Systematic Review

Expression of Yap Signaling Hippo Pathway in Cervical Pre-cancerous Lesions and Cervical Cancer

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Abstract

Objective: To determine the expression of YAP in cervical pre-cancerous and cervical cancer lesions.

Methods: Researchers systematically searched five databases using the checklist for Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) guideline and Newcastle-Ottawa Scale (NOS).. Inclusion criteria were the original study of YAP expression in cervical pre-cancerous lesions and cervical cancer, observational and experimental study, and using immunohistochemical techniques. The study protocol was registered in the PROSPERO database of systematic review (IDCRD42023407469).

Results: The data search in this study followed the PRISMA Guideline, which includes phases of identification, screening, and inclusion of studies. Initially, 245 articles were identified across five databases: Pubmed (105), ScienceDirect (8), Scopus (29), Web of Science (26), and ProQuest (77). After removing duplicates, 157 studies remained. During the initial screening, 142 studies were excluded, leaving 15 studies for further evaluation. These were assessed based on the use of immunohistochemistry staining for YAP expression and staining result. Subsequently, ten studies were excluded for either not using immunohistochsmistry or lacking staining result, resulting in five studdies selected for qualitative analysis. These five studies were evaluated using the New Ottawa Scale, as detailed in Table 1, and their YAP Expression characteristics are summarized in Table 2.

Conclusion: This systematic review showed that YAP expression at all levels ranging from normal tissue, cervical intraepithelial neoplasia, squamous cell carcinoma, and adenocarcinoma had increased expression in the cytoplasm or cell nucleus following the development of cervical cancer and tumorigenesis influenced by intra-tumor heterogeneity for YAP expression. YAP is expressed in the cytoplasm and nucleus, with different functions. YAP expression in these two sites Excessive YAP expression will trigger epithelial changes into mesenchyme which also plays a role in cancer development. This YAP expression also correlates with HPV, in which YAP levels will be maintained and increased.

Keywords: cervical cancer, cervical pre-cancerous lesions, YAP expression.

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INTRODUCTION

Cancer is a medical condition that initiates when regular cells transform into irregular cells, proliferating excessively and surpassing their typical boundaries within the body. This ailment can originate in nearly any body organ or tissue and has the potential to propagate to other parts of the body. The final phase of the cancer progression involves metastases, which is the primary cause of cancer-related deaths.[1]. Cervical cancer, a significant health concern predominantly affecting women, is primarily linked to Human Papillomavirus (HPV) infection. While most HPV infections are harmless and self-limiting, persistent infection by high-risk HPV strains, notably type 16, can escalate to the development of various cancers in the cervix, vagina, anal region, penis, and oropharynx. Besides viral infection, genetic mutations and

epigenetic modifications also play a crucial role in the pathogenesis of cervical cancer [2].

In 2018, the number of new cases of cervical cancer in the world was 570,000, and the number of deaths caused by cervical cancer was 311,000. Cervical cancer is the second leading disease in incidence and mortality after breast cancer. In Indonesia, cervical cancer ranks second out of the 35 most common cancers, with 9.2% of new cases in 2018, and ranks third with 9.0% of deaths[3,4].

The approach to manage with cancer depends on its stage and how far it has spread within the body. Initial strategies for managing cancer involve surgical interventions (such as conization, different types of hysterectomy, and lymph node removal) or a combination of radiation and chemotherapy[5]. Nevertheless, these treatments come with various unwanted effects. Recent studies have delved into alternative methods for managing cancer growth and inducing cancer cell death through the Hippo Signaling Pathway. This pathway, initially identified in fruit flies and later found in mammals, involves key molecules like Hippo, Salvador, Warts, Mats, Yorkie, and Scalloped in fruit flies, and Mst1-2, Sav1/WW45, Lats 1-2, MOBKL 1A-B, YAP, TAZ, TEAD1-4 in humans[6]. YAP and TAZ, critical components in this process, assume a vital role as co-activators during hippo signalling. They enter the cell's nucleus and bind with TEAD, prompting the activation of genes that encourage growth. This mechanism also supports the regeneration of organs following injury. When YAP and TAZ are excessively activated due to abnormalities in the Hippo pathway or their overexpression, the risk of cancer development is heightened[7]. Leveraging the Hippo Pathway signal could offer a promising alternative for managing cancer. This research aims to evaluate the expression levels of YAP in pre-cancerous cervical lesions and cervical cancer through a systematic review, incorporating a comprehensive literature search across major scientific databases.

METHODS

This systematic review was conducted and reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. An electronic search was conducted using the keywords: (YAP Expression) AND ((Cervical Cancer) OR (Cervical Lesion) OR (Cervical Carcinoma)) with a journal time range from 2010 to 2022. The databases used in the literature search in this study are Pubmed, Science Direct, Scopus, Web of Science, and Proquest.

Inclusion criteria for this study included; Cervical pre-cancerous lesions in the form of cervical intraepithelial neoplasia based on WHO classification; Cervical cancer with squamous cell carcinoma and adenocarcinoma types based on FIGO classification; Observational and experimental studies; and Research that is an original study, Staining with immunohistochemical techniques. Meanwhile, the exclusion criteria in this study include Other cancers other than cervical cancer were found; Observations with western blot analysis, Quantitative Real-Time PCR, Immunofluorescent, and Haemotoxyline staining; The results observed are not related to YAP expression; not available in full-text. The PICO (Patients, Index, Comparability, Objective) approach was used in this study. Patients, Patients with cervical pre-cancerous lesions and cervical cancer; Index, YAP expression; Comparison, Staging criteria for cervical cancer; Outcome, Percentage of YAP expression in cervical pre-cancerous lesions and cervical cancer. Literature that has been filtered based on the elimination of duplicated literature and inclusion and exclusion criteria will be processed in two stages: selection based on titles and abstracts that do not match the specified keywords or PICO and cannot be accessed. The second stage is reading full-text articles that meet the inclusion and exclusion criteria. Literature that meets the requirements is called eligible. Eligible literature will be assessed using the Newcastle Ottawa Scale.

The authors extracted data from all the retrieved studies and evaluated their quality using full-text articles. If there are differences of opinion, researchers will check and discuss them with each other. The authors, the year of the study, study location, study design, population characteristics, the number of samples, the age of the samples, diagnostic method, and the expression of YAP in the study were among the data picked.

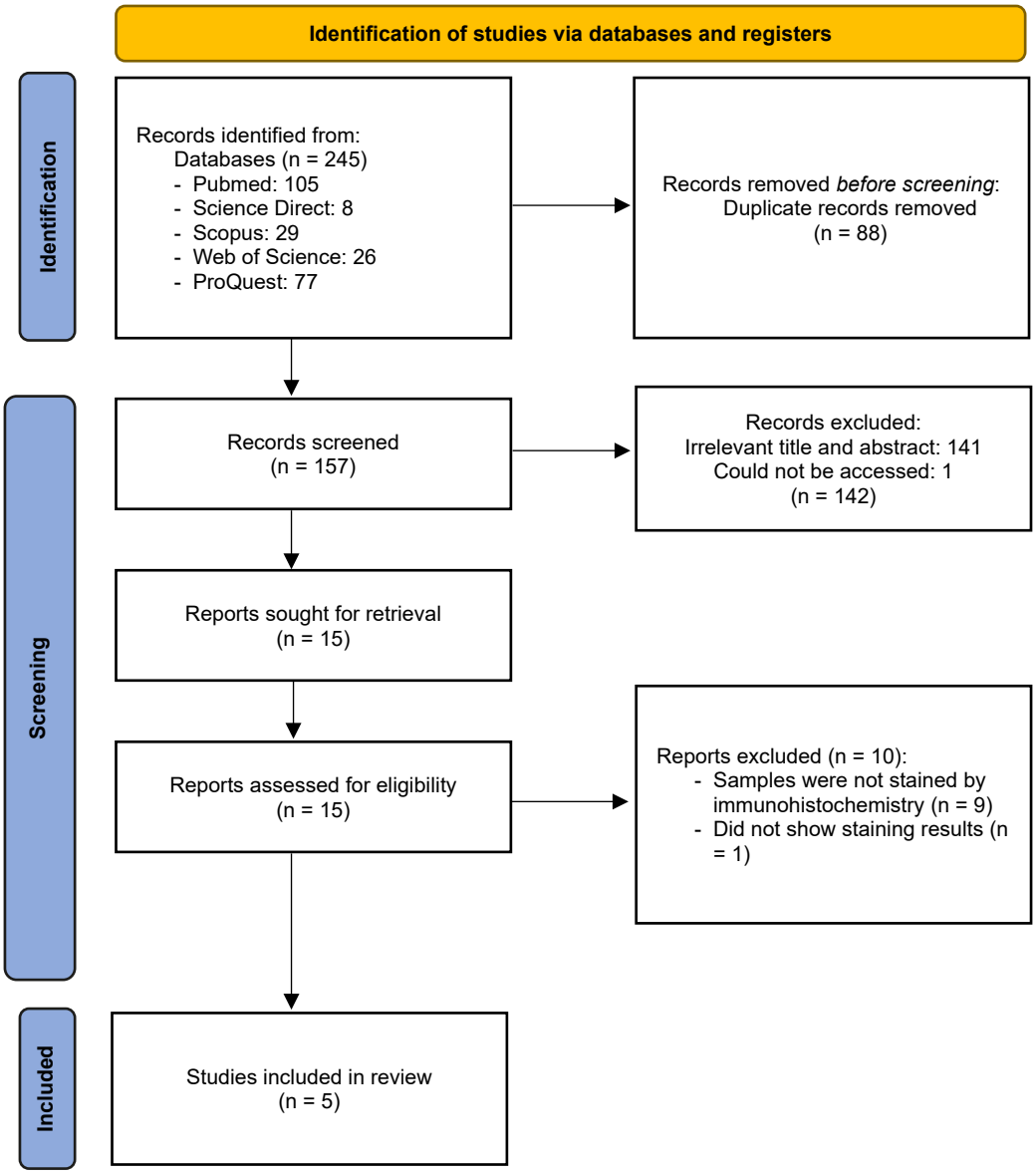

Figure 1. PRISMA 2020 flow diagram.

RESULTS

The data search in this study followed the PRISMA guidelines, as shown in Figure 1. This process is divided into three phases: identification, screening, and inclusion of studies. During the identification phase, researchers searched for articles across five different databases: PubMed, ScienceDirect, Scopus, Web of Science, and ProQuest, using automation tools. The search yielded 105 studies from PubMed, eight from ScienceDirect, 29 from Scopus, 26 from Web of Science, and 77 from ProQuest, totaling 245 articles. Duplicate studies were removed before proceeding to the screening phase, resulting in the exclusion of 88 studies.

At the initial screening stage, 142 studies were excluded. So there are 15 studies to be continued to the next step. In the second stage, the reading of the entire text focused on the staining method using the Immunohistochemical Technique, YAP expression, and the staining results. From the results of this second stage, ten studies were excluded, with details of 9 studies not stained with immunohistochemistry, and 1 study did not show staining results, so five studies would be used as sample material for this study.

Table 1. New ottawa scale.

	Liu et al. **[8]**	Xiao et al. **[9]**	He et al. **[10]**	He et al. **[11]**	Zhang et al. **[12]**
Is the case definition adequate (SELECTION)	-	*	*	*	-
Representativeness of the cases (SELECTION)	*	*	*	*	*
Selection of controls (SELECTION)	-	-	-	-	-
Definition of controls (SELECTION)	*	*	-	-	*
Comparability of cases and controls on the basis of the design or analysis (COMPARABILITY)	*	-	-	-	-
Ascertainment of exposure (EXPOSURE)	*	*	*	*	*
Same method of ascertainment for cases and controls (EXPOSURE)	*	*	*	*	*
Non-response rate (EXPOSURE)	-	-	-	-	-
Total	5	5	4	4	4

The research was then assessed qualitatively using the New Ottawa Scale. The New Ottawa Scale uses five aspects to evaluate research quality. These aspects are whether the case definition is adequate, representativeness of cases, selection of controls, definition of controls, Comparability of cases and controls on the basis of the design or analysis, Ascertainment of exposure, Same method of ascertainment for cases and controls, and non-response rate. The table presents a qualitative assessment of five studies on YAP expression using the New Ottawa Scale, evaluating aspects such as case definition, representativeness, control selection, comparability, and exposure ascertainment[8] received a total score of 5 points, excelling in representativeness, control definition, comparability, and exposure ascertainment, though it lacked an adequate case definition and selection of controls, also scored 5 points[9], with strengths in representativeness, control definition, and exposure ascertainment, but fell short in control selection and comparability, both scored 4 points[10,11]. These studies were strong in representativeness and exposure ascertainment but did not adequately define or select controls and lacked comparability. [12] also scored 4 points, with good performance in representativeness and exposure ascertainment but with limitations in case definition, control selection, and comparability. Overall, the assessment reveals that most studies were robust in ensuring representativeness and consistent exposure ascertainment but had varying weaknesses in control selection and comparability, affecting their overall quality ratings.

Table 2. Characteristics of included studies

Author, Year	Location	Design	Study Population	Total Sample	Age (yr)	Diagnostic Methods	Groups (n)	YAP Expression (%)
Liu et al., 2013 [8]	China	Case-control	Patients who underwent surgery at the Department of Gynecology of the Third Affiliated Hospital of Harbin Medical University between January 2003 December 2006	184	43.54±8.149	IHC	SCC (120)	Cytoplasm High: 30.83 Low: 69.17 Nuclear High: 0 Low: 0
							AC (42)	Cytoplasm High: 45.24 Low: 54.76 Nuclear High: 26.2 Low: 73.81

Xiao et al., 2014[9]	China	Case-control	Patients from the Pathology Department of the First Hospital affiliated with Shanxi Medical University during the period January 2006 to December 2011	180	NA	IHC	Chronic cervicitis (10) CIN 1 (49) CIN 2 (55) CIN 3 (34) SCC (32)	(0) 50 (1) 40 (2) 0 (3) 10 (0) 40.82 (1) 36.74 (2) 18.37 (3) 4.08 (0) 7.27 (1) 9.09 (2) 40 (3) 43.64 (0) 5.88 (1) 8.82 (2) 32.35 (3) 52.94 (0) 3.13 (1) 3.13 (2) 28.13 (3) 65.63
He et al., 2015 [10]	USA	Experimental, *in vivo*	Female athymic nude mice	79	6-week-old	IHC	Tumor (69) Normal (10)	Negative: 2.9 Weak: 5.8 Moderate: 13.04 Strong: 78.26 Negative: 60 Weak: 40 Moderate: 0 Strong: 0
He et al., 2019[11]	USA	Experimental, *in vivo*	KRT-rtTA and KRT14-	87	NA	IHC	Normal CIN I CIN II	Positivity: 0.36 Intensity (10^8): 0.286 Positivity: 0.41 Intensity (10^8): 0.286 Positivity: 1.10 Intensity (10^8): 6.43
Zhang et al., 2020[12]	China	Case-control	Patients who underwent surgically resected or biopsied from the First Affiliated Hospital of Bengbu Medical College from January 1, 2013, to December 31, 2014	151	27 – 70	IHC	CIN III	Positivity: 1.45 Intensity (10^8): 1.214

Characteristic results in five studies evaluating Yes-Associated Protein (YAP) expression in terms of location, study design, study population, total sample, age, diagnostic methods, study group, and YAP expression. The table summarizes five studies evaluating Yes-associated protein (YAP) expression using immunohistochemistry (IHC) in different populations and experimental conditions. A case-control study in China involving 184 patients from the Department of Gynecology[8], Third Affiliated Hospital of Harbin Medical University. They found that in squamous

cell carcinoma (SCC), cytoplasmic YAP expression was high in 30.83% of cases and low in 69.17%, while in adenocarcinoma (AC), 45.24% showed high cytoplasmic YAP expression and 26.2% had high nuclear YAP expression. Performed a similar study with 180 patients from Shanxi Medical University and observed that YAP expression increased progressively from chronic cervicitis to CIN and SCC,[9] with the highest expression in SCC (65.63%). Examined 79 female athymic nude mice and reported strong YAP expression in 78.26% of tumors compared to negligible expression in normal tissues.[10] In a follow-up experimental study.[11] used KRT-rtTA and KRT14-YAPS127A transgenic mice and found that YAP positivity and intensity increased with the severity of cervical intraepithelial neoplasia (CIN I to CIN III). Lastly,[12] investigated YAP expression in 151 patients at the First Affiliated Hospital of Bengbu Medical College, noting the highest expression (+++ 36.96%) in SCC, while normal tissues showed predominantly low expression levels. Overall, these studies collectively highlight the increasing YAP expression with disease progression, particularly in malignancies, underscoring its potential as a biomarker for disease severity and progression.

DISCUSSION

Cancer encompasses a collection of illnesses characterized by the unregulated proliferation and dissemination of irregular cells. The origins of cancer are varied, stemming from both internal and external factors, and their complexity means that our understanding remains partial. These causal elements can trigger the commencement of the cancer-forming process within the human body, potentially leading to fatality[13]. Cervical cancer, the most prevalent malignancy affecting the female cervix, emerges due to an infection by the Human Papilloma Virus (HPV)[2]. This form of cancer poses a significant global health challenge, ranking as the fourth leading cancer among women. In 2018, approximately 569,000 new cases were reported worldwide, contributing to around 311,000 cervical cancer-related deaths[14]. Various methods exist for managing cervical cancer, including primary, supplementary, and secondary treatment approaches[15].

Out of all these treatments, each one comes with its own set of side effects[15]. In recent times, numerous researchers have explored alternative methods to restrain the excessive growth of cancer cells and enhance the natural process of cancer cell death by utilizing the Hippo Signaling Pathway. The human hippo pathway comprises several fundamental routes, including Mst1-2, Sav1/WW45, Lats 1-2, MOBKL 1A-B, YAP, TAZ, and TEAD1-4. Within this crucial aspect, YAP and TAZ hold a significant role as transcriptional co-activators in contrast to the conventional hippo signaling. YAP and TAZ enter the nucleus of the cell and attach to TEAD, thereby prompting the activation of genes that promote growth. This mechanism also supports the regeneration of organs after they've been injured. However, irregular activation of YAP and TAZ, either due to disturbances in the Hippo pathway or an excessive presence of YAP, TAZ, and TEAD, can contribute to the development of cancer[6,7].

YAP overexpression was observed in cervical cancer across all five studies. This increased expression found in a wide range of human cancers indicates the potential of YAP to act as an oncogene. Similarly, the levels of YAP expression in Laryngeal Squamous Cell Carcinoma indicate that YAP overexpression serves as an independent prognostic biomarker functioning as an oncogene[16]. YAP can be classified as an oncogene due to its role in enhancing the regulation of cell replication, DNA synthesis, and repair. It also controls cyclin levels to facilitate entry into the "S" phase of the cell cycle and promotes completion of mitosis by triggering proto-oncogenic transcription factors, ultimately contributing to the manifestation of cancer cells[8,17].

Overexpression of YAP can lead to changes in cells that shift them from an epithelial to a mesenchymal state, a transformation commonly linked to the invasive and metastatic behavior of cancer cells. This shift, known as epithelial-mesenchymal transition, imparts aggressive traits like invasion, resistance to cell death, and reduced responsiveness to chemotherapy in advanced stages of disease. This process initiates when cell growth reaches a certain density. At this point, the Hippo pathway becomes active, prompting the expression of the Lats1/2 gene and its subsequent phosphorylation through a cascade of kinase reactions. YAP role involves diminishing the binding interaction of proteins within the nucleus, thereby impeding their function. Suppression of YAP/TAZ transcriptional function induces a state of cellular dormancy in the G1/S and G2/M phases, effectively stalling cell proliferation. Even when the Hippo pathway is deactivated, YAP/TAZ

continues its transcriptional activities without repression. Once YAP/TAZ enters the nucleus and binds to TEAD, it triggers cellular mitosis and proliferation, consequently promoting the transition from epithelial to mesenchymal state. Within cancer cells, YAP and TAZ are crucial in driving the epithelial-mesenchymal transition (EMT). This transition initiates processes such as self-renewal in cancer stem cells via TAZ activation and promotes EMT through interaction with AP-1 FOS components via YAP. During EMT, epithelial cells lose their apical-basal polarity, detach from the basement membrane, and weaken intercellular connections. In cancer cells, EMT is closely associated with characteristics such as cancer stem cell traits, resistance to apoptosis, and decreased susceptibility to drugs[8,17–21].

The process of epithelial-mesenchymal transition, in which YAP plays a role, plays a part in the development of cancer and the formation of tumors[20]. Another way in which YAP is involved in the development of tumors is through the varying levels of its expression within a tumor. This happens because tumor cells that express YAP at different intensities will engage in competition with neighboring cells. As these cells interact, the ones with higher YAP expression will experience boosted growth and stimulate the activation of genes associated with cancer[22].

YAP expression is found in two distinct cellular locations: the cytoplasm and the nucleus. In the normal and CIN I groups, YAP expression is primarily observed in small amounts within the cell cytoplasm. This indicates that when YAP is located in the cytoplasm, its role as a cancer initiator is diminished, although it might still contribute to the onset of cervical cancer and play a critical role in the differentiation of mature airway epithelial progenitors. Conversely, in the CIN II, III, SCC, AC, Early, and Advanced Cancer groups, YAP expression is predominantly concentrated within the cell nucleus. This suggests that YAP presence in the nucleus influences tumor development and cellular growth, suppresses differentiation, and hampers programmed cell death. Hence, YAP function within the nucleus is pivotal in the progression of CIN (cervical intraepithelial neoplasia) towards cancer. These differing subcellular distributions of YAP expression across tissue samples correspond to variations in its functionality, depending on whether YAP is located in the cytoplasm or the nucleus. In the cytoplasm, the presence of LATS 1/2 prompts phosphorylation of YAP, leading to its interaction with 14-3-3 proteins and subsequent ubiquitination, resulting in YAP degradation. However, when YAP is transported into the nucleus, it interacts with TEAD1-4 and releases VGLL4 to activate gene transcription, fostering tissue growth and restraining programmed cell death[9,23,24].

Past research has indicated that maintaining a proper balance of YAP in both the nucleus and cytoplasm is essential for controlling the way lungs develop in mice. If YAP is situated in the cytoplasm, its ability to encourage the advancement of tumors diminishes. On the other hand, when YAP is present in the nucleus, it influences the activation of different genes that play a role in the growth and multiplication of cells. This phenomenon is linked to changes and reduced activity of the main elements of the Hippo pathway[25].

The excessive activity of YAP has a significant impact on the health of patients. Individuals who exhibited high levels of YAP, TAZ, and β-catenin had unfavorable prospects, as indicated by lower chances of survival and shorter survival times compared to those with lower expressions. Another investigation suggested that the excessive presence and distribution of YAP in Ovarian Serous Cystadenocarcinoma were connected to unfavorable survival rates. Additionally, a separate study[11] found that patients with notable YAP1 amplification/ deletion or mutations in tumor suppressor genes experienced worse outcomes compared to those without any genetic alterations[11,12,26].

YAP plays a crucial part in determining the functions of cells in different subtypes of cervical carcinoma. These functions encompass cell proliferation, apoptosis, cell survival, and cell migration. Changes in how YAP is expressed and where it's located within cells can hold varying clinical significance depending on the type of tumor. As a result, it's reasonable to consider YAP role as a possible indicator of prognosis for cervical cancer. This is because higher levels of YAP expression in human cervical cancer tissues correlate with the advancement of cervical cancer. Furthermore, there's potential to target YAP for therapeutic purposes in cervical cancer treatment, given that cancer cells frequently resist cell death by inhibiting pathways related to apoptosis[10,17].

Cervical cancer develops due to an infection with high-risk forms of Human Papilloma Virus (HPV), specifically HPV 16 and 18. These types

of HPV are commonly found in healthy women and can sometimes regress on their own. While high-risk HPV infection is a crucial factor in the development of cervical cancer, it alone isn't sufficient to initiate and propel the progression of this cancer. The irregular functioning of the Hippo pathway might play a role in starting and advancing HPV-triggered cervical cancer. In cervical cancer cells, HPV E6/E7 can hinder the degradation of YAP through mechanisms involving the suppression of negative YAP regulators like MST1, PTPN14, or SOCS6. Furthermore, HPV E6 encourages the buildup of YAP, TAZ, and TEAD proteins and the genes they regulate. As a result, elevated YAP levels could lead to persistent HPV infection by increasing the expression of HPV membrane receptors and dampening the host's innate immune response[10,27–29].

Besides YAP, the TAZ protein also plays a role in cancer development. TAZ is a protein that is easily degraded and becomes unstable in densely packed cell environments. This relationship between TAZ expression, stability, and cancer development is significant in carcinogenesis and has been observed in various types of human cancer. Although previous research has shown elevated TAZ levels in cervical cancer, the precise mechanisms of TAZ expression and function in cervical cancer cells are not yet fully understood. Immunofluorescence studies have identified TAZ expression in a specific group of cells in both normal cervical tissue and squamous cell carcinoma (SCC)[30].

Examination using immunofluorescence revealed that TAZ was notably more prevalent in the nucleus and cytosol of normal tissues compared to both SCC tissues and metastatic SCC tissues. This distinct pattern of TAZ expression was particularly noticeable in the basal layer cells of normal cervical tissue but was absent in SCC tissues. These locations of TAZ expression indicate a widespread process of controlled breakdown, while the movement of TAZ into the nucleus could suggest that TAZ is triggering cancer-causing genetic programs. This implies that the Hippo pathway mainly influences TAZ by regulating its movement between the cell's fluid and the nucleus. The presence of TAZ in the cytoplasm might play a role in initiating or advancing abnormal tissue growth. This investigation established a connection between TAZ expression in both the nucleus and cytosol and SCC, partly because TAZ was observed to relocate to the cytosol within SCC tissues[30].

Based on the qualitative assessment of studies on Yes-associated protein (YAP) expression in cervical pre-cancerous lesions and cervical cancer, it is evident that YAP plays a critical role in the progression of cervical cancer. The systematic review identified five studies that were qualitatively evaluated using the New Ottawa Scale, focusing on aspects like case definition, representativeness, control selection, comparability, and exposure ascertainment. The studies showed variations in quality, scoring the highest (5 points each), indicating robust methodologies in control definition, exposure ascertainment, and representativeness[8,9], albeit with minor shortcomings in case definition and control selection. In contrast, scored 4 points each,[10-12] demonstrating strengths in representativeness and exposure ascertainment but lacking in control definition and selection. Across all studies, the consistent finding is the elevated expression of YAP in both the cytoplasm and nucleus of cervical cancer cells compared to normal tissues. This heightened expression correlates with the severity and advancement of the disease, highlighting YAP's potential as both a biomarker for cervical cancer and a therapeutic target. These findings substantiate the hypothesis that YAP expression plays a pivotal role in cervical cancer development and progression, influenced by its localization within cells and its interactions with components of the Hippo signaling pathway.

Further meta-analysis studies concerning YAP expression in cervical cancer is recommended to provide a unified perspective by integrating quantitative data and outcomes from randomized controlled trials (RCTs), thereby aiding in the evaluation of YAP's viability as both a therapeutic target and biomarker.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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