67%)
Schmid et al., USA & Australia, 2017	To determine the perceptual word associations that women hold with regards to cervical cancer screening tools in the US and Australia	Electronic Survey	Opportunistic	No	776	Survey Monkey's US and Australian databases	18–64	Co-occurrence network graphs	Low (64%)
Silver et al., USA, 2015	To explore and understand women's attitudes towards new cervical cancer screening options	Interviewer-administered survey	Opportunistic	Yes	551	Johns Hopkins Hospital affiliated outpatient OB/GYN clinics in Baltimore, MD	36–62	Poisson regression with robust error variance	Low (67%)
Vanslyke et al., USA, 2008	To explore the knowledge, attitudes and beliefs related to cervical cancer, HPV and HPV testing of low-income, Hispanic women	Focus groups	Opportunistic	No	54	Community-based settings in Albuquerque, New Mexico	18–60	Thematic analysis	Low (69%)
Waller et al., UK, 2005	To examine the understanding and beliefs about HPV and cervical cancer among women who have already participated in HPV testing	Structured Interviews	Organized	No	74	Clinical trials of HPV testing and a colposcopy clinic that utilizes HPV testing	20–64	Thematic framework analysis	Low (64%)

Note: * percentage points were calculated as recommended by the authors of the Quality Assessment Tool for Studies with Diverse Designs (QATSDD); 100% reflects no risk of bias. For overall scores ≤60% and > 60% we report *high* and *low* risk of bias respectively.

that HPV testing is performed because HPV "must be a serious disease" (Leon-Maldonado et al., 2016) and the factor *perceived susceptibility of HPV infection* includes perceived risk of getting a HPV infection (Silver et al., 2015), including the relative protection offered by a monogamous relationship (Vanslyke et al., 2008).

Perceived benefits of the HPV test synthesize women's beliefs of the HPV test being accurate for early detection of cancer (Filade et al., 2017; Dieng et al., 2013; Roland et al., 2016; Ogilvie et al., 2016) despite possible concerns about the *HPV test safety* (Filade et al., 2017; Ogilvie et al., 2016) and *negative emotions and perceptions related to HPV testing* such as anxiety about the test results (Filade et al., 2017), stigma and problems with communicating of positive results to significant others (Waller et al., 2005).

Subjective norms comprise healthcare provider (HCP) recommendation (Filade et al., 2017; Alfaro et al., 2015; Dieng et al., 2013; Huang et al., 2008; Ogilvie et al., 2013; Roland et al., 2016; Gerend et al., 2017; Ogilvie et al., 2016), screening guidelines (Filade et al., 2017; Jayasinghe et al., 2016; Ogilvie et al., 2013; Ogilvie et al., 2016), and the opinions of spouse and friends (Filade et al., 2017; Jayasinghe et al., 2016; Marlow et al., 2008; Ogilvie et al., 2013; Ogilvie et al., 2016).

3.2.3. Health behaviors, adherence, emotional and behavioral control

HPV vaccination status (Jayasinghe et al., 2016), history of health check-up (Silver et al., 2015), including screening for breast cancer (Silver et al., 2015), usage of birth control methods (e.g., contraceptives) (Alfaro et al., 2015; Nene, 2007) and smoking history were synthesized as *health behaviors*. *Adherence to cervical cancer screening* depends on the age of the first Pap (Jayasinghe et al., 2016), history of time-appropriate Pap testing (Alfaro et al., 2015; Burger et al., 2014; Jayasinghe et al., 2016; Marlow et al., 2008; Silver et al., 2015) and intentions to screen with the Pap test (Silver et al., 2015). *Perceived emotional reaction to HPV results* plays an important role, because women could feel embarrassed (Vanslyke et al., 2008) or concerned (Silver et al., 2015) by a positive HPV test result and therefore be reluctant to share the test outcome with their partner or close friends (Silver et al., 2015) who could show variable level of understanding (Ogilvie et al., 2013; Ogilvie et al., 2016). *Perceived behavioral control* e.g., "I am confident that I could have an HPV test to screen for cervical cancer instead of a Pap smear" (Ogilvie et al., 2016) represents an emerging factor in the context of increased options for primary cervical cancer screening.

3.2.4. Health information channels, healthcare system factors and interventions

Women use multiple *health information channels* to increase their knowledge (Marlow et al., 2008), which emphasizes the importance of HCP in disseminating critical information about HPV testing (Waller et al., 2005). *Healthcare system factors* such as health insurance status (Agenor et al., 2017), availability of screening facilities (Filade et al., 2017), and type of primary care provider (e.g., family practitioner, gynecologist) (Silver et al., 2015) can determine screening acceptability. *Interventions* to increase cervical screening participation include: personalized screening invitation letters (Acera et al., 2014; Burger et al., 2014), information leaflets (Acera et al., 2014), screening reminder phone calls (Acera et al., 2014), and HPV and cervical cancer prevention education (Kwan et al., 2010; Papa et al., 2009).

3.2.5. Personal factors

General health status (Burger et al., 2014; Huang et al., 2008), history of abnormal Pap test (Dieng et al., 2013; Jayasinghe et al., 2016; Silver et al., 2015), past medical history e.g., cancer (Alfaro et al., 2015; Huang et al., 2008), cardiovascular disease, diabetes, depression (Alfaro et al., 2015), history of STI's (Agenor et al., 2017; Alfaro et al., 2015) are grouped under *personal medical history and health status*. Having a family member with cervical or other malignancies (Vanslyke et al., 2008; Alfaro et al., 2015; Huang et al., 2008; Jayasinghe et al., 2016) is grouped under *family medical history*. Age at first sexual intercourse (Alfaro et al., 2015; Jayasinghe et al., 2016), number of lifetime sexual partners (Alfaro et al., 2015; Ogilvie et al., 2013; Silver et al., 2015; Ogilvie et al., 2016) and sexual orientation (Agenor et al., 2017) are summarized as *sexual history*. Finally, *sociodemographics* encompass widely used categories, e.g., age (Marlow et al., 2009; Agenor et al., 2017; Burger et al., 2014; Dieng et al., 2013; Huang et al., 2008; Jayasinghe et al., 2016; Marlow et al., 2008; Nene, 2007; Ogilvie et al., 2013; Silver et al., 2015; Ogilvie et al., 2016), relationship status (Agenor et al., 2017; Alfaro et al., 2015; Burger et al., 2014; Huang et al., 2008; Jayasinghe et al., 2016; Marlow et al., 2008; Nene, 2007; Ogilvie et al., 2013; Silver et al., 2015; Ogilvie et al., 2016), and education (Agenor et al., 2017; Alfaro et al., 2015; Burger et al., 2014; Dieng et al., 2013; Huang et al., 2008; Jayasinghe et al., 2016; Marlow et al., 2008; Nene, 2007; Ogilvie et al., 2013; Silver et al., 2015; Ogilvie et al., 2016).

3.3. Integration of qualitative and quantitative results and quantitative synthesis

We used an integration matrix to match each factor (rows) with their influence on HPV test acceptability (e.g., facilitator) based on quantitative results of primary studies (columns) (see Appendix B). The overall effect of each factor on HPV test acceptability (e.g., possible facilitator) is provided in the last column, e.g., for high perceived benefits of the HPV test, evidence of no impact (NI) (Jayasinghe et al., 2016) and facilitator (F) (Ogilvie et al., 2013; Ogilvie et al., 2016) were found, thus this factor was synthesized as possible facilitator (PF). Final MMRS results are displayed in Fig. 3 where factors are organized based on their overall effect on HPV test acceptability and their theoretical framework roots (i.e., HBM or TPB or additional factor). The narrative synthesis of quantitative results of primary studies is organized by results of the integration matrix and results of qualitative synthesis i.e., for each direction of influence (e.g., possible facilitators), factors corresponding to each category (e.g., knowledge, then attitudes, beliefs and subjective norms, etc.) are described sequentially.

3.3.1. Possible facilitators

Increased HPV and HPV test knowledge were associated with higher HPV test acceptability (OR = 1.47; 95% CI = 1.13–1.90 and OR = 1.70; 95% CI = 1.17–2.45 respectively) (Burger et al., 2014).

Burger et al. found a significant association between higher *perceived severity* of cervical cancer and HPV test acceptability (OR = 1.92; 95% CI = 1.32–2.80) (Burger et al., 2014). Higher *perceived susceptibility* of cervical cancer was either associated with higher HPV test acceptability (OR = 1.47; 95% CI = 1.05–2.06) (Burger et al., 2014) or had no effect (Silver et al., 2015). Higher *perceived susceptibility of HPV infection* was associated with higher HPV test acceptability; the association was not significant for perceived susceptibility of genital warts (Silver et al., 2015).*General attitudes and beliefs* related to cervical cancer screening (i.e., considering the Pap test to be very important in preventing cervical cancer) was associated with increased HPV test acceptability (OR = 3.50; 95% CI = 1.64–7.50) (Burger et al., 2014). Based on a relative small sample of 149 Australian women, Jayasinghe et al. found no significant association between *perceived benefits of the HPV test* and HPV test acceptability (Fisher exact test, $p = 0.2$) (Jayasinghe et al., 2016) while Ogilvie et al., on a sample of 981 Canadian women concluded that perceiving higher benefits was associated with higher acceptability of HPV testing regardless of age the screening starts (OR = 1.22; 95% CI = 1.15–1.30) (Ogilvie et al., 2013) or at ≥25 years at a 4 years interval (OR = 1.26; 95% CI = 1.23–1.30) (Ogilvie et al., 2016). *Higher perceived HPV test safety* was associated with higher HPV test acceptability (Ogilvie et al., 2013). Higher *subjective norms* (i.e., higher perceived influence from significant others, HCP, screening guidelines) was associated with higher HPV test acceptability (Jayasinghe et al., 2016; Marlow et al., 2008; Ogilvie et al.,

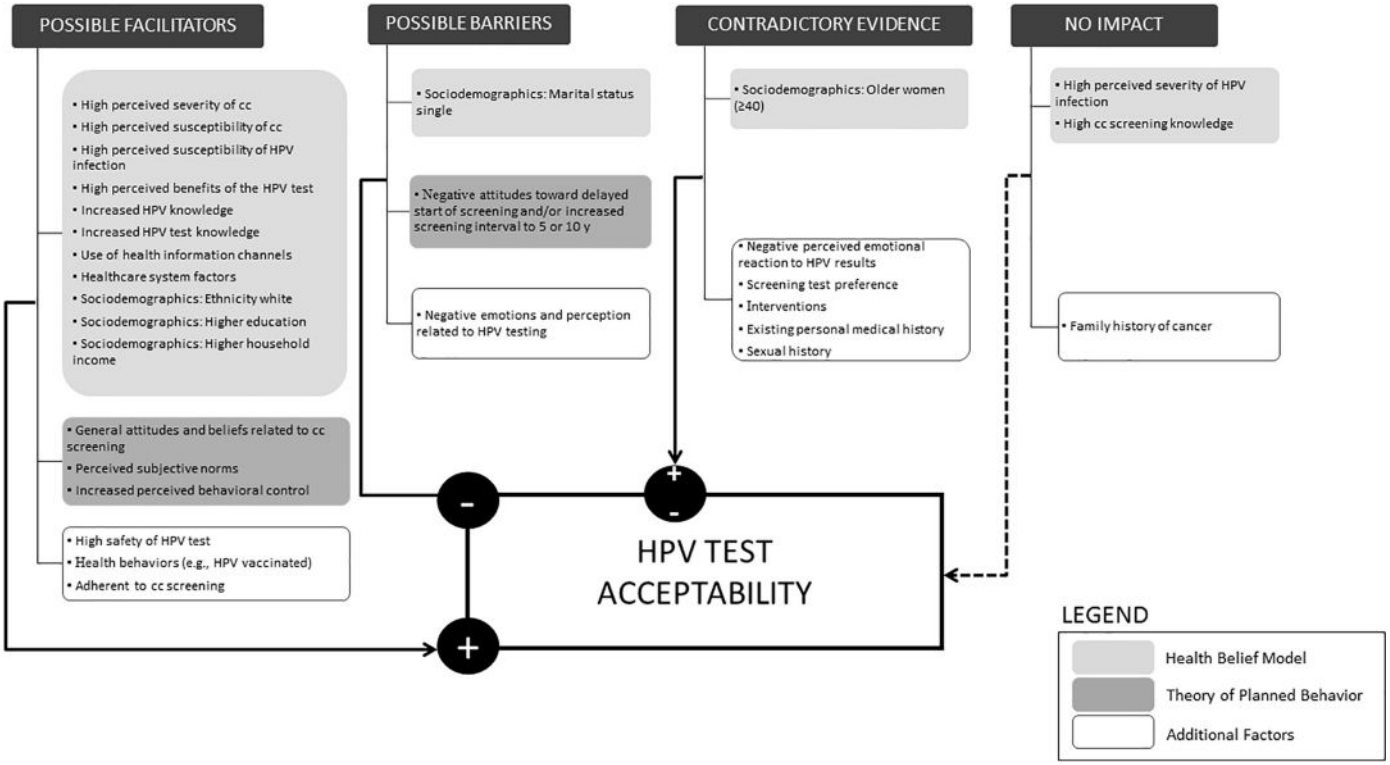


Fig. 3. Influence of factors on HPV test acceptability.
Note: cc = cervical screening; HPV = human papillomavirus.

2013; Ogilvie et al., 2016).

Related to *health behaviors*, positive HPV vaccination status was associated with higher acceptability to receive the HPV test starting at age 25 at a 5-year interval compared to Pap testing every 2 years (Jayasinghe et al., 2016). Contraception use was associated with higher HPV test acceptability (OR = 1.63; CI = 1.5–1.7) (Nene, 2007) and no association with the method of contraception was found (Alfaro et al., 2015). Smoking history did not significantly influence HPV test acceptability (Ogilvie et al., 2013; Silver et al., 2015; Ogilvie et al., 2016). *Adherence to cervical screening* recommendations (e.g., screening at intervals ≤3 years) was either associated with higher acceptability of HPV testing (Alfaro et al., 2015; Burger et al., 2014; Marlow et al., 2008) or no association was found (Huang et al., 2008; Jayasinghe et al., 2016; Silver et al., 2015). Increased *behavioral control* of getting the HPV test instead of the Pap test was found in two studies to increase HPV test acceptability (Ogilvie et al., 2013; Ogilvie et al., 2016), while in another study to have no effect on HPV test acceptability (Jayasinghe et al., 2016).

Women who communicated with friends about health issues, or, who gathered information from media or leaflets reported higher HPV test acceptability (Marlow et al., 2008). Surprisingly, discussing health issues with HCP and gathering information via internet were not significantly associated with HPV test acceptability (Marlow et al., 2008). Among *healthcare system factors*, being screened in a clinic that offered HPV testing in primary cervical cancer screening was associated with increased HPV test acceptability compared to Pap (Silver et al., 2015). Other factors, such as health insurance status (Agenor et al., 2017; Huang et al., 2008), and distance from the clinic and transportation facilities were not related to HPV test acceptability (Alfaro et al., 2015).

In terms of *sociodemographics*, non-whites were found to have lower acceptability than whites (Marlow et al., 2008), except for Latina (Huang et al., 2008). Education was found to either have no impact (Agenor et al., 2017; Alfaro et al., 2015; Burger et al., 2014; Dieng et al., 2013; Huang et al., 2008; Jayasinghe et al., 2016; Ogilvie et al., 2013; Silver et al., 2015) or increase (Marlow et al., 2008; Nene, 2007; Ogilvie et al., 2016) HPV test acceptability. Higher income is a possible facilitator as we found that income can increase (Burger et al., 2014; Silver et al., 2015) or have no effect (Agenor et al., 2017; Huang et al., 2008; Jayasinghe et al., 2016; Marlow et al., 2008) on HPV test acceptability.

3.3.2. Possible barriers

Women expressing concerns about *delayed start of screening* had significantly lower acceptability of the HPV test if the screening start is delayed to 25 years and continues at a 5-year interval (Jayasinghe et al., 2016). *Increasing the screening interval* from 1 to 3 years had no significant influence on HPV test acceptability (Jayasinghe et al., 2016; Silver et al., 2015). For five years between screening, acceptability was either similar to yearly intervals (Silver et al., 2015) or decreased (OR = 0.2; CI = 0.1–0.4) (Jayasinghe et al., 2016), while for 10-year screening interval acceptability was lower (OR = 0.05; CI = 0.03–0.1) (Jayasinghe et al., 2016). *Negative emotions and perception related to HPV testing* significantly increased acceptability of Pap compared to HPV testing (PR = 1.39; 95% CI = 1.07–1.80) (Silver et al., 2015). In most studies, marital status was not associated (Agenor et al., 2017; Alfaro et al., 2015; Huang et al., 2008; Marlow et al., 2008; Ogilvie et al., 2013; Silver et al., 2015; Ogilvie et al., 2016) with HPV test acceptability but evidence exists that being single (versus married) (Burger et al., 2014; Nene, 2007) is related to lower acceptability.

3.3.3. Contradictory evidence

Negative perceived emotional reaction to HPV results can either augment (i.e., higher concern about a positive HPV test) (Silver et al., 2015), diminish (i.e., women reluctant to share a positive HPV result with their partner) (Burger et al., 2014) or have no effect HPV test acceptability (Ogilvie et al., 2013; Ogilvie et al., 2016). In terms of *screening test preference*, when both Pap and HPV tests are offered, preference for a test is associated with higher acceptability i.e., increased HPV test acceptability (OR = 1.26; CI = 1.23–1.30) (Ogilvie et al., 2016) or increased Pap acceptability (60.7% for Pap,

CI = 56.5–65.7) (Silver et al., 2015).

Related to existing personal medical history, poor or very poor self-reported *health status* was found to decrease (OR = 0.49; CI = 0.27–0.91) (Burger et al., 2014) or have no significant effect (Huang et al., 2008) on HPV test acceptability. Reporting *personal history* of cancer (other than cervical) increased (Huang et al., 2008) or had no effect on HPV test acceptability (Alfaro et al., 2015). Reporting previous cervical cytological abnormalities either decreased (OR = 0.65; CI = 0.46–0.94) (Dieng et al., 2013) or had no impact (Silver et al., 2015) on HPV test acceptability. With respect to obstetric history, compared to nulligravidae, women who reported pregnancies had higher HPV test acceptability (OR = 2.10; CI = 1.80–2.40) (Nene, 2007). Other *personal medical history* correlates e.g., history of STI, menopausal status, Body Mass Index, cardiovascular diseases, diabetes and depression were not associated with HPV test acceptability (Agenor et al., 2017; Silver et al., 2015). Among *sexual history*, reporting 4 or more (Alfaro et al., 2015) or zero (Agenor et al., 2017) lifetime sexual partners was associated with lower HPV test acceptability and reporting both male and female lifetime partners increased HPV test acceptability (OR = 1.75; CI = 1.39–2.20) (Agenor et al., 2017). Evidence related to age is contradictory; older women (e.g., ≥40) were found to have either increased (Dieng et al., 2013; Huang et al., 2008) or decreased (Burger et al., 2014; Marlow et al., 2008; Nene, 2007) HPV test acceptability.

In 60–70 year old women, *interventions* in form of personalized letters signed by their physician and an informative leaflet explaining the most important reasons for screening for cervical cancer significantly increased HPV test acceptability (screening coverage increased with 31.6%, CI = 29.0–34.1, $p \leq 0.05$) (Acera et al., 2014). In a nationally representative sample of Norwegian women, Burger et al. found that using invitation letters for HPV testing (i.e., stating that HPV testing at a 6-year interval will replace Pap testing) resulted in marginally lower HPV test acceptability (strength of intention, $p = 0.008$) compared to using Pap testing invitation letters (i.e., at a 3-years interval) (Burger et al., 2014). Educational interventions were found to have either equivocal (Papa et al., 2009) or positive effect (Kwan et al., 2010) on HPV test acceptability.

3.3.4. No impact

Cervical cancer screening knowledge was not associated with HPV test acceptability (Jayasinghe et al., 2016; Silver et al., 2015). *Higher perceived severity of HPV infection* had no significant effect on women's acceptability of the HPV test (Burger et al., 2014).

Family medical history of cancer was not associated with HPV test acceptability (Alfaro et al., 2015; Huang et al., 2008).

4. Discussion

In our mixed methods research synthesis, we analyzed findings of empirical qualitative and quantitative studies and: a) provided an up-to-date and comprehensive list of factors specific for HPV test acceptability in primary screening for cervical cancer, b) synthesized factors' direction of influence on HPV test acceptability and c) described factors' impact on HPV test acceptability.

Our results show that factors associated with HPV test acceptability are complex; while many factors are included in the HBM and/or TPB (e.g., attitudes, perceived behavioral control), other relevant factors are not encompassed by these theoretical frameworks e.g., health behaviors, negative emotional reactions related to a positive HPV test result. Negative attitudes towards delayed start of screening (i.e. 25 years) and/or increased screening interval to 5 or 10 years and negative emotions and perceptions related to HPV testing are possible barriers to HPV test acceptability. In the context of the latest recommendations (von Karsa et al., 2015; Huh et al., 2015; Australian Government Department of Health, 2017; The American Congress of Obstetricians and Gynecologists, 2017; The American Cancer Society medical and editorial content team, 2017; Moyer, 2012) for primary screening for cervical cancer and ongoing plans of health authorities (Australian Government Department of Health, 2017; Elfstrom et al., 2015; Bruni et al., 2017; Tota et al., 2017; National Screening Unit, 2016; Public Health England, 2016; El-Zein et al., 2016; The Canadian Partnership Against Cancer, 2017) to implement HPV testing in primary cervical screening, addressing these attitudes and concerns should become part of the strategy to ensure a successful implementation of HPV test-based screening programs.

We found that women's increased HPV and HPV test knowledge and using information channels represent a possible facilitator of HPV test acceptability. Since women in the USA, Australia and UK were found to have low HPV (Marlow et al., 2013) and HPV test knowledge (Dodd et al., 2014), strategies that increase women's knowledge might also increase HPV test acceptability.

Healthcare providers play an important role in promoting preventive health measures; as our team has previously demonstrated, discussing with HCP's about HPV vaccination significantly increased acceptability of the HPV vaccine for their sons (Perez et al., 2017). However, when HCPs are unknowledgeable about, or uncomfortable with, recommendations, it can negatively impact preventive health behaviors. In the context of cervical cancer screening, Boone et al. (2016) found that US HCP's (e.g., OB/GYN, family physicians), contrary to existing guidelines for women aged 30 to 65 years (Moyer, 2012), recommended HPV co-testing on an every 3 year basis instead of 5 years (Boone et al., 2016). Similar results were obtained in Italy by Caglioti et al. (2017), who found that in women older than 30 years, 83.8% of gynecologists prefer to use the Pap test in primary screening, and only 44.9% of gynecologists knew that a negative HPV-DNA test allowed an increase in the screening interval to 5 years (Caglioti et al., 2017). Moreover, 20% of participants believed that HCP are insufficiently prepared to explain either positive or negative HPV test results to their patients (Caglioti et al., 2017). In our opinion, especially in health systems where cervical cancer screening is opportunistic, an age-appropriate HCP recommendation for HPV testing could increase women's HPV test acceptability as primary cervical cancer screening. Efforts are therefore needed to increase HCPs' awareness of, and comfort with the latest guidelines.

Moreover, adequate HPV vaccination coverage of females is important for secondary prevention of cervical cancer, as we found that women who were not vaccinated against HPV also had lower HPV test acceptability. Our results are concordant with results of a large US study which showed that cervical screening initiation and interval adherence were significantly higher in women who had been vaccinated against HPV (Chao et al., 2017).

Since our review shows that attitudes and beliefs are important factors of HPV test acceptability but have been measured with scales that were not rigorously psychometrically tested (Jayasinghe et al., 2016; Ogilvie et al., 2013; Ogilvie et al., 2016), we recommend that future research address this knowledge gap. While a comprehensive and psychometrically validated scale for measuring HPV knowledge has been published (Perez et al., 2016), in our opinion, the only validated HPV test knowledge scale available (Dodd et al., 2014; Waller et al., 2013) needs to be modified to include items related to differences between Pap and HPV testing (Marlow et al., 2009; Vanslyke et al., 2008; Waller et al., 2005) (e.g., reasons for doing a HPV instead of Pap test), risks (Filade et al., 2017; Leon-Maldonado et al., 2016) (e.g., pain, infection) and practicalities of the HPV test (Marlow et al., 2009) (e.g., what it involves).

Our study is not without limitations. Because most included studies were observational, interventions are needed for assessing the effect of factors on HPV test acceptability. Given that HPV testing as primary screening has only recently been recommended and only in some countries, there is a paucity of studies of psychosocial correlates of *actual* HPV testing uptake. Therefore, we defined HPV test acceptability comprehensively and included HPV test uptake as well as intentions/

willingness to receive the HPV test in our synthesis. Our results relate to the overarching significant factors of organized or opportunistic screening environments, while some differences e.g., previous adherence to cervical screening are possible. We conducted a sensitivity analysis by removing studies with high risk of bias (Jayasinghe et al., 2016; Marlow et al., 2008; Papa et al., 2009) from our synthesis (i.e., integration of quantitative evidence) and results remained largely unchanged. However, the facilitator effects of using health information channels (Marlow et al., 2008), being of white ethnicity (Marlow et al., 2008) and the barrier effect of expressing negative attitudes towards delayed start of screening and/or increased screening interval to 5 or 10 years (Jayasinghe et al., 2016) require further validation. We encourage researchers to further study the effect of factors on women's HPV test acceptability for which we found contradictory evidence i.e., cervical screening test preference, negative perceived emotional reaction to HPV results, the type of intervention, existing personal medical history and women's age. These contradictory findings may be attributed to the heterogeneity of factors (outcomes), population and interventions measured across included studies.

5. Conclusions

By synthesizing findings of both qualitative and quantitative studies, our review provides a wide perspective related to factors of HPV testing in primary cervical cancer screening. Our results can inform designing interventions to increase primary HPV-based cervical cancer screening uptake in high income countries, but even more so in low and middle income countries where the incidence of cervical cancer is highest and where, as suggested by previous research (Sankaranarayanan et al., 2009), implementing a primary HPV testing program could be lifesaving.

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Conflict of interest

Zeev Rosberger reports personal fees from Merck outside the submitted work at a consultation meeting in November 2015; and speaker to family physicians in April 2015. Gregory Zimet reports grants from Merck, grants from Roche, personal fees from Merck, outside the submitted work.

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