Pathology – Research and Practice 213 (2017) 723–729

Contents lists available at ScienceDirect

Pathology – Research and Practice

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

Review

Immunohistochemical expression of p16, Ki-67 and p53 in cervical lesions – A systematic review

Daliana Caldas Silva[a,*], Ana Katherine Gonçalves[a], Ricardo Ney Cobucci[b], Roberta Cecília Mendonça[c], Paulo Henrique Lima[c], Geraldo Cavalcanti Júnior[a]

[a] Health Science Post Graduation Program, Universidade Federal do Rio Grande do Norte – UFRN, Natal, RN, Brazil
[b] Gynaecology and Obstetrics Department, Universidade Potiguar – UnP, Natal, RN, Brazil
[c] Januário Cicco Maternity School, Universidade Federal do Rio Grande do Norte – UFRN, Natal, RN, Brazil

ARTICLE INFO

Article history:
Received 31 December 2016
Received in revised form 2 March 2017
Accepted 4 March 2017

Keywords:
Cervical intraepithelial neoplasia
Cancer
p16INK4
Ki-67
p53

ABSTRACT

This study evaluated the immunohistochemical (IHC) expression of p16, p53 and Ki-67 in precancerous lesions and in cervical cancer (CC). Identification and review of publications assessing IHC expression in cervical intraepithelial neoplasia (CIN) and CC until February 15, 2017. Systematic review of studies in women with and without cervical lesions in order to evaluate whether there is overexpression of these biomarkers. A total of 28 publications met the criteria which included 6005 patients. The analysis showed that there is higher IHC expression of these biomarkers associated with the more severe lesions. Nineteen out of 22 evaluated studies have shown that there is a higher p16 expression in more severe lesions (CC), while in p53 expression only 4 out of the 9 studies showed a higher expression among more severe cases. Regarding the Ki-67 expression, it was observed that 9 out of 14 studies showed higher expression in more severe lesions. A complete absence of or just minimal IHC expression was observed in the normal cervical epithelium, whilst a significant increase in the expression of these biomarkers was detected according to the severity of lesions. Results suggest that these biomarkers can be considered useful tools for discriminating between the stages of the progressive cervical disease.

Contents

1. Introduction

Screening programs based on cytological staining techniques (Pap test) has led to a remarkable decline in incidence and mortality from invasive cervical cancer (CC). However, the Pap test efficacy is hampered by the high inter-observer variability and false negative/positive rates [1]. Epidemiological and experimental data

* Corresponding author at: Av. Gal. Gustavo Cordeiro de Farias, s/n, 2° andar do Centro de Ciências da Saúde, Campus da Saúde, Natal, RN 59012-570, Brazil.
E-mail address: dalicaldas@hotmail.com (D.C. Silva).

http://dx.doi.org/10.1016/j.prp.2017.03.003
0344-0338/

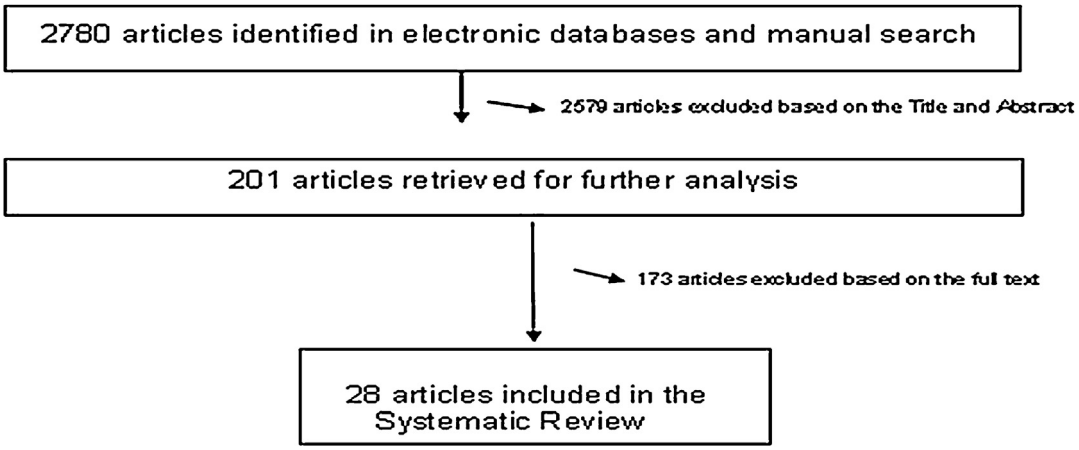

Fig. 1. Study selection.

have linked cervical cancer to infections by certain human papillomavirus (HPV) genotypes. Of the 120 types of HPV, it is known that at least 40 of them infect the genital epithelium; many of them are transient, but the main risk factor for cervical intraepithelial neoplasia (CIN) is persistent cervical infection by high-risk HPV (HR-HPV) [2].

Although the main causal agent associated with CIN and CC is well established, an accurate diagnosis of these precursor lesions of cervical cancer remains a challenge since it is a determinant of prognosis and survival. The association of HPV in the genesis of most cervical lesions is unquestionable. On the other hand, not all patients infected by the virus show the same evolution of the disease, since this behavior is linked to environmental factors, immunity, host genetics and cellular factors. The use of molecular markers has aided histopathology to identify women at high risk for recurrence and in the definition of doubtful cases [3].

The p16INK4a protein (p16) is a kinase inhibitor of cyclin-dependence, which negatively regulates progression through the G1-S transition checkpoint of the cell cycle [4]. Ki-67 is a nuclear protein that is associated with cell proliferation and has been suggested as a sensitive biological indicator of CIN progression [5]. The p53 as a tumor suppressor is one of the main factors that control cell proliferation. As genome's guardian, p53 holds the cell cycle in response to DNA damage or directs a damaged cell to its apoptotic pathway [6].

The expression of these biomarkers has been found to be associated with the severity and progression of cervical neoplasia in recent studies [7–9]. Current studies also relate overexpression of these biomarkers with worst or best prognosis. Zhou et al. and Grace et al. showed that p53 expression indicates a poor prognosis for cervical cancer [10,11]. Other authors have described the p16 role in the CIN to confirm equivocal cytological results, for its importance linked to the HPV-test, as a diagnostic tool, or in the prognostic analysis of lesions [12,13].

Although there is real evidence that some biomarkers immunostaining correlates with the severity of cytological/histological abnormalities, the only marker that has well established utility in the evaluation of progression, and not recurrence, of these lesions is p16INK4a [1,4,14]. The other markers are still poorly studied and, therefore, there are few published papers regarding Ki-67 and p53, lacking accuracy established for use in clinical practice, despite they seem to show difference according to their expression between high and low grade lesions [10,11,14,15].

In this systematic review, we focused on biomarkers that have potential usefulness in the clinical setting. Taking into consideration factors that will increase screening and diagnostic accuracy of cervical specimens and tissue biopsies, and we provide information regarding studies where p16, p53, and Ki-67 were associated with the risk of progression to a more severe lesion.

2. Methods

2.1. Literature search strategy

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [16] we performed a comprehensive literature search of PubMed, Embase, Web of Science, Scopus and Scielo electronic databases to identify comparative studies of p16, p53 and Ki-67 protein expression in women with and without cervical lesions until February 15, 2017. The following search terms and their combinations were used:" cervical intraepithelial neoplasia, "cervical cancer", "cervical carcinoma of the uterus", "Human Papilloma Virus", "HPV", "p16″, "p16INK4a", "Ki-67" and "p53". The reference lists associated with all studies

Table 1
Characteristics of the studies included in the systematic review.

Author/year/ reference	Country	Design of study	Sample size
Mitildzans/2017 [37]	Turkey	Case–control	58
Yu/2016 [24]	China	Cohort	211
Lim/2016 [25]	South Korea	Cross-sectional	103
Chaloob/2016 [26]	Iran	Cross-sectional	127
Zhong/2015 [28]	China	Case–control	1144
Zouheir/2015 [27]	Morocco	Cross-sectional	75
Kim/2015 [23]	South Korea	Cohort	149
Tagle/2014 [38]	Mexico	Cohort	101
Calil/2014 [21]	Brazil	Cross-sectional	174
Wu/2014 [6]	China	Cohort	203
Stănculescu/2013 [22]	Romania	Case–control	80
Yang/2013 [20]	China	Cohort	166
Son/2012 [29]	South Korea	Cross-sectional	91
Samarawardana/2011 [14]	USA	Cohort	296
Bao/2011 [18]	China	Case–control	79
Gupta/2010 [30]	India	Cross-sectional	100
Missaoui/2010 [19]	Tunisia	Case–control	87
Ozaki/2011 [7]	Japan	Cohort	252
Lesnikova/2009 [31]	Denmark	Cross-sectional	806
Ozgul/2008 [32]	Turkey	Cross-sectional	83
Godoy/2008 [33]	Brazil	Cross-sectional	104
Focchi/2007 [34]	Brazil	Cross-sectional	258
Lee/2004 [36]	South Korea	Cross-sectional	54
Branca/2004 [35]	Italy	Cross-sectional	292
Agoff/2003 [41]	USA	Cohort	569
Grace/2003 [11]	India	Cohort	105
Carrilho/2003 [39]	Mozambique	Case–control	67
Dimitrakakis/2000 [40]	Greece	Case–control	171