REVIEW ARTICLE
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PROGNOSTIC IMPACT OF MICRO-RNA EXPRESSION IN BREAST CANCER: SYSTEMATIC REVIEW

Impacto prognóstico da expressão de micrornas no câncer de mama: revisão sistemática

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ABSTRACT

Breast cancer is an important health problem worldwide and the identification of new prognostic markers is important in establishing the best treatment for each patient. MicroRNAs (miRNAs) are non-coding RNAs that regulate gene expression and that can be useful biomarkers for prognosis in breast cancer. The objective of this systematic review was to investigate tumor miRNA expression potentially associated with the prognostic factors of breast carcinomas. The search was done in the PubMed database; 1457 articles were initially found and 20 studies were included in the review. MiRNA-21 and miRNA-200b were the most commonly investigated in breast cancer prognosis. Lymph node metastasis was associated with the hyperexpression of miRNA-211, miRNA-301a and miRNA-370 and also associated with the hypoexpression of miRNA-124, miRNA-127, miRNA-129-5p, miRNA199-5p, miRNA-206, miRNA-218 and miRNA-339-5p. Distant metastasis was associated with miRNA-204 hypoexpression. Tumor size was associated with hyperexpression of miRNA-21 and miRNA-301a and also to the hypoexpression of miRNA-29b and miRNA129-5p. Lower survival rates were associated with the hyperexpression of miRNA-21, miRNA-301a and microRNA-711, and hypoexpression of miRNA-15a, miRNA-29b, miRNA-124, miRNA-129-5p, miRNA 199b -5p, miRNA-200b, miRNA-204, miRNA-206 and miRNA-218. On the other hand, higher survival rates were associated with the hyperexpression of miRNA-339-5p and miRNA-127 and also to the hypoexpression of miRNA-210. The results of this review emphasize the need to validate these findings in additional studies.

KEYWORDS: microRNA; breast cancer; prognosis.

RESUMO

O câncer de mama é um importante problema de saúde em todo o mundo e a identificação de novos marcadores prognósticos é necessária para estabelecer o melhor tratamento para cada paciente. MicroRNAs (miRNAs) são RNAs não codificadores reguladores da expressão gênica que têm sido evidenciados como biomarcadores úteis no prognóstico do câncer de mama. O objetivo desta revisão sistemática foi verificar o papel da expressão de miRNAs tumorais associados aos fatores prognósticos dos carcinomas de mama. A busca de estudos foi feita no banco de dados PubMed; 1.457 artigos foram inicialmente encontrados e 20 estudos foram incluídos na revisão. MiRNA-21 e miRNA-200b foram os mais comumente investigados em relação ao prognóstico do câncer de mama. A presença de metástase linfonodal foi significativamente associada à hiperexpressão de miRNA-211, miRNA-301a e miRNA-370 e também associada à hipoexpressão de miRNA-124, miRNA-127, miRNA-129-5p, miRNA199-5p, miRNA-206, miRNA-218 e miRNA-339-5p. Metástase a distância foi associada à hipoexpressão de miRNA-204. O tamanho do tumor foi associado à hiperexpressão de miRNA-21 e miRNA-301a e também à hipoexpressão de miRNA-29b e miRNA129-5p. Em relação à sobrevida global, menores taxas de sobrevida foram associadas à hiperexpressão de miRNA-21, miRNA-301a e microRNA-711 e à hipoexpressão de miRNA-15a, miRNA-29b, miRNA-124, miRNA-129-5p, miRNA 199b-5p, miRNA-200b, miRNA-204, miRNA-206 e miRNA-218. Por outro lado, maiores taxas de sobrevida foram associadas à hiperexpressão de miRNA-339-5p e miRNA-127 e também à hipoexpressão de miRNA-210. Os resultados desta revisão enfatizam a necessidade de validar esses achados em estudos adicionais.

PALAVRAS-CHAVE: microRNA, câncer de mama, prognóstico.

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INTRODUCTION

Breast cancer is one of the most frequent neoplasms in women and represents a major public health problem in the world due to its high incidence and mortality. Each year, more than 1.67 million women are diagnosed with this disease and about 522,000 still die from it, despite improvements in diagnosis and treatment[1]. In Brazil, 59,700 new cases of breast cancer are estimated for 2018, corresponding to a predicted risk of 56.33 cases per 100,000 women[2].

Cancer staging is a process used to determine the extent of disease in the body and the location of the tumor. It assists the clinician in the choice of treatment and in determining the patient's prognosis. According to the 8th edition of the American Joint Committee on Cancer (AJCC), the main aspects used in staging and determining prognosis in breast cancer include: tumor size or extent, presence of lymph node metastasis, presence of distant metastasis, estrogen and progesterone receptor expression, epidermal growth factor receptor (HER-2) overexpression, tumor grade, and histologic type[3].

Despite advances in the diagnosis and treatment of breast cancer, the molecular heterogeneity of this disease still poses a great challenge. It is, therefore, necessary to identify new biomarkers for it, in order to better predict the clinical outcomes, as well as to establish the most appropriate treatment for each patient. Recent researches have explored the possibility of using microRNAs (miRNAs) as diagnostic and/or prognostic biomarkers, since these molecules are implicated in the progression of breast cancer[4-6].

The miRNAs are defined as small, non-coding RNA sequences of approximately 22 nucleotides in length. They originate from genes that are transcribed by RNA polymerase II. During the miRNA transcription step, clamp or hairpin structures, named pri-miRNAs (primary transcript RNA), are generated by RNA polymerase II activity and, less frequently, by RNA polymerase III. Still within the nucleus, pri-miRNAs, by action of ribonuclease III, DROSHA and the DGCR8/Pasha cofactor, generate pre-miRNAs (miRNA precursor). The pre-miRNAs are then transported from the nucleus to the cytoplasm by the aid of Protein Exportin 5. The pre-miRNAs are subsequently processed by a second ribonuclease III, called Dicer, releasing mature miRNAs, which in turn are incorporated in the miRNA-induced silencing complex, which may target messenger RNA (mRNA) encoding a specific protein. Mature miRNAs regulate the expression of protein coding genes at the post-transcriptional level. Regulation is partial or complete, by pairing of mature miRNA to the 3' untranslated region (UTR) of the correlated messenger RNA (mRNA), inducing translation inhibition or degradation of the target messenger RNA (Figure 1)[7-9].

The miRNAs are involved in several physiological processes such as proliferation, differentiation, apoptosis and resistance to stress, but, when deregulated they can influence pathological processes, such as tumorigenesis[10,11]. Studies indicate that miRNAs are involved in the initiation and progression of human cancers because of their ability to regulate the actions of many oncogenes and tumor suppressor genes. Deregulation of miRNA expression is described in several types of cancer, including breast cancer[10,12,13]. The miRNAs can be studied in tumor tissues and biological fluids, such as serum or plasma. Differences in the expression of certain miRNAs in breast carcinoma tissues compared to normal tissues have been described in several studies and suggest that miRNAs may be promising biomarkers, useful for early detection and prognosis of breast cancer[4-6,14].

The study of the expression of miRNAs in breast cancer constitutes an area of growing research and of great relevance in the current scientific scenario. However, in the scientific literature, recent systematic reviews that have evaluated the association between the expression of tumor miRNAs and the prognostic aspects of breast cancer are scarce. In addition, the types of tumors evaluated, the miRNA expression quantification method, and the types of biological samples evaluated vary considerably, producing disconnected and even conflicting results

Some studies available in the literature have evaluated the expression of miRNAs only in triple negative breast tumors, others have evaluated the expression of circulating miRNAs, in serum or plasma, while others have investigated the expression

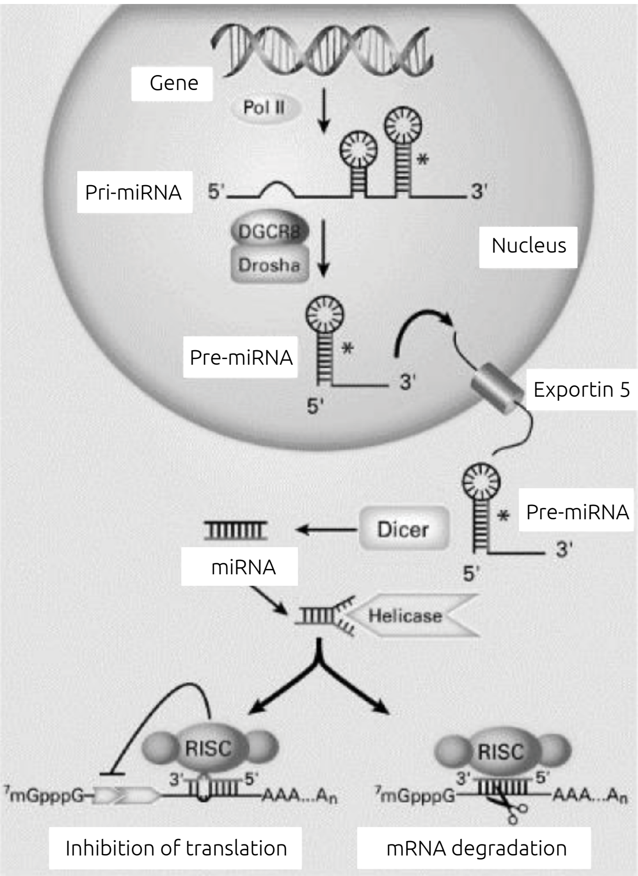

Figure 1. Biogenesis of miRNAs. Adapted from Iorio and Croce[9].

of miRNAs in association with specific clinical aspects, such as the presence of lymph node metastasis or disease recurrence, but there are few studies investigating the overall survival of patients as a function of miRNA expression. This study aimed to review the specific literature on the subject, with emphasis on the studies that evaluated the expression of miRNAs associated with the main prognostic factors in breast carcinomas, especially highlighting the impact of these biomarkers on patient survival.

METHOD

For the preparation of this study, a bibliographic review was performed in the PubMed database to identify relevant studies. Relevance criteria for the classification of studies included:

- studies published from 2002 to 2017;
- primary and descriptive studies;
- studies published in English;
- studies that evaluated the expression of miRNAs as a prognostic fator in breast cancer.

The search strategy adopted the following descriptors (microRNA OR miRNA OR miR) AND (breast cancer) AND (prognosis OR prognostic OR survival).

Relevance criteria for the study design included:

- studies that evaluated the prognosis of breast cancer through survival and/or the disease free interval;
- studies that evaluated miRNA expression through quantitative real-time polymerase chain reaction (RT-qPCR);
- studies that evaluated the expression of miRNAs in relation to tumor size, lymph node involvement by metastasis, distant metastasis, and triple and non-triple negative phenotype;
- studies that evaluated miRNA expression in freshly harvested or formalin-fixed tumor and included in paraffin specimens.

As exclusion criteria, publications that belonged to the category of case reports, literature reviews and meta-analyzes were not included. Two researchers reviewed the titles and abstracts of articles identified in the initial survey to determine the relevance of these publications.

The following data were extracted from the studies: first author, year of publication, number of participants, sample types, case origin, miRNAs studied, methods of miRNA expression evaluation and main results. The data were qualitatively reviewed and summarized in tables.

RESULT

Study selection

A total of 1,457 studies were initially identified through the electronic data search. After reviewing the titles and abstracts of these articles, 74 of them were selected, evaluating the expression of miRNAs in association with the prognosis of breast cancer. Then, careful reading of the full texts of these articles resulted in the exclusion of 54 of them. In total, 20 articles were eligible for systematic review. A flowchart of the study selection process is shown in Figure 2.

Characteristics of included studies

A total of 2,654 breast cancer patients were evaluated in the 20 included studies. The number of patients analyzed ranged from 30 to 344 per study. The researches considered were developed in countries such as Italy, South Korea, Iran, China and Japan — the last two were the ones with the most publications on the subject. The studies reported the prognostic values of 16 different miRNAs; the most studied were miRNA-21 and miRNA-200b: the first was investigated in four surveys, while the second, in two. The other selected studies investigated only a single miRNA. The selected studies used the quantitative real-time polymerase chain reaction (RT-qPCR) to evaluate the expression of miRNAs with TaqMan and SYBR Green quantification methodologies: TaqMan, used in 13 studies, was the most used one. SYBR Green was used in 7. The characteristics of the surveys included in the systematic review are shown in Table 1.

Studies evaluating the prognosis of breast cancer through survival and disease-free intervals have shown that miRNA hypoexpression was more associated with poorer prognosis than hyperexpression of miRNA. Regarding clinical-pathological characteristics, most of the studies showed that miRNA hypoexpression was more associated with lymph node metastasis than with miRNA hyperexpression. Table 2 shows the prognostic aspects related to the expression of miRNAs.

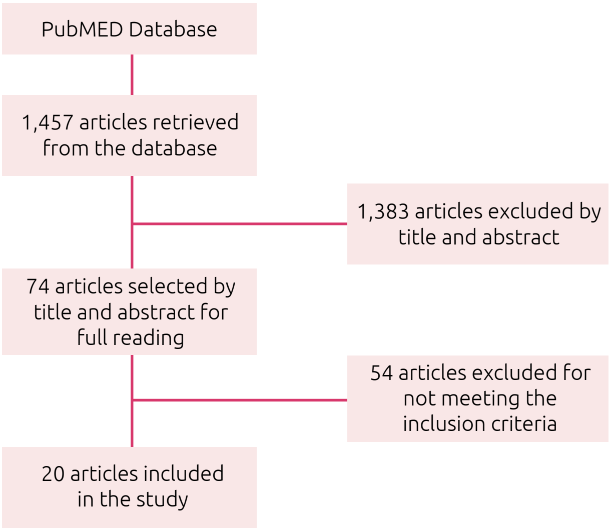

Figure 2. Flowchart of the study selection process.

Table 1. Characteristics of the studies included in the systematic review.

Author/year	miRNAs studied	Cases (n)	Origin of the cases	Quantification method	Results	Reference
Yan et al., 2008[14]	miRNA-21	Breast Ca (n=113) and normal tissue (n=40)	China	RT-qPCR TaqMan	Hyperexpression was associated with the worst prognosis.	14
Qian et al., 2009[10]	miRNA-21	Breast Ca (n=344)	Italy	RT-qPCR TaqMan	Hyperexpression was associated with lower disease-free survival in patients in the early stages.	10
Wu et al., 2010[19]	miRNA-339-5p	Breast Ca (n=90) and normal tissue (n=26)	China	RT-qPCR SYBR Green	Hypoexpression was associated with increased lymph node metastasis.	19
Lee et al., 2011[22]	miRNA-21	Breast Ca (n=109)	South Korea	RT-qPCR Taqman	Hyperexpression was associated with the largest tumor size and the lowest disease-free survival.	22
Toyama et al., 2012[24]	miRNA-210	Breast Ca (n=161)	Japan	RT-qPCR TaqMan	Hypoexpression was associated with better overall survival and better disease-free survival.	24
Li et al., 2013[18]	miRNA-206	Breast Ca (n=128)	China	RT-qPCR Taqman	Hypoexpression was associated with worse prognosis and distant metastasis.	18
Li et al., 2014[20]	miRNA-204	Breast Ca (n=129)	China	RT-qPCR Taqman	Hypoexpression was associated with lower overall survival, lower disease-free survival, and increased metastasis.	20
Dong et al., 2014[23]	miRNA-21	triple negative (n=72) and non-triple negative (n=14) Breast Ca	China	RT-qPCR SYBR Green	Hyperexpression was associated with worse prognosis and triple negative tumors.	23
Wang et al., 2014[16]	miRNA-127	Breast Ca (n=100)	China	RT-qPCR Taqman	Hypoexpression associated with lower overall survival.	16
Yu et al., 2014[11]	miRNA-301a	Triple negative Breast Ca (n=118)	China	RT-qPCR TaqMan	Hyperexpression was associated with lower overall survival, larger tumor size and lymph node metastasis.	11
Ye et al., 2014[21]	miRNA-200b	Breast Ca (n=40)	China	RT-qPCR SYBR Green	Hypoexpression was associated with a worse prognosis.	21
Shinden et al., 2015[26]	miRNA-15a	Breast Ca (n=230)	Japan	RT-qPCR TaqMan	Hypoexpression was associated with lower disease-free survival and lower overall survival.	26
Sim et al., 2015[15]	miRNA-370	Breast Ca (n=60)	South Korea	RT-qPCR SYBR Green	Hyperexpression was associated with lymph node metastasis and reduced disease-free survival.	15
Shinden et al., 2015[12]	miRNA-29b	Breast Ca (n=94)	Japan	RT-qPCR TaqMan	Hypoexpression was associated with lower overall survival and lower disease-free survival.	12
Dong et al., 2015[13]	miRNA-124	Breast Ca and normal tissue (n=133)	China	RT-qPCR SYBR Green	Hypoexpression was associated with lower overall survival, lymph node metastasis and low histopathological differentiation.	13
Yu et al., 2015[17]	miRNA-129-5p	Breast Ca and normal tissue (n=30)	China	RT-qPCR TaqMan	Hypoexpression was associated with lower survival.	17
Yao et al., 2015[25]	miRNA-200b	Breast Ca and normal tissue (n=278)	China	RT-qPCR SYBR Green	Hypoexpression was associated with lower survival.	25
Fang et al., 2016[4]	miRNA-199b-5p	Breast Ca and normal tissue (n=131)	China	RT-qPCR Taqman	Hypoexpression was associated with lymph node metastasis and decreased overall survival.	4
Hu et al., 2016[5]	miRNA-711	Breast Ca (n=161)	China	RT-qPCR TaqMan	Hyperexpression was associated with lower overall survival and lower disease-free survival.	5
Ahmadinejad et al., 2017[6]	miRNA-218	Breast Ca and normal tissue (n=33)	Iran	RT-qPCR SYBR Green	Hypoexpression was associated with lymph node metastasis, high grade and worse prognosis.	6

Breast Ca: breast cancer; RT-qPCR: quantitative real-time polymerase chain reaction.

microRNAs and the prognostic of breast cancer

miRNAs associated with the presence of lymph node metastasis

Three studies demonstrated hyperexpression of miRNA-21[14], miRNA-301a[11] and miRNA-370[15] associated with the presence of lymph node metastasis. On the other hand, seven of them demonstrated hypoexpression of miRNA-124[13], miRNA-127[16], miRNA-129-5p[17], miRNA-199b-5p[4], microRNA-206[18], miRNA-218[6] and miRNA-339-5p[19] associated with the presence of lymph node metastasis (Table 2).

miRNAs associated with the presence of distant metastasis

The hypoexpression of miRNA-204[20] and miRNA-200b[21] was associated with the presence of distant metastasis in two studies. No other study showed associations between hyperexpression of miRNAs and the presence of distant metastasis (Table 2).

miRNAs associated with tumor size

Hyperexpression of miRNA-21[22,23] and miRNA-301a[11] associated with tumor size was reported in three studies. The hypoexpression of miRNA-29b[12] and miRNA-129-5p[17] associated with tumor size was reported in two studies (Table 2).

miRNAs associated with triple negative phenotype

The triple negative phenotype is characterized by the absence of expression of estrogen, progesterone and HER-2 receptors in breast cancer. The hyperexpression of miRNA-210[24] and miRNA-301a[11] was associated with the triple negative phenotype in two studies, and miRNA-21[23] hypoexpression was associated with triple negative phenotype in a single study (Table 2).

miRNAs associated with the HER-2 positive phenotype

Hyperexpression of miRNA-21[22] was associated with HER-2 positive phenotype in one study, and miRNA-200b[25] hypoexpression was also associated with HER-2 positive phenotype in one study (Table 2).

miRNAs associated with overall survival

The hyperexpression of miRNA-21[10], miRNA-301a[11] and miRNA-711[5] was associated with poorer prognosis (lower overall survival) in six studies, while miRNA-127[16] and miRNA-339-5p[19] hyperexpression were associated with better prognosis (greater overall survival) in two studies. On the other hand, the hypoexpression of miRNA-15a[26], miRNA-29b[12], miRNA-124[13], miRNA-129-5p[17], miRNA-199b-5p[4], miRNA-200b[21,25], miRNA-204[20], miRNA-20[18] and miRNA-218[6] was associated to the worst prognosis in nine studies, and miRNA-210[24] hypoexpression was associated with better prognosis in a single study (Table 2).

miRNAs associated with disease-free survival

Hyperexpression of miRNA-21[10], miRNA-370[15] and miRNA-711[5] was associated with lower disease-free survival in three studies, while miRNA-339-5p[19] hyperexpression was associated with greater disease-free survival in a single study. On the other hand,

Table 2. Expression of miRNAs associated with prognostic aspects.

Prognostic aspect	Hypoexpressed miRNAs	Hyperexpressed miRNAs
Lymph node metastasis	miRNA-124[13], miRNA-127[16], miRNA-129-5p[17], miRNA-199b-5p[4], microRNA-206[18], miRNA-218[6] and miRNA-339-5p[19]	miRNA-21[14], miRNA-301a[11] and miRNA-370[15]
Distant metastasis	miRNA-204[20] and miRNA-200b[21]	
Tumor size	miRNA-29b[12] and miRNA-129-5p[17]	miRNA-21[22,23] and miRNA-301a[11]
Tumor phenotype (TN)	miRNA-21[23]	miRNA-210[24] and miRNA-301a[11]
Overall survival		
Poor survival	miRNA-15a[26], miRNA-29b[12], miRNA-124[13], miRNA-129-5p[17], miRNA-199b-5p[4], miRNA-200[21,25], miRNA-204[20], miRNA-206[18] and miRNA-218[6]	miRNA-21[10], miRNA-301a[11] and miRNA-711[5]
Best survival	miRNA-210[24]	miRNA-127[16] and miRNA-339-5p[19]
Disease-free survival		
Poor survival	miRNA-15a[26], miRNA-29b[12] and miRNA-204[20]	miRNA-21[10], miRNA-370[15] and miRNA-711[5]
Best survival	miRNA-210[24]	miRNA-339-5p[19]
Estrogen receptor		
Positive		
Negative	miRNA-200b[25]	miRNA-21[22]
Progesterone receptor		
Positive		
Negative	miRNA-129-5p[17]	miRNA-21[10]
HER-2		
Positive	miRNA-200b[25]	miRNA-21[22]
Negative		

TN: triple negative.

hypoexpression of miRNA-15a[26], miRNA-29b[12] and miRNA-204[20] was associated with lower disease-free survival in three studies, while miRNA-210[24] hypoexpression was associated with greater disease-free survival in a single study (Table 2).

DISCUSSION

The studies evaluated in this systematic review have shown that tumor miRNAs are useful biomarkers to predict the prognosis of breast cancer patients. Analysis of its expression allowed to differentiate characteristic expression profiles in this cancer in relation to normal mammary tissue and the expression of miRNAs in breast cancer was also correlated with conventional prognostic characteristics, such as tumor size, lymph node metastasis, distant metastasis and lower survival , suggesting the potential prognosis of these biomarkers.

The miRNAs can be investigated in two ways, either in tumor tissues or in circulating form, in serum or plasma. In this study, we prioritized the miRNAs evaluated in tumor tissues compared to normal tissues. The miRNAs may be hyper- and hypoexpressed in tumor tissues. Hyperexpressed ones can act as oncogenes because of their ability to suppress tumor suppressor genes[8]. The major oncogenic miRNAs were miRNA-21[10,14,22,23], miRNA-301a[11], miRNA-370[15] and miRNA-711[5] and their hyperexpression was associated with more aggressive characteristics of the tumor. In contrast, hypoexpressed microRNAs may act as tumor suppressors, as long as they suppress the expression of oncogenes[8]. Tumor suppressor miRNAs included miRNA-339-5p[19], miRNA-206[18], miRNA-204[20], miRNA-127[16], miRNA-200b[21,25], miRNA-15a[26], miRNA-29b[12], miRNA-124[13], miRNA-129-5p[17], miRNA- 199-5p[4] and miRNA-218[6], and the hypoexpression of most of these was associated with the presence of lymph node metastasis.

In the present study, miRNA-21 and miRNA-200b were the most commonly investigated in the prognosis of breast cancer. The miRNA-21, considered as an oncogenic miRNA, was investigated in four studies and its expression was significantly increased in breast cancers compared to normal tissues. Hyperexpression of this miRNA was significantly associated with more aggressive tumor characteristics, such as larger tumors and lymph node metastasis. Patients with breast cancer with hyperexpression of miRNA-21 presented worse prognosis, that is, lower overall survival[10,14,22,23].

The miRNA-200b, considered a tumor suppressor, was investigated in two studies and its expression was significantly lower in breast cancers than in normal tissues. The hypoexpression of miRNA-200b was associated with the most advanced clinical stage and the presence of distant metastases in breast cancer. Patients with miRNA-200b hypoexpression presented worse prognosis compared to those with overexpression of miRNA-200b[21,25].

Other miRNAs were also associated with the prognosis of breast carcinomas, but most of them were evaluated in only one study. The lowest survival rates were associated with hyperexpression of miRNA-301a[11] and microRNA-711[5] and hypoexpression of miRNA-15a[26], miRNA-29b[12], miRNA-124[13], miRNA-129-5p[17], miRNA-199b-5p[4], miRNA-204[20], miRNA -206[18] and miRNA-218[6]. On the other hand, higher survival rates were associated with the hyperexpression of miRNA-127[16] and miRNA-339-5p[19] and also to the hypoexpression of miRNA-210[24]. Thus, these miRNAs can be considered as having the most promising prognostic potential for breast cancer.

The findings of this study were similar to those found in three systematic reviews available in the literature. Nassar et al.[27] demonstrated that miRNA-21, miRNA-210 and miRNA-711, when hyperexpressed, were associated with lower survival rates. Other miRNAs suggested as prognostic biomarkers were reported by this study, including miRNA-9, miRNA-30a, let-7b, miRNA-106b, miRNA-122, miRNA-18b, miRNA-103, miRNA-107, miRNA-652, miRNA -155, miRNA-19a, miRNA-181b, miRNA-24, miRNA-27a, miRNA-27b-3p, miRNA-23a, miRNA-324-5p, miRNA-122, miRNA-375, miRNA-126, miRNA-10a. Van Schooneveld et al.[28] also reported miRNA-21 and miRNA-210 as associated with poor prognosis in breast cancer. Bertoli et al.[29] reported that miRNA-21, miRNA-29b, miRNA-204, miRNA-210 and miRNA-339-5p are the major prognostic biomarkers for breast cancer.

A discordant point to our systematic review over those previously published is that many miRNAs that appear in the other reviews were not included in our study. It is important to emphasize the heterogeneity of the previously published reviews, which evaluated the expression of miRNAS not only in tumor tissues, but also in blood, serum or plasma of patients with breast cancer. In addition to the diversity of biological samples evaluated, some included studies analyzing the expression of miRNAs in cell lines and not in tumor tissues or that used different quantification methods, such as microarrays and ***in situ*** hybridization.

Some limitations should be considered when interpreting the results of the present study. First, the analysis was limited to articles published in English. Second, the large number of miRNAs evaluated in individual studies makes it difficult to validate the results and to conduct qualitative and quantitative analyses, as a meta-analysis.

It is likely that the use of miRNAs as prognostic biomarkers has important implications for predicting the survival of breast cancer patients and that they will be incorporated as a new tool in clinical practice in the future. However, the results emphasize the need to systematically validate these findings in additional independent cohorts or through preclinical/clinical verification studies. In addition, it is necessary to select the most relevant miRNAs in breast cancer and to carry out global studies with a greater number and diversity of patients. In this way, the miRNAs can be used in clinical practice.

CONCLUSION

Specific tissue miRNAs can be considered as promising new biomarkers for prognosis in breast cancer patients. In this review, the expression of miRNAs associated with the prognosis of breast carcinomas was demonstrated. However, our results emphasize the need to systematically validate these findings in additional studies so that miRNAs are incorporated as a new tool in clinical practice.

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