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SELF-SAMPLING FOR HUMAN PAPILLOMAVIRUS (HPV) IN CERVICAL CANCER SCREENING: A SYSTEMIC REVIEW WITH VISUALIZATION USING ADJUTANT

Review
Article

Keywords

*Cervical cancer;
Self-sampling;
Human papillomavirus (HPV);
Adjutant;
Visualization;*

Abstract

The aim of this study is to perform an automatic systemic review analysis with visualization on (current) research articles about HPV self-sampling as screening test for cervical cancer. It were searched articles from PubMed databases up to August 2020, using Adjutant R package. The resulted document corpus included 275 researches between 1996 and 2020, grouped in five cluster topics. Word Cloud Generator (by Monkey Learn) open source tool for visualization was also employed. Acceptability of self-sampling methods and HPV collection devices/kits is also discussed. Self-collection HPV methodologies and tools are increasing accessibility, awareness, privacy and availability of populational screening for cervical cancer. Beside the fact that these methods may improve screening coverage, they are in agreement with physician-collected cervical specimens methods in detecting HPV. The cases diagnosed early can be included in a complex bimodal therapeutic plan according to the degree of severity – optimal medical and surgical treatment, which will lead to healing of cervical lesions, which in terms will maintain the women's reproductive prognosis during their reproductive age, where the highest incidence of chronic genital HPV infection is encountered.

INTRODUCTION

Cervical cancer is the fourth most frequent cancer in women and seventh in the general population worldwide. The main etiological factor of cervical cancer and its precursors is the persistent infection with high-risk strains of Human Papilloma Virus (HPV). Virology and molecular biology studies have shown that, of 99% of HPV infections, 80% are transient (mainly in the female population aged 24, adolescents) and the rest are persistent (especially within oncogenic strains of type 16 and 18, out of all 14 oncogenic strains). According to the theory of lesion continuity in regards to dysplastic lesion's neoplasia, especially in the female population aged 30 years and over, which due to the accumulation of genomic alterations in somatic cells (representing *primum movens* in the process of tumorigenesis) make them more susceptible to infection or malignant transformation, it has been found that the disease is preceded by an infection caused by any of the 14 oncogenic types of the human papilloma virus (HPV) (16, 18, 31, 33, 35, 45, 51, 53, 68) defined as "high risk" (hr-HPV) by the International Agency for Research on Cancer (IARC) in 2009. Following a hr-HPV infection, a small percentage of women develop cervical epithelium abnormalities known as squamous intraepithelial lesions (SIL) in cytology, or also as "intraepithelial neoplasms" (CIN). CIN1 has a high probability of regression (60-80%) within the first two years after detection and do not require treatment (Ginfalean, 2018). However, in 10% of cases, they may persist and progress to high grade neoplasms (CIN2 or CIN3), and 30% of these progress to carcinoma and, consequently, need to be treated. The frequency of cervical cancer and mortality caused by this type of cancer remains high. In Globocan (2018) it was mentioned that the occurrence of cervical cancer in Romania was 8.6%, and the mortality was 19.5/10,000 women. Worldwide, the following have been implemented: (i) primary prevention programs (via immunization) and (ii) secondary prevention programs – traditional cytological testing, to which (iii) co-tests have been added. Cervical cancer screening strategies, like regular Papanicolaou (Pap smear) test, ThinPrep, visual inspection with acetic acid or Iodine solution are among the most used screening methods for controlling cancer. However, the rates of women's participation to the screening programs tend to be reduced due to factors / barriers like: accessibility, (non)attendance / awareness about screening programs / cancer awareness education, costs / (un)insurance / low socio-economic status, (high) medical resource facilities, sociocultural barriers (subjective patient

experience, (lack of) knowledge about the test, experience of discomfort or pain, embarrassment and shame) (Gupta et al., 2018). In this context, self-sample HPV testing represents an alternative to Pap test for cervical cancer screening (Mayrand et al., 2007; Montealegre, Mullen, Jibaja-Weiss, Vargas Mendez & Scheurer, 2015; Montealegre, et al., 2015).

HPV self-sampling methods are not providing a diagnosis of cervical (pre) cancer, they are useful in identifying women at higher risk. This testing aims to signal the presence of highly oncogenic strains, extrapolation can lead to early identification of the number of cases of precancerous lesions of the cervix and implicitly of cervical cancer.

The purpose of the present study was to (i) perform an automatic systemic, in-depth, updated review analysis with visualization on (current) research articles about HPV self-sampling as screening test in order to (ii) identify main perspectives and trends, accomplish a comprehensive overview and to better understand of HPV self-sampling research directions, methodologies and tools.

AUTOMATED LITERATURE MINING

Adjutant (Crisan, Munzner, Gardy and Wren, 2019) is an R-based application specialized in topic discovery for systematic and literature reviews (Maniu and Maniu, 2020). The author searched for articles related to self-sampling methods used in detecting HPV infections. The PubMed databases were searched up to August 2020, using Adjutant R package with the following query: *Screening AND HPV AND (home OR self) AND sample AND cervical AND cancer*. Using this text mining based instrument the following data were extracted for each research: PubMed article ID, publication year, journal, authors, title, abstract, article type, language, PMC ID and citation count, DOI and mesh terms. This dataset generated with Adjutant can be further analyzed using statistical, data mining, geospatial and other data analysis and visualization methods (Maniu, 2014, Maniu, Maniu and Hunyadi, 2014a; Maniu, Maniu and Hunyadi, 2014b; Maniu and Maniu, 2015; Maniu and Maniu, 2016; Maniu, Wandschneider and Neamtu, 2017; Maniu, Maniu, Dospinescu and Visa, 2018; Maniu, Maniu, Visa, Costea and Neamtu, 2018a; Mocan, 2005). Word Cloud Generator (WCG) from Monkey Learn (2020), an open source tool, was used for visualization of (i) articles distribution in scientific journals and (ii) mesh terms distribution in scientific documents.

RESULTS

Literature mining

The resulted document corpus included 275 researches from 108 journals between 1996 and 2020. There were 227 journal articles, nine reviews and five meta-analyses, 10 multicenter studies and 25 randomized controlled trails.

Left graphic from Figure 1 presents the number of publications per year. After 2010 more than 10 papers were published a year, since 2013 the number increased at over 20 papers a year and reached to more than 30 per year since 2017. In the right side of Figure 1 are presented the top five journals where articles were published. The distribution of all journals in line with their appearance in the present collection is presented in Figure 2. Concretely, the top five journals were: BMC women's health, Gynecologic oncology, International journal of cancer, Journal of clinical virology and PloS one. In figure 3 the distribution of mesh terms from scientific documents is depicted.

Topic clusters

For the results of search analysis, Adjutant suggests five clusters, including 90% of all the retrieved articles. The list of the resulted clusters topics include: attend-report (211), methyl-triag (8), mrna-preval (6), vaccine-mother (6). These clusters are visually represented in Figure 4.

The attend-report cluster topics are referring to subjects like: (text analysis on titles) DNA testing, acceptability of self-sampling, tests performance / predictive value, self-collected vaginal / vulvar / urine samples, screening programs, (text analysis of abstracts) genotypes, neoplasia grades, collection devices, questionnaires, lesions.

Many studies are comparing results from (different) self-sampling collecting methods with results from physician screenings methods. These articles are suggesting the fact that self-sampling methods may improve screening coverage and are in agreement with physician-collected cervical specimens methods in detecting hrHPV types (Arbyn et al., 2014; Toliman et al., 2016). The highly oncogenic HPV strains, identified when the self-collection sample is taken (genitally, urinary), are: 16, 18, 31, 33, 45, 52, 58, 35, 39, 51, 56, 59, 66 and 68. (Cui et al., 2014; Ginfalean, 2016). Self-testing for primary HPV is considered reliable methods for the detection of stage 2+ intraepithelial cervical neoplasia (CIN 2+), according to Polman et al. (2019). Although the procedure has a low sensitivity to tests collected in a medical environment, the detection rate of CIN 2+ was 29.4%, cases that were additionally reassessed colposcopically, thus avoiding congestion in the medical environment, amid the COVID-19 pandemic.

HPV collection devices/kits

Types of collection devices for the identification and preservation of high-risk HPV include: brushes (Viba brush (Rovers Medical Devices, B.V., The Netherlands), Evalyn Brush (Disclosure Axlab, Danish)), cervicovaginal lavage (Delphi Screener (Rovers Medical Devices)), spatula, swabs (cobas CT/ NG Swab (Roche Diagnostics NZ), HerSwab® device/Eve kit (Eve Medical, Toronto, ON)), tampons (Bais et al., 2007; Bonilla-Osma, Amaya-Guio, Olaya-García & Bonilla-Bula, 2018; Brink et al., 2006; Fairley et al., 1992; Giorgi Rossi et al., 2015; Gök et al., 2010; Gustavsson et al., 2018; Longatto-Filho et al., 2012; Spees et al., 2019; Tranberg et al., 2018; van Baars et al., 2012).

Acceptability of self-sampling

Acceptability of self-sample HPV testing among women is assessed by using questionnaires / surveys. Questionnaires items could be closed-ended and/or open-ended and inquired about: (i) willingness to use the test if available; (ii) test comfort, (iii) easy to use, (iv) preference regarding self-collection versus physician-collection, (v) concerns regarding the self-sampling, (vi) willingness to redo the test. Additionally the questionnaires are including items about demographics, healthcare access and utilization, history of cervical cancer screening, knowledge of HPV, etc. (Brewer et al., 2019; Gottschlich et al., 2017; Montealegre et al., 2015). Most of the analyzed studies concluded that self-sample HPV testing is a method accepted by women's. The acceptability measurement instruments can be used simultaneously with other PROMs (patient-reported outcome measurement instruments for assessing quality of life, therapy/treatment management, etc.) (Maniu, Maniu, Visa, Costea and Neamtu, 2018b; Maniu, Maniu and Neamtu, 2019) in order to achieve a comprehensive overview.

CONCLUSIONS

The current study presents general steps that can be followed for performing a systemic, in-depth, automated, scientific review analysis with visualization. Considering the specific domain of HPV self-sampling as screening test, the article (i) highlights main research directions and trends from specific literature, (ii) offers comprehensive and broad overview about HPV self-sampling collection devices/kits and acceptability issues.

In comparison with traditional screening programs, self-collection HPV methodologies and tools are (i) increasing rates of women's participation to the screening programs - accessibility and (ii) reducing resources / costs / infrastructure facilities - less

infrastructure (self-collection HPV kits are allowing women's to collect their own cervicovaginal samples at home or at medical facilities) - availability. These methods increase the number of cases diagnosed early, which can be included in a complex bimodal therapeutic plan according to the degree of severity – optimal medical and surgical treatment, which will lead to healing of cervical lesions, which in terms will maintain the women's reproductive prognosis during their reproductive age, where the highest incidence of chronic genital HPV infection is faced.

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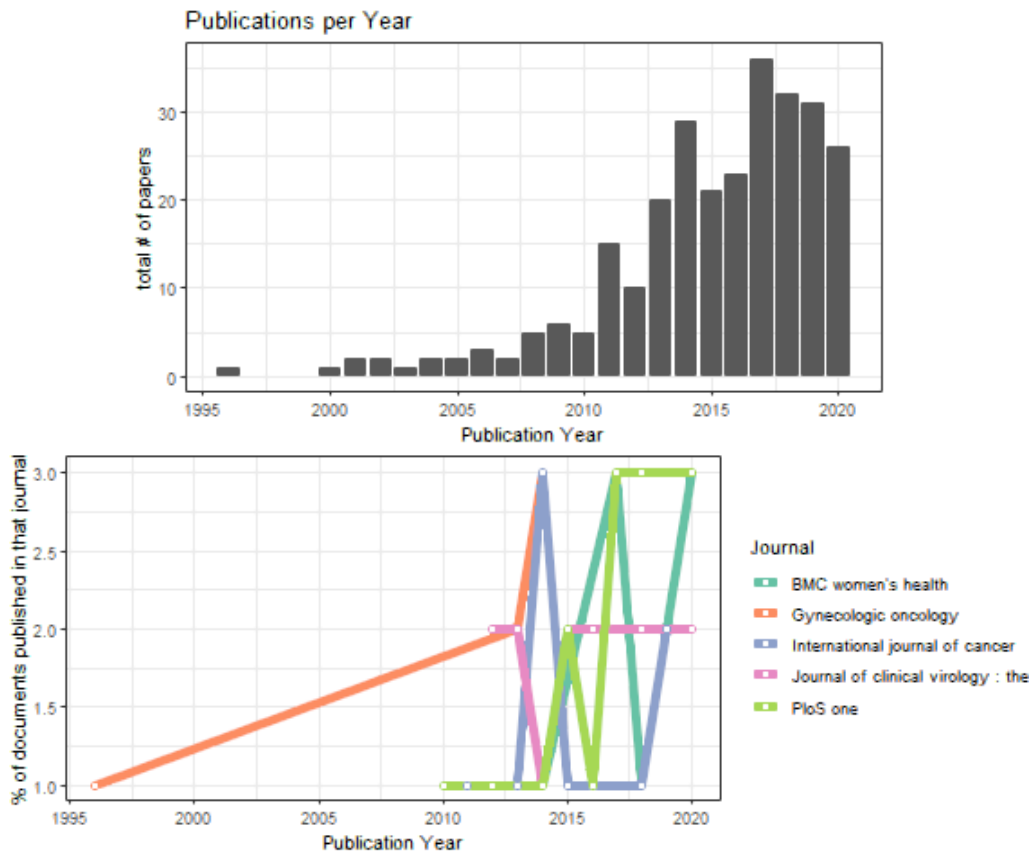


Figure 1
(left) The annual publication trend in Pub Med related to self-sampling methods used in detecting HPV infections, (right) Top five journals with published documents related to self-sampling methods used in detecting HPV infections



Figure 2
Distribution of articles in scientific journals. Word cloud generated using Word Cloud Generator by Monkey Learn
Source: Monkey Learn, 2020

