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Human papillomavirus DNA testing as a screen for cervical cancer: a meta-analysis of randomized controlled trials

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Summary

Purpose: The aim was to evaluate the effectiveness of cervical screening when HPV DNA testing is implemented. *Materials and Methods:* Medline (PubMed) was searched and experts were contacted for references. Odds ratio (OR) and 95% confidence intervals (CI) were used as measures of effect sizes. *Results:* The rate of CIN3 and worse decreased about two-fold, from 1.19% in round 1 to 0.67% in round 2, and CIN2 decreased from 1.70% in round 1 to 0.80% in round 2. When primary cervical screening with LBC was combined with HPV testing, there was a statistically significant reduction in the detection of CIN2 and CIN3+ at the next screening round compared with liquid-based cytology (LBC) alone. *Conclusions:* HPV DNA-based screening is more effective than cytology in CIN3 and invasive cervical cancers, by detecting persistent high-grade lesions earlier, and providing a longer low-risk period. However, in younger women, HPV screening leads to over-diagnosis of regressive CIN2.

Key Words: Human papillomavirus; Cervical cancer; Screening

Introduction

Cervical cancer is the fourth most common cancer in women worldwide and the most common cancer in many developing countries. Infections of human papillomaviruses (HPVs) are established as a major risk factor for cervical cancer [1, 2]. Liquid-based cytology (LBC) and conventional methods of cervical cytology (Pap smear) have been the mainstay of cervical cancer screening for many years. These measures did reduce the morbidity and mortality of cervical cancer [3]. Therefore, screening is typically recommended to women to avoid progression to cervical cancer.

Several studies have shown that testing for the DNA HPV is more sensitive than cytology in detecting high-grade cervical intraepithelial neoplasia (CIN)[4, 5]. The sensitivity of cytological testing for cervical intraepithelial neoplasia grade 3 and cervical cancer (CIN3+) is only moderate and this is compensated for by frequent screening [6]. Moreover, variability of HPV DNA testing, both between and within laboratories, is lower than that of cytological testing[7]. However, whether the long-term effectiveness of cervical screening is improved when HPV DNA testing is implemented is unknown. There has been much debate about necessity and economic value of testing HPV DNA in cervical screening.

Materials and Methods

The present authors performed a literature search for studies and technical reports published on Medline (via PubMed) for randomized controlled trials (RCTs) using the words or phrases " 'randomize' OR 'randomise' OR 'randomized' OR 'randomised' OR 'randomized controlled trial' OR 'randomized controlled trials' OR 'randomized controlled trial' " AND " 'HPV' OR 'human papillomavirus' " AND "screening" AND "cervical cancer". Only English language literature was included.

The data was carefully extracted from all eligible publications independently by two of the authors according to selection criteria listed above.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [8] was considered in this study. Heterogeneity across trials was assessed using the I^2-statistic. If I^2 was > 50%, a random effect model was used. However, if I^2 was < 50%, a fixed effect model was used. $P \leq 0.05$ was considered significant. All these analyses were performed with Rev Man 5.3 software.

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Table 1. — *General features of the included studies.*

Studies	Country	Number of Women	Age (years)	Publication type
Kitchener *et al.*, 2009 [9]	UK	24,510	20-64	RCT
Leinonen *et al.*, 2009 [10]	Finland	54,207	20-60	RCT
Stoler *et al.*, 2011 [11]	US	47,208	21-60	RCT
Ronco *et al.*, 2010 [12]	Italy	47,001	35-60	RCT
Rijkaart*et al.*, 2012 [13]	Netherland	22,420	29-56	RCT
Ogilvie *et al.*, 2012 [14]	North America	44,099	25-65	RCT
Ronco *et al.*, 2014 [15]	Belgium	176,464	20-64	RCT

RCT=Randomized Controlled Trial.

Table 2. — *Results of this meta-analysis*

Processes	Number of studies involved (n)	OR With 95% CI	*p* value	I^2 value (%)
CIN3 + round 1	4	1.19 [1.03, 1.36]	0.07	58
CIN2 round 1	4	1.70 [1.45, 2.00]	0.04	65
CIN3 + round 2	4	0.67 [0.54, 0.82]	0.13	46
CIN2 round 2	4	0.80 [0.64, 1.00]	0.02	69
CIN3 + total	6	0.72 [0.61, 0.85]	0.02	64
CIN2 total	5	1.01 [0.84, 1.21]	0.0004	80

Results

A number of 201 articles have been identified from Medline (via PubMed). After eliminating the duplicate studies and studies not related to the present topic, seven full text articles were finally assessed for eligibility. The flow diagram for the study selection is illustrated in Figure 1. Table 1 represents the general features of the included studies.

Table 2 represents the results of this meta-analysis. Total seven studies for HPV tests and cervical smears were pooled, with a total of 415,909 participants. Figure 2 shows a summary of the findings of this comparison.

The cytology and histology results by HPV status for both groups in round 1 and 2 are shown in Table 2. A large reduction in cytological abnormality rates from round 1 to round 2 was seen in both groups. The rate of CIN3 and worse decreased about two-fold, from 1.19% in round 1 to 0.67% in round 2, and CIN2 decreased from 1.70% in round 1 to 0.80% in round 2. This difference reflected a decrease in the reported abnormality rate after the introduction of HPV DNA screening. When primary cervical screening with LBC was combined with HPV testing, there was a statistically significant reduction in the detection of CIN2 and CIN3+ at the next screening round compared with LBC alone.

Discussion

The present pooled analysis of seven randomized controlled trials of HPV-based cervical screening versus conventional cytology showed a significant reduction in invasive cervical cancers in women who had HPV-based screening. Furthermore, HPV DNA testing with cytology triage was more sensitive than conventional cytology in detecting CIN 2 lesions. However, HPV DNA testing with cytology triage was also more sensitive than conventional cytology in detecting CIN 3 and worse lesions.

Perhaps there are three main factors contributing to the lower cytological abnormality rates seen in round 2 than in round 1. First, some prevalent disease detected in round 1 had presumably been missed at the previous routine smear. The possible reason might be that LBC in this study might have been more sensitive than earlier cytology in this routinely screened population. The additional sensitivity achieved by LBC or HPV testing must, however, depend on the protocol for colposcopic follow-up, and also on the sensitivity of the conventional cytology against which they are compared, which has varied widely between different regions and over time. The sensitivity of conventional cytology for detecting high-grade CIN varied between 30% and 80% in different European centers [4]. A systematic review of both screening and referral studies found no difference in sensitivity to detect high-grade CIN between LBC and conventional cytology [16]. However, a Dutch randomized study reported no difference in test positives, but without histological outcomes [17].

A second factor may have been additional detection of CIN2 or lesser pathology by LBC, the treatment of which might prevent some CIN3 lesions in the next screening round. An Italy randomized reported 66% more cytological abnormalities detected by LBC than by conventional cytology, which led to increased detection of CIN2 although not CIN3+ [18]. Comparisons of sensitivity and specificity for the detection of high-grade disease over a single screening round might therefore be misleading, particularly if LBC leads to increased detection and biopsy or treatment of low-grade disease, which prevents

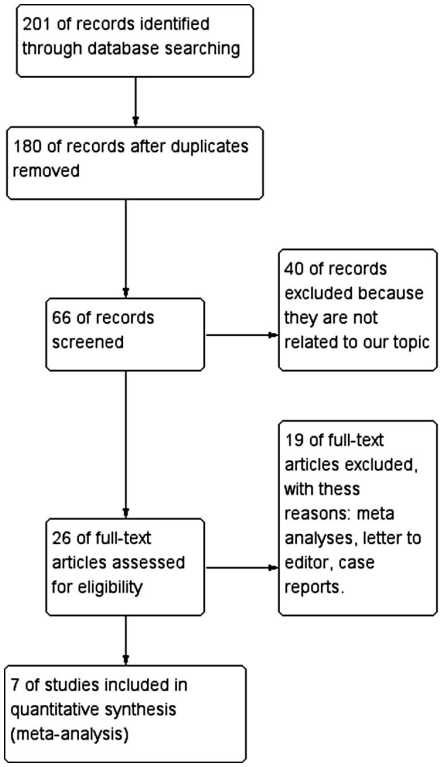

Figure 1. — The flow diagram for the study selection

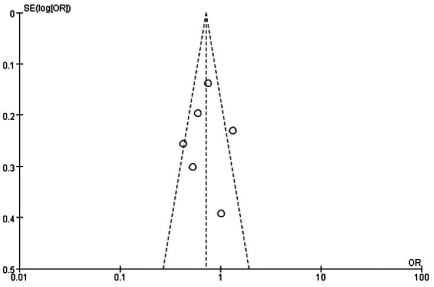

Figure 3. — Funnel plot showing the sensitivity analysis

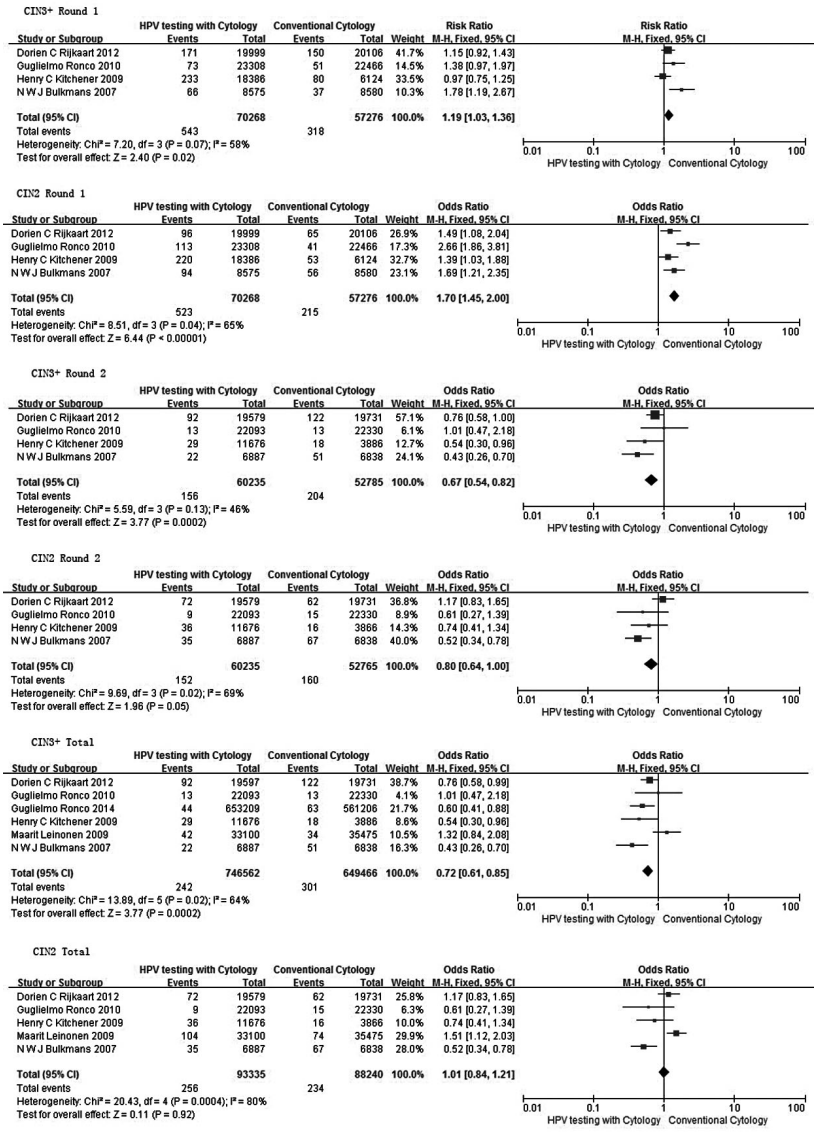

Figure 2. — Forest plot showing the outcomes between HPV testing with cytology and conventional cytology

progression [19].

The third factor, the most important one, in the present authors' opinion, may be that HPV16 and 18 were more common in younger women with cervical cancer than in older women. Women with cervical cancer who are HPV16 or HPV18 positive tend to be younger at diagnosis than women who are positive for other types such as HPV31 and 33 [20]. The difference in age-specific prevalence could be the result of more rapid progression of HPV16 and HPV18 positive precancerous lesions compared with pre-cancers attributed to other carcinogenic HPV genotypes [21]. In this study, although the overall colposcopy referral rate was the same in both screening arms, the youngest women, that is, those younger than 35 years, were referred for colposcopy more often in the HPV DNA screening arm than in the conventional screening arm. In addition, the intensified follow-up screening visits may further increase the rate of referral for colposcopy in the HPV DNA screening arm, especially among women younger than 35 years because they were targeted for intensified follow-up in excess. Thus, additional data concerning cervical lesions detected during follow-up are needed for a final evaluation of the demands on colposcopic resources *vs.* rates of any CIN or cancer with HPV DNA testing.

There are unavoidable statistical deficiencies in the present study, despite strict randomization, but the principal

conclusions are that the increased sensitivity achieved with HPV testing was small at entry and negligible over two screening rounds, and that cytological and histological abnormality prevalence rates were greatly reduced in round 2.

Conclusion

Data from follow-up analysis of seven large randomized cohorts show that HPV-based cervical screening provides greater protection against invasive cancer compared with cytology-based screening. Prevention of cancer in younger women is a priority.

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