European Journal of Obstetrics & Gynecology and Reproductive Biology 210 (2017) 275–280

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Review article

Diagnostic performance of dual-staining cytology for cervical cancer screening: A systematic literature review

Wiebren A.A. Tjalma

Multidisciplinary Breast Clinic, Unit Gynecologic Oncology, Antwerp University Hospital, University of Antwerp, Wilrijkstraat 10, 2650 Edegem, Belgium

ARTICLE INFO

Article history:
Received 29 October 2016
Received in revised form 30 December 2016
Accepted 4 January 2017
Available online xxx

Keywords:
Screening
Diagnostic cytology
Dual-stain cytology
CINtec® PLUS cytology test
Triage
ASCUS (abnormal squamous cells of undetermined significance)
LSIL (low-grade squamous intraepithelial lesion)
p16/Ki-67 dual-stain cytology
p16
Ki-67

ABSTRACT

Cervical cancer screening saves lives. Secondary prevention in cervical cancer screening relies on the results of primary cytology and/or HPV testing. However, primary screening with cytology has a low sensitivity, and HPV screening has a low specificity. This means that either cancers are missed, or women are over-treated. To improve performance outcomes, the concept of dual-stain cytology (CINtec® PLUS Cytology test) has been introduced. In this approach, additional staining with p16/Ki-67 is performed in cases where cytology results are abnormal (LSIL or ASCUS) and/or HPV-positive. Another way to describe this approach might be "diagnostic" cytology. In order to assess the value of this "diagnostic cytology", a systematic literature review was conducted of dual-stain cytology performance across multiple studies until May 2016. In a Belgian screening population (women age 25–65 years), dual-stain cytology was significantly more sensitive (66%) and slightly less specific (−1.0%) than cytology. In the population referred to colposcopy or with abnormal cytology (ASCUS, LSIL), dual-staining showed a significantly higher increase in specificity, and a slightly lower sensitivity than HPV testing. Specificity gains resulted in fewer false positives and an increase in the number of correct referrals to colposcopy. Dual-staining with p16/Ki-67 cytology is an attractive biomarker approach for triage in cervical cancer screening.

Contents

Introduction

Cervical cancer screening started almost 90 years ago. Over the years, we have moved from direct sampling with an Ayre's spatula and object glass to liquid-based cytology. Since then, research showing that nearly all cervical cancers are caused by the human papilloma virus has resulted in screening programs based on HPV detection, thus moving away from reliance on cytological abnormalities alone [1]. The discovery of HPV has increased the detection of abnormalities considerably. A downside, however, is that there is also an increase in "false positive" results. False

E-mail addresses: Wiebren.Tjalma@uza.be, wiebren.tjalma@telenet.be (W.A.A. Tjalma).

http://dx.doi.org/10.1016/j.ejogrb.2017.01.009
0301-2115/

positive should be differentiated in true (real) false positives, which are considered those HPV infections and lesions which will clear over time and in women who are falsely positive due to the limitations and errors of the test itself. At present, it is difficult to predict which HPV infections will progress to (pre)cancerous lesions, and which infections are transient and will regress. In order to improve the detection of severe abnormalities and cancers and reduce the number of "silent" infections, there is a need for colposcopy triage after an HPV infection is found. Triage for colposcopy can be determined based on HPV type, viral load, and cytology findings. Recently, dual-stain cytology has been proposed as a biomarker for colposcopy triage. In a recent ANOVA (analysis of variance) model for network meta-analyses of diagnostic test accuracy, 11 tests for detecting cervical precancer were evaluated [2]. From the full dataset, the superiority index consistently identified p16/Ki-67 as the optimal test in detecting cervical precancer with equivocal or mildly abnormal cervical cells.

This article seeks to evaluate the sensitivity and specificity of dual-stain cytology in cervical cancer screening based on a systematic literature review. We also include a meta-analysis component to summarize and synthesize results, given the increasing availability of complex quantitative test data on cervical cancer screening, and the accompanying need to assess and draw conclusions about existing knowledge.

Methods

Literature search and data extraction

We performed a literature search of studies published as of May 1, 2016, in the electronic databases MEDLINE and EMBASE, without geographical or language restrictions. The review was undertaken according to the CRD (Centre for Reviews and Dissemination), PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and NICE (National Institute for Health and Care Excellence) guidelines [3]. To be eligible for meta-analysis, a study needed to report a measure of diagnostic performance such as sensitivity, specificity, detection rate, odds ratio, positive predictive value, negative predictive value, true positive (TP) (or true negative (TN)), false positive (FP) (or false negative (FN)). These outcomes were chosen since they are the most significant as well as widely used outcomes to compare test performance, and can be calculated from one another using established formulas [4]. Sensitivity and specificity were chosen as the outcome measures in the final meta-analysis based on guidance from the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy [4].

The search was comprised of 3 components: [1] Population/disease area: "Cervical cancer"; [2] Diagnostic performance measure: "Sensitivity" OR "Specificity" OR "Detection rate" OR "Diagnostic odds ratio" OR "Positive predictive value" OR "Negative predictive value"; [3] Clinical information: The CINtec® PLUS Cytology test: "CINtec® PLUS" OR ("ki67" AND "p16") OR "dual stain". In all studies measuring performance of the CINtec® PLUS Cytology test, true disease state–determined from histopathological assessment of cervical biopsies with hematoxylin and eosin (H&E)– was used as ground truth. The studies found in the dual-staining literature review included both Pap cytology and HPV DNA testing in most cases the Hybrid Capture 2 (hc2) HPV DNA test® by Digene (QIAGEN, Gaithersburg, MD) as the comparator screening test [5].

We extracted data from each study regarding its design, setting, population, screening strategies employed, data and study quality, metrics used to describe data, follow-up and triage (where appropriate), and outcomes. The study details and results were extracted into specifically designed data extraction forms. If TP, FN, FP, TN values were not reported in the study reviewed, these values were calculated based on diagnostic performance (i.e. sensitivity, specificity, detection rate, odds ratio, positive predictive value or negative predictive value), total number of patients (i.e. diagnoses of ≥CIN2 or ≥CIN3), and total number in the study population, if available. Authors of studies were not contacted because additional

Table 1
Search Strategies for studies which assessed the performance of dual staining.

Index	Description	Search terms	Number of hits
1	Terms for population	cervical AND ('cancer'/exp OR cancer)	92766
2	Terms for diagnostic		
3	test/clinical		
4	information		
2		CINtec® AND plus	36
3		p16	15499
4		ki AND 67	33611
5		'dual stain' OR 'dual stained' OR 'dual staining' OR 'dual-stain' OR 'dual-stained' OR 'dual-staining'	790
6		#2 OR (#3 AND #4 AND # 5)	67
7		'cell'/exp OR cell AND cycle AND ('deregulation'/exp OR deregulation)	2477
8		cellular AND oncogenic AND transformation	2906
9		oncogenically AND transformed AND basal AND ('cell'/exp OR cell)	6
10		oncogenically AND transformed AND epithelial AND ('cell'/exp OR cell)	25
11		• #7 OR #8 OR #9 OR #10	5372
12		• #2 OR (#3 AND #4 # 5) OR (#7 OR #8 OR #9 OR #10)	5432
13	Terms for diagnostic	#6 AND ('sensitivity' OR 'specificity' OR ('detection' AND 'rate'))	48
14	performance measures	#6 AND ('Diagnostic Odds Ratio' OR 'DOR')	0
15		#6 AND ('Positive predictive value' OR 'Negative predictive value' OR 'Predictive value')	18
16		#6 AND ('sensitivity' OR 'specificity' OR 'detection rate' OR 'Diagnostic Odds Ratio' OR 'DOR' OR 'Positive predictive value' OR 'Negative predictive value' OR 'Predictive value')	49
17		#12 AND ('sensitivity' OR 'specificity' OR 'detection rate' OR 'Diagnostic Odds Ratio' OR 'DOR' OR 'Positive predictive value' OR 'Negative predictive value' OR 'Predictive value')	462
18	Combination	#1 AND #16	42
19		#1 AND #17	59
20		#1 AND #17 After Year 2000 (search selected for review)	55

The first round of the initial literature search found 55 studies which assessed the CINtec® *PLUS* Cytology test.