Systematic review

Serum microRNAs dysregulation in cervical cancer and their diagnostic role: A systematic review

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ABSTRACT

Cervical cancer is the fourth-highest prevalent tumor among women in the world. Though the development in the early diagnosis of cervical cancer in developed countries, developing countries are still suffering from it. Among the different biomarkers, serum microRNAs (miRNAs) were reported as valuable tools in the diagnosis of cervical cancer. To highlight the most recent studies of the serum miRNAs in cervical cancer diagnosis, we systematically searched science direct and Web of Science databases using keywords, and the articles that meet inclusion criteria and do not meet exclusion criteria are included in the current review for further analysis. After applying the current study inclusion and exclusion criteria we found 42 dysregulated miRNAs, among them miR-21 was the most investigated, and most of them were capable of distinguishing between healthy and cervical cancer subjects. The current study shows the importance of serum miRNAs as biomarkers in cervical cancer diagnosis.

Keywords: Cervical cancer; miRNA; dysregulation; diagnosis.

INTRODUCTION

Cervical cancer is one of the highest prevalence cancers with over 600000 new cases yearly and around half of them die each year worldwide, It is the most gynecological and fourth-highest prevalent cancer among women globally (1-3). Several factors increase the probability of cervical malignancy including infection with the human papillomavirus, smoking habit, and immune system dysfunction, the majority of the cervical cancer deaths are reported in low or medium-income countries (4). More than 90 % of cervical cancers are caused by the infection with the most oncogenic subtypes of the human papillomavirus; HPV16 and HPV 18 (5). Diagnosis of cervical cancer at an earlier stage would enhance the survival rate. The American cancer society recommended that screening for cervical cancer to be initiated from 21 years of age, screening for cervical cancer may be done either by Papanikolaou test (PAP) or by using the human papillomavirus molecular test (6). One of the attractive methods of non-invasive identification is by using the serum. Different types of serum proteins have been reported in cervical cancer patients with dysregulated expression patterns (7).

MiRNAs are small non-coding RNA molecules that regulate the gene expression at the post-transcription regulation, they are about 18-24 nucleotides in length. MiRNAs are biosynthesized by the transcription of DNA to produce "primary microRNAs" followed by creating "precursor microRNAs" The latter are then producing the final miRNAs "mature miRNAs", the mature miRNA interacts with the untranslated region (3′ UTR) of the messenger RNA of its target gene to degrade the transcript or repress the translation as well as miRNA may interact with some gene regions like gene promoter, 5′ UTR or protein-coding regions (8). The miRNA genes are found on all chromosomes except the Y chromosome, single miRNA capable of regulating dozens of genes (9).

Serum biomarkers are promising non-invasive tools to screen and diagnose many diseases. MiRNAs are tissue specific in their expression patterns (9). Circulating miRNAs may serve as a biomarker for different diseases including tumor as the expression pattern of these non-coding RNA molecules can reveal the tissues status (10). In cervical cancer, most of studies investigated the miRNAs expression in cervix tissues, however, the serum related study still needs more efforts. The number of serum miRNA studies started increasing in recent years and many studies have reported a dysregulation in miRNAs expression in the cervical cancer patient's serum compared to healthy people (11-13). Spotlighting the status of these circulating RNA molecules will help to better understand and explore their usage as a possible biomarker.

In this systematic review, we systematically reviewed the dysregulated miRNAs in the serum of cervical cancer patients and their counterparts' healthy women.

MATERIALS AND METHODS

Searching strategy

According to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, we systematically searched the databases; Science Directs and Web of Science for any down or up-regulated miRNAs in the serum of cervical cancer patients for the period from January 2017 to November 2022. We approached any article that may contain the two terms miRNA and cervical cancer.

The databases were searched for the following terms: "microRNA" AND "cervical cancer" OR "miRNA" and "cervical cancer" or "miR" and "cervical" in all fields. The study strategy is illustrated in Fig. 1.

Inclusion and exclusion criteria

The following criteria are applied for the inclusion of the research articles in the present study: (i) original research studies that written in the English language; (ii) research articles which are published from January 2017 to December 2022 (iii) contain both miRNAs and cervical cancer or their synonyms; (iv) the miRNAs are profiled in serum.

The following criteria were used to exclude and the paper meets them, (i) The review articles, meta-analysis, *in silico* studies and retracted research articles; (ii) non-human serum (iii) the papers which are not written in the English language; (iv) the profiling of the miRNAs done in cell lines, tissues or other biological materials and fluids but not serum; (v) profiling the miRNAs after treatment with specific medicine.

RESULTS

Data extraction

The two databases searched for the study keywords and the eligible articles were 1434 from the web of science and 75 from Science Direct. Two independent researchers read the titles and abstracts of all the papers. Then the inclusion and exclusion criteria were applied and removed the duplicated articles the number of papers became 34. The second examination was done by the researchers in a separate manner and the final lists merged. Thirty-four papers were checked entirely for their eligibility and further analysis. The final included papers are 32 papers. From each study, the following data were extracted: (i) Title of study; (ii) country of study; (iii) number of serum samples and number of controls; (iv) down-regulated miRNAs; (v) up-regulated miRNA; (vi) target gene; (vii) abstract.

Down-regulated miRNAs and their role in cervical cancer

The miRNAs have been reported to be dysregulated in several types of cancers. There are many miRNAs down-regulated in the serum of cervical cancer patients.MiR-1254 is found to be down-regulated and correlated with poor prognosis in both serum and tissues of cervical cancer, furthermore, its expression is negatively correlated with the long-chain noncoding RNA ABHD11-AS1(12). A study that combined serum, urine, and tissues for the investigation of miRNAs, established that miR-34a-5p, miR-218-5p, and miR-145-5p expression is less in cervical cancer patients though the target genes did not explain (13). The low expression of miR-34a and miR-218 is related to the poor cervical cancer prognosis as well as it is an indicator of cancer metastasis and differentiation degree (14).

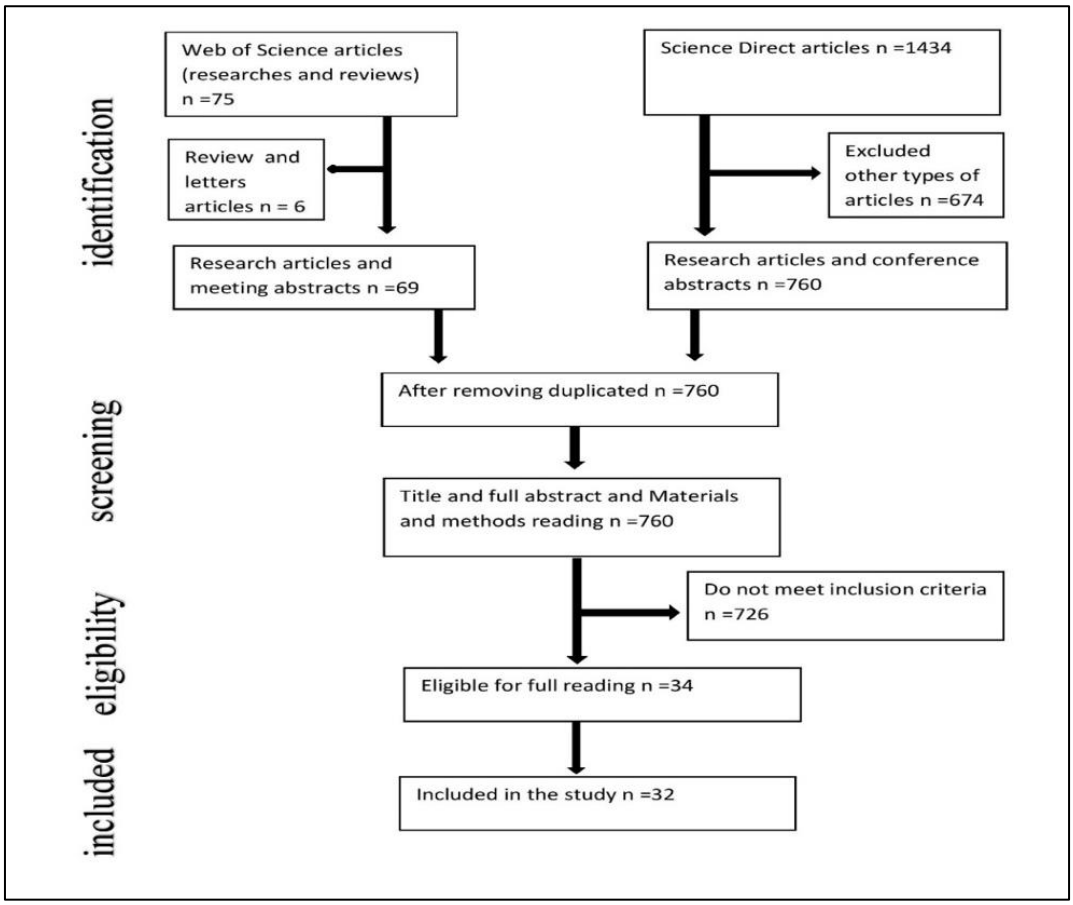

Fig. 1: Flowchart of the study strategy using PRISMA guidelines

Table 1: The down-regulated serum miRNAs in cervical cancer

miRNA	No. of samples	No. of controls	Target gene	Reference
miR-1254	72	78	None	14
miR-34a-5p, miR-218-5p, and miR-145-5p	100	80	None	15,16
miR-378a-3p	48	48	None	17
miR-144-3p, miR-337-3p	72	62	None	11
miR-375-3p	124	119	None	18
miR-125b, miR-370	157	90	None	13
miR-485-5p	78	78	*FLOT-1*	19
miR-124	68	57	None	20
miR-638, miR-521	40	41	None	21
miR-139-5p	99	50	*ZEB1*	22
miR-29b	98	76	*TUG1*	23
miR-409-3p	115	115	*MTF2*	24
miR-200b	80	138	None	24
miR-100	110	34	None	25

The advanced cancer stage and metastasis can be identified by the positive relationship with the low expression of mR-378a-3p in extracellular and intracellular in females with cervical cancer compared to their healthy counterparts (17). The miRNAs, miR-144-3p and miR-337-3p have been found with low expression and to be increased after treating the patients, and showed prognosis evaluating importance (11). In another study on over 200 cervical cancer patients compared to healthy control, miR-375-3p was used as a molecular indicator to differentiate patients from normal females, interestingly, the low miR-375-3p expression was suppressed by SNHG17 (18). A combination of the decreased expression miRNAs, miR-125b and miR-370 with the highly expressed miR-21 worked well to diagnose the early stages (I and IIA) of cervical cancer (13). MiR-485-5p and its target gene *FLOT-1* were able to discriminate cervical tumor from normal serum samples (19).

Low expression of miR-124 and high expression of miR-21 as well as high macrophage colony-stimulating factor showed better capability for the diagnosis of primary cervical carcinogenesis (20). Independently, miR-638 and miR-521 combined with Squamous Cell Carcinoma-Related Antigen were capable of diagnosis of cervical carcinoma (21). In different studies, miR-139-5p and miR-29b were profiled by qPCR and showed low expression in contrast to their counterparts' genes *ZEB1* and *TUG1* respectively (22,23). The gene *MTF2* appeared to be the target of the down-regulated miR-409-3p in serum and tissues of the cervical cancer samples (24). Long non-coding RNA reported as a repressor of miR-200b and enhances cervical cancer development (24). The survival rate is reported to be proportional with the low expression of miR-100, the low expression, the worse survival rate (29). The down-regulated miRNAs listed in Table 1.

Up-regulated miRNAs and their role in cervical cancer

Different researchers have linked the over expression of several miRNAs to tumor initiation, and diagnosis of tumors. Many miRNAs are over expressed in cervical cancer, among them miR-21 is studied by different groups, this small non coding RNA was found to have a key role in cervical cancer proliferation and its target gene *TIMP3* was identified by one group (13,15,20,26-28). The overexpression of miR-1468-5p enables the cervical cancer cells to escape from the immunity system (29). In HPV 16 cervical cancer patients the miR-221 was highly expressed, and *SOCS1* was the target gene which is down-regulated (30). MiR-27a-3p expression showed high levels in cervical tumors in females with folic acid deficiency (31). A study combined miR-486-5p and two proteins as a predictive tool for the diagnosis of early stages of cervical cancer, the same miRNA was reported to be overexpressed and to target the *PTEN* gene by another research group (32,33). The high level of squamous cell carcinoma antigen together with miR-152 can predict cervical cancer but is not sensitive enough to diagnose the primary stages (12). Using a quantification method based on a universal primer set frame, the level of miR-155 is elevated in the serum of cervical cancer patients, that was confirmed later by different studies (15,27). The early diagnosis of cervical cancer achieved by two different studies using miR-3142 and miR-15b (34,35). Five different studies found eight of up-regulated miRNAs (miR-199a-5p, miR-18a, miR-766-5p, miR-29a, miR-25, miR-9, miR-192, miR-205) in cervical cancer patient compared to healthy controls (15,32,36-38). A research group in India indicated a significant high expression of three miRNAs; miR-17-5p, miR-32-5p, and miR-454-3p, more over the study found the expression of miR-454-3p is negatively correlated to the gene *ST18* (24).

Table 2: The up-regulated serum miRNAs in cervical cancer

miRNA	No. of samples	No. of controls	Target gene	Reference
miR-21-5p	374	352	None	13,15,20,26-28
miR-155-5p	56	56	None	15,27
miR-199a-5p	50	50	None	15
miR-1468-5p	102	102	None	29
miR-18a	84	191	None	36
miR-766-5p	67	67	*SCAI*	37
miR-15b	23	17	None	35
miR-29a,miR-25	140	140	None	32
miR-27a-3p	60	30	None	31
miR-9, miR-192 ,miR-205	18	36	None	38
miR-454-3p	115	115	*ST18*	24
miR-17-5p, miR-32-5p	115	115	None	24
miR-152	100	50	None	12
miR-G-1	15	25	*LMNB1, TMED5*	39
miR-221	32	32	*SOCS1*	30
miR-3142	Not Available	Not Available	None	34
miR-1266	100	50	*DAB2IP*	40
miR-486-5p	161	161	*PTEN*	32,33
miR-150	50	50	*PDCD4*	41

A miRNA called miR-G-1 was found in high expression in the cervical patients serum and it is reported to promote cervical cancer via upregulation of its target genes; *LMNB1*, and *TMED5* (39). MiR-1266 represents an indicator of the development stage of scervical cancer and its high expression is inversely correlated with the survival rate (40). The over expressed miR-150 was found to inhibit its target gene *PDCD4* and that led to promote cervical cancer development (41). The up-regulated miRNAs in cervical cancer are illustrated in Table 2.

DISCUSSION

The association between miRNAs and cancer has been reported in the past two decades, however the full understanding of these non-coding RNA molecules is still to be covered. Many studies have linked different cancers to miRNAs dysregulation, among them was cervical cancer. The expression patterns of miRNAs have been studied in different types of body's tissues and fluids including serum. The present systematic review approached highlighting the importance of serum miRNAs in cervical cancer patients by conducting a systematic search in two data sets (web of science and science direct) in the last six years. The search results highlighted 23 up-regulated and 19 down-regulated miRNAs. The most miRNA studied was miR-21 in 374 patients and 352 healthy controls by different studies, miR-21 found to be up-regulated in five studies. We found that most studies were able to use the miRNAs to differentiate between healthy and cervical cancer groups. The current review supports the previous evidence of the high value of miRNAs in the cancer biomarker field. Whether it is up or downregulated, the serum miRNAs may work as biomarker tools efficiently.

Most of the included studies were conducted on subjects from Asia and a lot of studies experimented on a limited number of patients. In comparison to the tissue miRNA studies serum miRNA research are quietly less though they have shown credible results.

Finally, this systematic review concluded the last findings of miRNAs in cervical cancer and that can help in bringing more attention to these molecules' roles as non-invasive biomarkers.

CONCLUSION

The serum miRNAs are considered as biomarkers in different diseases including tumors. Finding a non-invasive biomarker is the aim of biomarker research. In this systematic review we highlighted how different studies have used the miRNA expression patterns in cervical cancer study. We also found that in different studies the miRNAs are promising tools and easy to handle for the diagnosis of cervical cancer.

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CONFLICT OF INTEREST

The authors declare no conflict of interest

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