Georgeta GINFALEAN
Faculty of Medicine, Lucian Blaga University of Sibiu

CERVICAL CANCER SCREENING: PAP TEST AND ITS ALTERNATIVES. A REVIEW WITH VISUALIZATION USING ADJUTANT

Review Article

Keywords
Pap test;
Screening;
Cervical cancer;
Human papillomavirus (HPV);
Adjutant, visualization;

Abstract

The objective of this study is to perform a review analysis with visualization on research articles related to Pap test and alternative methods of screening for cervical cancer. Articles from PubMed databases up to October 2020 were searched and filtered using Adjutant application. The resulted document corpus included 527 researches, published between 1953 and 2020. This automated search tool also performs topic cluster identification, resulting ten cluster topics in this study research context. The cluster's topics highlight the main perspectives and trends in research regarding cervical cancer programs. The presentation of these clusters provide an assemble, comprehensive and broad overview of existing research on: access / participation / compliance / knowledge / implementation / limitations / guidelines of/to/for cervical cancer screening programs (especially Pap test), HPV molecular screening tests, HPV vaccination programs, screening strategies cost-effectiveness.

INTRODUCTION

Cervical cancer (CC, cancer of cervix uteri) is one of the most common sexually transmitted diseases with an increasing incidence, especially in populations from developing countries. It was reported in 2018 in Europe a cervical cancer incidence of 61,072 cases and a mortality of 25,829 cases (Bruni et al., 2019). The global estimated crude incidence rate of cervical cancer in 2018 is geographically presented in figure 1.

Cervical cancer Papanicolau test (or pap-test) is a manual, widespread method used for (i) screening / diagnosing cervical cancer, (ii) follow-up test for women with prior abnormalities. It was proposed in the 1940s by George N. Papanicolaou and H.F. Traut (Papanicolaou and Traut 1997). However, in 1927, the Romanian physician Aurel Babes collected samples of cells (smear) from the surface of the cervix and detected presence of cervical cancer (Tan & Tatsumura 2015). When it's performed regularly, the early Pap test identifies abnormal cells in the cervix before they turn into cancer cells. It is one of the easiest medical investigations; however, too few women periodically perform this test. The proof is the sad leading place in Europe in cervical cancer mortality.

Despite the fact that it is a widespread cervical cancer screening method, the Papanicolaou test presents a series of limitations, given by the following aspects: subjective interpretation of cell morphological alterations, incorrect sampling of cellular material without intercepting the transformation area (squamous-cylindrical junction for example migrates in perimenopause to the interior of the cervical canal), errors in interpretation (due to incorrect sampling, non-uniform distribution of cells, blood and mucus obscuration etc.), false negative results (30-50%), speed and costs, etc. (Siebers et al., 2009; Venkatesulu, Mallick, & Rath, 2017).

Additional / alternative / modified / prevention methods have been proposed in order to be used in screening / triage / follow-up and to increase the sensitivity of cervical cytological screening. Among these methods are the following: UltraFast / REAP / Enviro staining methods liquid-based cytology (Thin Prep, SurePath techniques), visual inspection (by acetic acid, Lugol's iodine techniques), HPV testing ((viral) markers deterction - HPV DNA, HPV mRNA, proteins, methylation).

It is unanimously accepted and demonstrated by studies of virology and molecular biology that HPV infection is the main cause (99%) of cervical tumors, respectively of neoplastic precursor lesions. Therefore, vaccines that prevent these infections will also prevent cervical cancer.

Currently, there are HPV vaccines, all of which target the two most common types of high-risk HPV (16 and 18) that together cause most cases of cervical cancer. Vaccination is extremely effective in preventing persistent HPV 16 and 18 infections when given to adolescent girls and young women before starting their sexual life. These vaccines also provide a low level of protection against several other high-risk HPVs.

The purpose of the present study was to perform a review analysis with visualization of research articles on the Pap-test and its alternative methods in screening / triage / follow-up / prevention of cervical cancer.

AUTOMATED LITERATURE MINING

Adjutant (Crisan, Munzner, Gardy and Wren, 2019) is an open-source, interactive R-based application specialized in topic discovery using text mining techniques for systematic and literature reviews (Maniu and Maniu, 2020). Articles related to Papanicolau test as a screening program for cervical cancer were searched. The search was conducted on PubMed databases, using Ajutant R package with the following query: *(Pap AND smear AND test) OR (Papanicolaou AND test) AND screening AND programs AND cervical AND cancer,* up to September 2020. For each retrieved document were extracted: PubMed article ID, publication year, journal, authors, title, abstract, article type, language, PMC ID and citation count, DOI and mesh terms. The document corpus retrieved by Adjutant can be further used for 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, 2018; Mocan, 2005). Also, an open source tool: Word Cloud Generator (WCG) from Monkey Learn (2020) was used for visualization tasks.

RESULTS

Literature mining
The search conducted using Adjutant tool resulted in 527 research documents from 237 journals published from1953 to 2020. There were 442 journal articles, 62 reviews and one meta-analysis, 11 randomized controlled trails, seven multicenter studies and four other type of documents (letters, editorial).

The number of publications per year is presented in the Figure 2. More than 30 papers are published per year since 2014. The top journals where articles

were published are presented in the Figure 3, and were: Journal of cancer (49 documents), Obstetrics (46 documents), Cancer Prevention (41 documents), Public Health (35 documents), Asian Pacific Journal (31 documents). In figure 4 the distribution of mesh terms from scientific documents is depicted.

Survey on existing literature on Papanicolau test based on the retrieved topic clusters

For the results of search analysis, Adjutant suggests ten clusters, including 57% of all the retrieved articles. The list of the resulted clusters topics include: papanicola-popul (133), dna-type (30), knowledge-belief (28), abnorm-lesion (20), vaccine-infect (18), knowledge-practic (17), cost-effect (16), immigr-sampl (14), collect-sampl (13), intervent-effect (13). These clusters are visually represented in Figure 5.

From the papanicola-popul cluster (133 documents) were mainly analyzed the results of studies from 2010 to 2020 (58 documents, almost a half from these cluster documents). These studies are addressing issues like (i) screening, diagnosis, staging, prevention/control, (factors associated with) access/participation/compliance, incidence, implementation strategies, disparities, inequalities, performance, limitations, guidelines of/to/for cervical cancer screening programs. Among the major ideas / recommendations from these studies are: using HPV test instead of Papanicolau test, screening every five years, with the option of self-sampling, and triage based on HPV 16/18 or Papanicolaou typing (Ferreccio, 2018), effective screening programs should consider factors like starting age and screening intervals. Pan American Health Organization in collaboration with WHO (World Health Organization) proposed a Plan of Action for Cervical Cancer Prevention and Control 2018-2030, and suggested four strategic lines of action: (1) improve cervical cancer program organization and governance, information systems, and cancer registries; (2) strengthen primary prevention through information, education, and HPV vaccination; (3) improve cervical cancer screening and precancer treatment through innovative strategies; (4) improve access to services for cancer diagnosis, treatment, rehabilitation, and palliative care (Pan American Health Organization, 2018).

HPV molecular screening tests – dna-type cluster

Most of the studies from this cluster are presented the prevalence and genotype distribution of HPV in different populations. Also, in this cluster, some of the studies are comparing the methods HPV DNA (human papillomavirus deoxyribonucleic acid, HPV genotypes 16, 18, 31, 33, 45) and HPV mRNA (human papillomavirus messenger ribonucleic acid, viral oncoproteins (biomarkers) E6 and E7). HPV DNA-based screening method is more effective than a Pap test (in preventing cervical cancer), but is less specific. The HPV mRNA test showed a similar or slightly lower sensitivity than the HPV DNA tests but with a higher specificity (Maggino et al., 2016). Agreement of both diagnostic approaches was encontered in case of (i) women with low-grade and high-grade squamous intraepithelial lesion, (ii) type-specific agreement regardless of cytology (Salimović-Bešić, Tomić-Čiča, Smailji, and Hukić, 2013). These studies are concluding that furthet studys are needed to test the specificity and superiority of HPV (E6/E7) mRNA testing (Salimović-Bešić et al., 2013) and recommanding that comparison of the HPV mRNA and HPV DNA tests must be interpreted cautiously (Maggino et. al., 2016).

HPV vaccination programs – vaccine-infect cluster

Cervical cancer develops in the presence of a persistent high-risk HPV infection. Therefore, vaccines that prevent these infections will also prevent cervical cancer. The approved vaccines for HPV are quadrivalent Gardasil/Silgard (targets HPV 6, 11, 16, 18), Cervarix (targets HPV 16, 18), nonavalent Gardasil 9 (targets HPV 6, 11, 16, 18, 31, 33, 45, 52, 58) (Schülein et al., 2016; Dilley, Miller and Huh, 2018; Chrysostomou, Stylianou, Constantinidou and Kostrikis, 2018). However, this available HPV vaccine does not provide protection against all types of high-risk HPV, and although the vaccine reduces the risk of cancer, it does not provide complete protection. That is why it is important for all women to have a cervical screening, even if they have had the vaccine. The results of the study of Chao et al. (2017) suggested that (i) vaccinated women (compared to unvaccinated women) were more likely to subsequently initiate cervical cancer screening, (ii) there is need for targeted interventions among unvaccinated women to to improve vaccination rates and/or cervical cancer screening.

Cost-effectiveness cluster

Cost-effectiveness studies of cervical screening strategies (Pap smear screening usually compared with others strategies like HPV DNA testing) are analytical tools which can help the health policy makers in their decision-making process of designing / implementing / scale specific target-population screening programs (Sawaya, Kerlikowske, Lee, Gildengorin and Washington, 2000; Nahvijou et al., 2014; Nahvijou et al., 2016; Shen, Olwanda, Kahn, and Huchko, 2018). Cost-effectiveness analysis performed by Nahvijou (Nahvijou et al., 2016) uses, as model parameters, characteristics such as: transition (regression,

progression, persistent) probabilities, test characteristics (sensitivity/specificity), utility characteristics (quality of life questionnaires – QALY, EuroQol EQ-5D (Mandelblatt et al., 2002; Szende, Oppe and Devlin, 2007; Maniu et al., 2018; Maniu, Maniu and Neamtu, 2019), medical screening costs from a health provider perspective (cost of the test, physician visit, colposcopy, biopsy, conization, treatment costs for different stages (Nahvijou, Sari, Zendehdel and Marnani, 2014; Daroudi, Zendehdel, Nahvijou, Zahmatkesh and Akbarisari, 2014)), gross domestic product (GDP) per capita (as threshold). When performing cost-effectiveness studies different screening strategies are analyzed. These strategies are taking into consideration: type of screening test (Pap smear vs. HPV DNA testing), different target / starting ages (21, 30, 35 years), screening intervals (3, 5, 10 years) (Nahvijou et al., 2014). Other studies are analyzing time and travel costs (Woolley et al., 2007) and cost items like personnel, recurrent goods, services, capital goods, and facility overhead (Shen et al., 2018).

CONCLUSIONS

The widespread Pap smear test is used in screening programs to detect cervical cancer and routine Pap screening is an useful way to prevent it. There is currently a huge amount of scientific evidence demonstrating the benefits and safety of the HPV vaccine. Based on this evidence, the HPV vaccine is accepted by doctors and scientists as an extremely effective way to reduce the risk of cervical cancer, and the European Center for Disease Prevention and Control has emphasized that national health authorities across Europe should make greater efforts to ensure that all adolescent girls are vaccinated against HPV. Population-based vaccination and screening programs should work together to optimize cervical cancer prevention (Kim et al., 2016).

The clusters' topics identified with the automated search tool Adjutant are highlighting main perspectives and trends in research regarding cervical cancer programs. The presentation of these clusters provide an assemble, comprehensive and broad overview of existing research on: access / participation / compliance / knowledge / implementation / limitations / guidelines of/to/for cervical cancer screening programs (especially Pap test), HPV molecular screening tests, HPV vaccination programs, screening strategies cost-effectiveness. Beside Adjutant, other automated analytical tools for literature mining can be used in order to assemble a broad overview of the research field (Maniu et al., 2020).

REFERENCES

[1] Bruni, L., Albero, G., Serrano, B., Mena, M., Gómez, D., Muñoz, J., Bosch, F.X. and de Sanjosé, S. (2019). *ICO/IARC Information Centre on HPV and Cancer (HPV Information Centre)*. Human Papillomavirus and Related Diseases in Europe. Summary Report.

[2] Chao, C., Silverberg, M. J., Becerra, T. A., Corley, D. A., Jensen, C. D., Chen, Q., & Quinn, V. P. (2017). Human papillomavirus vaccination and subsequent cervical cancer screening in a large integrated healthcare system. *American journal of obstetrics and gynecology*, *216*(2), 151.e1–151.

[3] Chrysostomou, A. C., Stylianou, D. C., Constantinidou, A., & Kostrikis, L. G. (2018). Cervical Cancer Screening Programs in Europe: The Transition Towards HPV Vaccination and Population-Based HPV Testing. *Viruses*, *10*(12), 729.

[4] Crisan, A., Munzner, T., Gardy, J.L., Wren, J. (2019). Adjutant: An R-based tool to support topic discovery for systematic and literature reviews. Bioinformatics, 35, 1070–1072.

[5] Dilley, S., Miller, K.; Huh, W. (2018). HPV vaccination. *Gynecol. Oncol.*, 148, 3–4.

[6] Daroudi, A., Zendehdel, K., Nahvijou, A., Zahmatkesh, H., Akbarisari, A. (2014). A Review of Methods for Estimating Economic Burden of Cancer.

[7] Ferreccio, C. (2018). Nuevas estrategias de prevención y control de cáncer de cuello uterino en Chile [New strategies for the prevention and control of cervical cancer in Chile]. *Salud Pública de México*, *60*(6), 713-721.

[8] Kim, J., Bell, C., Sun, M., Kliewer, G., Xu, L., McInerney, M., Svenson, L. W., & Yang, H. (2016). Effect of human papillomavirus vaccination on cervical cancer screening in Alberta. *CMAJ : Canadian Medical Association journal - journal de l'Association medicale canadienne, 188*(12), E281–E288.

[9] Mandelblatt, J.S., Lawrence, W.F., Womack, S.M., Jacobson, D., Yi, B., Hwang, Y., et al. (2002). Benefits and costs of using HPV testing to screen for cervical cancer. *JAMA: the journal of the American Medical Association 287*: 2372–2381.

[10] Maggino, T., Sciarrone, R., Murer, B., Dei Rossi, M. R., Fedato, C., Maran, M., Iorio, M., Soldà, M., Zago, F., Giorgi Rossi, P., & Zorzi, M. (2016). Screening women for cervical cancer carcinoma with a HPV mRNA test: first results from the Venice pilot program. *British journal of cancer*, *115*(5), 525–532.

[11] Maniu, I. (2014). *Tehnici de analiză a datelor: statistica [Data analysis techniques:*

statistics]. Ed. Univ. Lucian Blaga Sibiu, ISBN 978 – 606 – 12 – 0891 – 3, 9-127.

[12] Maniu, I., Maniu, G., & Hunyadi, D. (2014a). *Feature discovering in medical data sets using cluster algorithms.* Ovidius University Annals Series, Section Applied Mathematics and Computer Science, Issue 16, Ovidius University Press, ISSN 1584-5990, 143-150.

[13] Maniu, I., Maniu, G., & Hunyadi, D. (2014b). *Computational intelligence in medical data sets, Modeling and development of intelligent systems.* ISSN 2067-3965, 69-74.

[14] Maniu, I., & Maniu, G.C. (2015). Data analysis techniques for examine factors influencing student's enrollment decision. International Conference on collaboration in complex systems. Fusion between Arts, Theology, Engineering, Management & Social Sciences, *SEA – Practical Application of science, Issue 8: Collaboration in complex systems, 2*(8), 61-64.

[15] Maniu, I., & Maniu, G. (2016). *Analiza datelor: arbori de decizie [Data analysis: decision trees].* Ed. Univ. „Lucian Blaga" Sibiu, ISBN 978-606-12-1418-1, 54-88.

[16] Maniu, I., Wandschneider, A., & Neamtu, B. (2017). Practical recommendations of data preprocessing and geospatial measures for optimizing the neurological and other pediatric emergencies management. 17 Cross-cultural knowledge exchange. Interactions between law, education, tourism & culture. – SEA International Conferenece, 8-9 july, Constanta, *SEA Practical Application of science Journal*, ISSN-L:2360-2554, *Fascicle Health and medical management, V*(14), 305-311.

[17] Maniu, I., Maniu, G., Dospinescu, C., & Visa, G. (2018). A Factor Analysis Model for Dimension Reduction of Outcome Factors in Neonatal Seizure Context, BRAIN. *Broad Research in Artificial Intelligence and Neuroscience , 9*(2), ISSN 2067-8957, 95-103.

[18] Maniu, I., Maniu, G., Visa, G., Costea, R., & Neamtu, B. (2018). Measurement instruments for screening and assessing differnet headache and migraine aspects. *SEA - PRACTICAL APPLICATION OF SCIENCE" Journal, Volume VI*, Issue 18 (3), 369-378.

[19] Maniu, I., Maniu, G., & Neamțu, B. (2019). Quality of life measurement instruments for headache and migraine disorders. *Applied Medical Informatics, 41*(1).

[20] Maniu, I., & Maniu, G. (2020). A Systemic Review with Visualization using Adjutant: Application in Case of Febrile Seizure Research, 8th IEEE International Conference on E-Health and Bioengineering - EHB 2020 Grigore T. Popa University of Medicine and Pharmacy Iasi, Web Conference, Romania, October 29-30.

[21] Mocan, I. (2005). *SPSS Introducere în analiza datelor [SPSS Introduction in data analysis].* Ed. Univ. „Lucian Blaga" Sibiu, ISBN 973 – 739 – 189 – 6, 12-93.

[22] Nahvijou, A., Sari, A.A., Zendehdel, K., Marnani, A.B. (2014). Management of Precancerous Cervical Lesions in Iran: A Cost Minimizing Study. *Asian Pacific Journal of Cancer Prevention, 15*: 8209–8213.

[23] Nahvijou, A., Hadji, M., Barati Marnani, A., Tourang, F., Neda Bayat, E., Daroudi, R., et al. (2014). A Systematic Review of Economic Aspects of Cervical Cancer Screening Strategies Worldwide: Discrepancy between Economic Analysis and Policymaking. *Asian Pacific Journal of Cancer Prevention 15*: 8229– 8237.

[24] Nahvijou, A., Daroudi, R., Tahmasebi, M., Amouzegar Hashemi, F., Rezaei Hemami, M., Akbari Sari, A., Barati Marenani, A., & Zendehdel, K. (2016). Cost-Effectiveness of Different Cervical Screening Strategies in Islamic Republic of Iran: A Middle-Income Country with a Low Incidence Rate of Cervical Cancer. *PloS one*, *11*(6), e0156705.

[25] Pan American Health Organization (2018). *Plan of Action for Cervical Cancer Prevention and Control 2018-2030.* Washington, D.C.: PAHO.

[26] Papanicolaou, G. N., & Traut, H. F. (1997). The diagnostic value of vaginal smears in carcinoma of the uterus. 1941. *Archives of pathology & laboratory medicine*, *121*(3), 211–224

[27] Salimović-Bešić, I., Tomić-Čiča, A., Smailji, A., & Hukić, M. (2013). Comparison of the detection of HPV-16, 18, 31, 33, and 45 by type-specific DNA- and E6/E7 mRNA-based assays of HPV DNA positive women with abnormal Pap smears. *Journal of virological methods*, *194*(1-2), 222–228.

[28] Sawaya, G.F., Kerlikowske, K., Lee, N.C., Gildengorin, G., Washington, A.E. (2000). Frequency of cervical smear abnormalities within 3 years of normal cytology. *Obstetrics & Gynecology 96*: 219–223

[29] Schülein, S., Taylor, K. J., König, J., Claus, M., Blettner, M., & Klug, S. J. (2016). Factors influencing uptake of HPV vaccination among girls in Germany. *BMC public health*, *16*, 995.

[30] Shen, J., Olwanda, E., Kahn, J. G., & Huchko, M. J. (2018). Cost of HPV screening at community health campaigns (CHCs) and health clinics in rural Kenya. *BMC health services research*, *18*(1), 378.

[31] Siebers, A. G., Klinkhamer, P. J., Grefte, J. M., Massuger, L. F., Vedder, J. E., Beijers-Broos, A., Bulten, J., & Arbyn, M. (2009). Comparison of liquid-based cytology with conventional cytology for detection of cervical

cancer precursors: a randomized controlled trial. *JAMA*, *302*(16), 1757–1764.

[32] Szende, A., Oppe, M., Devlin, N.J. (2007). *EQ-5D value sets: inventory, comparative review and user guide*. Springer Netherlands, ISBN 978-1-4020-5510-2.

[33] Tan, S. Y., & Tatsumura, Y. (2015). George Papanicolaou (1883-1962): Discoverer of the Pap smear. *Singapore medical journal*, *56*(10), 586–587.

[34] Woolley, C., Philips, Z., Whynes, D. K., Cotton, S. C., Gray, N. M., Sharp, L., Little, J., Waugh, N. R., & The TOMBOLA group (2007). United Kingdom cervical cancer screening and the costs of time and travel. *International Journal of Technology Assessment in Health Care, 23*(2), 232-239.

[35] Venkatesulu, B. P., Mallick, S., & Rath, G. K. (2017). Patterns of care of cervical cancer in the elderly: A qualitative literature review. *Journal of geriatric oncology*, *8*(2), 108–116

[36] International Agency for Research on Cancer (2020). *Online analysis map*. https://gco.iarc.fr/today/online-analysis-map

[37] Monkey Learn (2020). *Word Cloud Generator*. https://monkeylearn.com/word-cloud/

LIST OF FIGURES

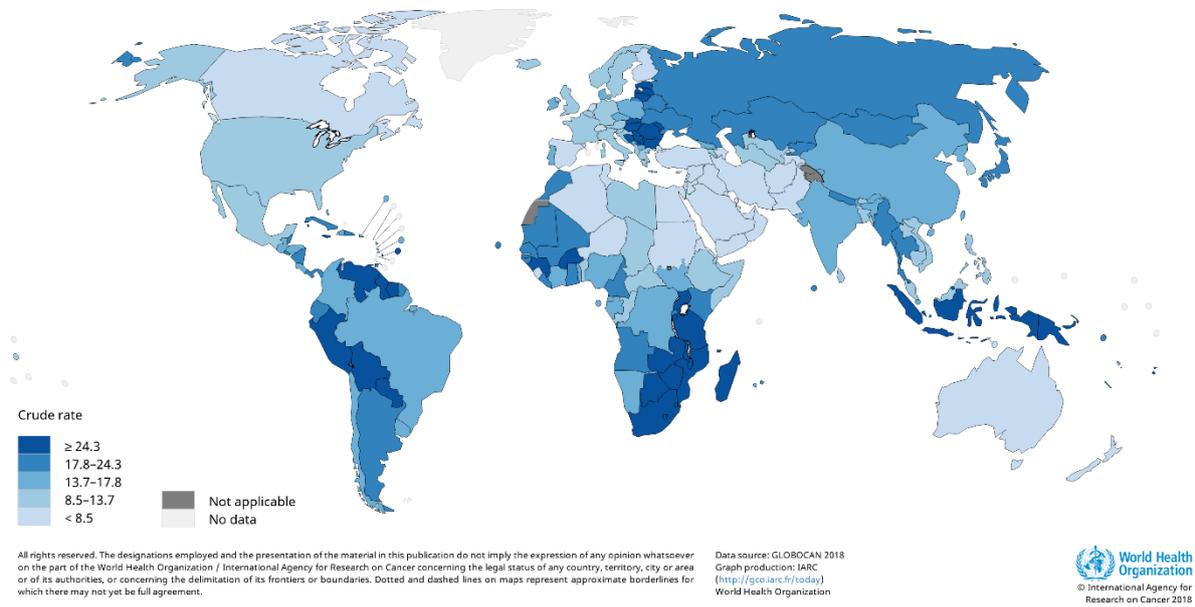Estimated crude incidence rates in 2018, cervix uteri, all ages

Figure 1
Incidence crude rate of cervical cancer in 2018
Source: author analysis using online analysis map instruments from International Agency for Research on Cancer (2020)
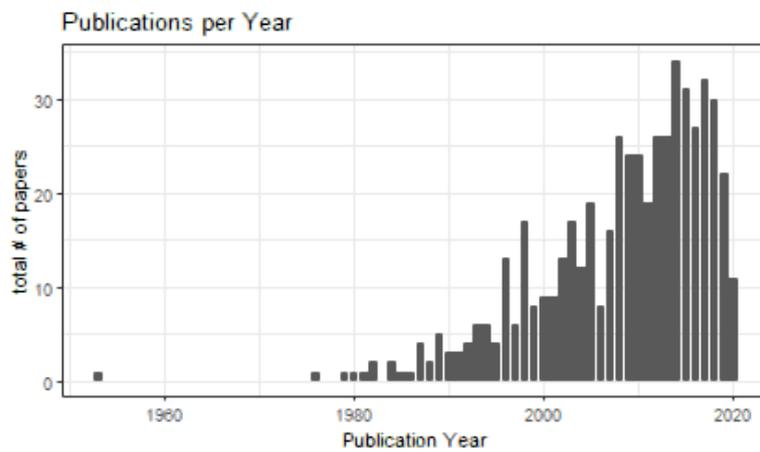

Figure 2
The annual publication trend in Pub Med related to Papanicolau test

Figure 3
**Distribution of articles in scientific journals. Word cloud generated using Word Cloud Generator by
Monkey Learn**
Source: author analysis using Monkey Learn (2020)

Figure 4
**Distribution of mesh terms in scientific documents. Word cloud generated using Word Cloud Generator by
Monkey Learn**
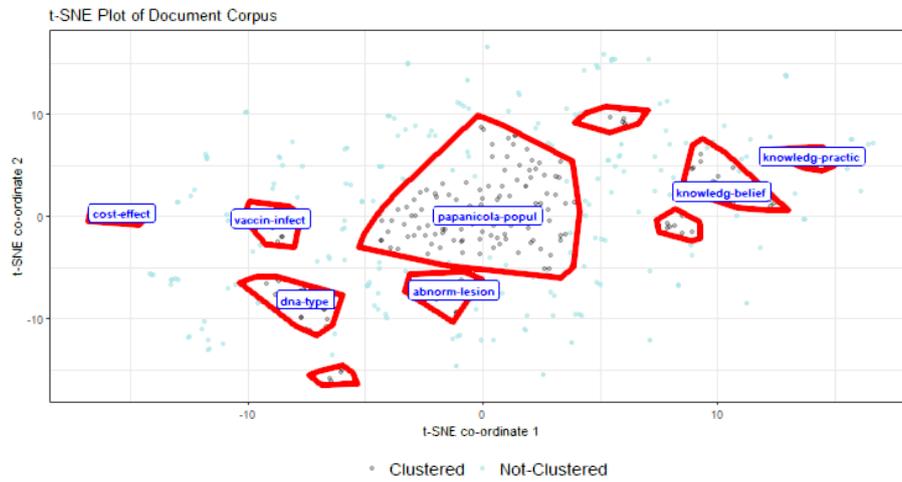*Source: author analysis using Monkey Learn (2020)*

Figure 5
Topic clusters representation of the retrieved literature review analysis related to Papanicolau test, generated with Adjutant