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Evaluation of the MiR-513a-5p Impinges on Progesterone Receptor Protein Expression in Breast Cancer Cells: A Systematic Review and Meta-analysis

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ABSTRACT

Background and aim: MicroRNAs can be considered as a predictor or cause of breast cancer. The present study was conducted to evaluate MiR-513a-5p's impacts on progesterone receptor protein expression in breast cancer cells.

Material and methods: The present study was based on the PRISMA 2020-27-item checklist. By giving the keywords microRNAs, breast cancer, MiR-513a-5p, progesterone, all articles available in the international databases, PubMed, Web of Science, Scopus, Science Direct, Web of Knowledge, EBSCO, Wiley, ISI, Elsevier, Embase databases and Google Scholar search engine were reviewed until August 2023. STATA/MP. V17 software was used in this meta-analysis.

Results: Three articles were included in the present study. MiR-513a-5p upregulation was directly and statistically significantly associated with breast cancer risk (OR = 1.45; 95% CI 1.07–1.83; P<0.01).

Conclusions: The results of the present study can affect different aspects of breast cancer development. The use and identification of miR-513-a-5p as a long-term biomarker to identify the pathways involved in the early development of breast cancer should be considered.

1. Introduction

Progesterone is one of the steroid hormones; the main place of its secretion is the ovary and the placenta in pregnant women.[1] Progesterone is one of the main and necessary factors in the process of the natural lobule and alveolar development of the breast and after that during pregnancy and to prepare the breast for breastfeeding.[2] Along with estrogen and prolactin, progesterone also plays an important role in the differentiation of the mammary epithelium and changes in breast cycles during a monthly menstrual cycle.[3] Breast cancer is the most common type of cancer and the most common cause of cancer death among women.[4] Mammography and core-needle biopsy have increased the rate of diagnosis of this disease, but unfortunately, there has been no noticeable change in the death rate of these patients in the past 60 years.[5] It has been known for many years that some breast cancers respond to hormonal treatments.[6] Today, it has been proven that about half of breast cancers have estrogen and progesterone receptors on tumor cells, which cause tumor growth in the presence of the above hormones.[6] Numerous studies show that breast cancer patients are positive in terms of estrogen receptors.[7-10] Today, the measurement of estrogen and progesterone receptors is widely performed for therapeutic purposes and to determine prognosis in breast cancer.[11, 12] Molecular cell studies have shown that three main groups of genes, including oncogenes (cancer accelerators), tumor suppressors (inhibitors of cell proliferation), and DNA repair genes, play a key role in causing cancer.[13] Among them, microRNAs (miRNAs) can act both as oncogenes and as tumor suppressors.[14] MiRNAs are single-stranded ribonucleic acids and a large subgroup of non-coding RNAs with a length of 18 to 25 nucleotides,[15] which exert their effect by regulating and controlling the expression of genes at the post-transcriptional level, and in the cells of different tissues of the body, fluid Plasma and other body fluids such as tears, urine and amniotic fluid are found.[16] Research has proven that miRNAs are the most stable nucleic acids in peripheral blood. This topic has accelerated the investigation of circulating miRNAs as a new marker for rapid cancer diagnosis.[17] Considering the importance of breast cancer diagnosis and the consensus of the results of previous studies, the present systematic review and meta-

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analysis study was conducted to evaluate MiR-513a-5p impinges on progesterone receptor protein expression in breast cancer cells.

2. Material and methods

Search strategy and Information sources

The present study was based on the PRISMA 2020-27-item checklist.[18] By giving the keywords microRNAs, breast cancer, MiR-513a-5p, progesterone, all articles available in the international databases, PubMed, Web of Science, Scopus, Science Direct, Web of Knowledge, EBSCO, Wiley, ISI, Elsevier, Embase databases and Google Scholar search engine were reviewed until August 2023. In addition to this list of sources, the selected articles were screened to find relevant references. The search was done independently by two researchers to avoid bias. The keywords studied based on the MeSH term were:

(((((("Neoplasms"[Mesh]) OR "Breast Neoplasms"[Mesh]) AND "MicroRNAs"[Mesh]) AND ("Progesterone"[Mesh] OR "Receptors, Progesterone"[Mesh])) AND "Risk Factors"[Mesh])) AND "Hormones"[Mesh]) AND "MIRN513A1 microRNA, human" [Supplementary Concept].

Study selection criteria

Inclusion and exclusion criteria

breast cancer patients, Hormone assay, and availability of the full text of the article. Studies with incomplete results, case studies, case reports, in vivo studies, and review articles were excluded.

Selection and data collection process

Two researchers independently collected data from the selected studies using a pre-prepared standard checklist to reduce reporting bias and errors. This checklist included demographic information, clinical information, and study results.

Study risk of bias assessment

The grading method recommended by the GRADE system was used To evaluate the quality of the evidence.[19] According to GRADE, the quality of the evidence is classified into four groups: 1. Studies that do not change the validity of the evaluation results regarding the therapeutic effect (high quality); 2. Studies that are more effective on the validity of the evaluation results regarding the therapeutic effect (moderate quality); 3. Studies that affect the validity of the evaluation results about the therapeutic effect and change the evaluation results (low quality); 4. Studies in which the results of evaluating the therapeutic effect are unclear (low quality).

Data analysis

STATA/MP. v17 software was used in this meta-analysis. Firstly, heterogeneity between studies was assessed by X2-based Q-tests and I^2 tests (25%: low heterogeneity, 25-75%: moderate heterogeneity, and more than 75%: high heterogeneity) or was considered significantly heterogeneous ($p<0.05$). Meta-analysis was performed using mean differences with a 95% confidence interval; the results were combined using the fixed effect model (Inverse–variance method) in meta-analysis. (Table 1)

3. Results

Study selection

In the initial search, 90 articles were found, and all articles were entered into EndNote.X8 software; in the first stage, by studying the titles of the articles, 30 articles were deleted due to being repetitive. In the second step, by studying the abstract of 60 articles, 48 unrelated articles (based on the inclusion and exclusion criteria) were excluded from the study. In the third step, after carefully reading the full text of 12 articles, nine articles were deleted due to inconsistency with the purpose of the study. Finally, three articles were used in this study.

MiRNA-513a-5p constitutes a risk factor for breast cancer

According to Fig.2, miR-513a-5p upregulation was directly and statistically significantly associated with breast cancer risk (OR = 1.45; 95% CI 1.07–1.83; P<0.01). MiR-513a-5p expression was directly and significantly associated with an almost 66% increase in breast cancer risk (ES = 66%; 95% CI 36%–96%; P<0.01) (Fig. 3).

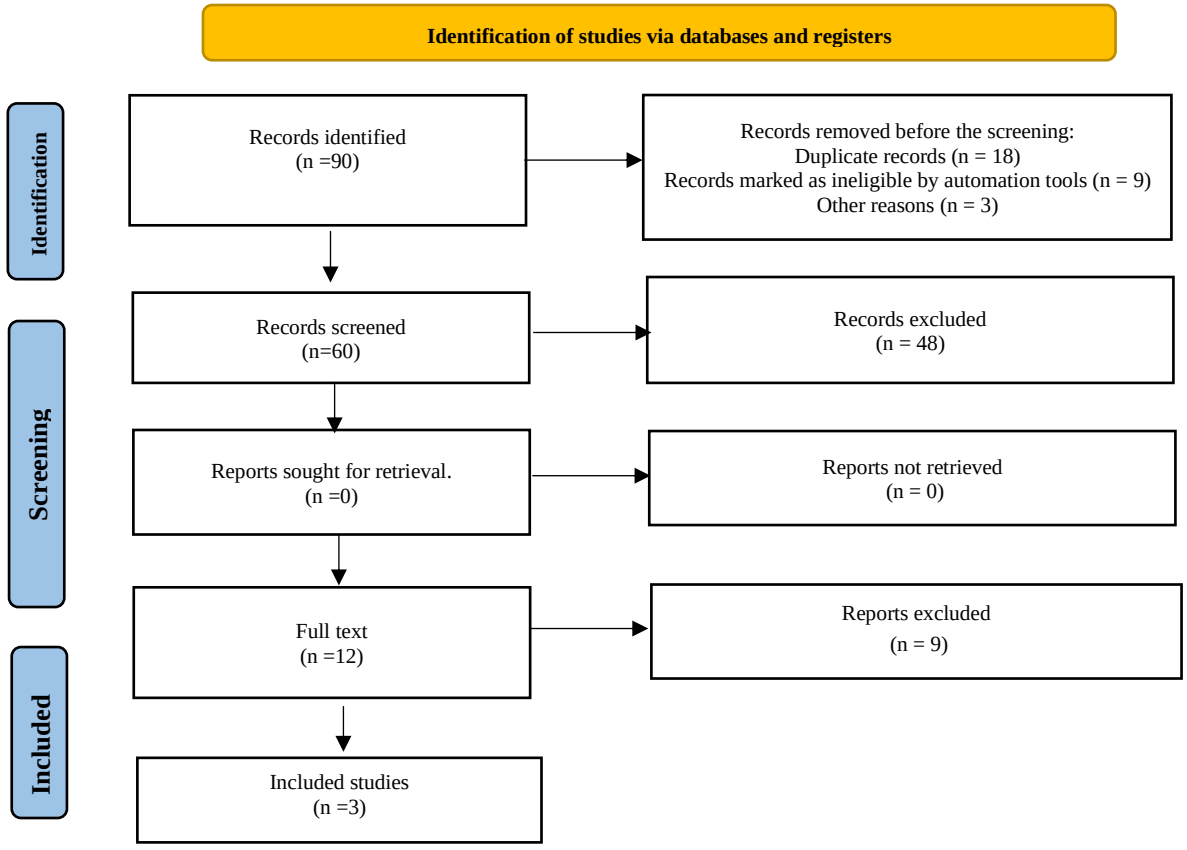

Fig. 1. PRISMA 2020 Checklist.

Table 1. Characteristics of the selected studies.

Study. Years	Clinical Samples		Cell Culture	Type of MiRNAs	Outcome
	Breast Cancer Cases	Control			
Fu et al., 2021[20]	17	17	Human breast epithelial cell line MCF-10A and four BC cell lines, MCF7, MDA-MB-231, MDA-MB-468, and MDA-MB-453	miR-382-5p, miR-506-5p, miR-513a-5p, and miR-134-5p	MiR-513a-5p is a target of ZBED3-AS1
Muti et al., 2018[21]	191	191	Human luminal breast cancer cell lines MCF-7, T47D, ZR-75-1 and BT-474	miR-513-a-5p, miR513b-5p and miR-513c-5p	The progesterone receptor is a direct target of miR-513a-5p
Cochrane et al., 2012[22]	28		T47D and MCF7 breast cancer cells	miR-29a, miR-29b and miR-29c, miR-141, miR-200, miR-513a-5p and miR-513a-3p	The progesterone progestin downregulates the progesterone receptor itself, upregulated miRNA miR-513a-5p

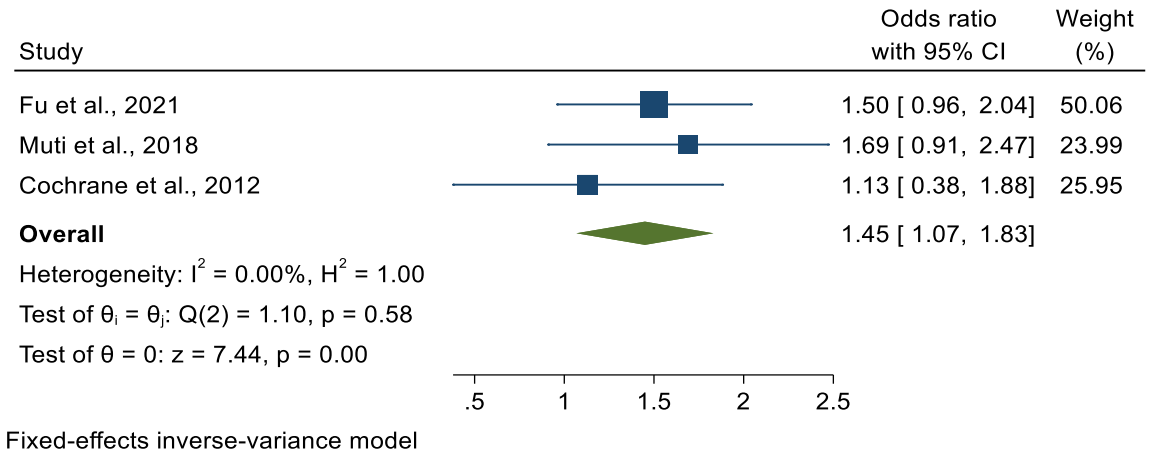

Fig. 2. MiR-513a-5p differential expression was directly and significantly associated with the risk of breast cancer.

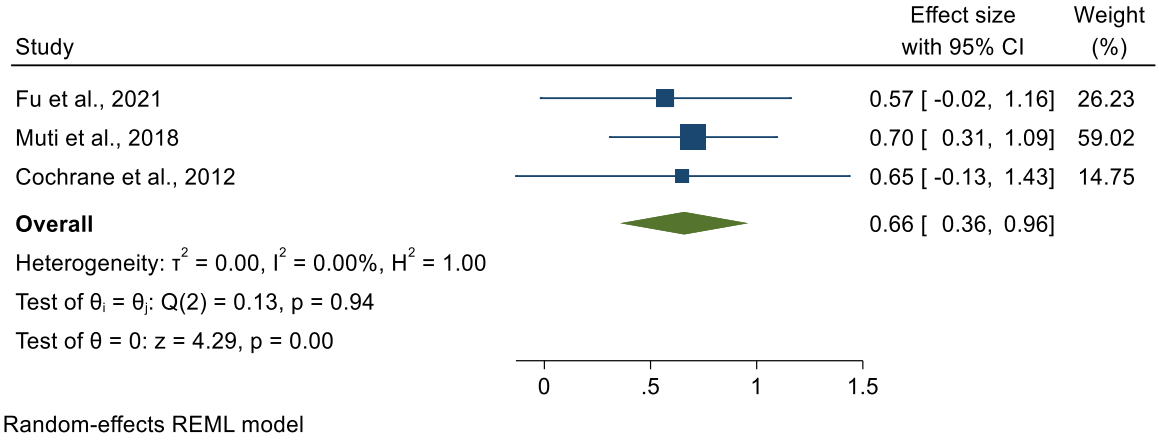

Fig. 3. Breast cancer risk.

4. Discussion

According to our knowledge, this study is the first systematic review and meta-analysis conducted to evaluate MiR-513a-5p impacts on progesterone receptor protein expression in breast cancer cells. In selected studies, miR-513a-5p have been identified as prognostic miRNAs that can reduce progesterone receptor levels and potentially reduce the biological function of progesterone. Through the searches, only three studies were found that investigated the association of MiR-513a-5p with breast cancer. In one of the studies, miR-513a-5p upregulation was directly and statistically significantly associated with breast cancer risk.[21] The following study showed that miR-513a-5p provides a novel mechanism for controlling progesterone receptor protein expression.[22] In another study, the effects of ZBED3-AS1 on the malignant behaviors of BC cells were assessed, and it was observed that miR-513a-5p is a target of ZBED3-AS1 and the relationship between miR-513a-5p and KLF6 in breast cancer.[20] Studies have shown that progesterone has anti-inflammatory properties, can inhibit oncogenic pathways, and plays an important role in the development of breast cancer.[23] The evidence of the present study also confirms these findings that the low expression of progesterone receptors can be a facilitating condition for the development of cancer. However, the exact role of progesterone in the course of breast cancer is an unsolved scientific issue. In postmenopausal women, changes in progesterone serum concentration have been challenged.[24] Few studies have investigated the progesterone receptor as the main result of the functional activity of miR-513a-5p; by studying the available literature in this field, they have described the correlation between progesterone receptor expression and different miRNAs.[25] The findings of the study showed that increased miR-513a-5p expression levels were observed in breast cancer cells after progesterone treatment.[22] Based on the findings of various studies, increased testosterone levels are associated with breast cancer; the association of miR-513a-5p upregulation with increased testosterone levels should be investigated in future studies. The present study had limitations, such as very few studies evaluating MiR-513a-5p impacts on progesterone receptor protein expression in breast cancer cells. Also, the sample size was small, and on the other hand, the follow-up of patients was only investigated in one study; more studies are needed to confirm the evidence.

5. Conclusion

According to the present meta-analysis, the positive regulation of miR-513-a-5p had a direct and statistically significant relationship with the increased risk of breast cancer. The results of the present study can affect different aspects of breast cancer development. The use and identification of miR-513-a-5p as a long-term biomarker to identify the pathways involved in the early development of breast cancer should be considered.

Conflict of Interest

The authors declared that there is no conflict of interest.

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